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THE CONCISE GUIDE TO PHARMACOLOGY 2017/18

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THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Enzymes

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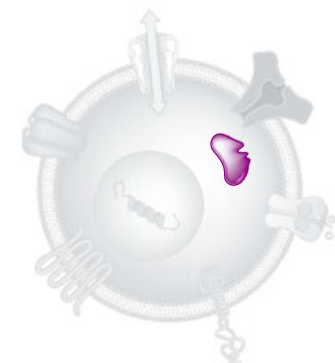
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Abstract

The Concise Guide to PHARMACOLOGY 2017/18 provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at <http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full>. Enzymes are one of the eight major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, other ion channels, nuclear hormone receptors, catalytic receptors and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2017, and supersedes data presented in the 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature Committee of the Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

Conflict of interest

The authors state that there are no conflicts of interest to declare.

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Overview: Enzymes are protein catalysts facilitating the conversion of substrates into products. The Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB) classifies enzymes into families, using a four number code, on the basis of the reactions they catalyse. There are six main families:

- EC 1.-.- Oxidoreductases;
- EC 2.-.- Transferases;
- EC 3.-.- Hydrolases;
- EC 4.-.- Lyases;
- EC 5.-.- Isomerases;
- EC 6.-.- Ligases.

Although there are many more enzymes than receptors in biology, and many drugs that target prokaryotic enzymes are effective medicines, overall the number of enzyme drug targets is relatively small [392, 430], which is not to say that they are of modest importance.

The majority of drugs which act on enzymes act as inhibitors; one exception is metformin, which appears to stimulate activity of AMP-activated protein kinase, albeit through an imprecisely-defined mechanism. Kinetic assays allow discrimination of competitive, non-competitive, and un-competitive inhibitors. The majority of inhibitors are competitive (acting at the enzyme's ligand recognition site), non-competitive (acting at a distinct site;

potentially interfering with co-factor or co-enzyme binding) or of mixed type. One rare example of an uncompetitive inhibitor is lithium ions, which are effective inhibitors at inositol 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 available from the indicated literature.

Many enzymes require additional entities for functional activity. Some of these are used in the catalytic steps, while others pro-

mote 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

S275	Kinases (EC 2.7.x.x)	–	ATR subfamily	–	RAD53 family
–	AGC: Containing PKA, PKG, PKC families	S278	FRAP subfamily	–	Testis specific kinase (TSSK) family
–	DMPK family	–	SMG1 subfamily	–	Trbl family
–	GEK subfamily	–	TRRAP subfamily	–	Trio family
–	Other DMPK family kinases	–	Other PIKK family kinases	–	CK1: Casein kinase 1
S276	Rho kinase	–	RIO family	–	Casein kinase 1 (CK1) family
–	G protein-coupled receptor kinases (GRKs)	–		–	Tau tubulin kinase (TTBK) family
–	Beta-adrenergic receptor kinases (βARKs)	–	RIO1 subfamily	–	Vaccina related kinase (VRK) family
–	Opsin/rhodopsin kinases	–	RIO2 subfamily	–	CMGC: Containing CDK, MAPK, GSK3, CLK families
–	GRK4 subfamily	–	RIO3 subfamily	–	CLK family
–	MAST family	–	PDHK family	S279	Cyclin-dependent kinase (CDK) family
–	NDR family	–	Pyruvate dehydrogenase kinase (PDHK) family	–	CCRK subfamily
–	PDK1 family	–	TAF1 family	–	
–	Protein kinase A	–	TIF1 family	–	CDK1 subfamily
–	Akt (Protein kinase B)	–	CAMK: Calcium/calmodulin-dependent protein kinases	S279	CDK4 subfamily
S276	Protein kinase C (PKC)	–	CAMK1 family	–	CDK5 subfamily
S277	Alpha subfamily	–	CAMK2 family	–	CDK7 subfamily
S277	Delta subfamily	–	CAMK-like (CAMKL) family	–	CDK8 subfamily
S277	Eta subfamily	–	AMPK subfamily	–	CDK9 subfamily
–	Iota subfamily	–	BRSK subfamily	–	CDK10 subfamily
–	Protein kinase G (PKG)	–	CHK1 subfamily	–	CRK7 subfamily
–	Protein kinase N (PKN) family	–	HUNK subfamily	–	PITSLRE subfamily
–	RSK family	–	LKB subfamily	–	TAIRE subfamily
–	MSK subfamily	–	MARK subfamily	–	Cyclin-dependent kinase-like (CDKL) family
–	p70 subfamily	–	MELK subfamily	–	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase (DYRK) family
–	RSK subfamily	–	NIM1 subfamily	–	Dyrk1 subfamily
–	RSKR subfamily	–	NuaK subfamily	–	Dyrk2 subfamily
–	RSKL family	–	PASK subfamily	–	HIPK subfamily
–	SGK family	–	QIK subfamily	–	PRP4 subfamily
–	YANK family	–	SNRK subfamily	–	Glycogen synthase kinase (GSK) family
–	Atypical	–	CAMK-unique family	S279	GSK subfamily
–	ABC1 family	–	CASK family	–	Mitogen-activated protein kinases (MAP kinases)
–	ABC1-A subfamily	–	DCAMKL family	–	ERK subfamily
–	ABC1-B subfamily	–	Death-associated kinase (DAPK) family	–	Erk7 subfamily
–	Alpha kinase family	–	MAPK-Activated Protein Kinase (MAPKAPK) family	–	JNK subfamily
–	ChaK subfamily	–	MAPKAPK subfamily	–	p38 subfamily
–	eEF2K subfamily	–	MKN subfamily	–	nmo subfamily
–	Other alpha kinase family kinases	–	Myosin Light Chain Kinase (MLCK) family	–	RCK family
–	BCR family	–	Phosphorylase kinase (PHK) family	–	SRPK family
–	Bromodomain kinase (BRDK) family	–	PIM family	–	Other protein kinases
–	G11 family	–	Protein kinase D (PKD) family	–	CAMKK family
–	Phosphatidyl inositol 3' kinase-related kinases (PIKK) family	–	PSK family	–	

-	Meta subfamily	-	PAKA subfamily	S284	C14: Caspase
-	Aurora kinase (Aur) family	-	PAKB subfamily	-	CE: Cysteine (C) Peptidases
-	Bub family	-	SLK subfamily	-	C48: Ulp1 endopeptidase
-	Bud32 family	-	STLK subfamily	-	M-: Metallo (M) Peptidases
-	Casein kinase 2 (CK2) family	-	TAO subfamily	-	M79: Prenyl protease 2
-	CDC7 family	-	YSK subfamily	-	MA: Metallo (M) Peptidases
-	Haspin family	-	STE20 family	S285	M1: Aminopeptidase N
-	IKK family	-	STE-unique family	S285	M2: Angiotensin-converting (ACE and ACE2)
-	IRE family	-	TK: Tyrosine kinase	S286	M10: Matrix metalloproteinase
-	MOS family	-	Non-receptor tyrosine kinases (nRTKs)	S286	M12: Astacin/Adamalysin
-	NAK family	S281	Abl family	-	M13: Neprilysin
-	NIMA (never in mitosis gene a)	S281	Ack family	-	M49: Dipeptidyl-peptidase III
-	- related kinase (NEK) family	-	Csk family	-	MC: Metallo (M) Peptidases
-	NKF1 family	-	Fak family	-	M14: Carboxypeptidase A
-	NKF2 family	-	Fer family	-	ME: Metallo (M) Peptidases
-	NKF4 family	S281	Janus kinase (JAK) family	-	M16: Pitrilysin
-	NKF5 family	S282	Src family	-	MF: Metallo (M) Peptidases
-	NRBP family	-	Syk family	-	M17: Leucyl aminopeptidase
-					MG: Metallo (M) Peptidases
-	Numb-associated kinase (NAK) family	S282	Tec family	-	M24: Methionyl aminopeptidase
-	Other-unique family	-	TKL: Tyrosine kinase-like	-	MH: Metallo (M) Peptidases
S280	Polo-like kinase (PLK) family	-	Interleukin-1 receptor-associated	-	M18: Aminopeptidase I
-	PEK family	-	kinase (IRAK) family	-	M20: Carnosine dipeptidase
-	GCN2 subfamily	-	Leucine-rich repeat kinase (LRRK) family	-	M28: Aminopeptidase Y
-	PEK subfamily	-	LIM domain kinase (LISK) family	S286	MJ: Metallo (M) Peptidases
-	Other PEK family kinases	-	LIMK subfamily	-	M19: Membrane dipeptidase
-	Sgk493 family	-	TESK subfamily	S287	MP: Metallo (M) Peptidases
-	Slob family	-	Mixed Lineage Kinase (MLK) family	-	M67: PSMD14 peptidase
-	TBCK family	-	HH498 subfamily	-	PA: Serine (S) Peptidases
-	TOPK family	-	ILK subfamily	-	S1: Chymotrypsin
-	Tousled-like kinase (TLK) family	-	LZK subfamily	S287	PB: Threonine (T) Peptidases
-	TTK family	-	MLK subfamily	-	Phosphoribosyl pyrophosphate
-	Unc-51-like kinase (ULK) family	-	TAK1 subfamily	-	C44: amidotransferase
-	VPS15 family	S283	RAF family	-	T1: Proteasome
-	WEE family	-	Receptor interacting protein	S288	T2: Glycosylasparaginase precursor
-	Wnk family	-	kinase (RIPK) family	-	PC: Cysteine (C) Peptidases
-	Miscellaneous protein kinases	-	TKL-unique family	-	C26: Gamma-glutamyl hydrolase
-	actin-binding proteins ADF family	S284	Peptidases and proteinases	-	SB: Serine (S) Peptidases
-	Twinfilin subfamily	-	AA: Aspartic (A) Peptidases	-	S8: Subtilisin
-	SCY1 family	S284	A1: Pepsin	S289	SC: Serine (S) Peptidases
-	Hexokinases	-	AD: Aspartic (A) Peptidases	-	S9: Prolyl oligopeptidase
-	STE: Homologs of yeast Sterile 7,	S284	A22: Presenilin	S289	S10: Carboxypeptidase Y
-	Sterile 11, Sterile 20 kinases	-	CA: Cysteine (C) Peptidases	-	S28: Lysosomal Pro-Xaa carboxypeptidase
S280	STE7 family	-	C1: Papain	-	S33: Prolyl aminopeptidase
-	STE11 family	-	C2: Calpain	-	AAA ATPases
-	STE20 family	-	C12: Ubiquitin C-terminal hydrolase	-	Acetylcholine turnover
-	FRAY subfamily	-	C19: Ubiquitin-specific protease	S290	Adenosine turnover
-	KHS subfamily	-	C54: Aut2 peptidase	S291	Amino acid hydroxylases
-	MSN subfamily	-	C101: OTULIN peptidase	S292	L-Arginine turnover
-	MST subfamily	-	CD: Cysteine (C) Peptidases	S293	2.1.1.- Protein arginine N-methyltransferases
-	NinaC subfamily	-	C13: Legumain	S294	

S294	Arginase	S312	Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase	S346	Nucleoside synthesis and metabolism
S294	Arginine:glycine amidinotransferase	S313	Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs)	S347	Sphingosine 1-phosphate turnover
S294	Dimethylarginine dimethylaminohydrolases	S317	Cytochrome P450	S348	Sphingosine kinase
S295	Nitric oxide synthases	S317	CYP1 family	S348	Sphingosine 1-phosphate phosphatase
S296	Carboxylases and decarboxylases	S317	CYP2 family	S349	Sphingosine 1-phosphate lyase
S296	Carboxylases	S318	CYP3 family	S349	Thyroid hormone turnover
S298	Decarboxylases	S319	CYP4 family	–	1.-.- Oxidoreductases
S299	Catecholamine turnover	S320	CYP5, CYP7 and CYP8 families	–	1.1.1.42 Isocitrate dehydrogenases
S302	Ceramide turnover	S320	CYP11, CYP17, CYP19, CYP20 and CYP21 families	–	1.4.3.13 Lysyl oxidases
S302	Serine palmitoyltransferase	S321	CYP24, CYP26 and CYP27 families	–	1.13.11.- Dioxygenases
–	3-ketodihydro sphingosine reductase	S321	CYP39, CYP46 and CYP51 families	S350	1.14.11.29 2-oxoglutarate oxygenases
S303	Ceramide synthase	S323	Endocannabinoid turnover	S351	1.14.13.9 kynurenine 3-monoxygenase
S304	Sphingolipid Δ^4 -desaturase	S323	N-Acylethanolamine turnover	–	1.17.4.1 Ribonucleoside-diphosphate reductases
S304	Sphingomyelin synthase	S324	2-Acylglycerol ester turnover	–	2.1.1.- Methyltransferases
S305	Sphingomyelin phosphodiesterase	S325	Eicosanoid turnover	–	2.1.2.- Hydroxymethyl-, formyl- and related transferases
S305	Neutral sphingomyelinase coupling factors	S325	Cyclooxygenase	–	2.3.-.- Acyltransferases
S305	Ceramide glucosyltransferase	S326	Prostaglandin synthases	–	2.4.2.1 Purine-nucleoside phosphorylase
S306	Acid ceramidase	S327	Lipoxygenases	S351	2.4.2.30 poly(ADP-ribose)polymerases
S306	Neutral ceramidases	S328	Leukotriene and lipoxin metabolism	S352	2.5.1.58 Protein farnesyltransferase
S307	Alkaline ceramidases	S329	GABA turnover	–	2.6.1.42 Branched-chain-amino-acid transaminase
S307	Ceramide kinase	S330	Glycerophospholipid turnover	–	3.1.-.- Ester bond enzymes
S308	Chromatin modifying enzymes	S331	Phosphoinositide-specific phospholipase C	–	3.1.1.- Carboxylic Ester Hydrolases
–	Enzymatic bromodomain-containing proteins	S332	Phospholipase A ₂	–	3.2.1.- Glycosidases
–	Bromodomain kinase (BRDK) family	S333	Phosphatidylcholine-specific phospholipase D	–	3.4.21.46 Complement factor D
–	TAF1 family	S334	Lipid phosphate phosphatases	S353	3.5.1.- Histone deacetylases (HDACs)
–	TIF1 family	S335	Phosphatidylinositol kinases	–	3.5.1.2 Glutaminases
–	1.14.11.- Histone demethylases	S336	Phosphatidylinositol phosphate kinases	S353	3.5.3.15 Peptidyl arginine deiminases (PADI)
S309	2.1.1.- Protein arginine N-methyltransferases	S339	Haem oxygenase	–	3.6.5.2 Small monomeric GTPases
–	2.1.1.43 Histone methyltransferases (HMTs)	S340	Hydrogen sulphide synthesis	S354	RAS subfamily
–	2.3.1.48 Histone acetyltransferases (HATs)	S341	Hydrolases	–	RAB subfamily
S309	3.5.1.- Histone deacetylases (HDACs)	S342	Inositol phosphate turnover	S355	4.2.1.1 Carbonate dehydratases
–	3.6.1.3 ATPases	S342	Inositol 1,4,5-trisphosphate 3-kinases	–	5.-.- Isomerases
S310	Cyclic nucleotide turnover/signalling	S343	Inositol polyphosphate phosphatases	–	5.2.-.- Cis-trans-isomerases
S310	Adenylyl cyclases (ACs)	S343	Inositol monophosphatase	S355	5.99.1.2 DNA Topoisomerases
S311	Exchange protein activated by cyclic AMP (EPACs)	S344	Lanosterol biosynthesis pathway	–	6.3.3.- Cyclo-ligases
		–	LPA synthesis		

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 (divided into 15 subfamilies), with over 100 protein kinase-like pseudogenes [335]. It is beyond the

scope of the Concise Guide to list all these protein kinase activities, but full listings are available on the 'Detailed page' provided for each enzyme.

Most inhibitors of these enzymes have been assessed in cell-free investigations and so may appear to 'lose' potency and selectiv-

ity 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 [110].

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 [282].

