


















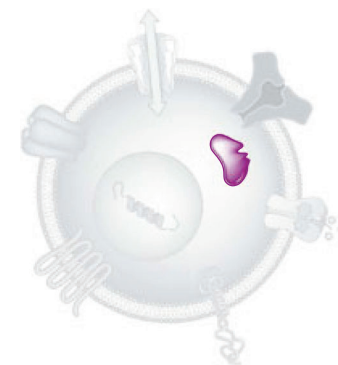


The Concise Guide to PHARMACOLOGY 2023/24: Enzymes

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Abstract

The Concise Guide to PHARMACOLOGY 2023/24 is the sixth in this series of biennial publications. The Concise Guide provides concise overviews, mostly in tabular format, of the key properties of approximately 1800 drug targets, and nearly 6000 interactions with about 3900 ligands. There is an emphasis on selective pharmacology (where available), plus links to the open access knowledgebase source of drug targets and their ligands (<https://www.guidetopharmacology.org/>), which provides more detailed views of target and ligand properties. Although the Concise Guide constitutes almost 500 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.16181>. Enzymes are one of the six major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, 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-2023, and supersedes data presented in the 2021/22, 2019/20, 2017/18, 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature and Standards Committee of the International 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 disclose.

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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 [523, 565], 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 ingenol mebutate, which is a non-selective protein kinase C activator approved for the topical treatment of actinic keratoses. 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 mono-phosphatase 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 promote a particular conformational change. Co-factors are tightly bound to the enzyme and include metal ions and heme groups. Co-enzymes are typically small molecules which accept or donate functional groups to assist in the enzymatic reaction. Examples include ATP, NAD, NADP and S-adenosylmethionine, as well as a number of vitamins, such as riboflavin (vitamin B1) and thiamine (vitamin B2). Where co-factors/co-enzymes have been identified, the Guide indicates their involvement.

Family structure

S293	AAA ATPases	S308	Acid ceramidase	S319	CYP3 family
S293	Acetylcholine turnover	S309	Neutral ceramidases	S319	CYP4 family
–	Acyl-CoA synthetases	S309	Alkaline ceramidases	S320	CYP5, CYP7 and CYP8 families
S294	Adenosine turnover	S309	Ceramide kinase	S320	CYP11, CYP17, CYP19, CYP20 and CYP21 families
S295	Amino acid hydroxylases	–	Chitinases	S321	CYP24, CYP26 and CYP27 families
S296	L-Arginine turnover	S310	Chromatin modifying enzymes	S322	CYP39, CYP46 and CYP51 families
S297	2.1.1.- Protein arginine N-methyltransferases	–	1.14.11.- Histone demethylases	–	DNA glycosylases
S297	Arginase	S311	2.1.1.- Protein arginine N-methyltransferases	S323	DNA topoisomerases
S297	Arginine:glycine amidinotransferase	–	2.1.1.43 Histone methyltransferases (HMTs)	–	E2 ubiquitin-conjugating enzymes
S298	Dimethylarginine dimethylaminohydrolases	–	2.3.1.48 Histone acetyltransferases (HATs)	S323	E3 ubiquitin ligase components
S298	Nitric oxide synthases	S311	3.5.1.- Histone deacetylases (HDACs)	S324	Endocannabinoid turnover
S299	Carbonic anhydrases	–	3.6.1.3 ATPases	S324	N-Acylethanolamine turnover
S300	Carboxylases and decarboxylases	–	Enzymatic bromodomain-containing proteins	S325	2-Acylglycerol ester turnover
S300	Carboxylases	–	Bromodomain kinase (BRDK) family	S326	Eicosanoid turnover
S301	Decarboxylases	–	TAF1 family	S326	Cyclooxygenase
S303	Catecholamine turnover	–	TIF1 family	S327	Prostaglandin synthases
S305	Ceramide turnover	S312	Cyclic nucleotide turnover/signalling	S328	Lipoxygenases
S305	Serine palmitoyltransferase	S312	Adenylyl cyclases (ACs)	S329	Leukotriene and lipoxin metabolism
–	3-ketodihydrospingosine reductase	–	Cyclic GMP-AMP synthase	S330	GABA turnover
S306	Ceramide synthase	S313	Exchange protein activated by cyclic AMP (EPACs)	S331	Glycerophospholipid turnover
S306	Sphingolipid Δ 4-desaturase	S314	Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs)	S331	Phosphoinositide-specific phospholipase C
S307	Sphingomyelin synthase	S316	Cytochrome P450	S332	Phospholipase A ₂
S307	Sphingomyelin phosphodiesterase	S317	CYP1 family	S333	Phosphatidylcholine-specific phospholipase D
S308	Neutral sphingomyelinase coupling factors	S317	CYP2 family: drug metabolising subset	S334	Lipid phosphate phosphatases
S308	Ceramide glucosyltransferase	S318	CYP2 family: physiological enzymes subset	S335	Phosphatidylinositol kinases