Nomenclature	Rho associated coiled-coil containing protein kinase 1	Rho associated coiled-coil containing protein kinase 2
Systematic nomenclature	ROCK1	ROCK2
HGNC, UniProt	<i>ROCK1</i> , Q13464	<i>ROCK2</i> , O75116
EC number	2.7.11.1	2.7.11.1
Common abbreviation	Rho kinase 1	Rho kinase 2
Inhibitors	RKI-1447 (pIC ₅₀ >9) [414], Y27632 (pIC ₅₀ 5.9–7.3) [328, 575], fasudil (pK _i 7) [434], Y27632 (pK _i 6.8) [540], fasudil (pIC ₅₀ 5.5–5.6) [328, 434]	RKI-1447 (pIC ₅₀ >9) [414], compound 11d [DOI: 10.1039/c0md00194e] (pIC ₅₀ >9) [90], GSK269962A (pIC ₅₀ 8.4) [126], compound 32 (pIC ₅₀ 8.4) [49], compound 22 (pIC ₅₀ 7.7) [575], Y27632 (pIC ₅₀ 6.3–7.2) [328, 575], Y27632 (pK _i 6.8–6.9) [328, 540], fasudil (pIC ₅₀ 5.9–5.9) [328, 434]
Selective inhibitors	GSK269962A (pIC ₅₀ 8.8) [126]	–

Further reading on Rho kinases

Feng, Y, PV LoGrasso, O Defert and R Li 2016 Rho Kinase (ROCK) Inhibitors and Their Therapeutic Potential *J Med Chem* 59: 2269-300 [PMID:26486225]

Nishioka, T, MH Shohag, M Amano and K Kaibuchi 2015 Developing novel methods to search for substrates of protein kinases such as Rho-kinase *Biochim Biophys Acta* 1854: 1663-6 [PMID:25770685]

Shimokawa, H, S Sunamura and K Satoh 2016 RhoA/Rho-Kinase in the Cardiovascular System *Circ Res* 118: 352-66 [PMID:26838319]

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 , and PKC γ 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 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
HGNC, UniProt	<i>PRKCB</i> , P05771	<i>PRKCG</i> , P05129
EC number	2.7.11.13	2.7.11.13
Common abbreviation	PKC β	PKC γ
Inhibitors	sotrastaurin (pIC ₅₀ 8.7) [548], Gö 6983 (pIC ₅₀ 8.1) [195], GF109203X (pIC ₅₀ 7.8) [533] – Bovine, 7-hydroxystaurosporine (pIC ₅₀ 7.5) [468]	Gö 6983 (pIC ₅₀ 8.2) [195], 7-hydroxystaurosporine (pIC ₅₀ 7.5) [469]
Selective inhibitors	ruboxistaurin (pIC ₅₀ 8.2) [250], enzastaurin (pIC ₅₀ 7.5) [140], CGP53353 (pIC ₅₀ 6.4) [75]	–

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
HGNC, UniProt	<i>PRKCA</i> , P17252	<i>PRKCD</i> , Q05655
EC number	2.7.11.13	2.7.11.13
Common abbreviation	PKC α	PKC δ
Activators	–	ingenol mebutate (pK _i 9.4) [263]
Inhibitors	sotrastaurin (pIC ₅₀ 8.7) [548], Gö 6983 (pIC ₅₀ 8.1) [195], 7-hydroxystaurosporine (pIC ₅₀ 7.5) [468]	sotrastaurin (pIC ₅₀ 8.9) [548], Gö 6983 (pIC ₅₀ 8) [195]

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
HGNC, UniProt	PRKCE , Q02156
EC number	2.7.11.13
Common abbreviation	PKC ϵ
Inhibitors	sotrastaurin (pIC ₅₀ 8.2) [548]

Further reading on Protein kinase C

Igumenova TI. (2015) Dynamics and Membrane Interactions of Protein Kinase C. *Biochemistry* **54**: 4953-68 [PMID:26214365]

Newton AC *et al.* (2017) Reversing the Paradigm: Protein Kinase C as a Tumor Suppressor. *Trends Pharmacol Sci* **38**: 438-447 [PMID:28283201]

Salzer E *et al.* (2016) Protein Kinase C delta: a Gatekeeper of Immune Homeostasis. *J Clin Immunol* **36**: 631-40 [PMID:27541826]

FRAP subfamily

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

Nomenclature	mechanistic target of rapamycin
HGNC, UniProt	MTOR , P42345
EC number	2.7.11.1
Common abbreviation	mTOR
Inhibitors	ridaforolimus (pIC ₅₀ 9.7) [441], torin 1 (pIC ₅₀ 9.5) [310], INK-128 (pIC ₅₀ 9) [231], INK-128 (pK _i 8.9) [231], gedatolisib (pIC ₅₀ 8.8) [544], dactolisib (pIC ₅₀ 8.2) [332], PP-242 (pIC ₅₀ 8.1) [15], PP121 (pIC ₅₀ 8) [15], XL388 (pIC ₅₀ 8) [511], PF-04691502 (pK _i 7.8) [309], apitolisib (pK _i 7.8) [506]
Selective inhibitors	everolimus (pIC ₅₀ 8.7) [464], temsirolimus (pIC ₅₀ 5.8) [278]

Further reading on FRAP subfamily

Hukelmann JL *et al.* (2016) The cytotoxic T cell proteome and its shaping by the kinase mTOR. *Nat. Immunol.* **17**: 104-12 [PMID:26551880]

Saxton RA *et al.* (2017) mTOR Signaling in Growth, Metabolism, and Disease. *Cell* **169**: 361-371 [PMID:28388417]

Cyclin-dependent kinase (CDK) family

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

Overview: The development of CDK inhibitors as anticancer drugs is reviewed in [508], with detailed content covering CDK4 and CDK6 inhibitors under clinical evaluation.

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
HGNC, UniProt	CDK4 , P11802	CDK6 , Q00534
EC number	2.7.11.22	2.7.11.22
Common abbreviation	CDK4	CDK6
Inhibitors	R547 (pK _i 9) [117], palbociclib (pIC ₅₀ 8) [160], Ro-0505124 (pIC ₅₀ 7.7) [129], riviciclib (pIC ₅₀ 7.2) [258], alvociclib (pK _i 7.2) [70]	palbociclib (pIC ₅₀ 7.8) [160]

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
HGNC, UniProt	GSK3B , P49841
EC number	2.7.11.26
Common abbreviation	GSK3B
Inhibitors	CHIR-98014 (pIC ₅₀ 9.2) [440], LY2090314 (pIC ₅₀ 9) [133], CHIR-99021 (pIC ₅₀ 8.2) [440], SB 216763 (pIC ₅₀ ~8.1) [95], 1-azakenpauillone (pIC ₅₀ 7.7) [285], SB-415286 (pIC ₅₀ ~7.4) [95], IM-12 (pIC ₅₀ 7.3) [460]
Selective inhibitors	AZD2858 (pK _i 8.3) [31]
Comments	Due to its Tau phosphorylating activity, small molecule inhibitors of GSK-3β are being investigated as potential treatments for Alzheimer's disease (AD) [31]. 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 [320].

Further reading on GSK subfamily

Beurel E *et al.* (2015) Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacol Ther* **148**: 114-31 [PMID:25435019]
Domoto T *et al.* (2016) Glycogen synthase kinase-3beta is a pivotal mediator of cancer invasion and resistance to therapy. *Cancer Sci* **107**: 1363-1372 [PMID:27486911]

Khan I *et al.* (2017) Natural and synthetic bioactive inhibitors of glycogen synthase kinase. *Eur J Med Chem* **125**: 464-477 [PMID:27689729]
Maqbool M *et al.* (2016) Pivotal role of glycogen synthase kinase-3: A therapeutic target for Alzheimer's disease. *Eur J Med Chem* **107**: 63-81 [PMID:26562543]

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
HGNC, UniProt	PLK4 , O00444
EC number	2.7.11.21
Common abbreviation	PLK4
Inhibitors	CFI-400945 (pIC ₅₀ 8.6) [343]

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
HGNC, UniProt	MAP2K1 , Q02750	MAP2K2 , P36507
EC number	2.7.12.2	2.7.12.2
Common abbreviation	MEK1	MEK2
Inhibitors	trametinib (pIC ₅₀ 9–9.1) [183, 589], PD 0325901 (pIC ₅₀ 8.1) [208]	trametinib (pIC ₅₀ 8.7) [589]
Allosteric modulators	binimetinib (Negative) (pIC ₅₀ 7.9) [428], refametinib (Negative) (pIC ₅₀ 7.7) [242], CI-1040 (Negative) (pK _d 6.9) [112]	binimetinib (Negative) (pIC ₅₀ 7.9) [428], refametinib (Negative) (pIC ₅₀ 7.3) [242]
Selective allosteric modulators	cobimetinib (Negative) (pIC ₅₀ 9.1) [457]	–

Abl family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Abl family

Nomenclature	ABL proto-oncogene 1, non-receptor tyrosine kinase
HGNC, UniProt	ABL1, P00519
EC number	2.7.10.2
Common abbreviation	Abl
Inhibitors	compound 8h (pIC ₅₀ 9.7) [529], dasatinib (pIC ₅₀ 9.6) [270], compound 24 (pIC ₅₀ 9.3) [118], PD-173955 (pK _d 9.2) [112], bosutinib (pIC ₅₀ 9) [186], PD-173955 (pIC ₅₀ ~8.3) [362], bafetinib (pIC ₅₀ 7.6–8.2) [228, 269], ponatinib (pIC ₅₀ 8.1) [232], nilotinib (pIC ₅₀ 7.8) [372], PP121 (pIC ₅₀ 7.7) [15], imatinib (pIC ₅₀ 6.7) [228], GNF-5 (pIC ₅₀ 6.7) [597]

Ack family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Ack family

Nomenclature	tyrosine kinase non receptor 2
HGNC, UniProt	TNK2, Q07912
EC number	2.7.10.2
Common abbreviation	Ack
Inhibitors	compound 30 (pIC ₅₀ 9) [122]

Janus kinase (JakA) family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Janus kinase (JakA) family

Nomenclature	Janus kinase 1	Janus kinase 2	Janus kinase 3	tyrosine kinase 2
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
Common abbreviation	JAK1	JAK2	JAK3	Tyk2

(continued)				
Nomenclature	Janus kinase 1	Janus kinase 2	Janus kinase 3	tyrosine kinase 2
Inhibitors	ruxolitinib (pIC ₅₀ 8.5–10.1) [203, 423], filgotinib (pIC ₅₀ 8) [541]	NS-018 (pIC ₅₀ 9.1) [374], BMS-911543 (pIC ₅₀ 9) [420], AT-9283 (pIC ₅₀ 8.9) [230], XL019 (pIC ₅₀ 8.7) [152], fedratinib (pIC ₅₀ 8.5) [333, 566], gandotinib (pIC ₅₀ 8.4) [330]	AT-9283 (pIC ₅₀ 9) [230]	–
Selective inhibitors	–	compound 1d (pIC ₅₀ >9) [554]	–	–
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 [64, 115]. 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 → Non-receptor tyrosine kinases (nRTKs) → 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
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
Common abbreviation	Blk	FRK	Fyn	Lyn	Src
Inhibitors	–	–	PP1 (pIC ₅₀ 8.2) [205]	bafetinib (pIC ₅₀ 8) [228]	WH-4-023 (pIC ₅₀ 8.2) [340], PD166285 (pK _i 8.1) [396], PP121 (pIC ₅₀ 7.8) [15], ENMD-2076 (pIC ₅₀ 7.7) [416]

Tec family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Tec family

Nomenclature	BMX non-receptor tyrosine kinase	Bruton tyrosine kinase	TXK tyrosine kinase
HGNC, UniProt	<i>BMX</i> , P51813	<i>BTK</i> , Q06187	<i>TXK</i> , P42681
EC number	2.7.10.2	2.7.10.2	2.7.10.2
Common abbreviation	Etk	Btk	TXK
Inhibitors	compound 38 (pIC ₅₀ 9.1) [300], ibrutinib (pIC ₅₀ 9.1) [318], compound 31 (pIC ₅₀ 8.7) [300]	ibrutinib (pIC ₅₀ 9.3) [395], compound 31 (pIC ₅₀ 8.4) [300], compound 38 (pIC ₅₀ > 8.4) [300]	–
Selective inhibitors	BMX-IN-1 (pIC ₅₀ 8.1) [307]	CGI1746 (pIC ₅₀ 8.7) [120], CHMFL-BTK-11 (Irreversible inhibition) (pIC ₅₀ 7.6) [576]	–

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
HGNC, UniProt	<i>BRAF</i> , P15056	<i>RAF1</i> , P04049
EC number	2.7.11.1	2.7.11.1
Common abbreviation	B-Raf	c-Raf
Inhibitors	GDC-0879 (pIC ₅₀ 9.7–9.9) [112, 206], dabrafenib (pIC ₅₀ 8.5) [305], regorafenib (pIC ₅₀ 7.6) [594], vemurafenib (pIC ₅₀ 7) [555], PLX-4720 (pK _d 6.5) [112], compound 2 (pK _d 6.3) [227], CHIR-265 (pK _d 5.9) [112]	–
Selective inhibitors	–	GW5074 (pIC ₅₀ 8.1) [88]

Further reading on Kinases (EC 2.7.x.x)

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. *Neuropharmacology* **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]

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 (exo-peptidases and exo-proteinases) at the amino terminus (amino-peptidases) or carboxy terminus (carboxy-peptidases). Non-terminal peptide bonds are cleaved by endo-peptidases and endo-proteinases, which are divided into

serine endo-peptidases (EC 3.4.21.-), cysteine endo-peptidases (EC 3.4.22.-), aspartate endo-peptidases (EC 3.4.23.-), metallo-endo-peptidases (EC 3.4.24.-) and threonine endo-peptidases (EC 3.4.25.-).

Since 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 that have ligands (mostly small-molecules) directed against them. For those interested in detailed background we recommend the MEROPS database [450] (with whom we collaborate) as an information resource [432].

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) [580]

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) [260] in the generation of amyloid beta (A β) [7, 510]. Given that the accumulation and aggregation of A β in the brain is piv-

otal in the development of Alzheimer's disease (AD), inhibition of PS activity is one mechanism being investigated as a therapeutic option for AD [187]. 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 [119]. The most active small peptides in this report were P4 and P8, from the amino-terminal domain of PS-1.

Information on members of this family may be found in the [online database](#).

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 cas-

pases (caspases 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 prote-

olysed 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.

Information on members of this family may be found in the [online database](#).

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 [522].

Information on members of this family may be found in the [online database](#).

M2: Angiotensin-converting (ACE and ACE2)

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

Nomenclature	Angiotensin-converting enzyme
HGNC, UniProt	ACE, P12821
EC number	3.4.15.1
Common abbreviation	ACE
Endogenous substrates	angiotensin I (AGT, P01019) > angiotensin II (AGT, P01019)
Inhibitors	zofenoprilat (pK _i 9.4) [283] – Rabbit, captopril (pK _i 8.4) [354], zofenopril
Selective inhibitors	perindoprilat (pIC ₅₀ 9) [73], cilazaprilat (pIC ₅₀ 8.7) [559] – Rabbit, imidaprilat (pIC ₅₀ 8.7) [443], lisinopril-tryptophan (C-domain assay) (pIC ₅₀ 8.2) [560], RXP-407 (N-domain selective inhibition) (pIC ₅₀ 8.1) [472], fosinoprilat (pIC ₅₀ 8) [113] – Rabbit, enalaprilat (pIC ₅₀ 7.5) [87], benazeprilat (pIC ₅₀ 6.6) [296]
Comments	Reports of ACE GPI hydrolase activity [277] have been refuted [298]

M10: Matrix metallopeptidase

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

Overview: Matrix metalloproteinases (MMP) are calcium- and zinc-dependent proteinases regulating the extracellular matrix and are often divided (*e.g.* [545]) on functional and structural bases into gelatinases, collagenases, stromelylinases 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 [537]	–
Comments	MMP2 is categorised as a gelatinase with substrate specificity for gelatinase A.	MMP8 is categorised as a collagenase.

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.

Information on members of this family may be found in the [online database](#).

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	<i>FOLH1</i> , Q04609
EC number	3.4.17.21
Antibodies	capromab (Binding)
Comments	Folate hydrolase is also known as NAALADase as it is responsible for the hydrolysis of N-acetylaspartylglutamate to form N-acetylaspartate and L-glutamate (L-glutamic acid). 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.

Comments: 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 (pK _i 6) [189]

S1: Chymotrypsin

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

Nomenclature	complement C1r	coagulation factor II, thrombin	coagulation factor X
HGNC, UniProt	C1R , P00736	F2 , P00734	F10 , P00742
EC number	3.4.21.41	3.4.21.5	3.4.21.6
Inhibitors	nafamostat (pIC ₅₀ 4.9) [216]	lepirudin (pK _i 13) [506], desirudin (pK _i 12.7) [254], AZ12971554 (pK _i 9.5) [19], melagatran (pK _i 8.7) [198], bivalirudin (pK _i 8.6) [573], dabigatran (pK _i 8.3) [211], argatroban (pK _i 7.7) [238]	rivaroxaban (pK _i 9.4) [407], edoxaban (pK _i 9.2) [412], apixaban (pK _i 9.1) [574]
Selective inhibitors	–	Dup-714 (pK _i 10.4) [175], AR-H067637 (pIC ₅₀ 8.4) [114]	–

Nomenclature	elastase, neutrophil expressed	plasminogen	plasminogen activator, tissue type	protease, serine 1	tryptase alpha/beta 1
HGNC, UniProt	ELANE , P08246	PLG , P00747	PLAT , P00750	PRSS1 , P07477	TPSAB1 , Q15661
EC number	3.4.21.37	3.4.21.7	3.4.21.68	3.4.21.4	3.4.21.59
Inhibitors	alvelestat (pK _i 8) [502], sivelestat (pIC ₅₀ 7.4) [103]	aprotinin {Bovine} (Binding) (pIC ₅₀ 6.8) [492], tranexamic acid (Binding) (pIC ₅₀ 3.6) [492]	–	nafamostat (pIC ₅₀ 7.8) [216]	nafamostat (pIC ₅₀ 10) [365]
Selective inhibitors	–	6-aminocaproic acid (Binding) (pIC ₅₀ 4.4) [86]	–	–	gabexate (pIC ₅₀ 8.5) [135]

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 [93]. 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 subunit beta 5
HGNC, UniProt	PSMB5 , P28074
EC number	3.4.25.1
Inhibitors	bortezomib (pIC ₅₀ 7.7) [371]
Selective inhibitors	ixazomib (pK _i 9) [286]

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 [[315](#), [452](#), [501](#)]. 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 [[106](#), [147](#), [155](#)].

Information on members of this family may be found in the [online database](#).

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 (pK _i 9.2) [196], linagliptin (pK _i 9) [130], sitagliptin (pIC ₅₀ 8.1) [111], vildagliptin (pK _i 7.8) [196]

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 neuromus-

cular 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 (Cartwright blood group)	butyrylcholinesterase
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 ⁺
Common abbreviation	ChAT	AChE	BChE
Inhibitors	compound 2 (pIC ₅₀ 6.5) [190] – Mouse	tacrine (pK _i 7.5) [58], galantamine (pIC ₅₀ 6.3) [94], rivastigmine (pIC ₅₀ 5.4) [325]	rivastigmine (pIC ₅₀ 7.4) [325], tacrine (pK _i 7.2) [58]
Sub/family-selective inhibitors	–	physostigmine (pIC ₅₀ 7.6–7.8) [325]	physostigmine (pIC ₅₀ 7.6–7.8) [325]
Selective inhibitors	–	donepezil (pIC ₅₀ 7.7–8.3) [68 , 170 , 325], BW284C51 (pIC ₅₀ 7.7) [182]	bambuterol (pIC ₅₀ 8.5) [182]
Comments	Splice variants of choline O-acetyltransferase are suggested to be differentially distributed in the periphery and CNS (see [30]).	–	–

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 [[570](#)].

Further reading on Acetylcholine turnover

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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
Systematic nomenclature	–	–	CD73	–
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
Common abbreviation	ADA	ADK	NT5E	SAHH
Rank order of affinity	2'-deoxyadenosine > adenosine	adenosine	adenosine 5'-monophosphate , 5'-GMP , 5'-inosine monophosphate , 5'-UMP > 5'-dAMP , 5'-dGMP	–
Endogenous substrates	–	–	–	S-adenosylhomocysteine
Products	2'-deoxyinosine , inosine	adenosine 5'-monophosphate	uridine , inosine , guanine , adenosine	adenosine
Inhibitors	–	–	–	DZNep (p <i>K</i> _i 12.3) [184] – Hamster
Selective inhibitors	pentostatin (p <i>C</i> ₅₀ 10.8) [4], EHNA (p <i>K</i> _i 8.8) [4]	A134974 (p <i>C</i> ₅₀ 10.2) [348], ABT702 (p <i>C</i> ₅₀ 8.8) [248]	αβ-methyleneADP (p <i>C</i> ₅₀ 8.7) [56]	3-deazaadenosine (p <i>C</i> ₅₀ 8.5) [197]
Comments	–	The enzyme exists in two isoforms derived from alternative splicing of a single gene product: a short isoform, ADK-S, located in the cytoplasm is responsible for the regulation of intra- and extracellular levels of adenosine and hence adenosine receptor activation; a long isoform, ADK-L, located in the nucleus contributes to the regulation of DNA methylation [48, 569].	Pharmacological inhibition of CD73 is being investigated as a novel cancer immunotherapy strategy [552].	–

Comments: An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, [CECRI](#), [Q9NZK5](#)) has been identified [[101](#), [331](#)], which is insensitive to [EHNA](#) [[595](#)]. Other forms of adenosine deaminase act on ribonucleic acids and may be divided into two families: [ADAT1](#) ([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); [ADARB1](#) ([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 severe 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 [[259](#)].

Further reading on Adenosine turnover

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Sawynok J (2016) Adenosine receptor targets for pain. *Neuroscience* **338**: 1-18 [[PMID:26500181](#)]
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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 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⁺	–	–
Endogenous activators	Protein kinase A-mediated phosphorylation (Rat) [2]	Protein kinase A-mediated phosphorylation [251]	Protein kinase A-mediated phosphorylation [252]	Protein kinase A-mediated phosphorylation [252]
Inhibitors	–	methyltyrosine	telotristat ethyl [267]	–
Selective inhibitors	α-methylphenylalanine [191] – Rat, fenclonine	α-propyldopacetamide , 3-chlorotyrosine , 3-iodotyrosine , alpha-methyltyrosine	α-propyldopacetamide , 6-fluorotryptophan [377], fenclonine , fenfluramine	α-propyldopacetamide , 6-fluorotryptophan [377], fenclonine , fenfluramine

(continued)				
Nomenclature	L-Phenylalanine hydroxylase	L-Tyrosine hydroxylase	L-Tryptophan hydroxylase 1	L-Tryptophan hydroxylase 2
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	TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [109].	–	–

Further reading on Amino acid hydroxylases

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- Flydal MI *et al.* (2013) Phenylalanine hydroxylase: function, structure, and regulation. *IUBMB Life* **65**: 341-9 [PMID:23457044]
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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 on L-Arginine turnover

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2.1.1.- Protein arginine N-methyltransferases

Enzymes → L-Arginine turnover → 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 di-methylated products; these may be symmetric (SDMA) or asymmetric (N^G,N^G-dimethyl-L-arginine) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.

Information on members of this family may be found in the [online database](#).

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.

Information on members of this family may be found in the [online database](#).

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 [525], S-(2-boronoethyl)-L-cysteine [97, 268] and 2(S)-amino-6-boronoheptanoic acid [24, 97].

Arginine:glycine amidinotransferase

Enzymes → L-Arginine turnover → Arginine:glycine amidinotransferase

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

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
HGNC, UniProt	<i>DDAH1</i> , O94760	<i>DDAH2</i> , O95865
EC number	3.5.3.18	3.5.3.18
Common abbreviation	DDAH1	DDAH2
Cofactors	Zn ²⁺	–
Inhibitors	compound 2e (p <i>K</i> _i 5.7) [279]	–

Nitric oxide synthases

Enzymes → L-Arginine turnover → Nitric oxide synthases

Overview: Nitric oxide synthases (NOS, E.C. 1.14.13.39) are a family of oxidoreductases that synthesize nitric oxide (NO) via the NADPH and oxygen-dependent consumption of L-arginine with the resultant by-product, L-citrulline. There are 3 NOS isoforms and they are related by their capacity to produce NO, highly conserved organization of functional domains and significant homology at the amino acid level. NOS isoforms are functionally distinguished by the cell type where they are expressed, intracellular targeting and transcriptional and post-translation mechanisms regulating enzyme activity. The nomenclature suggested by **NC-IUPHAR** of NOS I, II and III [363] has not gained wide acceptance, and the 3 isoforms are more commonly referred

to as neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) which reflect the location of expression (nNOS and eNOS) and inducible expression (iNOS). All are dimeric enzymes that shuttle electrons from NADPH, which binds to a C-terminal reductase domain, through the flavins FAD and FMN to the oxygenase domain of the other monomer to enable the BH₄-dependent reduction of heme bound oxygen for insertion into the substrate, L-arginine. Electron flow from reductase to oxygenase domain is controlled by calmodulin binding to canonical calmodulin binding motif located between these domains. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affin-

ity for Ca²⁺/calmodulin (*CALM1 CALM2 CALM3*, P62158) with great avidity and is essentially calcium-independent and constitutively active. Efficient stimulus-dependent coupling of nNOS and eNOS is achieved *via* subcellular targeting through respective N-terminal PDZ and fatty acid acylation domains whereas iNOS is largely cytosolic and function is independent of intracellular location. nNOS is primarily expressed in the brain and neuronal tissue, iNOS in immune cells such as macrophages and eNOS in the endothelial layer of the vasculature although exceptions in other cells have been documented. L-NAME and related modified arginine analogues are inhibitors of all three isoforms, with IC₅₀ values in the micromolar range.

Nomenclature	Endothelial NOS	Inducible NOS	Neuronal NOS
HGNC, UniProt	NOS3 , P29474	NOS2 , P35228	NOS1 , P29475
EC number	1.14.13.39	1.14.13.39	1.14.13.39
Common abbreviation	eNOS	iNOS	nNOS
Endogenous Substrate	L-arginine	L-arginine	L-arginine
Products	NO , L-citrulline	NO , L-citrulline	L-citrulline , NO
Cofactors	oxygen, BH4 , Zn²⁺ , flavin mononucleotide , NADPH , heme , flavin adenine dinucleotide	heme , flavin mononucleotide , flavin adenine dinucleotide , oxygen, NADPH , Zn²⁺ , BH4	flavin adenine dinucleotide , heme , oxygen, BH4 , flavin mononucleotide , NADPH , Zn²⁺
Selective inhibitors	–	1400W (pIC ₅₀ 8.2) [178], 2-amino-4-methylpyridine (pIC ₅₀ 7.4) [139], PIBTU (pIC ₅₀ 7.3) [179], NIL (pIC ₅₀ 5.5) [364], aminoguanidine [99]	3-bromo-7NI (pIC ₅₀ 6.1–6.5) [43], 7NI (pIC ₅₀ 5.3) [20]

Comments: The reductase domain of NOS catalyses the reduction of cytochrome c and other redox-active dyes [[345](#)]. NADPH:O₂ oxidoreductase catalyses the formation of superoxide anion/H₂O₂ in the absence of [L-arginine](#) and [sapropterin](#).

Further reading on Nitric oxide synthases

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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	Propionyl-CoA carboxylase	γ -Glutamyl carboxylase
HGNC, UniProt	PC, P11498	ACACA, Q13085	ACACB, O00763	–	GGCX, P38435
Subunits	–	–	–	Propionyl-CoA carboxylase β subunit, Propionyl-CoA carboxylase α subunit	–
EC number	6.4.1.1	6.4.1.2	6.4.1.2	6.4.1.3	4.1.1.90
Common abbreviation	PC	ACC1	ACC2	PCCA,PCCB	GGCX
Endogenous substrates	ATP, pyruvic acid	ATP, acetyl CoA	acetyl CoA, ATP	propionyl-CoA, ATP	glutamyl peptides
Products	P_i , ADP, oxalacetic acid	P_i , ADP, malonyl-CoA	P_i , ADP, malonyl-CoA	ADP, methylmalonyl-CoA, P_i	carboxyglutamyl peptides
Cofactors	biotin	biotin	biotin	biotin	vitamin K hydroquinone, NADPH
Inhibitors	–	–	–	–	anisindione
Selective inhibitors	–	TOFA (pIC ₅₀ 4.9) [599]	TOFA (pIC ₅₀ 4.9) [599]	–	–
Comments	–	Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase.		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 GGXX 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	Glutamic acid decarboxylase 1	Glutamic acid decarboxylase 2	Histidine decarboxylase
HGNC, UniProt	<i>GAD1</i> , Q99259	<i>GAD2</i> , Q05329	<i>HDC</i> , P19113
EC number	4.1.1.15: L-glutamic acid + H ⁺ -> GABA + CO ₂	4.1.1.15: L-glutamic acid + H ⁺ -> GABA + CO ₂	4.1.1.22
Common abbreviation	GAD1	GAD2	HDC
Endogenous substrates	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid	L-histidine
Products	GABA	GABA	histamine
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate
Selective inhibitors	s-allylglycine	s-allylglycine	AMA, FMH [174]
Comments	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [577]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading).		–

Nomenclature	L-Arginine decarboxylase	L-Aromatic amino-acid decarboxylase	Malonyl-CoA decarboxylase	Ornithine decarboxylase	Phosphatidylserine decarboxylase	S-Adenosylmethionine decarboxylase
HGNC, UniProt	<i>AZIN2</i> , Q96A70	<i>DDC</i> , P20711	<i>MLYCD</i> , O95822	<i>ODC1</i> , P11926	<i>PSD</i> , Q9UG56	<i>AMD1</i> , P17707
EC number	4.1.1.19	4.1.1.28: levodopa -> dopamine + CO ₂ 5-hydroxy-L-tryptophan -> 5-hydroxytryptamine + CO ₂ This enzyme also catalyses the following reaction:: L-tryptophan -> tryptamine + CO ₂	4.1.1.9	4.1.1.17	4.1.1.65	4.1.1.50
Common abbreviation	ADC	AADC	MLYCD	ODC	PSDC	SAMDC

(continued)						
Nomenclature	L-Arginine decarboxylase	L-Aromatic amino-acid decarboxylase	Malonyl-CoA decarboxylase	Ornithine decarboxylase	Phosphatidylserine decarboxylase	S-Adenosylmethionine decarboxylase
Endogenous substrates	L-arginine	levodopa, 5-hydroxy-L-tryptophan, L-tryptophan	malonyl-CoA	L-ornithine	phosphatidylserine	S-adenosyl methionine
Products	agmatine [601]	5-hydroxytryptamine, dopamine	acetyl CoA	putrescine	phosphatidylethanolamine	S-adenosyl-L-methioninamine
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	pyruvic acid	pyruvic acid
Selective inhibitors	–	3-hydroxybenzylhydrazine, L- α -methyldopa, benserazide [108], carbidopa	–	APA (pIC ₅₀ 7.5) [494], eflornithine (pK _d 4.9) [422]	–	sardomozide (pIC ₅₀ 8) [493]
Comments	The presence of a functional ADC activity in human tissues has been questioned [96].	AADC is a homodimer.	Inhibited by AMP-activated protein kinase-evoked phosphorylation [451]	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 [393].	s-allylglycine is also an inhibitor of SAMDC [393].

Further reading on Carboxylases and decarboxylases

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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-Tyrosine hydroxylase	Dopamine beta-hydroxylase (dopamine beta-monoxygenase)	L-Aromatic amino-acid decarboxylase
HGNC, UniProt	<i>PAH</i> , P00439	<i>TAT</i> , P17735	<i>TH</i> , P07101	<i>DBH</i> , P09172	<i>DDC</i> , P20711
EC number	1.14.16.1: L-phenylalanine + O ₂ -> L-tyrosine	2.6.1.5: L-tyrosine + α-ketoglutaric acid -> 4-hydroxyphenylpyruvic acid + L-glutamic acid	1.14.16.2: L-tyrosine + O ₂ -> levodopa	1.14.17.1: dopamine + O ₂ = (-)-noradrenaline + H ₂ O	4.1.1.28: levodopa -> dopamine + CO ₂ 5-hydroxy-L-tryptophan -> 5-hydroxytryptamine + CO ₂ This enzyme also catalyses the following reaction:: L-tryptophan -> tryptamine + CO ₂
Common abbreviation	–	TAT	–	DBH	AADC
Endogenous substrates	L-phenylalanine	–	L-tyrosine	–	levodopa, 5-hydroxy-L-tryptophan, L-tryptophan
Products	L-tyrosine	–	levodopa	–	5-hydroxytryptamine, dopamine
Cofactors	sapropterin	pyridoxal phosphate	sapropterin, Fe ²⁺	Cu ²⁺ , L-ascorbic acid	pyridoxal phosphate
Endogenous activators	Protein kinase A-mediated phosphorylation (Rat) [2]	–	Protein kinase A-mediated phosphorylation [251]	–	–

(continued)					
Nomenclature	L-Phenylalanine hydroxylase	Tyrosine aminotransferase	L-Tyrosine hydroxylase	Dopamine beta-hydroxylase (dopamine beta-monooxygenase)	L-Aromatic amino-acid decarboxylase
Selective inhibitors	α -methylphenylalanine [191] – Rat, fenclonine	–	α -propylidopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine	nepicastat (pIC ₅₀ 8) [496]	3-hydroxybenzylhydrazine, L- α -methyldopa, benserazide [108], 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.	TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [109].	DBH is a homotetramer. A protein structurally-related to DBH (MOXD1, Q6UVY6) has been described and for which a function has yet to be identified [76].	AADC is a homodimer.

Nomenclature	Phenylethanolamine N-methyltransferase	Monoamine oxidase A	Monoamine oxidase B	Catechol-O-methyltransferase
HGNC, UniProt	PNMT, P11086	MAOA, P21397	MAOB, P27338	COMT, P21964
EC number	2.1.1.28: (-)-noradrenaline -> (-)-adrenaline	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
Common abbreviation	PNMT	MAO-A	MAO-B	COMT
Cofactors	S-adenosyl methionine	flavin adenine dinucleotide	flavin adenine dinucleotide	S-adenosyl methionine

(continued)				
Nomenclature	Phenylethanolamine N-methyltransferase	Monoamine oxidase A	Monoamine oxidase B	Catechol-O-methyltransferase
Inhibitors	LY134046 (pK _i 7.6) [163]	moclobemide (pK _i 8.3) [247], phenelzine (Irreversible inhibition) (pK _i 7.3) [39], tranylcypromine (pI _C ₅₀ 4.7) [587], selegiline (pK _i 4.2) [357], befloxatone [107], clorgiline, pirlindole [350]	rasagiline (pI _C ₅₀ 7.8) [591], phenelzine (Irreversible inhibition) (pK _i 7.8) [39], lazabemide (pK _i 7.1) [200, 532], selegiline (pK _i 5.7–6) [121, 357], tranylcypromine (pI _C ₅₀ 4.7) [587]	tolcapone (soluble enzyme) (pK _i 9.6) [317], tolcapone (membrane-bound enzyme) (pK _i 9.5) [317], entacapone (soluble enzyme) (pK _i 9.5) [317], entacapone (membrane-bound enzyme) (pK _i 8.7) [317]
Selective inhibitors	–	–	safinamide (pK _i 6.3) [38]	–
Comments	–	–	–	COMT appears to exist in both membrane-bound and soluble forms. COMT has also been described to methylate steroids, particularly hydroxyestradiols

Further reading on Catecholamine turnover

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Ramsay RR. (2016). Molecular aspects of monoamine oxidase B. *Prog Neuropsychopharmacol Biol Psychiatry* **69**: 81-9 [PMID:26891670]
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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

reduced 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 galactosylce-

ramides. 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 [202]. Complexes involving SPT3 appeared more broad in substrate selectivity, with incorporation of myristoylCoA prominent for SPT1/SPT3/ssSPTa complexes, while SPT1/SPT3/ssSPTb complexes had similar activity with C16, C18 and C20 acylCoAs [202].