S336	Phosphatidylinositol phosphate kinases	–	G11 family	–	CK1: Casein kinase 1
–	Glycine recycling	–	Phosphatidyl inositol 3' kinase-related kinases	–	Casein kinase 1 (CK1) family
S337	Haem oxygenase	–	(PIKK) family	–	Tau tubulin kinase (TTBK) family
S338	Hydrogen sulphide synthesis	–	ATR subfamily	–	Vaccinia related kinase (VRK) family
S338	Hydrolases	S344	FRAP subfamily	–	CMGC: Containing CDK, MAPK, GSK3, CLK families
S340	Inositol phosphate turnover	–	SMG1 subfamily	–	CLK family
S340	Inositol 1,4,5-trisphosphate 3-kinases	–	TRRAP subfamily	–	Cyclin-dependent kinase (CDK) family
S340	Inositol polyphosphate phosphatases	–	Other PIKK family kinases	S345	CDK5 subfamily
S341	Inositol monophosphatase	–	RIO family	–	CDK7 subfamily
–	Itaconate biosynthesis	–	RIO1 subfamily	–	CDK8 subfamily
S341	Kinases (EC 2.7.x.x)	–	RIO2 subfamily	S345	CDK9 subfamily
–	AGC: Containing PKA, PKG, PKC families	–	RIO3 subfamily	–	CDK10 subfamily
–	DMPK family	–	PDHK family	–	CRK7 subfamily
–	GEK subfamily	–	Pyruvate dehydrogenase kinase (PDHK) family	–	PITSLRE subfamily
–	Other DMPK family kinases	–	TAF1 family	–	TAIRE subfamily
S342	Rho kinase	–	TIF1 family	–	Cyclin-dependent kinase-like (CDKL) family
–	G protein-coupled receptor kinases (GRKs)	–	CAMK: Calcium/calmodulin-dependent protein kinases	–	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase (DYRK) family
–	Beta-adrenergic receptor kinases (bARKs)	–	CAMK1 family	–	Dyrk1 subfamily
–	Opsin/rhodopsin kinases	–	CAMK2 family	–	Dyrk2 subfamily
–	GRK4 subfamily	–	CAMK-like (CAMKL) family	–	HIPK subfamily
–	MAST family	–	AMPK subfamily	–	PRP4 subfamily
–	NDR family	–	BRSK subfamily	–	Glycogen synthase kinase (GSK) family
–	PDK1 family	–	CHK1 subfamily	–	GSK subfamily
–	Protein kinase A (PKA) family	–	HUNK subfamily	–	Mitogen-activated protein kinases (MAP kinases)
–	Akt (Protein kinase B, PKB) family	–	LKB subfamily	–	ERK subfamily
S342	Protein kinase C (PKC) family	–	MARK subfamily	–	Erk7 subfamily
S342	Alpha subfamily	–	MELK subfamily	S345	JNK subfamily
S343	Delta subfamily	–	NIM1 subfamily	–	p38 subfamily
S343	Eta subfamily	–	NuaK subfamily	–	nmo subfamily
S344	Iota subfamily	–	PASK subfamily	–	RCK family
–	Protein kinase G (PKG) family	–	QIK subfamily	–	SRPK family
–	Protein kinase N (PKN) family	–	SNRK subfamily	–	Other protein kinases
–	RSK family	–	CAMK-unique family	–	CAMKK family
–	MSK subfamily	–	CASK family	–	Meta subfamily
–	p70 subfamily	–	DCAMKL family	–	Aurora kinase (Aur) family
–	RSK subfamily	–	Death-associated kinase (DAPK) family	–	Bub family
–	RSKR subfamily	–	MAPK-Activated Protein Kinase (MAPKAPK) family	–	Bud32 family
–	RSKL family	–	MAPKAPK subfamily	–	Casein kinase 2 (CK2) family
–	SGK family	–	MKN subfamily	–	CDC7 family
–	YANK family	–	Myosin Light Chain Kinase (MLCK) family	–	Haspin family
–	Atypical	–	Phosphorylase kinase (PHK) family	–	IKK family
–	ABC1 family	–	PIM family	–	IRE family
–	ABC1-A subfamily	–	Protein kinase D (PKD) family	–	MOS family
–	ABC1-B subfamily	–	PSK family	–	NAK family
–	Alpha kinase family	–	RAD53 family	–	
–	ChaK subfamily	–	Testis specific kinase (TSSK) family	–	
–	eEF2K subfamily	–	Trbl family	–	
–	Other alpha kinase family kinases	–	Trio family	–	
–	BCR family	–		–	
–	Bromodomain kinase (BRDK) family	–		–	

-	NIMA (never in mitosis gene a)- related kinase (NEK) family	S347	Ack family	-	C13: Legumain
-	NKF1 family	-	Csk family	S355	C14: Caspase
-	NKF2 family	-	Fak family	-	CE: Cysteine (C) Peptidases
-	NKF4 family	S348	Fer family	-	C48: Ulp1 endopeptidase
-	NKF5 family	S349	Janus kinase (JakA) family	-	M-: Metallo (M) Peptidases
-	NRBP family	S349	Src family	-	M79: Prenyl protease 2
-	Numb-associated kinase (NAK) family	-	Tec family	-	MA: Metallo (M) Peptidases
-	Other-unique family	-	TKL: Tyrosine kinase-like	S356	M1: Aminopeptidase N
S346	Polo-like kinase (PLK) family	-	Interleukin-1 receptor-associated kinase (IRAK) family	S356	M2: Angiotensin-converting enzymes (ACE and ACE2)
-	PEK family	-	Leucine-rich repeat kinase (LRRK) family	S357	M10: Matrix metallopeptidase
-	GCN2 subfamily	-	LIM domain kinase (LISK) family	S357	M12: Astacin/Adamalysin
-	PEK subfamily	-	LIMK subfamily	-	M13: Neprilysin
-	Other PEK family kinases	-	TESK subfamily	-	M49: Dipeptidyl-peptidase III
-	SgK493 family	-	Mixed Lineage Kinase (MLK) family	-	MC: Metallo (M) Peptidases
-	Slob family	-	HH498 subfamily	-	M14: Carboxypeptidase A
-	TBCK family	-	ILK subfamily	-	ME: Metallo (M) Peptidases
-	TOPK family	-	LZK subfamily	-	M16: Pitrilysin
-	Tousled-like kinase (TLK) family	-	MLK subfamily	-	MF: Metallo (M) Peptidases
-	TTK family	-	TAK1 subfamily	-	M17: Leucyl aminopeptidase
-	Unc-51-like kinase (ULK) family	S350	RAF family	-	MG: Metallo (M) Peptidases
-	VPS15 family	-	Receptor interacting protein kinase (RIPK) family	-	M24: Methionyl aminopeptidase
-	WEE family	-	TKL-unique family	-	MH: Metallo (M) Peptidases
-	Wnk family	-	Lanosterol biosynthesis pathway	-	M18: Aminopeptidase I
-	Miscellaneous protein kinases	S350	LPA synthesis	-	M20: Carnosine dipeptidase
-	actin-binding proteins ADF family	-	Membrane bound O-acyltransferases	S358	M28: Aminopeptidase Y
-	Twinfilin subfamily	-	Methionine turnover	-	MJ: Metallo (M) Peptidases
-	SCY1 family	-	Mitofusin proteins	S358	M19: Membrane dipeptidase
-	Hexokinases	-	NADPH oxidases	-	MP: Metallo (M) Peptidases
-	STE: Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases	-	Nucleoside synthesis and metabolism	-	M67: PSMD14 peptidase
S346	STE7 family	S352	Nucleotide salvage	-	PA: Serine (S) Peptidases
-	STE11 family	-	Pyrimidine salvage	S358	S1: Chymotrypsin
-	STE20 family	-	Nucleotide turnover	-	PB: Threonine (T) Peptidases
-	FRAY subfamily	S353	Paraoxonase (PON) family	-	C44: Phosphoribosyl pyrophosphate amidotransferase
-	KHS subfamily	S354	Peptidases and proteinases	S359	T1: Proteasome
-	MSN subfamily	S354	Blood coagulation components	-	T2: Glycosylasparaginase precursor
-	MST subfamily	-	AA: Aspartic (A) Peptidases	-	PC: Cysteine (C) Peptidases
-	NinaC subfamily	S355	A1: Pepsin	-	C26: Gamma-glutamyl hydrolase
-	PAKA subfamily	-	AD: Aspartic (A) Peptidases	-	SB: Serine (S) Peptidases
-	PAKB subfamily	S355	A22: Presenilin	S359	S8: Subtilisin
-	SLK subfamily	-	CA: Cysteine (C) Peptidases	-	SC: Serine (S) Peptidases
-	STE20 subfamily	-	C1: Papain	S360	S9: Prolyl oligopeptidase
-	STLK subfamily	-	C2: Calpain	-	S10: Carboxypeptidase Y
-	TAO subfamily	-	C12: Ubiquitin C-terminal hydrolase	-	S28: Lysosomal Pro-Xaa carboxypeptidase
-	YSK subfamily	-	C19: Ubiquitin-specific protease	-	S33: Prolyl aminopeptidase
-	STE-unique family	-	C54: Aut2 peptidase	S360	Peptidyl-prolyl cis/trans isomerases
-	TK: Tyrosine kinase	-	C65: Otubains	-	Phosphatases
-	Non-receptor tyrosine kinases (nRTKs)	-	C101: OTULIN peptidase	-	Class I classical (Cys-based) phosphatases
S347	Abl family	-	CD: Cysteine (C) Peptidases	-	Dual specificity phosphatases