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
HGNC, UniProt	SPTLC1, O15269	SPTLC2, O15270	SPTLC3, Q9NUV7	SPTSSA, Q969W0	SPTSSB, Q8NFR3
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	–	–
Common abbreviation	SPT1	SPT2	SPT3	SPTSSA	SPTSSB
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	–	–
Selective inhibitors	myriocin (pK _i 9.6) [358] – Mouse	myriocin [358]	myriocin [358]	–	–

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, fumonisins B1.

Nomenclature	ceramide synthase 1	ceramide synthase 2	ceramide synthase 3	ceramide synthase 4	ceramide synthase 5	ceramide synthase 6
HGNC, UniProt	CERS1, P27544	CERS2, Q96G23	CERS3, Q8IU89	CERS4, Q9HA82	CERS5, Q8N5B7	CERS6, Q6ZMG9
EC number	2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A					
Common abbreviation	CERS1	CERS2	CERS3	CERS4	CERS5	CERS6
Substrates	C18-CoA [543]	C24- and C26-CoA [292]	C26-CoA and longer [361, 424]	C18-, C20- and C22-CoA [438]	C16-CoA [288, 438]	C14- and C16-CoA [360]

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
Inhibitors	RBM2-1B (pIC ₅₀ 4.7) [63]	–
Comments	Myristoylation of DEGS1 enhances its activity and targets it to the mitochondria [28].	–

Comments: DEGS1 activity is inhibited by a number of natural products, including [curcumin](#) and [\$\Delta^9\$ -tetrahydrocannabinol](#) [138].

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	SGMS1, Q86VZ5	SGMS2, Q8NHU3	SAMD8, 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
Inhibitors	compound 1j (pIC ₅₀ 5.7) [301]	compound D24 (pIC ₅₀ 4.9) [116]	–
Comments	–	Palmitoylation of sphingomyelin synthase 2 may allow targeting to the plasma membrane [517].	–

Sphingomyelin phosphodiesterase

Enzymes → Ceramide turnover → Sphingomyelin phosphodiesterase

Overview: Also known as sphingomyelinase.

Nomenclature	sphingomyelin phosphodiesterase 1	sphingomyelin phosphodiesterase 2	sphingomyelin phosphodiesterase 3	sphingomyelin phosphodiesterase 4	sphingomyelin phosphodiesterase acid-like 3A	sphingomyelin phosphodiesterase acid-like 3B
HGNC, UniProt	<i>SMPD1</i> , P17405	<i>SMPD2</i> , O60906	<i>SMPD3</i> , Q9NY59	<i>SMPD4</i> , Q9NXE4	<i>SMPDL3A</i> , Q92484	<i>SMPDL3B</i> , Q92485
EC number		3.1.4.12: sphingomyelin -> ceramide + phosphocholine			3.1.4.-: sphingomyelin -> ceramide + phosphocholine	
Inhibitors	–	inhibitor A (p <i>K</i> _i 5.8) [586] – Bovine	–	–	–	–

Neutral sphingomyelinase coupling factors

Enzymes → Ceramide turnover → Neutral sphingomyelinase coupling factors

Overview: Protein FAN [3] and polycomb protein EED [410] allow coupling between TNF receptors and neutral sphingomyelinase phosphodiesterases.

Nomenclature	embryonic ectoderm development	neutral sphingomyelinase activation associated factor
HGNC, UniProt	<i>EED</i> , O75530	<i>NSMAF</i> , Q92636
Selective inhibitors	A-395 (Binding) (p <i>K</i> _i 9.4) [217]	–

Ceramide glucosyltransferase

Enzymes → Ceramide turnover → Ceramide glucosyltransferase

Nomenclature	UDP-glucose ceramide glucosyltransferase
HGNC, UniProt	UGCG , Q16739
EC number	2.4.1.80: UDP-glucose + ceramide = uridine diphosphate + glucosylceramide
Inhibitors	miglustat (p <i>K</i> _i 5.1) [63]
Comments	Glycosceramides 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 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 [274].

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 2	N-acylsphingosine amidohydrolase 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 [516].	–

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 [505].	ACER2 is associated with the Golgi apparatus [582].	ACER3 is associated with the ER and Golgi apparatus [336].

Ceramide kinase

Enzymes → Ceramide turnover → Ceramide kinase

Nomenclature	ceramide kinase
HGNC, UniProt	CERK, Q8TCTO
EC number	2.7.1.138: ceramide + ATP -> ceramide 1-phosphate + ADP
Inhibitors	NVP 231 (pIC ₅₀ 7.9) [188]

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

Further reading on Ceramide turnover

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- Iqbal J *et al.* (2017) Sphingolipids and Lipoproteins in Health and Metabolic Disorders. *Trends Endocrinol Metab* **28**: 506-518 [PMID:28462811]
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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 [280]. 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) [280].

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 [137], where a wide variety of cellular and

protein aberrations are known to perturb chromatin structure, gene transcription and ultimately cellular pathways [27, 477]. 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 [175, 565]) and erasers (*e.g.* the HDAC inhibitors **vorinostat**, **romidepsin** and **belinostat** for the treatment of T-cell lymphomas [153, 265]) 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 [61]. Current progress in this field is reviewed by Simó-Riudalbas and Esteller (2015) [478].

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.

Information on members of this family may be found in the [online database](#).

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 into five subfamilies 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 Zn²⁺ 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 [456].

HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [90] such as microtubules [233], the hsp90 chaperone [281] and the tumour suppressor p53 [322].

Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [305, 444], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [567]. Several small molecule HDAC inhibitors are already approved for clinical use: romidepsin, belinostat, vorinostat, panobinostat, belinostat, valproic acid and tucidinostat. HDACs and HDAC inhibitors currently in development as potential anti-cancer therapeutics are reviewed by Simó-Riudalbas and Esteller (2015) [478].

Information on members of this family may be found in the [online database](#).

Cyclic nucleotide turnover/signalling

Enzymes → Cyclic nucleotide turnover/signalling

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 (ACs)

Enzymes → Cyclic nucleotide turnover/signalling → Adenylyl cyclases (ACs)

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, [419]) and G_{αs} (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 [527]. 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	adenylyl cyclase 1	adenylyl cyclase 2 (brain)	adenylyl cyclase 3	adenylyl cyclase 4
HGNC, UniProt	ADCY1, Q08828	ADCY2, Q08462	ADCY3, O60266	ADCY4, Q8NFM4
Common abbreviation	AC1	AC2	AC3	AC4
Endogenous activators	calmodulin (CALM1 CALM2 CALM3 , P62158), PKC-evoked phosphorylation [246 , 515]	Gβγ, PKC-evoked phosphorylation [80 , 326 , 520]	calmodulin (CALM1 CALM2 CALM3 , P62158), PKC-evoked phosphorylation [89 , 246]	Gβγ [173]
Endogenous inhibitors	Gα _i , Gα _o , Gβγ [520 , 521]	–	Gα _i , RGS2 , CaM kinase II-evoked phosphorylation [479 , 521 , 562]	PKC-evoked phosphorylation [603]

Nomenclature	adenylyl cyclase 5	adenylyl cyclase 6	adenylyl cyclase 7	adenylyl cyclase 8	adenylyl cyclase 9
HGNC, UniProt	ADCY5, O95622	ADCY6, O43306	ADCY7, P51828	ADCY8, P40145	ADCY9, O60503
Common abbreviation	AC5	AC6	AC7	AC8	AC9
Endogenous activators	PKC-evoked phosphorylation [262]	–	PKC-evoked phosphorylation [561]	Ca ²⁺ [62]	–
Endogenous inhibitors	Gα _i , Ca ²⁺ , PKA-evoked phosphorylation [240 , 243 , 521]	Gα _i , Ca ²⁺ , PKA-evoked phosphorylation, PKC-evoked phosphorylation [83 , 289 , 521 , 590]	–	–	Ca ²⁺ /calcineurin [402]
Inhibitors	NKY80 (pIC ₅₀ 5.2) [52 , 390]	NKY80 (pIC ₅₀ 4.8) [52]	–	–	–

Comments: Nitric oxide has been proposed to inhibit AC5 and AC6 selectively [[223](#)], although it is unclear whether this phenomenon is of physiological significance. A soluble adenylyl cyclase has been described ([ADCY10, Q96PN6](#) [[54](#)]), unaffected by either Gα or Gβγ subunits, which has been suggested to be a cytoplasmic bicarbonate (pH-insensitive) sensor [[82](#)]. It can be inhibited selectively by KH7 (pIC₅₀ 5.0–5.5) [[221](#)].

Further reading on Adenylyl cyclases

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Exchange protein activated by cyclic AMP (EPACs)

Enzymes → Cyclic nucleotide turnover/signalling → Exchange protein activated by cyclic AMP (EPACs)

Overview: Epacs are members of a family of guanine nucleotide exchange factors (ENSEM00250000000899), which also includes *RapGEF5* (GFR, KIAA0277, MR-GEF, Q92565) and *RapGEFL1* (Link-GEFII, Q9UHV5). They are activated endoge-

nously by cyclic AMP and with some pharmacological selectivity by 8-pCPT-2'-O-Me-cAMP [134]. 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 [459].

Nomenclature	Rap guanine nucleotide exchange factor 3	Rap guanine nucleotide exchange factor 4
HGNC, UniProt	RAPGEF3 , O95398	RAPGEF4 , Q8WZA2
Common abbreviation	Epac1	Epac2
Inhibitors	ESI-09 (pIC ₅₀ 5.5) [12]	HJC 0350 (pIC ₅₀ 6.5) [78], ESI-09 (pIC ₅₀ 4.4–5.2) [12, 79]

Further reading on Exchange protein activated by cyclic AMP (EPAC)

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Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase

Enzymes → Cyclic nucleotide turnover/signalling → Guanylyl cyclases (GCs) → Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase

Overview: Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase (GTP diphosphate-lyase (cyclising)), E.C. 4.6.1.2, is a heterodimer comprising a β_1 subunit and one of two alpha subunits (α_1 , α_2) giving rise to two functionally indistinguishable isoforms, GC-1 ($\alpha_1\beta_1$) and GC-2 ($\alpha_2\beta_1$) [449, 593]. A haem group is associated with the β subunit and is the target for the endogenous ligand NO, and, potentially, carbon monoxide [159]. The enzyme converts guanosine-5'-triphosphate to the intracellular second messenger cyclic guanosine-3',5'-monophosphate (cyclic GMP).

Nomenclature	Guanylyl cyclase, $\alpha_1\beta_1$	Guanylyl cyclase, $\alpha_2\beta_1$
Subunits	Guanylyl cyclase β_1 subunit, Guanylyl cyclase α_1 subunit	Guanylyl cyclase β_1 subunit, Guanylyl cyclase α_2 subunit
Common abbreviation	GC-1	GC-2
Endogenous ligands	NO, CO	NO, CO
Selective activators	YC-1 [159, 272, 449], cinaciguat [apo-GC-1] [500], riociguat [498, 499]	YC-1 [272, 449], cinaciguat [apo-GC-2] [500], riociguat [500, 499]
Selective inhibitors	NS 2028 (pIC ₅₀ 8.1) [389] – Bovine, ODQ (pIC ₅₀ 7.5) [177]	ODQ

Subunits

Nomenclature	Guanylyl cyclase α_1 subunit	Guanylyl cyclase α_2 subunit	Guanylyl cyclase β_1 subunit	Guanylyl cyclase β_2 subunit
HGNC, UniProt	<i>GUCY1A3</i> , Q02108	<i>GUCY1A2</i> , P33402	<i>GUCY1B3</i> , Q02153	<i>GUCY1B2</i> , O75343

Comments: ODQ also shows activity at other haem-containing proteins [142], while YC-1 may also inhibit cGMP-hydrolysing phosphodiesterases [158, 169].

Further reading on Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase

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Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs)

Enzymes → Cyclic nucleotide turnover/signalling → Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs)

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	phosphodiesterase 1A	phosphodiesterase 1B	phosphodiesterase 1C
HGNC, UniProt	PDE1A , P54750	PDE1B , Q01064	PDE1C , Q14123
Common abbreviation	PDE1A	PDE1B	PDE1C
Rank order of affinity	cyclic GMP > cyclic AMP	cyclic GMP > cyclic AMP	cyclic GMP = cyclic AMP
Endogenous activators	calmodulin (CALM1 CALM2 CALM3 , P62158)	calmodulin (CALM1 CALM2 CALM3 , P62158)	calmodulin (CALM1 CALM2 CALM3 , P62158)
Inhibitors	crisaborole (pIC ₅₀ 5.2) [8]	–	–
Selective inhibitors	SCH51866 (pIC ₅₀ 7.2) [542], vinpocetine (pIC ₅₀ 5.1) [319]	SCH51866 (pIC ₅₀ 7.2) [542]	SCH51866 (pIC ₅₀ 7.2) [542], vinpocetine (pIC ₅₀ 4.3) [319]

Nomenclature	phosphodiesterase 2A	phosphodiesterase 3A	phosphodiesterase 3B
HGNC, UniProt	PDE2A , O00408	PDE3A , Q14432	PDE3B , Q13370
Common abbreviation	PDE2A	PDE3A	PDE3B
Rank order of affinity	cyclic AMP ≫ cyclic GMP	–	–
Endogenous activators	cyclic GMP	–	–
Endogenous inhibitors	–	cyclic GMP	cyclic GMP
Inhibitors	milrinone (pIC ₅₀ <6.5) [504]	cilostazol (pIC ₅₀ 6.7) [504], inamrinone (pIC ₅₀ 4.8) [480]	–
Selective inhibitors	BAY607550 (pIC ₅₀ 8.3–8.8) [47], EHNA (pIC ₅₀ 5.3) [355]	cilostamide (pIC ₅₀ 7.5) [504], anagrelide (pIC ₅₀ 7.1–7.3) [257 , 341 , 349], milrinone (pIC ₅₀ 6.3–6.4) [131 , 504]	cilostamide (pIC ₅₀ 7.3) [504], cilostazol (pIC ₅₀ 6.4) [504], milrinone (pIC ₅₀ 6) [504], inamrinone (pIC ₅₀ 4.5) [504]
Comments	EHNA is also an inhibitor of adenosine deaminase (E.C. 3.5.4.4).	–	–

Nomenclature	phosphodiesterase 4A	phosphodiesterase 4B	phosphodiesterase 4C	phosphodiesterase 4D	phosphodiesterase 5A
HGNC, UniProt	<i>PDE4A</i> , P27815	<i>PDE4B</i> , Q07343	<i>PDE4C</i> , Q08493	<i>PDE4D</i> , Q08499	<i>PDE5A</i> , O76074
Common abbreviation	PDE4A	PDE4B	PDE4C	PDE4D	PDE5A
Rank order of affinity	cyclic AMP \gg cyclic GMP	cyclic AMP \gg cyclic GMP	cyclic AMP \gg cyclic GMP	cyclic AMP \gg cyclic GMP	cyclic GMP > cyclic AMP
Endogenous activators	–	–	–	PKA-mediated phosphorylation [229]	Protein kinase A, protein kinase G [100]
Inhibitors	<i>ibudilast</i> (pIC ₅₀ 7.3) [275], <i>RS-25344</i> (pIC ₅₀ 7.2) [453]	<i>roflumilast</i> (pIC ₅₀ 9.4) [321], <i>ibudilast</i> (pIC ₅₀ 7.2) [275], <i>RS-25344</i> (pIC ₅₀ 6.5) [453]	<i>RS-25344</i> (pIC ₅₀ 8.1) [453], <i>ibudilast</i> (pIC ₅₀ 6.6) [275]	<i>RS-25344</i> (pIC ₅₀ 8.4) [453]	<i>gisadenafil</i> (pIC ₅₀ 8.9) [433], <i>milrinone</i> (pIC ₅₀ 7.3)
Sub/family-selective inhibitors	<i>rolipram</i> (pIC ₅₀ 9) [553], <i>CDP840</i> (pK _i 8) [406], <i>Ro20-1724</i> (pIC ₅₀ 6.5) [553]	<i>rolipram</i> (pIC ₅₀ 9) [553], <i>Ro20-1724</i> (pIC ₅₀ 6.4) [553]	<i>CDP840</i> (pK _i 7.7) [406], <i>rolipram</i> (pIC ₅₀ 6.5) [553], <i>Ro20-1724</i> (pIC ₅₀ 5.4) [553]	<i>CDP840</i> (pK _i 8.1) [406], <i>rolipram</i> (pIC ₅₀ 7.2) [553], <i>Ro20-1724</i> (pIC ₅₀ 6.2) [553]	–
Selective inhibitors	<i>YM976</i> (pIC ₅₀ 8.3) [14], <i>apremilast</i> (pIC ₅₀ 7.8) [457]	–	<i>apremilast</i> (pIC ₅₀ 6.9) [457]	<i>apremilast</i> (pIC ₅₀ 7.5) [457]	<i>ildenafil</i> (pIC ₅₀ 9.7) [51], <i>T0156</i> (pIC ₅₀ 9.5) [362], <i>sildenafil</i> (pIC ₅₀ 8.4–9) [538], <i>551</i> , <i>tadalafil</i> (pIC ₅₀ 8.5) [379], <i>SCH51866</i> (pIC ₅₀ 7.2) [542], <i>zaprinast</i> (pIC ₅₀ 6.8) [538]

Nomenclature	phosphodiesterase 6A	phosphodiesterase 6B	phosphodiesterase 6C	phosphodiesterase 6D	phosphodiesterase 6G	phosphodiesterase 6H
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
Common abbreviation	PDE6A	PDE6B	PDE6C	PDE6D	PDE6G	PDE6H
Inhibitors	–	–	<i>sildenafil</i> (pIC ₅₀ 7.4) [551]	–	–	–

Nomenclature	phosphodiesterase 7A	phosphodiesterase 7B	phosphodiesterase 8A	phosphodiesterase 8B
HGNC, UniProt	PDE7A, Q13946	PDE7B, Q9NP56	PDE8A, O60658	PDE8B, O95263
Common abbreviation	PDE7A	PDE7B	PDE8A	PDE8B
Rank order of affinity	cyclic AMP ≫ cyclic GMP [353]	cyclic AMP ≫ cyclic GMP [176]	cyclic AMP ≫ cyclic GMP [146]	cyclic AMP ≫ cyclic GMP [214]
Inhibitors	crisaborole (pIC ₅₀ 6.1) [8]	BRL50481 (pIC ₅₀ 4.9) [9]	–	–
Selective inhibitors	BRL50481 (pIC ₅₀ 6.7–6.8) [9, 486]	dipyridamole (pIC ₅₀ 5.7–6) [179, 455], SCH51866 (pIC ₅₀ 5.8) [455]	dipyridamole (pIC ₅₀ 5.1) [146]	dipyridamole (pIC ₅₀ 4.3) [214]
Comments	PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively	–	–	–

Nomenclature	phosphodiesterase 9A	phosphodiesterase 10A	phosphodiesterase 11A
HGNC, UniProt	PDE9A, O76083	PDE10A, Q9Y233	PDE11A, Q9HCR9
Common abbreviation	PDE9A	PDE10A	PDE11A
Rank order of affinity	cyclic GMP ≫ cyclic AMP [145]	cyclic AMP , cyclic GMP [161]	cyclic AMP , cyclic GMP [141]
Inhibitors	SCH51866 (pIC ₅₀ 5.8) [145], zaprinast (pIC ₅₀ 4.5) [145]	–	tadalafil (pIC ₅₀ 6.5) [379], BC11-38 (pIC ₅₀ 6.5) [79]

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 [224, 225]. PDE4A–D splice variants can be membrane-bound or cytosolic [229]. 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.

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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 en-

dogenous 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.

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 [503]

CYP2 family

Enzymes → Cytochrome P450 → CYP2 family

Nomenclature	CYP2A6	CYP2A7	CYP2C8	CYP2J2	CYP2R1
HGNC, UniProt	CYP2A6, P11509	CYP2A7, P20853	CYP2C8, P10632	CYP2J2, P51589	CYP2R1, Q6VVX0
EC number	1.14.14.1	1.14.14.1	1.14.14.1	1.14.14.1	1.14.13.15
Inhibitors	–	–	phenelzine (pK_i 5.1) [150]	terfenadine (pIC_{50} 5.1) [287]	–
Comments	Metabolises nicotine.	CYP2A7 does not incorporate haem and is functionally inactive [162]	Converts arachidonic acid to 11(R)-12(S)-epoxyeicosatrienoic acid or 14(R)-15(S)-epoxyeicosatrienoic acid [596].	Converts arachidonic acid to 14(R)-15(S)-epoxyeicosatrienoic acid [579].	Converts vitamin D3 to calcifediol [85].

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 [155], codeine [155], diazepam [155], tamoxifen [155], erlotinib [155]
Products	4-hydroxy-tamoxifen quinone methide [469], 4-hydroxy-tamoxifen [469]
Inhibitors	ritonavir (pK_i > 7) [266]
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 [166].

CYP4 family

Enzymes → Cytochrome P450 → CYP4 family

Nomenclature	CYP4A11	CYP4F2	CYP4F3	CYP4F8
HGNC, UniProt	CYP4A11, Q02928	CYP4F2, P78329	CYP4F3, Q08477	CYP4F8, P98187
EC number	1.14.15.3	1.14.13.30	1.14.13.30	1.14.14.1
Inhibitors	–	17-octadecynoic acid (p <i>K</i> _i 5.9) [470]	–	–
Comments	Converts lauric acid to 12-hydroxylauric acid.	Responsible for ω -hydroxylation of LTB ₄ , LXB ₄ [359], and tocopherols, including vitamin E [491]	Responsible for ω -hydroxylation of LTB ₄ , LXB ₄ [359], and polyunsaturated fatty acids [143, 207]	Converts PGH ₂ to 19-hydroxyPGH ₂ [60] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [378].

Nomenclature	CYP4F12	CYP4F22	CYP4V2	CYP4X1	CYP4Z1
HGNC, UniProt	CYP4F12, Q9HCS2	CYP4F22, Q6NT55	CYP4V2, Q6ZWL3	CYP4X1, Q8N118	CYP4Z1, Q86W10
EC number	1.14.14.1	1.14.14.-	1.14.-.-	1.14.14.1	1.14.14.1
Comments	AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12	Converts arachidonic acid to 16-HETE and 18-HETE [378].	Converts myristic acid to 14-hydroxymyristic acid [372].	Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [497].	Converts lauric acid to 12-hydroxylauric acid.

Comments: Converts lauric acid to 12-hydroxylauric acid.

CYP5, CYP7 and CYP8 families

Enzymes → Cytochrome P450 → CYP5, CYP7 and CYP8 families

Nomenclature	CYP5A1	CYP7A1	CYP7B1	CYP8A1	CYP8B1
HGNC, UniProt	<i>TBXAS1</i> , P24557	<i>CYP7A1</i> , P22680	<i>CYP7B1</i> , O75881	<i>PTGIS</i> , Q16647	<i>CYP8B1</i> , Q9UNU6
EC number	5.3.99.5: PGH ₂ = thromboxane A ₂	1.14.13.17	1.14.13.100	5.3.99.4	1.14.13.95
Common name	Thromboxane synthase	–	–	Prostacyclin synthase	–
Comments	Inhibited by dazoxiben [427] and camonagrel [194].	Converts cholesterol to 7α-hydroxycholesterol [379].	Converts dehydroepiandrosterone to 7α-DHEA [445].	Converts PGH₂ to PGI₂ [209]. Inhibited by tranylcypromine [193]	Converts 7α-hydroxycholest-4-en-3-one to 7-α,12α-dihydroxycholest-4-en-3-one (in rabbit) [239] 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
HGNC, UniProt	<i>CYP11A1</i> , P05108	<i>CYP11B1</i> , P15538	<i>CYP11B2</i> , P19099
EC number	1.14.15.6	1.14.15.4	1.14.15.4 1.14.15.5
Common name	–	–	Aldosterone synthase
Inhibitors	mitotane [297, 303]	metyrapone (pIC ₅₀ 7.8) [602], mitotane	osilodrostat (pIC ₅₀ 9.7) [585]
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 [558]	Converts corticosterone to aldosterone

Nomenclature	CYP17A1	CYP19A1	CYP20A1	CYP21A2
HGNC, UniProt	CYP17A1 , P05093	CYP19A1 , P11511	CYP20A1 , Q6UW02	CYP21A2 , P08686
EC number	1.14.99.9	1.14.14.1	1.14.-.-	1.14.99.10
Common name	–	Aromatase	–	–
Inhibitors	abiraterone (pIC ₅₀ 7.1–8.4) [413 , 417]	anastrozole (pIC ₅₀ 7.8) [367], aminoglutethimide [405]	–	(2S,4S)-ketoconazole (pIC ₅₀ 5.3) [447] – Rat
Selective inhibitors	galeterone (pIC ₅₀ 6.5) [204]	letrozole (pK _i 10.7) [346], exemestane (pIC ₅₀ 7.3) [92], testolactone (pK _i 4.5) [102]	–	–
Comments	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 .	Converts androstenedione and testosterone to estrone and 17β-estradiol , respectively. Inhibited by anastrozole [415], and letrozole [35]	–	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
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
Common name	–	–	–	Sterol 27-hydroxylase	–
Comments	Converts 1,25-dihydroxyvitamin D3 (calcitriol) to 1α,24R,25-trihydroxyvitamin D3 .	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 D3 to 1,25-dihydroxyvitamin D3 (calcitriol)

CYP39, CYP46 and CYP51 families

Enzymes → Cytochrome P450 → CYP39, CYP46 and CYP51 families

Nomenclature	CYP39A1	CYP46A1	CYP51A1
HGNC, UniProt	CYP39A1, Q9NYLS	CYP46A1, Q9Y6A2	CYP51A1, Q16850
EC number	1.14.13.99	1.14.13.98	–
Common name	–	Cholesterol 24-hydroxylase	Lanosterol 14- α -demethylase
Inhibitors	–	–	azalanstat (pK _i 9.1) [549]
Comments	Converts 24-hydroxycholesterol to 7 α ,24-dihydroxycholesterol [302].	Converts cholesterol to 24(S)-hydroxycholesterol.	Converts lanosterol to 4,4-dimethylcholesta-8.14.24-trienol.

Further reading on Cytochrome P450

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Endocannabinoid turnover

Enzymes → Endocannabinoid turnover

Overview: The principle endocannabinoids are 2-acylglycerol esters, such as [2-arachidonoylglycerol](#) (2AG), and *N*-acylethanolamines, such as [anandamide](#) (*N*-arachidonylethanolamine, AEA). The glycerol esters and ethanolamides are synthesised and hydrolysed by parallel, independent pathways. 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 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, [476]). A transacylation enzyme which forms *N*-acylphosphatidylethanolamines has recently

been identified as a cytosolic enzyme, [PLA2G4E](#) (Q3MJ16) [383]. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism *via* cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [11, 154, 488].

N-Acylethanolamine turnover

Enzymes → Endocannabinoid turnover → *N*-Acylethanolamine turnover

Nomenclature	N-Acylphosphatidylethanolamine-phospholipase D	Fatty acid amide hydrolase	Fatty acid amide hydrolase-2	N-Acylethanolamine acid amidase
HGNC, UniProt	NAPEPLD , Q6IQ20	FAAH , O00519	FAAH2 , Q6GMR7	NAAA , Q02083
EC number	–	3.5.1.99 : anandamide + H ₂ O ⇌ arachidonic acid + ethanolamine oleamide + H ₂ O ⇌ oleic acid + NH ₃ The enzyme is responsible for the catabolism of neuromodulatory fatty acid amides, including anandamide and oleamide: anandamide + H ₂ O ⇌ arachidonic acid + ethanolamine oleamide + H ₂ O ⇌ oleic acid + NH ₃	3.5.1.99 : anandamide + H ₂ O ⇌ arachidonic acid + ethanolamine oleamide + H ₂ O ⇌ oleic acid + NH ₃ The enzyme is responsible for the catabolism of neuromodulatory fatty acid amides, including anandamide and oleamide: anandamide + H ₂ O ⇌ arachidonic acid + ethanolamine oleamide + H ₂ O ⇌ oleic acid + NH ₃	3.5.1.-
Common abbreviation	NAPE-PLD	FAAH	FAAH2	NAAA
Rank order of affinity	–	anandamide > oleamide > N-oleylethanolamide > N-palmitoylethanolamine [563]	oleamide > N-oleylethanolamide > anandamide > N-palmitoylethanolamine [563]	N-palmitoylethanolamine > MEA > SEA ≥ N-oleylethanolamide > anandamide [539]
Selective inhibitors	–	JNJ1661010 (pIC ₅₀ 7.8) [264], PF750 (pIC ₅₀ 6.3–7.8) [5], OL135 (pIC ₅₀ 7.4) [563], URB597 (pIC ₅₀ 6.3–7) [563], PF3845 (pIC ₅₀ 6.6) [6]	OL135 (pIC ₅₀ 7.9–8.4) [261, 563], URB597 (pIC ₅₀ 7.5–8.3) [261, 563]	S-OOPP (pIC ₅₀ 6.4) [489] – Rat, CCP (pIC ₅₀ 5.3) [535]

(continued)				
Nomenclature	<i>N</i> -Acylphosphatidylethanolamine-phospholipase D	Fatty acid amide hydrolase	Fatty acid amide hydrolase-2	<i>N</i> -Acylethanolamine acid amidase
Comments	NAPE-PLD activity appears to be enhanced by polyamines in the physiological range [311], but fails to transphosphatidylate with alcohols [408] unlike phosphatidylcholine-specific phospholipase D.	–	The FAAH2 gene is found in many primate genomes, marsupials, and other distantly related vertebrates, but not a variety of lower placental mammals, including mouse and rat [563].	–

Comments: Routes for *N*-acylethanolamine biosynthesis other than through NAPE-PLD activity have been identified [536].

2-Acylglycerol ester turnover

Enzymes → Endocannabinoid turnover → 2-Acylglycerol ester turnover

Nomenclature	Diacylglycerol lipase α	Diacylglycerol lipase β	Monoacylglycerol lipase	$\alpha\beta$ -Hydrolase 6
HGNC, UniProt	<i>DAGLA</i> , Q9Y4D2	<i>DAGLB</i> , Q8NCG7	<i>MGLL</i> , Q99685	<i>ABHD6</i> , Q9BV23
EC number	3.1.1.-	3.1.1.-	3.1.1.23	3.1.1.23
Common abbreviation	DAGL α	DAGL β	MAGL	ABHD6
Endogenous substrates	diacylglycerol	diacylglycerol	2-oleoyl glycerol = 2-arachidonoylglycerol \gg anandamide [181]	1-arachidonoylglycerol > 2-arachidonoylglycerol > 1-oleoylglycerol > 2-oleoyl glycerol [375]
Selective inhibitors	orlistat (pIC ₅₀ 7.2) [40], RHC80267 (pIC ₅₀ 4.2) [255]	orlistat (pIC ₅₀ 7) [40], RHC80267	JJKK 048 (pIC ₅₀ 9.3) [1], KML29 (pIC ₅₀ 8.5) [77], JZL184 (pIC ₅₀ 8.1) [314]	WWL70 (pIC ₅₀ 7.2) [299], WWL123 (pIC ₅₀ 6.4) [21]
Comments	–	–	–	WWL70 has also been suggested to have activity at oxidative metabolic pathways independent of ABHD6 [513].

Comments on Endocannabinoid turnover: Many of the compounds described as inhibitors are irreversible and so potency estimates will vary with incubation time. FAAH2 is not found in rodents [563] and a 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 [ABHD2](#) ([P08910](#)) [356], [ABHD12](#) ([Q8N2K0](#)) [44], neuropathy target esterase ([PNPLA6](#), [Q8IY17](#) [338]) and carboxylesterase 1 ([CES1](#), [P23141](#) [581]). [ABHD2](#) ([P08910](#)) has also been described as a triacylglycerol

lipase and ester hydrolase [329], while [ABHD12](#) ([Q8N2K0](#)) is also able to hydrolyse lysophosphatidylserine [531]. [ABHD12](#) ([Q8N2K0](#)) has been described to be inhibited selectively by triterpenoids, such as betulinic acid [401].