-	Protein tyrosine phosphatases non-receptor type (PTPN)	-	1.2.3.1 Aldehyde oxidase	-	2.7.1.40 Pyruvate kinases
-	Metal-dependent protein phosphatase (PPM) family	-	1.4.3.13 Lysyl oxidases	-	3.1.-.- Ester bond enzymes
-	Sugar phosphatases	S366	1.13.11.- Dioxygenases	-	3.1.1.- Carboxylic Ester Hydrolases
-	Phosphodiesterases (other)	-	1.14.13.9 Kynurenine 3-monooxygenase	-	3.2.1.- Glycosidases
S361	Poly ADP-ribose polymerases	-	1.17.4.1 Ribonucleoside-diphosphate reductases	-	3.4.21.46 Complement factor D
S362	Prolyl hydroxylases	-	2.1.1.- Methyltransferases	S367	3.5.1.- Histone deacetylases (HDACs)
S362	Sphingosine 1-phosphate turnover	-	2.1.2.- Hydroxymethyl-, formyl- and related transferases	-	3.5.1.2 Glutaminases
S362	Sphingosine kinase	-	2.3.1.- Acyltransferases	S367	3.5.3.15 Peptidyl arginine deiminases (PADI)
S363	Sphingosine 1-phosphate phosphatase	-	2.3.2.- Aminoacyltransferases	S368	3.6.5.2 Small monomeric GTPases
S364	Sphingosine 1-phosphate lyase	-	2.3.2.13 Transglutaminases	S368	RAS subfamily
S365	Thyroid hormone turnover	-	2.3.2.27 RING-type E3 ubiquitin transferase	S369	RAB subfamily
-	UDP glucuronosyltransferases (UGT)	-	2.4.2.1 Purine-nucleoside phosphorylase	-	5.-.-.- Isomerases
-	1.-.-.- Oxidoreductases	S366	2.5.1.18 Glutathione transferases	-	6.3.3.- Cyclo-ligases
-	1.1.1.42 Isocitrate dehydrogenases	-	2.5.1.58 Protein farnesyltransferase	-	
		-	2.6.1.42 Branched-chain-amino-acid transaminase		

AAA ATPases

Enzymes → AAA ATPases

Overview: AAA or AAA+ (ATPases Associated with diverse cellular Activities) proteins couple chemical energy provided by ATP hydrolysis to the remodeling or translocation of macromolecules. They are involved in a wide range of cellular processes, including DNA replication, protein degradation, membrane fusion, microtubule severing, peroxisome biogenesis, signal transduction and the regulation of gene expression.

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

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

neuromuscular 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
Common abbreviation	ChAT	AChE	BChE
HGNC, UniProt	CHAT , P28329	ACHE , P22303	BCHE , P06276
EC number	2.3.1.6: acetyl CoA + choline = acetylcholine + coenzyme A	3.1.1.7: acetylcholine + H ₂ O = acetic acid + choline + H ⁺	3.1.1.7: acetylcholine + H ₂ O = acetic acid + choline + H ⁺

Inhibitors	naphthylvinylmethylpyridine (pIC ₅₀ 6.5) [251] – Mouse	tacrine (pK _i 7.5) [75], galantamine (pIC ₅₀ 6.3) [118], rivastigmine (pIC ₅₀ 5.4) [435]	rivastigmine (pIC ₅₀ 7.4) [435], tacrine (pK _i 7.2) [75]
Sub/family-selective inhibitors	–	physostigmine (pIC ₅₀ 7.6–7.8) [435]	physostigmine (pIC ₅₀ 7.6–7.8) [435]
Selective inhibitors	–	donepezil (pIC ₅₀ 7.7–8.3) [85, 220, 435], BW284C51 (pIC ₅₀ 7.7) [234]	bambuterol (pIC ₅₀ 8.5) [234]
Comments	Splice variants of choline O-acetyltransferase are suggested to be differentially distributed in the periphery and CNS (see [47]).	–	–

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 [731].

Further reading on Acetylcholine turnover

Akincioglu H *et al.* (2020) Acetylcholinesterase Inhibitors: Potential Drugs for Alzheimer's Disease *Mini Rev Med Chem* **20**: 703-715 [PMID:31902355]

Lockridge O. (2015) Review of human butyrylcholinesterase structure, function, genetic variants, history of use in the clinic, and potential therapeutic uses. *Pharmacol Ther* **148**: 34-46 [PMID:25448037]

Sussman JL *et al.* (2020) Computational studies on cholinesterases: Strengthening our understanding of the integration of structure, dynamics and function *Neuropharmacology* **179**: 108265 [PMID:32795461]

Taylor P *et al.* (2021) Ligand design for human acetylcholinesterase and nicotinic acetylcholine receptors, extending beyond the conventional and canonical *J Neurochem* [PMID:33638151]

Winek K *et al.* (2021) Regulators of cholinergic signaling in disorders of the central nervous system *J Neurochem* [PMID:33638173]

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 adenyl 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 transporters, *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	–
Common abbreviation	ADA	ADK	NT5E	SAHH
HGNC, UniProt	ADA , P00813	ADK , P55263	NT5E , P21589	AHCY , P23526
EC number	3.5.4.4: adenosine + H₂O = inosine + NH₃	2.7.1.20	3.1.3.5	3.3.1.1
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	adenosine, guanine, inosine, uridine	adenosine
Inhibitors	–	–	–	DZNep (pK _i 12.3) [239] – Hamster
Selective inhibitors	pentostatin (pIC ₅₀ 10.8) [8], EHNA (pK _i 8.8) [8]	A134974 (pIC ₅₀ 10.2) [460], ABT702 (pIC ₅₀ 8.8) [332]	αβ-methyleneADP (pIC ₅₀ 8.7) [73]	3-deazaadenosine (pIC ₅₀ 8.5) [265]
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 [64, 729].	Pharmacological inhibition of CD73 is being investigated as a novel cancer immunotherapy strategy [709].	–

Comments: An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, *CECRI*, *Q9NZK5*) has been identified [128, 440], which is insensitive to EHNA [765]. 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 [345].

Further reading on Adenosine turnover

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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	<i>PAH</i> , P00439	<i>TH</i> , P07101	<i>TPH1</i> , P17752	<i>TPH2</i> , 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

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16181/full>

Amino acid hydroxylases S295

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 [336]	Protein kinase A-mediated phosphorylation [337]	Protein kinase A-mediated phosphorylation [337]
Inhibitors	–	–	rodatristat (pIC ₅₀ 7.5) [242], compound 23a (pIC ₅₀ 7.4) [31], telotristat ethyl (pIC ₅₀ 7.2) [31, 358], LP533401 (pIC ₅₀ 6.2) [31]	rodatristat (pIC ₅₀ 8.1) [242]
Selective inhibitors	α-methylphenylalanine [253] – Rat, fenclonine	α-propylidopacetamide , 3-chlorotyrosine , 3-iodotyrosine , alpha-methyltyrosine	α-propylidopacetamide , 6-fluorotryptophan [500], fenclonine , fenfluramine	α-propylidopacetamide , 6-fluorotryptophan [500], fenclonine , fenfluramine
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 [141].	–	–

Further reading on Amino acid hydroxylases

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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 [creatinine](#) 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 modification 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](#).

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 [673], S-(2-boronoethyl)-L-cysteine [121, 359] and 2(S)-amino-6-borono-hexanoic acid [37, 121].

Arginine:glycine amidinotransferase

Enzymes → L-Arginine turnover → Arginine:glycine amidinotransferase

Overview: Arginine:glycine amidinotransferase is a mitochondrial enzyme that is involved in creatine biosynthesis.

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

Comments: Missense mutations in *GATM* which disrupt creatine synthesis, underlie creatine deficiency syndromes which are characterised by cognitive disability, language impairment, and behavioural disorders.

Dimethylarginine dimethylaminohydrolases

Enzymes → L-Arginine turnover → Dimethylarginine dimethylaminohydrolases

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

Nomenclature	N^G,N^G -Dimethylarginine dimethylaminohydrolase 1	N^G,N^G -Dimethylarginine dimethylaminohydrolase 2
Common abbreviation	DDAH1	DDAH2
HGNC, UniProt	DDAH1 , O94760	DDAH2 , O95865
EC number	3.5.3.18	3.5.3.18
Cofactors	Zn ²⁺	–
Inhibitors	compound 2e (pK _i 5.7) [371]	–

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 (NO₂) 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 [[480](#)] 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

affinity 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
Common abbreviation	eNOS	iNOS	nNOS
HGNC, UniProt	NOS3 , P29474	NOS2 , P35228	NOS1 , P29475
EC number	1.14.13.39	1.14.13.39	1.14.13.39
Endogenous Substrate	L-arginine	L-arginine	L-arginine
Products	NO, L-citrulline	NO, L-citrulline	NO, L-citrulline
Cofactors	heme, flavin adenine dinucleotide, flavin mononucleotide, NADPH, oxygen, BH ₄ , Zn ²⁺	heme, flavin adenine dinucleotide, flavin mononucleotide, NADPH, oxygen, BH ₄ , Zn ²⁺	heme, flavin adenine dinucleotide, flavin mononucleotide, NADPH, oxygen, BH ₄ , Zn ²⁺

Inhibitors	–	–	NANT
Selective inhibitors	–	1400W (pIC ₅₀ 8.2) [230], 2-amino-4-methylpyridine (pIC ₅₀ 7.4) [189], PIBTU (pIC ₅₀ 7.3) [231], NIL (pIC ₅₀ 5.5) [481], aminoguanidine [125]	3-bromo-7NI (pIC ₅₀ 6.1–6.5) [60], 7NI (pIC ₅₀ 5.3) [28]

Comments: The reductase domain of NOS catalyses the reduction of cytochrome c and other redox-active dyes [454]. 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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Further reading on L-Arginine turnover

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Wu Q *et al.* (2021) Protein arginine methylation: from enigmatic functions to therapeutic targeting. *Nat Rev Drug Discov* [PMID:33742187]

Carbonic anhydrases

Enzymes → Carbonic anhydrases

Overview: Carbonic anhydrases facilitate the interconversion of water and carbon dioxide to 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	carbonic anhydrase 13	carbonic anhydrase 14
Common abbreviation	CA I	CA VII	CA XII	CA XIII	CA XIV
HGNC, UniProt	CA1, P00915	CA7, P43166	CA12, O43570	CA13, Q8N1Q1	CA14, Q9ULX7
EC number	4.2.1.1	4.2.1.1	4.2.1.1	4.2.1.1	4.2.1.1
Inhibitors	chlorthalidone (pK _i 6.5)	methazolamide (pK _i 8.7) [610], acetazolamide (pK _i 8.6) [27], brinzolamide (pK _i 8.6) [610], chlorthalidone (pK _i 8.6) [672]	SLC-0111 (pK _i 8.4) [122]	–	–

Further reading on Carbonic anhydrases

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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	Propionyl-CoA carboxylase
Common abbreviation	PCCA,PCCB
Subunits	Propionyl-CoA carboxylase α subunit, Propionyl-CoA carboxylase β subunit
EC number	6.4.1.3
Endogenous substrates	ATP, propionyl-CoA
Products	ADP, methylmalonyl-CoA, P_i
Cofactors	biotin
Comments	Propionyl-CoA carboxylase is able to function in both forward and reverse activity modes, as a ligase (carboxylase) or lyase (decarboxylase), respectively.