Further reading on Endocannabinoid turnover

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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

conjugation 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 [PGG₂](#) from [arachidonic acid](#). Hydroperoxidase activity inherent in the enzyme catalyses the formation of [PGH₂](#) from [PGG₂](#). COX-1 and -2 can be nonselectively inhibited by [ibuprofen](#), [ketoprofen](#), [naproxen](#), [indomethacin](#) and [paracetamol](#) (acetaminophen). [PGH₂](#) 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 ₂ O + 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 ₂ O + PGH ₂ arachidonic acid => PGG ₂ => PGH ₂ This enzyme is also associated with the following reaction:: docosahexaenoic acid => PGH ₃
Selective inhibitors	ketorolac (pIC ₅₀ 9.7) [557], FR122047 (pIC ₅₀ 7.5) [382]	celecoxib (pIC ₅₀ 8.7) [41], valdecoxib (pIC ₅₀ 8.3) [512], diclofenac (pIC ₅₀ 7.7) [45], rofecoxib (pIC ₅₀ 6.1–6.5) [557], lumiracoxib (pK _i 6.5) [46], meloxicam (pIC ₅₀ 6.3) [294], etoricoxib (pIC ₅₀ 6) [439]

Prostaglandin synthases

Enzymes → Eicosanoid turnover → Prostaglandin synthases

Overview: Subsequent to the formation of PGH₂, 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 (see

Cytochrome P450s). Additionally, multiple enzyme 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 multifunctional 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	mPGES1	mPGES2	cPGES	L-PGDS
HGNC, UniProt	<i>PTGES</i> , O14684	<i>PTGES2</i> , Q9H7Z7	<i>PTGES3</i> , Q15185	<i>PTGDS</i> , P41222
EC number	5.3.99.3: PGH ₂ = PGE ₂	5.3.99.3: PGH ₂ = PGE ₂	5.3.99.3: PGH ₂ = PGE ₂	5.3.99.2: PGH ₂ = PGD ₂
Cofactors	glutathione	dihydrolipoic acid	–	–
Comments	–	–	Phosphorylated and activated by casein kinase 2 (CK2) [370]. Appears to regulate steroid hormone function by interaction with dimeric hsp90 [74, 253].	–

Nomenclature	H-PGDS	AKR1C3	CBR1	HPGD
HGNC, UniProt	HPGDS, O60760	AKR1C3, P42330	CBR1, P16152	HPGD, P15428
EC number	5.3.99.2: PGH ₂ = PGD ₂	1.3.1.20 1.1.1.188: PGD ₂ + 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: PGE ₂ + NADP ⁺ = PGF _{2α} + NADPH + H ⁺ 1.1.1.197	1.1.1.141 15-hydroxyprostaglandins => 15-ketoprostaglandins LXA ₄ => 15-keto-lipoxin A ₄
Cofactors	–	NADP ⁺	NADP ⁺	–
Inhibitors	HQL-79 (pIC ₅₀ 5.3–5.5) [16]	tolfenamic acid (pK _i 8.1) [421] flufenamic acid, indomethacin, flavonoids [344, 484]	wedelolactone (pIC ₅₀ 5.4) [604]	–
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 [276].

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.-

(continued)	5-LOX	12R-LOX	12S-LOX	15-LOX-1	15-LOX-2	E-LOX
Nomenclature	5-LOX	12R-LOX	12S-LOX	15-LOX-1	15-LOX-2	E-LOX
Endogenous substrates	arachidonic acid	–	–	–	–	12R-HPETE
Endogenous activators	5-LOX activating protein (ALOX5AP, P20292)	–	–	–	–	–
Endogenous inhibitors	Protein kinase A-mediated phosphorylation [324]	–	–	–	–	–
Selective inhibitors	CJ13610 (pIC ₅₀ 7.2) [144], PF-04191834 (pIC ₅₀ 6.6) [342], zileuton	–	–	compound 34 (pK _i > 8) [425]	–	–
Comments	FLAP activity can be inhibited by MK-886 [124] and BAY-X1005 [210] 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 [592].

Comments: An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 [167]. 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 [450].

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 [429]. 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](#) [384].

Nomenclature	Leukotriene C4 synthase	γ -Glutamyltransferase	Dipeptidase 1	Dipeptidase 2
HGNC, UniProt	<i>LTC4S</i> , Q16873	<i>GGCT</i> , O75223	<i>DPEP1</i> , P16444	<i>DPEP2</i> , 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) [189]	–

Comments: LTA₄H is a member of a family of arginyl aminopeptidases (ENSFM0025000001675), which also includes aminopeptidase B (*RNPEP*, 9H4A4) and aminopeptidase B-like 1 (*RNPEPL1*, Q9HAU8). Dipeptidase 1 and 2 are members of a family of membrane dipeptidases, which also includes (*DPEP3*, Q9H4B8) for which LTD₄ appears not to be a substrate.

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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 subservise 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 [136] 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 neurones, 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	Glutamic acid decarboxylase 2
HGNC, UniProt	GAD1, Q99259	GAD2, Q05329
EC number	4.1.1.15: L-glutamic acid + H ⁺ -> GABA + CO ₂	4.1.1.15: L-glutamic acid + H ⁺ -> GABA + CO ₂
Common abbreviation	GAD1	GAD2
Endogenous substrates	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid
Products	GABA	GABA
Cofactors	pyridoxal phosphate	pyridoxal phosphate
Selective inhibitors	s-allylglycine	s-allylglycine
Comments	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [577]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading).	

Nomenclature	aldehyde dehydrogenase 9 family member A1	4-aminobutyrate aminotransferase	aldehyde dehydrogenase 5 family member A1
HGNC, UniProt	ALDH9A1, P49189	ABAT, P80404	ALDH5A1, P51649
EC number	1.2.1.19: 4-aminobutanal + NAD + H ₂ O = GABA + NADH + H ⁺ 1.2.1.47: 4-trimethylammoniobutanal + NAD + H ₂ O = 4-trimethylammoniobutanoate + 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-nonenate + NADH + 2H ⁺
Common abbreviation	–	GABA-T	SSADH
Cofactors	NAD	pyridoxal phosphate	NAD [469]
Inhibitors	–	vigabatrin (Irreversible inhibition) (pK _i 3.1) [306, 475]	4-acryloylphenol (pIC ₅₀ 6.5) [519]

Further reading on GABA turnover

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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).

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 PIP_2 to IP_3 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- ϵ 1 may represent a point of convergence of signalling via both G protein-coupled and catalytic receptors. Ca^{2+} ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC- δ

activity. PLC has been suggested to be activated non-selectively by the small molecule *m3M3FBS* [23], although this mechanism of action has been questioned [284]. The aminosteroid *U73122* has been described as an inhibitor of phosphoinositide-specific PLC [485], although its selectivity among the isoforms is untested and it has been reported to occupy the H1 histamine receptor [235].

Nomenclature	PLC β 1	PLC β 2	PLC β 3	PLC β 4	PLC γ 1	PLC γ 2
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	$G\alpha_q$, $G\alpha_{11}$, $G\beta\gamma$ [220, 399, 487]	$G\alpha_{16}$, $G\beta\gamma$, <i>Rac2</i> (<i>RAC2</i> , P15153) [65, 236, 237, 297, 399]	$G\alpha_q$, $G\beta\gamma$ [71, 295, 399]	$G\alpha_q$ [196]	PIP_3 [22]	PIP_3 , <i>Rac1</i> (<i>RAC1</i> , P63000), <i>Rac2</i> (<i>RAC2</i> , P15153), <i>Rac3</i> (<i>RAC3</i> , P60763) [22, 411, 550]
Inhibitors	–	–	–	–	–	<i>CCT129957</i> (pIC_{50} 5.5) [436]

Nomenclature	PLC δ 1	PLC δ 3	PLC δ 4	PLC ϵ 1	PLC ζ 1	PLC η 1	PLC η 2
HGNC, UniProt	<i>PLCD1</i> , P51178	<i>PLCD3</i> , Q8N3E9	<i>PLCD4</i> , Q9BRC7	<i>PLCE1</i> , Q9P212	<i>PLCZ1</i> , Q86YWO	<i>PLCH1</i> , Q4KWH8	<i>PLCH2</i> , O75038
Endogenous activators	Transglutaminase II, p122-RhoGAP {Rat}, spermine, $G\beta\gamma$ [199, 226, 368, 399]	–	–	Ras, rho [490, 571]	–	–	$G\beta\gamma$ [600]
Endogenous inhibitors	Sphingomyelin [404]	–	–	–	–	–	–

Comments: A series of PLC-like proteins (*PLCL1*, [Q15111](#); *PLCL2*, [Q9UPR0](#) and *PLCH1*, [Q4KWH8](#)) form a family with PLC δ and PLC ζ 1 isoforms, but appear to lack catalytic activity. PLC- δ 2 has been cloned from bovine sources [[351](#)].

Further reading on Phosphoinositide-specific phospholipase C

Cocco L *et al.* (2015) Phosphoinositide-specific phospholipase C in health and disease. *J Lipid Res* **56**: 1853-60 [[PMID:25821234](#)]
 Cockcroft S *et al.* (2016) Topological organisation of the phosphatidylinositol 4,5-bisphosphate-phospholipase C resynthesis cycle: PITPs bridge the ER-PM gap. *Biochem J* **473**: 4289-4310 [[PMID:27888240](#)]
 Litosch I. (2015) Regulating G protein activity by lipase-independent functions of phospholipase C. *Life Sci* **137**: 116-24 [[PMID:26239437](#)]

Nakamura Y *et al.* (2017) Regulation and physiological functions of mammalian phospholipase C. *J Biochem* **161**: 315-321 [[PMID:28130414](#)]
 Swann K *et al.* (2016) The sperm phospholipase C-zeta and Ca²⁺ signalling at fertilization in mammals. *Biochem Soc Trans* **44**: 267-72 [[PMID:26862214](#)]

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)

Further reading on Phospholipase A₂

Leslie CC. (2015) Cytosolic phospholipase A(2): physiological function and role in disease. *J Lipid Res* **56**: 1386-402 [[PMID:25838312](#)]
 Ong WY *et al.* (2015) Synthetic and natural inhibitors of phospholipases A2: their importance for understanding and treatment of neurological disorders. *ACS Chem Neurosci* **6**: 814-31 [[PMID:25891385](#)]

Ramanadham S *et al.* (2015) Calcium-independent phospholipases A2 and their roles in biological processes and diseases. *J Lipid Res* **56**: 1643-68 [[PMID:26023050](#)]

Nomenclature	sPLA ₂ -1B	sPLA ₂ -2A	sPLA ₂ -2D	sPLA ₂ -2E	sPLA ₂ -2F	sPLA ₂ -3
HGNC, UniProt	PLA2G1B , P04054	PLA2G2A , P14555	PLA2G2D , Q9UNK4	PLA2G2E , Q9NZK7	PLA2G2F , Q9BZM2	PLA2G3 , Q9NZ20

Nomenclature	cPLA ₂ -4A	cPLA ₂ -4B	cPLA ₂ -4C	cPLA ₂ -4D	cPLA ₂ -4E	cPLA ₂ -4F
HGNC, UniProt	PLA2G4A, P47712	PLA2G4B, P0C869	PLA2G4C, Q9UP65	PLA2G4D, Q86XP0	PLA2G4E, Q3MJ16	PLA2G4F, Q68DD2
EC number	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4
Inhibitors	compound 57 (pIC ₅₀ 8.4) [320]	–	–	–	–	–
Comments	cPLA ₂ -4A also expresses lysophospholipase (EC 3.1.1.5) activity [473].	–	–	–	–	–

Nomenclature	PLA ₂ -G5	iPLA ₂ -G6	PLA ₂ -G7	sPLA ₂ -10	sPLA ₂ -12A	platelet activating factor acetylhydrolase 2
HGNC, UniProt	PLA2G5, P39877	PLA2G6, O60733	PLA2G7, Q13093	PLA2G10, O15496	PLA2G12A, Q9BZM1	PAFAH2, Q99487
EC number	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.47
Inhibitors		–	darapladib (pIC ₅₀ 10) [42]	–	–	–
Selective inhibitors			rilapladib (Competitive) (pIC ₅₀ 9.6) [568]			

Comments: The sequence of PLA₂-2C suggests a lack of catalytic activity, while PLA₂-12B (GXIIIB, GXIII sPLA₂-like) appears to be catalytically inactive [448]. A further fragment has been identified with sequence similarities to Group II PLA₂ members. Otcocin 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 [13]. 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 [29].

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 3.1.4.4) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidylation reaction [428].

Nomenclature	PLD1	PLD2
HGNC, UniProt	PLD1 , Q13393	PLD2 , O14939
EC number	3.1.4.4	3.1.4.4
Endogenous activators	ADP-ribosylation factor 1 (ARF1 , P84077), PIP₂ , RhoA, PKC evoked phosphorylation, RalA [201 , 323]	A phosphatidylcholine + H ₂ O <=> choline + a phosphatidate ADP-ribosylation factor 1 (ARF1 , P84077), PIP₂ [316], oleic acid [454]
Endogenous inhibitors	Gβγ [418]	Gβγ [418]
Inhibitors	FIPI (pIC ₅₀ 8) [463]	FIPI (pIC ₅₀ 7.8) [484]
Selective inhibitors	compound 69 (pIC ₅₀ 7.3) [463]	VU0364739 (pIC ₅₀ 7.7) [293]

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 [[185](#)]). Additionally, an N-acylethanolamine-specific phospholipase D ([NAPEPLD](#), [Q6IQ20](#)) has been

characterized, which appears to have a role in the generation of [endocannabinoids](#)/endovanilloids, including [anandamide](#) [[388](#)]. This enzyme activity appears to be enhanced by polyamines in the physiological range [[311](#)] and fails to transphosphatidylate with alcohols [[408](#)].

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 [[391](#)]. PLD4 is described not to have phospholipase D catalytic activity [[588](#)], but has been associated with inflammatory disorders [[386](#), [507](#), [526](#)]. Sequence analysis suggests that PLD5 is catalytically inactive.

Further reading on Phospholipase D

Brown HA *et al.* (2017) Targeting phospholipase D in cancer, infection and neurodegenerative disorders. *Nat Rev Drug Discov* **16**: 351-367 [[PMID:28209987](#)]
Frohman MA. (2015) The phospholipase D superfamily as therapeutic targets. *Trends Pharmacol Sci* **36**: 137-44 [[PMID:25661257](#)]

Nelson RK *et al.* (2015) Physiological and pathophysiological roles for phospholipase D. *J Lipid Res* **56**: 2229-37 [[PMID:25926691](#)]

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>PLPP1</i> , O14494	<i>PLPP3</i> , O14495	<i>PLPP2</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

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, PI3Ks have common motifs of

at least one C2, calcium-binding domain and helical domains, alongside structurally-conserved catalytic domains. *Wortmannin* and *LY 294002* 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 β , and include Ras-binding, Phox homology and two C2domains.

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 alpha	phosphatidylinositol 4-kinase beta
HGNC, UniProt	<i>PI4KA</i> , P42356	<i>PI4KB</i> , Q9UBF8
EC number	2.7.1.67	2.7.1.67
Common abbreviation	PI4KIII α /PIK4CA	PI4KIII β /PIK4CB
Endogenous activation	–	PKD-mediated phosphorylation [212]
Sub/family-selective inhibitors	wortmannin (pIC ₅₀ 6.7–6.8) [180, 352]	wortmannin (pIC ₅₀ 6.7–6.8) [180, 352]
Selective inhibitors	–	PIK-93 (pIC ₅₀ 7.7) [26, 271]

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
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
Common abbreviation	C2 α /PIK3C2A	C2 β /PIK3C2B	C2 γ /PIK3C2G
Inhibitors	torin 2 (pIC ₅₀ 7.6) [312]	PI-103 (pIC ₅₀ 8) [213]	–

Enzymes → Glycerophospholipid turnover → Phosphatidylinositol phosphate kinases

Overview: PIP₂ is generated by phosphorylation of PI 4-phosphate or PI 5-phosphate by type I PI 4-phosphate 5-kinases or type II PI 5-phosphate 4-kinases.

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
HGNC, UniProt	<i>PIK3C3</i> , Q8NEB9
EC number	2.7.1.137
Common abbreviation	VPS34

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
HGNC, UniProt	<i>PIK3CA</i> , P42336	<i>PIK3CB</i> , P42338
EC number	2.7.1.153 2.7.11.1	2.7.1.153
Common abbreviation	PI3K α	PI3K β
Inhibitors	PIK-75 (pIC ₅₀ 9.5) [213], gedatolisib (pIC ₅₀ 9.4) [544], PF-04691502 (pK _i 9.2) [309], PI-103 (pIC ₅₀ 8.7) [435], BGT-226 (pIC ₅₀ 8.4) [337], KU-0060648 (pIC ₅₀ 8.4) [66], dactolisib (pIC ₅₀ 8.4) [332], apitolisib (pIC ₅₀ 8.3) [506]	KU-0060648 (pIC ₅₀ 9.3) [66], PI-103 (pIC ₅₀ 8.5) [435], AZD6482 (pIC ₅₀ 8) [380], ZSTK474 (pIC ₅₀ 7.4–7.8) [578, 583], apitolisib (pIC ₅₀ 7.6) [506], BGT-226 (pIC ₅₀ 7.2) [337]
Sub/family-selective inhibitors	pictilisib (pIC ₅₀ 8.5) [149]	pictilisib (pIC ₅₀ 7.5) [149]

Nomenclature	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
HGNC, UniProt	PIK3CG , P48736	PIK3CD , O00329
EC number	2.7.1.153	2.7.1.153
Common abbreviation	PI3K γ	PI3K δ
Inhibitors	dactolisib (pIC ₅₀ 8.3) [332], apitolisib (pIC ₅₀ 7.8) [506], PI-103 (pIC ₅₀ 7.8) [435], BGT-226 (pIC ₅₀ 7.4) [337], ZSTK474 (pIC ₅₀ 7.3–7.3) [578, 583], TG-100-115 (pIC ₅₀ 7.1) [394], alpelisib (pIC ₅₀ 6.6) [164], KU-0060648 (pIC ₅₀ 6.2) [66]	KU-0060648 (pIC ₅₀ > 10) [66], idelalisib (<i>in vitro</i> activity against recombinant enzyme) (pIC ₅₀ 8.6) [290], PI-103 (pIC ₅₀ 8.5) [435], ZSTK474 (pIC ₅₀ 8.2–8.3) [578, 583], apitolisib (pIC ₅₀ 8.2) [506], dactolisib (pIC ₅₀ 8.1) [332], alpelisib (pIC ₅₀ 6.5) [164]
Sub/family-selective inhibitors	pictilisib (pIC ₅₀ 7.1) [149]	pictilisib (pIC ₅₀ 8.5) [149]
Selective inhibitors	CZC 24832 (pK _d 7.7) [32]	–

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-type zinc finger containing
HGNC, UniProt	PIKFYVE , Q9Y217
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 [426]. This enzyme family is also known as type I PIP(5)Ks.

Nomenclature	phosphatidylinositol-4-phosphate 5-kinase type 1 alpha	phosphatidylinositol-4-phosphate 5-kinase type 1 gamma
HGNC, UniProt	PIPSK1A , Q99755	PIPSK1C , O60331
EC number	2.7.1.68	2.7.1.68
Common abbreviation	PIPSK1A	PIPSK1C
Inhibitors	ISA-2011B [465]	–

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 [426]. This enzyme family is also known as type II PIP(5)Ks.

Nomenclature	phosphatidylinositol-5-phosphate 4-kinase type 2 alpha	phosphatidylinositol-5-phosphate 4-kinase type 2 beta	phosphatidylinositol-5-phosphate 4-kinase type 2 gamma
HGNC, UniProt	PIP4K2A , P48426	PIP4K2B , P78356	PIP4K2C , Q8TBX8
EC number	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	2.7.1.149	2.7.1.149
Common abbreviation	PIP4K2A	PIP4K2B	PIP4K2C

Further reading on Phosphatidylinositol kinases

Bauer TM *et al.* (2015) Targeting PI3 kinase in cancer. *Pharmacol Ther* **146**: 53-60 [PMID:25240910]

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Singh P *et al.* (2016) p110alpha and p110beta isoforms of PI3K signaling: are they two sides of the same coin? *FEBS Lett* **590**: 3071-82 [PMID:27552098]

Zhu J *et al.* (2015) Discovery of selective phosphatidylinositol 3-kinase inhibitors to treat hematological malignancies. *Drug Discov Today* **20**: 988-94 [PMID:25857437]

Further reading on Glycerophospholipid turnover

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Irvine RF. (2016) A short history of inositol lipids. *J Lipid Res* **57**: 1987-1994 [PMID:27623846]

Poli A *et al.* (2016) Nuclear Phosphatidylinositol Signaling: Focus on Phosphatidylinositol Phosphate Kinases and Phospholipases C. *J Cell Physiol* **231**: 1645-55 [PMID:26626942]

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
HGNC, UniProt	HMOX1, P09601	HMOX2, P30519
EC number	1.14.14.18 Protoheme + 3 [reduced NADPH-hemoprotein reductase] + 3 O(2) <=> biliverdin + Fe(2+) + CO + 3 [oxidized NADPH-hemoprotein reductase] + 3 H(2)O	1.14.14.18 Protoheme + 3 [reduced NADPH-hemoprotein reductase] + 3 O(2) <=> biliverdin + Fe(2+) + CO + 3 [oxidized NADPH-hemoprotein reductase] + 3 H(2)O
Common abbreviation	HO1	HO2

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 [215]. The chemical [tin protoporphyrin IX](#) acts as a haem oxygenase inhibitor in rat liver with an IC₅₀ value of 11 nM [128].

Further reading on Haem oxygenase

Abraham NG *et al.* (2016) Translational Significance of Heme Oxygenase in Obesity and Metabolic Syndrome. *Trends Pharmacol Sci* **37**: 17-36 [PMID:26515032]
Naito Y *et al.* (2014) Heme oxygenase-1 and anti-inflammatory M2 macrophages. *Arch Biochem Biophys* **564**: 83-8 [PMID:25241054]

Otterbein LE *et al.* (2016) Heme Oxygenase-1 and Carbon Monoxide in the Heart: The Balancing Act Between Danger Signaling and Pro-Survival. *Circ Res* **118**: 1940-59 [PMID:27283533]
Poulos TL. (2014) Heme enzyme structure and function. *Chem. Rev.* **114**: 3919-62 [PMID:24400737]

Hydrogen sulphide synthesis

Enzymes → [Hydrogen sulphide synthesis](#)

Overview: Hydrogen sulfide is a gasotransmitter, with similarities to nitric oxide and carbon monoxide. Although the enzymes indicated below have multiple enzymatic activities, the focus here is the generation of hydrogen sulphide (H₂S) and the

enzymatic characteristics are described accordingly. Cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) are pyridoxal phosphate (PLP)-dependent enzymes. 3-mercaptopyruvate sulfurtransferase (3-MPST) functions to generate H₂S; only CAT

is PLP-dependent, while 3-MPST is not. Thus, this third pathway is sometimes referred to as PLP-independent. CBS and CSE are predominantly cytosolic enzymes, while 3-MPST is found both in the cytosol and the mitochondria.

Nomenclature	Cystathionine β-synthase	Cystathionine γ-lyase	L-Cysteine:2-oxoglutarate aminotransferase	3-Mercaptopyruvate sulfurtransferase
HGNC, UniProt	CBS, P35520	CTH, P32929	KYAT1, Q16773	MPST, P25325
EC number	4.2.1.22	4.4.1.1	4.4.1.13	2.8.1.2
Common abbreviation	CBS	CSE	CAT	MPST
Endogenous substrates	L-cysteine (K _m 6×10 ⁻³ M) [81], L-homocysteine	L-cysteine	L-cysteine	3-mercaptopyruvic acid (K _m 1.2×10 ⁻³ M) [369]
Products	cystathionine	NH₃ , pyruvic acid	NH₃ , pyruvic acid	pyruvic acid

(continued)				
Nomenclature	Cystathionine β -synthase	Cystathionine γ -lyase	L-Cysteine:2-oxoglutarate aminotransferase	3-Mercaptopyruvate sulfurtransferase
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	Zn ²⁺
Inhibitors	aminoxyacetic acid (pIC ₅₀ 5.1) [17]	aminoethoxyvinylglycine (pIC ₅₀ 6) [17], aminoxyacetic acid (pIC ₅₀ 6) [17], β -Cyano-L-alanine (pIC ₅₀ 5.8) [17], propargylglycine (pIC ₅₀ 4.4) [17]	–	–

Further reading on Hydrogen sulphide synthesis

Asimakopoulou A *et al.* (2013) Selectivity of commonly used pharmacological inhibitors for cystathionine α synthase (CBS) and cystathionine γ lyase (CSE). *British Journal of Pharmacology* **169**: 922-932 [PM:23488457]

Kanagy NL *et al.* (2017) Vascular biology of hydrogen sulfide. *Am J Physiol Cell Physiol* **312**: C537-C549 [PMID:28148499]

Meng G *et al.* (2017) Protein S-sulfhydration by hydrogen sulfide in cardiovascular system. *Br J Pharmacol* [PMID:28148499]

Wallace JL *et al.* (2015) Hydrogen sulfide-based therapeutics: exploiting a unique but ubiquitous gasotransmitter. *Nat Rev Drug Discov* **14**: 329-45 [PMID:28148499]

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 G, endothelial type	carboxylesterase 1	lipase E, hormone sensitive type
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
Common abbreviation	PNLIP	LIPG	CES1	LIPE
Inhibitors	orlistat (pIC ₅₀ 8.9) [61]	–	–	–

Nomenclature	ectonucleoside triphosphate diphosphohydrolase 1	ectonucleoside triphosphate diphosphohydrolase 2
Systematic nomenclature	CD39	CD39L1
HGNC, UniProt	ENTPD1, P49961	ENTPD2, Q9Y5L3
EC number	3.6.1.5 Hydrolyzes NTPs to nucleotide monophosphates (NMPs): A nucleoside 5'-triphosphate + 2 H ₂ O <=> a nucleoside 5'-phosphate + 2 phosphate	3.6.1.- Hydrolyzes extracellular nucleotide 5'-triphosphates: NTP > NMP + 2 phosphate
Common abbreviation	NTPDase-1	NTPDase-2
Selective inhibitors	–	PSB-6426 (pK _i 5.1) [53]
Comments	ENTPD1 sequentially converts extracellular purine nucleotides (ATP and ADP) to the monophosphate form. Adenosine is then generated by the action of Ecto-5'-Nucleotidase (CD73). ENTPD1 is the rate-limiting step. Extracellular ATP acts as a damage-associated molecular pattern (DAMP) that activates innate immune cells through adenosine-induced activation of P2X and P2Y purinogenic receptors.	–

Further reading on Hydrolases

Markey GM. (2011) Carboxylesterase 1 (Ces1): from monocyte marker to major player. *J. Clin. Pathol.* **64**: 107-9 [PMID:21177752]

Takenaka MC *et al.* (2016) Regulation of the T Cell Response by CD39. *Trends Immunol* **37**: 427-39 [PMID:27236363]

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, IP₃, which acts at intracellular ligand-gated ion channels, [IP₃ receptors](#) to

elevate intracellular calcium. IP₃ is recycled to inositol by phosphatases or phosphorylated to form other active inositol polyphosphates. Inositol produced from dephosphorylation of IP₃ 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 ([CALM1 CALM2 CALM3](#), P62158) [98].

Information on members of this family may be found in the [online database](#).

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, ENSFM0025000001432) generate 1,5,-IP₂ and 5-phosphatases (E.C. 3.1.3.36 or 3.1.3.56) generate 1,4,-IP₂.

Information on members of this family may be found in the [online database](#).

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 [458].

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, [347]; pIC_{50} 3.2, [385]) than IMPase 2 (pIC_{50} 1.8-2.1, [385]). IMPase activity may be inhibited competitively by L690330 (pK_i 5.5, [347]), 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 [347]	–
Inhibitors	Li ⁺ (pK_i 3.5) [347]	–

Comments: Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder [481, 482, 589]. Disruption of the gene encoding IMPase 1, but not IMPase 2, appears to mimic the effects of Li⁺ in mice [104, 105].

Further reading on Inositol phosphate turnover

Irvine R. (2016) A tale of two inositol trisphosphates. *Biochem Soc Trans* **44**: 202-11
[PMID:26862207]

Livermore TM *et al.* (2016) Phosphate, inositol and polyphosphates. *Biochem Soc Trans* **44**: 253-9
[PMID:26862212]

Miyamoto A *et al.* (2017) Probes for manipulating and monitoring IP₃. *Cell Calcium* **64**: 57-64
[PMID:27887748]

Windhorst S *et al.* (2017) Inositol-1,4,5-trisphosphate 3-kinase-A (ITPKA) is frequently over-expressed and functions as an oncogene in several tumor types. *Biochem Pharmacol* **137**: 1-9
[PMID:28377279]

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	<i>ACAT1</i> , P24752	<i>ACAT2</i> , Q9BWD1	<i>HMGCS1</i> , Q01581	<i>HMGCS2</i> , P54868
EC number	2.3.1.9: 2acetyl CoA = acetoacetyl CoA + coenzyme A	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	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.	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	<i>HMGCR</i> , P04035	<i>MVK</i> , Q03426	<i>PMVK</i> , Q15126	<i>MVD</i> , 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 -> ADP + (R)-5-phosphomevalonate	2.7.4.2: ATP + (R)-5-phosphomevalonate = ADP + (R)-5-diphosphomevalonate	4.1.1.33: ATP + (R)-5-diphosphomevalonate -> ADP + isopentenyl diphosphate + CO ₂ + PO ₃ ⁴⁻
Inhibitors	lovastatin (Competitive) (pK _i 9.2) [10], rosuvastatin (Competitive) (pIC ₅₀ 8.3) [241], cerivastatin (Competitive) (pK _i 8.2) [67], atorvastatin (Competitive) (pIC ₅₀ 8.1) [241], cerivastatin (Competitive) (pIC ₅₀ 8) [528], simvastatin (Competitive) (pIC ₅₀ 8) [241], fluvastatin (Competitive) (pIC ₅₀ 7.6) [241]	–	–	–

(continued) Nomenclature	hydroxymethylglutaryl-CoA reductase	mevalonate kinase	phosphomevalonate kinase	diphosphomevalonate decarboxylase
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 2	geranylgeranyl diphosphate synthase
HGNC, UniProt	<i>IDI1</i> , Q13907	<i>IDI2</i> , Q9BXS1	<i>GGPS1</i> , O95749
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

Nomenclature	farnesyl diphosphate synthase	squalene synthase	squalene monooxygenase	lanosterol synthase
HGNC, UniProt	<i>FDPS</i> , P14324	<i>FDFT1</i> , P37268	<i>SQLE</i> , Q14534	<i>LSS</i> , P48449
EC number	2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate 2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate	2.5.1.21: 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	risedronate (pIC ₅₀ 8.4) [33], zoledronic acid (pK _i 7.1) [129], alendronate (pIC ₅₀ 6.3) [33]	zaragozic acid A (pK _i 10.1) [34] – Rat, zaragozic acid A (pIC ₅₀ 9.2) [530]	–	–
Selective inhibitors	ibandronic acid (pK _i 6.7) [129], pamidronic acid (pIC ₅₀ 6.7) [129]	–	–	–

Further reading on Lanosterol biosynthesis pathway

Moutinho M *et al.* (2017) The mevalonate pathway in neurons: It's not just about cholesterol. *Exp Cell Res* [PMID:28232115]
 Mullen PJ *et al.* (2016) The interplay between cell signalling and the mevalonate pathway in cancer. *Nat Rev Cancer* **16**: 718-731 [PMID:27562463]
 Ness GC. (2015) Physiological feedback regulation of cholesterol biosynthesis: Role of translational control of hepatic HMG-CoA reductase and possible involvement of oxysterols. *Biochim Biophys Acta* **1851**: 667-73 [PMID:25701719]

Porter TD. (2015) Electron Transfer Pathways in Cholesterol Synthesis. *Lipids* **50**: 927-36 [PMID:26344922]
 Samaras K *et al.* (2016) Does statin use cause memory decline in the elderly? *Trends Cardiovasc Med* **26**: 550-65 [PMID:27177529]

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)	inosine monophosphate dehydrogenase 1	inosine monophosphate dehydrogenase 2	xanthine dehydrogenase
HGNC, UniProt	DHFR , P00374	DHODH , Q02127	IMPDH1 , P20839	IMPDH2 , P12268	XDH , P47989
EC number	1.5.1.3	1.3.5.2	1.1.1.205	1.1.1.205	1.17.1.4
Inhibitors	pemetrexed (p <i>K</i> _i 8.1) [171, 474], pralatrexate (p <i>K</i> _i 7.3) [244]	teriflunomide (p <i>K</i> _i 7.5) [214], leflunomide (p <i>K</i> _i 4.9) [397]	mycophenolic acid (p <i>C</i> ₅₀ 7.7) [376], ribavirin (p <i>C</i> ₅₀ 5.6–6) [572], thioguanine [132, 546]	mycophenolic acid (p <i>C</i> ₅₀ 7.7) [376], ribavirin (p <i>C</i> ₅₀ 5.6–6) [572], thioguanine [132, 546]	febuxostat (p <i>K</i> _i 9.9) [387] – Bovine, allopurinol (p <i>K</i> _i 5.2) [36]
Selective inhibitors	methotrexate (p <i>K</i> _i 8.9) [446]	–	–	–	–

Nomenclature	ribonucleotide reductase catalytic subunit M1	ribonucleotide reductase regulatory subunit M2	ribonucleotide reductase regulatory TP53 inducible subunit M2B	thymidylate synthetase	phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase	purine nucleoside phosphorylase
HGNC, UniProt	<i>RRM1</i> , P23921	<i>RRM2</i> , P31350	<i>RRM2B</i> , Q7LG56	<i>TYMS</i> , P04818	<i>GART</i> , P22102	<i>PNP</i> , P00491
EC number	1.17.14.1	1.17.4.1	1.17.1.4	2.1.1.45	2.1.2.2 6.3.3.1 6.3.4.13	–
Common abbreviation	–	–	–	–	GART	–
Inhibitors	clofarabine (pIC ₅₀ 8.3) [400], fludarabine (pIC ₅₀ 6) [534], hydroxyurea (pIC ₅₀ 3.8) [471], gemcitabine [219]	–	–	pemetrexed (pK _i 7) [474], capecitabine [69, 398]	pemetrexed (pK _i 5) [474] – Mouse	–
Selective inhibitors	–	–	–	raltitrexed (pIC ₅₀ 6.5) [172]	–	–

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 on Nucleoside synthesis and metabolism

Day RO *et al.* (2016) Xanthine oxidoreductase and its inhibitors: relevance for gout. *Clin Sci (Lond)* **130**: 2167–2180 [PMID:27798228]
 Okafor ON *et al.* (2017) Allopurinol as a therapeutic option in cardiovascular disease. *Pharmacol Ther* **172**: 139–150 [PMID:27916655]

Sramek M *et al.* (2017) Much more than you expected: The non-DHFR-mediated effects of methotrexate. *Biochim Biophys Acta* **1861**: 499–503 [PMID:27993660]

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 sphingosylphosphocholine 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.