Nomenclature	Pyruvate carboxylase	Acetyl-CoA carboxylase 1	Acetyl-CoA carboxylase 2	γ -Glutamyl carboxylase
Common abbreviation	PC	ACC1	ACC2	GGCX
HGNC, UniProt	PC, P11498	ACACA, Q13085	ACACB, O00763	GGCX, P38435
EC number	6.4.1.1	6.4.1.2	6.4.1.2	4.1.1.90
Endogenous substrates	ATP, pyruvic acid	ATP, acetyl CoA	ATP, acetyl CoA	glutamyl peptides
Products	ADP, oxalacetic acid, P_i	malonyl-CoA, ADP, P_i	malonyl-CoA, ADP, P_i	carboxyglutamyl peptides
Cofactors	biotin	biotin	biotin	NADPH, vitamin K hydroquinone

Inhibitors	–	–	compound 2e (pIC ₅₀ 8.7) [658], A-908292 (pIC ₅₀ 7.6) [713]	anisindione
Selective inhibitors	–	compound 21 (pIC ₅₀ 8) [255], TOFA (pIC ₅₀ 4.9) [773]	compound 21 (pIC ₅₀ 8.4) [255], TOFA (pIC ₅₀ 4.9) [773]	–
Selective allosteric modulators	–	firsocostat (Negative) (pIC ₅₀ 8.7) [282]	firsocostat (Negative) (pIC ₅₀ 8.2) [282]	–
Comments	–	Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase.	Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase.	Loss-of-function mutations in γ -glutamyl carboxylase are associated with clotting disorders .

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

Further reading on Carboxylases

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Decarboxylases

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

Overview: The decarboxylases generate CO₂ and the indicated products from acidic substrates, requiring [pyridoxal 5-phosphate](#) or [pyruvic acid](#) as a co-factor.

Nomenclature	Glutamic acid decarboxylase 1	Glutamic acid decarboxylase 2	Histidine decarboxylase
Common abbreviation	GAD1	GAD2	HDC
HGNC, UniProt	GAD1 , Q99259	GAD2 , Q05329	HDC , 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
Endogenous substrates	L-glutamic acid , L-aspartic acid	L-glutamic acid , L-aspartic acid	L-histidine
Products	GABA	GABA	histamine
Cofactors	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyridoxal 5-phosphate
Selective inhibitors	s-allylglycine	s-allylglycine	AMA , FMH [226]
Comments	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β -alanine [735]. 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
Common abbreviation	ADC	AADC	MLYCD	ODC	PSDC	SAMDC
HGNC, UniProt	AZIN2, Q96A70	DDC, P20711	MLYCD, O95822	ODC1, P11926	PISD, Q9UG56	AMD1, P17707
EC number	4.1.1.19	4.1.1.28: levodopa → dopamine + CO ₂ 5-hydroxy-L-tryptophan → 5-hydroxytryptamine + CO ₂	4.1.1.9	4.1.1.17	4.1.1.65	4.1.1.50
Endogenous substrates	L-arginine	5-hydroxy-L-tryptophan, L-tryptophan, levodopa	malonyl-CoA	L-ornithine	phosphatidylserine	S-adenosyl methionine
Products	agmatine [775]	5-hydroxytryptamine, dopamine	acetyl CoA	putrescine	phosphatidylethanolamine	S-adenosyl-L-methionin-amine
Cofactors	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyruvic acid	pyruvic acid
Selective inhibitors	–	3-hydroxybenzylhydrazine, L- α -methyldopa, benserazide [138], carbidopa	–	APA (pI _{C₅₀ 7.5) [642], eflornithine (pK_d 4.9) [556]}	–	sardomozide (pI _{C₅₀ 8) [641]}
Comments	The presence of a functional ADC activity in human tissues has been questioned [120].	AADC is a homodimer.	Inhibited by AMP-activated protein kinase-evoked phosphorylation [588]	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 [524].	S-allylglycine is also an inhibitor of SAMDC [524].

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 bloodstream, catecholamines are accumulated through the action 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)
Common abbreviation	–	TAT	–	DBH
HGNC, UniProt	PAH , P00439	TAT , P17735	TH , P07101	DBH , P09172
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
Endogenous substrates	L-phenylalanine	–	L-tyrosine	–
Products	L-tyrosine	–	levodopa	–
Cofactors	sapropterin	pyridoxal 5-phosphate	sapropterin, Fe ²⁺	L-ascorbic acid, Cu ²⁺
Endogenous activators	Protein kinase A-mediated phosphorylation (Rat) [2]	–	Protein kinase A-mediated phosphorylation [336]	–
Selective inhibitors	α-methylphenylalanine [253] – Rat, fenclonine	–	α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine	nepicastat (pIC ₅₀ 8) [644]
Comments	PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monoxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria	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 [141].	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 [95].

Nomenclature	L-Aromatic amino-acid decarboxylase	Phenylethanolamine N-methyltransferase	Catechol-O-methyltransferase
Common abbreviation	AADC	PNMT	COMT
HGNC, UniProt	DDC , P20711	PNMT , P11086	COMT , P21964
EC number	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	2.1.1.28: (-)-noradrenaline → (-)-adrenaline	2.1.1.6: S-adenosyl-L-methionine + a catechol = S-adenosyl-L-homocysteine + a guaiacol(-)-noradrenaline → normetanephrine(-)-adrenaline → metanephrine3,4-dihydroxymandelic acid → vanillylmandelic aciddopamine → 3-methoxytyramine
Endogenous substrates	5-hydroxy-L-tryptophan, L-tryptophan, levodopa	–	–
Products	5-hydroxytryptamine, dopamine	–	–
Cofactors	pyridoxal 5-phosphate	S-adenosyl methionine	S-adenosyl methionine
Inhibitors	–	LY134046 (pK _i 7.6) [214]	tolcapone (soluble enzyme) (pK _i 9.6) [425], tolcapone (membrane-bound enzyme) (pK _i 9.5) [425], entacapone (soluble enzyme) (pK _i 9.5) [425], entacapone (membrane-bound enzyme) (pK _i 8.7) [425]
Selective inhibitors	3-hydroxybenzylhydrazine, L-α-methyldopa, benserazide [138], carbidopa	–	–
Comments	AADC is a homodimer.	–	COMT appears to exist in both membrane-bound and soluble forms. COMT has also been described to methylate steroids, particularly hydroxysteroids