Sphingosine kinase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine kinase

Nomenclature	sphingosine kinase 1	sphingosine kinase 2
HGNC, UniProt	<i>SPHK1</i> , Q9NYA1	<i>SPHK2</i> , Q9NRA0
EC number	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP ATP + sphinganine = sphinganine 1-phosphate + ADP	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP ATP + sphinganine = sphinganine 1-phosphate + ADP
Common abbreviation	SPHK1	SPHK2
Cofactors	Mg ²⁺ [469]	Mg ²⁺
Sub/family-selective inhibitors	SKI-II (pIC ₅₀ 6.3) [156]	–
Selective inhibitors	PF-543 (pIC _{8.7}) [556],	ABC294640 (pK _i 5) [157], ROME (pIC ₅₀ 4.6) [304]

Further reading on Sphingosine kinases

Adams DR *et al.* (2016) Sphingosine Kinases: Emerging Structure-Function Insights. *Trends Biochem Sci* **41**: 395-409 [PMID:27021309]
 Marfe G *et al.* (2015) Sphingosine kinases signalling in carcinogenesis. *Mini Rev Med Chem* **15**: 300-14 [PMID:25723458]
 Pyne NJ *et al.* (2017) Sphingosine Kinase 2 in Autoimmune/Inflammatory Disease and the Development of Sphingosine Kinase 2 Inhibitors. *Trends Pharmacol Sci* **38**: 581-591 [PMID:28606480]

Pyne S *et al.* (2016) Sphingosine 1-phosphate and sphingosine kinases in health and disease: Recent advances. *Prog Lipid Res* **62**: 93-106 [PMID:26970273]
 Santos WL *et al.* (2015) Drugging sphingosine kinases. *ACS Chem Biol* **10**: 225-33 [PMID:25384187]

Sphingosine 1-phosphate phosphatase

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

Nomenclature	sphingosine-1-phosphate phosphatase 1	sphingosine-1-phosphate phosphatase 2
HGNC, UniProt	<i>SGPP1</i> , Q9BX95	<i>SGPP2</i> , Q8IWX5
EC number	3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate	3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate
Common abbreviation	SGPP1	SGPP2
Comments	Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [231].	–

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 (pIC ₅₀ 6.7) [564]
Comments	THI (2-Acetyl-5-tetrahydroxybutyl imidazole) inhibits the enzyme activity in intact cell preparations [462].

Further reading on Sphingosine 1-phosphate lyase

Ebenezer DL *et al.* (2016) Targeting sphingosine-1-phosphate signaling in lung diseases. *Pharmacol Ther* **168**: 143-157 [[PMID:27621206](#)]

Sanllehi P *et al.* (2016) Inhibitors of sphingosine-1-phosphate metabolism (sphingosine kinases and sphingosine-1-phosphate lyase). *Chem Phys Lipids* **197**: 69-81 [[PMID:26200919](#)]

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](#)).

Nomenclature	thyroid peroxidase
HGNC, UniProt	TPO , P07202
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
Common abbreviation	TPO
Cofactors	Ca ²⁺
Inhibitors	methimazole [373], propylthiouracil [373]
Comments	Carbimazole is a pro-drug for methimazole

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 (rT3, 3,3',5'-triiodothyronine, a relatively inactive analogue). DIO1 is also able to deiodinate RT3 to form 3,3'-diiodothyronine (T_2). Iodotyrosine deiodinase is a 1TM homodimeric enzyme.

Nomenclature	iodothyronine deiodinase 1	iodothyronine deiodinase 2	iodothyronine deiodinase 3	iodotyrosine deiodinase
HGNC, UniProt	<i>DIO1</i> , P49895	<i>DIO2</i> , Q92813	<i>DIO3</i> , P55073	<i>IYD</i> , Q6PHW0
EC number	1.97.1.10: $T_4 \rightarrow$ triiodothyronine $rT_3 \rightarrow T_2$	1.97.1.10: $T_4 \rightarrow$ triiodothyronine $rT_3 \rightarrow T_2$	1.97.1.11: $T_4 \rightarrow$ triiodothyronine $rT_3 \rightarrow T_2$	1.22.1.1: 3-iodotyrosine \rightarrow L-tyrosine + I ⁻ 3,5-diiodo-L-tyrosine \rightarrow 3-iodotyrosine + I ⁻
Common abbreviation	DIO1	DIO2	DIO3	IYD
Cofactors	–	–	–	flavin adenine dinucleotide, NADPH

Further reading on Thyroid hormone turnover

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]
 Gereben B *et al.* (2015) Scope and limitations of iodothyronine deiodinases in hypothyroidism. *Nat Rev Endocrinol* **11**: 642-52 [PMID:26416219]
 Mondal S *et al.* (2017) Novel thyroid hormone analogues, enzyme inhibitors and mimetics, and their action. *Mol Cell Endocrinol* [PMID:28408161]

Schweizer U *et al.* (2015) New insights into the structure and mechanism of iodothyronine deiodinases. *J Mol Endocrinol* **55**: R37-52 [PMID:26390881]
 van der Spek AH *et al.* (2017) Thyroid hormone metabolism in innate immune cells. *J Endocrinol* **232**: R67-R81 [PMID:27852725]

1.14.11.29 2-oxoglutarate oxygenases

Enzymes → 1.14.11.29 2-oxoglutarate oxygenases

Overview: Hypoxia inducible factor (HIF) is a transcriptional complex that is involved in oxygen homeostasis [466]. At normal oxygen levels, the alpha subunit of HIF (HIF-1 α) is targeted for degradation by prolyl hydroxylation by the prolyl hydroxylases PHD proteins 1-3 (HIF-PHs) which are 2-oxoglutarate oxygenases responsible for the post-translational modification of a specific proline in each of the oxygen-dependent degradation domains

of HIF-1 α . Hydroxylated HIFs are then targeted for proteasomal degradation *via* the von Hippel-Lindau ubiquitination complex [245]. 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 [151]. Small molecule HIF-PH inhibitors are in clinical trial as novel therapies for the amelioration of anemia associated with chronic kidney disease [50].

Nomenclature	egl-9 family hypoxia inducible factor 2	egl-9 family hypoxia inducible factor 1	egl-9 family hypoxia inducible factor 3
HGNC, UniProt	EGLN2, Q9GKS0	EGLN1, Q9GZT9	EGLN3, Q9H6Z9
EC number	–	1.14.11.29	1.14.11.29
Common abbreviation	PHD1	PHD2	PHD3
Inhibitors		IOX2 (pIC ₅₀ 7.7) [91]	

Further reading on 2-oxoglutarate oxygenases

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 Markolovic S *et al.* (2015) Protein Hydroxylation Catalyzed by 2-Oxoglutarate-dependent Oxygenases. *J Biol Chem* **290**: 20712-22 [[PMID:26152730](#)]
 Salminen A *et al.* (2015) 2-Oxoglutarate-dependent dioxygenases are sensors of energy metabolism, oxygen availability, and iron homeostasis: potential role in the regulation of aging process. *Cell Mol Life Sci* **72**: 3897-914 [[PMID:26118662](#)]

Wu Y *et al.* (2017) Application of in-vitro screening methods on hypoxia inducible factor prolyl hydroxylase inhibitors. *Bioorg Med Chem* **25**: 3891-3899 [[PMID:28625716](#)]
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1.14.13.9 kynurenine 3-monoxygenase

Enzymes → [1.14.13.9 kynurenine 3-monoxygenase](#)

Nomenclature	Kynurenine 3-monoxygenase
HGNC, UniProt	KMO, O15229
EC number	1.14.13.9
Comments	L-kynurenine + NADPH + O ₂ <=> 3-hydroxy-L-kynurenine + NADP(+) + H ₂ O Kynurenine 3-monoxygenase participates in metabolism of the essential amino acid tryptophan.

Further reading on Kynurenine 3-monoxygenases

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Smith JR *et al.* (2016) Kynurenine-3-monoxygenase: a review of structure, mechanism, and inhibitors. *Drug Discov Today* **21**: 315-24 [[PMID:26589832](#)]
 Song P *et al.* (2017) Abnormal kynurenine pathway of tryptophan catabolism in cardiovascular diseases. *Cell Mol Life Sci* **74**: 2899-2916 [[PMID:28314892](#)]

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
HGNC, UniProt	<i>PARP1</i> , P09874	<i>PARP2</i> , Q9UGN5	<i>PARP3</i> , Q9Y6F1
EC number	2.4.2.30	2.4.2.30	–
Common abbreviation	PARP1	PARP2	PARP3
Selective inhibitors	AG14361 (p <i>K</i> _i 8.2) [483]	–	–

Further reading on Poly(ADP-ribose)polymerases

- Bai P. (2015) Biology of Poly(ADP-Ribose) Polymerases: The Factotums of Cell Maintenance. *Mol Cell* **58**: 947-58 [[PMID:26091343](#)]
 Bai P *et al.* (2015) Poly(ADP-ribose) polymerases as modulators of mitochondrial activity. *Trends Endocrinol Metab* **26**: 75-83 [[PMID:25497347](#)]
 Bock FJ *et al.* (2016) New directions in poly(ADP-ribose) polymerase biology. *FEBS J* **283**: 4017-4031 [[PMID:27087568](#)]

- Bock FJ *et al.* (2015) RNA Regulation by Poly(ADP-Ribose) Polymerases. *Mol Cell* **58**: 959-69 [[PMID:26091344](#)]
 Ryu KW *et al.* (2015) New facets in the regulation of gene expression by ADP-ribosylation and poly(ADP-ribose) polymerases. *Chem Rev* **115**: 2453-81 [[PMID:25575290](#)]

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) [[72](#)]. 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, methionine, alanine or glutamine; leucine for EC 2.5.1.59) [[165](#)]. 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.

Information on members of this family may be found in the [online database](#).

Further reading on Protein farnesyltransferase

Gao S *et al.* (2016) The Role of Geranylgeranyltransferase I-Mediated Protein Prenylation in the Brain. *Mol Neurobiol* **53**: 6925–6937 [PMID:26666664]
Shen M *et al.* (2015) Farnesyltransferase and geranylgeranyltransferase I: structures, mechanism, inhibitors and molecular modeling. *Drug Discov Today* **20**: 267–76
<https://www.ncbi.nlm.nih.gov/pubmed/25450772>[PMID:25450772]

Shen Y *et al.* (2015) The Recent Development of Farnesyltransferase Inhibitors as Anticancer and Antimalarial Agents. *Mini Rev Med Chem* **15**: 837–57 [PMID:25963569]
Wang M *et al.* (2016) Protein prenylation: unique fats make their mark on biology. *Nat Rev Mol Cell Biol* **17**: 110–22 [PMID:26790532]

3.5.1.- Histone deacetylases (HDACs)

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 Zn²⁺ 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 [456].

HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [91] such as microtubules [233], the hsp90 chaperone [281] and the tumour suppressor p53 [322].

Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [305, 444], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [567]. Several small molecule HDAC inhibitors are already approved for clinical use: romidepsin, belinostat, vorinostat, panobinostat, belinostat, valproic acid and tucidinostat. HDACs and HDAC inhibitors currently in development as potential anti-cancer therapeutics are reviewed by Simó-Riudalbas and Esteller (2015) [478].

Information on members of this family may be found in the [online database](#).

Further reading on Histone deacetylases

Maolanon AR *et al.* (2017) Natural and Synthetic Macrocyclic Inhibitors of the Histone Deacetylase Enzymes. *Chembiochem* **18**: 5–49 [PMID:27748555]
Micelli C *et al.* (2015) Histone deacetylases: structural determinants of inhibitor selectivity. *Drug Discov Today* **20**: 718–35 [PMID:25687212]
Millard CJ *et al.* (2017) Targeting Class I Histone Deacetylases in a “Complex” Environment. *Trends Pharmacol Sci* **38**: 363–377 [PMID:28139258]

Roche J *et al.* (2016) Inside HDACs with more selective HDAC inhibitors. *Eur J Med Chem* **121**: 451–83 [PMID:27318122]
Zagni C *et al.* (2017) The Search for Potent, Small-Molecule HDACIs in Cancer Treatment: A Decade After Vorinostat. *Med Res Rev* [PMID:28181261]

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, generating peptidyl-

citrulline on histones, fibrinogen, and other biologically relevant proteins. The human isozymes exhibit tissue-specific expression patterns [256]. Overexpression and/or increased PADI activity is observed in several diseases, including rheumatoid arthritis,

Alzheimer's disease, multiple sclerosis, lupus, Parkinson's disease, and cancer [37]. Pharmacological PADI inhibition reverses protein-hypercitrullination and disease in mouse models of multiple sclerosis [366].

Information on members of this family may be found in the [online database](#).

Further reading on Peptidyl arginine deiminases

Koushik S *et al.* (2017) PAD4: pathophysiology, current therapeutics and future perspective in rheumatoid arthritis. *Expert Opin Ther Targets* **21**: 433-447 [PMID:28281906]
Tu R *et al.* (2016) Peptidyl Arginine Deiminases and Neurodegenerative Diseases. *Curr Med Chem* **23**: 104-14 [PMID:26577926]

Whiteley CG. (2014) Arginine metabolising enzymes as targets against Alzheimers' disease. *Neurochem Int* **67**: 23-31 [PMID:24508404]

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 [495], which leads to increased cell proliferation and

decreased apoptosis [598]. Because of their importance in oncogenic transformation these proteins have become the targets of intense drug discovery effort [25].

Information on members of this family may be found in the [online database](#).

Further reading on RAS subfamily

Dorard C *et al.* (2017) Deciphering the RAS/ERK pathway in vivo *Biochem Soc Trans* **45**: 27-36 [PMID:28202657]
Keeton AB *et al.* (2017) The RAS-Effector Interaction as a Drug Target. *Cancer Res* **77**: 221-226 [PMID:28062402]
Lu S *et al.* (2016) Ras Conformational Ensembles, Allosterity, and Signaling. *Chem Rev* **116**: 6607-65 [PMID:26815308]
Ostrem JM *et al.* (2016) Direct small-molecule inhibitors of KRAS: from structural insights to mechanism-based design. *Nat Rev Drug Discov* **15**: 771-785 [PMID:27469033]

Papke B *et al.* (2017) Drugging RAS: Know the enemy. *Science* **355**: 1158-1163 [PMID:28302824]
Quah SY *et al.* (2016) Pharmacological modulation of oncogenic Ras by natural products and their derivatives: Renewed hope in the discovery of novel anti-Ras drugs. *Pharmacol Ther* **162**: 35-57 [PMID:27016467]
Simanshu DK *et al.* (2017) RAS Proteins and Their Regulators in Human Disease. *Cell* **170**: 17-33 [PMID:28666118]

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 1	carbonic anhydrase 7	carbonic anhydrase 12
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) [467], acetazolamide (p <i>K</i> _i 8.6) [19], brinzolamide (p <i>K</i> _i 8.6) [467], chlorthalidone (p <i>K</i> _i 8.6) [524]	chlorthalidone (p <i>K</i> _i 8.4) [524], diclofenamide (p <i>K</i> _i 7.3) [547]

Further reading on 4.2.1.1 Carbonic anhydrases

Frost SC. (2014) Physiological functions of the alpha class of carbonic anhydrases. *Subcell Biochem* **75**: 9-30 [PMID:24146372]

Supuran CT. (2017) Advances in structure-based drug discovery of carbonic anhydrase inhibitors. *Expert Opin Drug Discov* **12**: 61-88 [PMID:27783541]

Supuran CT. (2016) Structure and function of carbonic anhydrases. *Biochem J* **473**: 2023-32 [PMID:27407171]

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
HGNC, UniProt	TOP1, P11387	TOP2A, P11388
EC number	5.99.1.2	5.99.1.2
Inhibitors	irinotecan [125, 518] – Bovine	etoposide (p <i>K</i> ₅₀ 7.3), teniposide [127] – Mouse

Further reading on DNA topoisomerases

Bansal S *et al.* (2017) Topoisomerases: Resistance versus Sensitivity, How Far We Can Go? *Med Res Rev* **37**: 404-438 [PMID:27687257]

Capranico G *et al.* (2017) Type I DNA Topoisomerases. *J Med Chem* **60**: 2169-2192 [PMID:28072526]

Nagaraja V *et al.* (2017) DNA topoisomerase I and DNA gyrase as targets for TB therapy. *Drug Discov Today* **22**: 510-518 [PMID:27856347]

Pommier Y *et al.* (2016) Roles of eukaryotic topoisomerases in transcription, replication and genomic stability. *Nat Rev Mol Cell Biol* **17**: 703-721 [PMID:27649880]

Seol Y *et al.* (2016) The dynamic interplay between DNA topoisomerases and DNA topology. *Biophys Rev* **8**: 101-111 [PMID:28510219]

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