Nomenclature	Monoamine oxidase A	Monoamine oxidase B
Common abbreviation	MAO-A	MAO-B
HGNC, UniProt	MAOA , P21397	MAOB , P27338
EC number	1.4.3.4dopamine → 3,4-dihydroxyphenylacetaldehyde + NH ₃ (-)-noradrenaline → 3,4-dihydroxymandelic acid + NH ₃ (-)-adrenaline → 3,4-dihydroxymandelic acid + NH ₃ 5-hydroxytryptamine → 5-hydroxyindole acetaldehyde + NH ₃ tyramine → 4-hydroxyphenyl acetaldehyde + NH ₃	1.4.3.4
Cofactors	flavin adenine dinucleotide	flavin adenine dinucleotide
Inhibitors	moclobemide (pK _i 8.3) [329], phenelzine (Irreversible inhibition) (pK _i 7.3) [58], tranylcypromine (pIC ₅₀ 4.7) [756], selegiline (pK _i 4.2) [472], befloxatone [136], clorgiline , pirlindole [463]	rasagiline (pIC ₅₀ 7.8) [761], phenelzine (Irreversible inhibition) (pK _i 7.8) [58], lazabemide (pK _i 7.1) [268 , 682], selegiline (pK _i 5.7–6) [156 , 472], tranylcypromine (pIC ₅₀ 4.7) [756]
Selective inhibitors	–	safinamide (pK _i 6.3) [57]

Further reading on Catecholamine turnover

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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 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 galactosylceramides.

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

Serine palmitoyltransferase

Enzymes → Ceramide turnover → Serine palmitoyltransferase

Overview: The functional enzyme is a heterodimer of SPT1 (LCB1) with either SPT2 (LCB2) or SPT3 (LCB2B); the small subunits of SPT (ssSPTa or ssSPTb) bind to the heterodimer to enhance enzymatic activity. The complexes of SPT1/SPT2/ssSPTa and SPT1/SPT2/ssSPTb were most active with palmitoylCoA as substrate, with the latter complex also showing some activity with stearoylCoA [274]. 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 [274].

Nomenclature	serine palmitoyltransferase long chain base subunit 1	serine palmitoyltransferase long chain base subunit 2	serine palmitoyltransferase long chain base subunit 3	serine palmitoyltransferase small subunit A	serine palmitoyltransferase small subunit B
Common abbreviation	SPT1	SPT2	SPT3	SPTSSA	SPTSSB
HGNC, UniProt	<i>SPTLC1</i> , O15269	<i>SPTLC2</i> , O15270	<i>SPTLC3</i> , Q9NUV7	<i>SPTSSA</i> , Q969W0	<i>SPTSSB</i> , 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	–	–
Cofactors	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyridoxal 5-phosphate	–	–
Inhibitors	–	–	–	–	compound 18 (pK _i 5.8) [302]
Selective inhibitors	myriocin (pK _i 9.6) [473] – Mouse	myriocin [473]	myriocin [473]	–	–

Ceramide synthase

Enzymes → Ceramide turnover → Ceramide synthase

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

Nomenclature	ceramide synthase 1	ceramide synthase 2	ceramide synthase 3	ceramide synthase 4	ceramide synthase 5	ceramide synthase 6
Common abbreviation	CERS1	CERS2	CERS3	CERS4	CERS5	CERS6
HGNC, UniProt	CERS1, P27544	CERS2, Q96G23	CERS3, Q8IU89	CERS4, Q9HA82	CERS5, Q8NSB7	CERS6, Q6ZMG9
EC number	2.3.1.24: acylCoA + dihydro sphingosine → dihydroceramide + coenzyme A sphingosine + acylCoA → ceramide + coenzyme A					
Substrates	C18-CoA [697]	C24- and C26-CoA [388]	C26-CoA and longer [476, 558]	C18-, C20- and C22-CoA [574]	C16-CoA [384, 574]	C14- and C16-CoA [475]

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, Q6QHCS
EC number	1.14.-.-	1.14.-.-
Cofactors	NAD	NAD
Inhibitors	SKI II (pK _i 6.5) [117], RBM2-1B (pI _{C50} 4.7) [80]	–
Comments	Myristoylation of DEGS1 enhances its activity and targets it to the mitochondria [43].	–

Comments: DEGS1 activity is inhibited by a number of natural products, including [curcumin](#) and Δ^9 -tetrahydrocannabinol [188].

Sphingomyelin synthase

Enzymes → Ceramide turnover → Sphingomyelin synthase

Overview: Following translocation from the ER to the Golgi under the influence of the ceramide transfer protein, sphingomyelin synthases allow the formation of sphingomyelin by the transfer of phosphocholine from the phospholipid phosphatidylcholine.

Sphingomyelin synthase-related protein 1 is structurally related but lacks sphingomyelin synthase activity.

Nomenclature	sphingomyelin synthase 1	sphingomyelin synthase 2	sterile alpha motif domain containing 8
HGNC, UniProt	<i>SGMS1</i> , Q86VZ5	<i>SGMS2</i> , Q8NHU3	<i>SAMD8</i> , Q96LT4
EC number	2.7.8.27: ceramide + phosphatidylcholine → sphingomyelin + diacylglycerol	2.7.8.27: ceramide + phosphatidylcholine → sphingomyelin + diacylglycerol	2.7.8.-: ceramide + phosphatidylethanolamine → ceramide phosphoethanolamine
Inhibitors	compound 1j (pIC ₅₀ 5.7) [404]	compound D24 (pIC ₅₀ 4.9) [148]	–
Comments	–	Palmitoylation of sphingomyelin synthase 2 may allow targeting to the plasma membrane [666].	–

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	3.1.4.12: sphingomyelin → ceramide + phosphocholine	3.1.4.12: sphingomyelin → ceramide + phosphocholine	3.1.4.12: sphingomyelin → ceramide + phosphocholine	3.1.4.-: sphingomyelin → ceramide + phosphocholine	3.1.4.-: sphingomyelin → ceramide + phosphocholine
Inhibitors	compound 21b (pIC ₅₀ 6.5) [752], WJYK50 (pIC ₅₀ 6.3) [751], WJYK50 (pIC ₅₀ 6.1) [752]	inhibitor A (pK _i 5.8) [755] – Bovine	–	–	–	–

Neutral sphingomyelinase coupling factors

Enzymes → Ceramide turnover → Neutral sphingomyelinase coupling factors

Overview: Protein FAN [4] and polycomb protein EED [541] 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) (pK _i 9.4) [292]	–

Ceramide glucosyltransferase

Enzymes → Ceramide turnover → Ceramide glucosyltransferase

Nomenclature	UDP-glucose ceramide glucosyltransferase
HGNC, UniProt	<i>UGCG</i> , Q16739
EC number	2.4.1.80: UDP-glucose + ceramide = UDP + glucosylceramide
Inhibitors	miglustat (pK _i 5.1) [76]
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	<i>ASAHI</i> , 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 [365].

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 [665].	–

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 [651].	ACER2 is associated with the Golgi apparatus [744].	ACER3 is associated with the ER and Golgi apparatus [444].

Ceramide kinase

Enzymes → Ceramide turnover → Ceramide kinase

Nomenclature	ceramide kinase
HGNC, UniProt	CERK, Q8TCT0
EC number	2.7.1.138 : ceramide + ATP → ceramide 1-phosphate + ADP
Inhibitors	NVP 231 (pIC ₅₀ 7.9) [249]

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

Further reading on Ceramide turnover

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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 [372]. 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) [372].

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 [186], where a wide variety of cellular and protein aberrations are known to perturb chromatin structure, gene transcription and ultimately cellular pathways [41, 621]. 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 [227, 725]) and erasers (*e.g.* the HDAC inhibitors vorinostat, romidepsin and belinostat for the treatment of T-cell lymphomas [203, 355]) 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 [78]. Current progress in this field is reviewed by Simó-Riudalbas and Esteller (2015) [622].

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 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](#).

3.5.1.- Histone deacetylases (HDACs)

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

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

The histone deacetylase family has been classified in to five 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 Zn⁺ as a co-factor, whereas catalysis by Class III enzymes requires NAD⁺ as a co-factor, and members of this subfamily have ADP-ribosylase activity in addition to protein deacetylase function [596].

HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [113] such as microtubules [314], the hsp90 chaperone [373] and the tumour suppressor p53 [432].

Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [409, 582], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [727]. 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) [622].

Nomenclature	histone deacetylase 6
HGNC, UniProt	HDAC6, Q9UBN7
EC number	3.5.1.98
Inhibitors	trichostatin A (pK _i 9) [69], vorinostat (pK _i 8.8) [69], romidepsin (pK _i 8) [69]
Selective inhibitors	ricolinostat (pIC ₅₀ 8.3) [593]

Further reading on 3.5.1.- Histone deacetylases (HDACs)

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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).

For details of the enzymes involved in cGMP synthesis see the **Receptor Guanylyl Cyclase (RGC) family**, in the Catalytic receptors section.

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-delimited adenylyl cyclases (**nomenclature as approved by the NC-IUPHAR Subcommittee on Adenylyl cyclases** [151]) 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 $G\alpha_s$ (the stimulatory G protein α subunit) and forskolin (except AC9, [552]). Adenosine and its derivatives (e.g. 2',5'-dideoxyadenosine), acting through the P-site, are inhibitors of adenylyl cyclase activity [675]. Four families of membranous adenylyl cyclase are distinguishable: calmodulin (CALM1 CALM2 CALM3, P62158)-stimulated (AC1,

AC3 and AC8), Ca^{2+} - and $G\beta\gamma$ -inhibitible (AC5, AC6 and AC9), $G\beta\gamma$ -stimulated and Ca^{2+} -insensitive (AC2, AC4 and AC7), and forskolin-insensitive (AC9) forms. A soluble adenylyl cyclase (AC10) lacks membrane spanning regions and is insensitive to G proteins. It functions as a cytoplasmic bicarbonate (pH-insensitive) sensor [101].

Nomenclature	adenylyl cyclase 1	adenylyl cyclase 2	adenylyl cyclase 3	adenylyl cyclase 4	adenylyl cyclase 5
Common abbreviation	AC1	AC2	AC3	AC4	AC5
HGNC, UniProt	ADCY1, Q08828	ADCY2, Q08462	ADCY3, O60266	ADCY4, Q8NFM4	ADCY5, O95622
EC number	4.6.1.1	4.6.1.1	4.6.1.1	4.6.1.1	4.6.1.1

Searchable database: <https://www.guidetopharmacology.org/>Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16181/full>

Adenylyl cyclases (ACs) S312

Endogenous activators	calmodulin (CALM1 CALM2 CALM3, P62158), PKC-evoked phosphorylation [328 , 664]	$G\beta\gamma$, PKC-evoked phosphorylation, Raf-evoked phosphorylation [99 , 161 , 436 , 669]	calmodulin (CALM1 CALM2 CALM3, P62158), PKC-evoked phosphorylation [111 , 328]	$G\beta\gamma$ [222]	PKC-evoked phosphorylation, $G\beta\gamma$, Raf-evoked phosphorylation [161 , 225 , 352]
Activators	compound 45 (pIC ₅₀ 7.7) [579] – Bovine	FD1 [518]	–	–	FD6 [518]
Endogenous inhibitors	$G\alpha_i$, $G\alpha_o$, $G\beta\gamma$ [669 , 670]	–	RGS2 , $G\beta\gamma$, CaM kinase II-evoked phosphorylation [157 , 624 , 720]	PKC-evoked phosphorylation [777]	$G\alpha_i$, Ca^{2+} , PKA-evoked phosphorylation, $G\beta\gamma$, NO [225 , 300 , 323 , 327 , 670]
Inhibitors	–	SKF-83566 [124]	–	–	NKY80 (pIC ₅₀ 5.2) [70 , 518]
Selective inhibitors	ST034307 (pIC ₅₀ 5.6) [72]	–	–	–	–

Nomenclature	adenylyl cyclase 6	adenylyl cyclase 7	adenylyl cyclase 8	adenylyl cyclase 9	adenylyl cyclase 10
Common abbreviation	AC6	AC7	AC8	AC9	AC10
HGNC, UniProt	ADCY6 , O43306	ADCY7 , P51828	ADCY8 , P40145	ADCY9 , O60503	ADCY10 , Q96PN6
EC number	4.6.1.1	4.6.1.1	4.6.1.1	4.6.1.1	–
Endogenous activators	$G\beta\gamma$, Raf-evoked phosphorylation [161 , 225]	$G\beta\gamma$, PKC-evoked phosphorylation [45 , 719]	calmodulin (CALM1 CALM2 CALM3, P62158) [79]	–	Bicarbonate, Ca^{2+} [101 , 411]
Endogenous inhibitors	$G\alpha_i$, Ca^{2+} , PKA-evoked phosphorylation, PKC-evoked phosphorylation, NO [102 , 300 , 385 , 670 , 759]	–	PKA-evoked phosphorylation [730]	Ca^{2+} /calcineurin [532]	–
Inhibitors	NKY80 (pIC ₅₀ 4.8) [70]	–	–	–	TDI-11861 (Binding) (pK _d 8.9) [469], TDI-11861 (pIC ₅₀ 8.3) [469], KH7 (pIC ₅₀ 5–5.5) [298], LRE1 (pIC ₅₀ 5) [561]

Comments: Many of the activators and inhibitors listed are only somewhat selective or have not been tested against all AC isoforms [[70](#), [124](#)]. AC3 shows only modest *in vitro* activation by Ca^{2+} /CaM.

Further reading on Adenylyl cyclases (ACs)

Antoni FA. (2020) The chilling of adenylyl cyclase 9 and its translational potential. *Cell Signal* **70**: 109589 [[PMID:32105777](#)]

Dessauer CW *et al.* (2017) International Union of Basic and Clinical Pharmacology. CI. Structures and Small Molecule Modulators of Mammalian Adenylyl Cyclases. *Pharmacol Rev* **69**: 93-139 [[PMID:28255005](#)]

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Wiggins SV *et al.* (2018) Pharmacological modulation of the CO₂/HCO₃⁻/pH-, calcium-, and ATP-sensing soluble adenylyl cyclase. *Pharmacol Ther* **190**: 173-186 [[PMID:29807057](#)]

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 ([ENSEM0025000000899](#)), which also includes [RapGEF5](#) (GFR, KIAA0277, MR-GEF, [Q92565](#)) and

[RapGEFL1](#) (Link-GEFII, [Q9UHV5](#)). They are activated endogenously by cyclic AMP and with some pharmacological selectivity by 8-pCPT-2'-O-Me-cAMP [[180](#)]. 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 [[599](#)].

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16181/full>

Exchange protein activated by cyclic AMP (EPACs) S313

Nomenclature	Rap guanine nucleotide exchange factor 3	Rap guanine nucleotide exchange factor 4
Common abbreviation	Epac1	Epac2
HGNC, UniProt	RAPGEF3, O95398	RAPGEF4, Q8WZA2
Inhibitors	ESI-09 (pIC ₅₀ 5.5) [19], CE3F4	HJC 0350 (pIC ₅₀ 6.5) [97], ESI-09 (pIC ₅₀ 4.4–5.2) [19, 98]

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

Bouvet M *et al.* (2019) The Epac1 Protein: Pharmacological Modulators, Cardiac Signalosome and Pathophysiology *Cells* **8**: 1543 [PMID:31795450]
 Fujita T *et al.* (2017) The role of Epac in the heart. *Cell Mol Life Sci* **74**: 591-606 [PMID:27549789]
 Luchowska-Stańska U *et al.* (2019) Selective small-molecule EPAC activators *Biochem Soc Trans* **47**: 1415-1427 [PMID:31671184]

Robichaux 3rd WG *et al.* (2018) Intracellular cAMP Sensor EPAC: Physiology, Pathophysiology, and Therapeutics Development. *Physiol Rev* **98**: 919-1053 [PMID:29537337]
 Wang P *et al.* (2017) Exchange proteins directly activated by cAMP (EPACs): Emerging therapeutic targets. *Bioorg Med Chem Lett* **27**: 1633-1639 [PMID:28283242]

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	phosphodiesterase 2A	phosphodiesterase 3A	phosphodiesterase 3B
Common abbreviation	PDE1A	PDE1B	PDE1C	PDE2A	PDE3A	PDE3B
HGNC, UniProt	PDE1A, P54750	PDE1B, Q01064	PDE1C, Q14123	PDE2A, O00408	PDE3A, Q14432	PDE3B, Q13370
EC number	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic GMP > cyclic AMP	cyclic GMP > cyclic AMP	cyclic GMP = cyclic AMP	cyclic AMP ≫ cyclic GMP	–	–
Endogenous activators	calmodulin (CALM1 CALM2 CALM3, P62158)	calmodulin (CALM1 CALM2 CALM3, P62158)	calmodulin (CALM1 CALM2 CALM3, P62158)	cyclic GMP	–	–
Endogenous inhibitors	–	–	–	–	cyclic GMP	cyclic GMP
Inhibitors	crisaborole (pIC ₅₀ 5.2) [13]	–	–	PF-05180999 (pIC ₅₀ 8.8) [294], milrinone (pIC ₅₀ <6.5) [649]	cilostazol (pIC ₅₀ 6.7) [649], inamrinone (pIC ₅₀ 4.8) [625]	–
Selective inhibitors	SCH51866 (pIC ₅₀ 7.2) [695], vinpocetine (pIC ₅₀ 5.1) [427]	lenrispodun (pIC ₅₀ 10.2) [399], SCH51866 (pIC ₅₀ 7.2) [695]	compound 3m (pIC ₅₀ 8.5) [739], SCH51866 (pIC ₅₀ 7.2) [695], vinpocetine (pIC ₅₀ 4.3) [427]	BAY607550 (pIC ₅₀ 8.3–8.8) [63], EHNA (pIC ₅₀ 5.3) [468]	cilostamide (pIC ₅₀ 7.5) [649], anagrelide (pIC ₅₀ 7.1–7.3) [340, 449, 462], milrinone (pIC ₅₀ 6.3–6.4) [177, 649]	cilostamide (pIC ₅₀ 7.3) [649], cilostazol (pIC ₅₀ 6.4) [649], milrinone (pIC ₅₀ 6) [649], inamrinone (pIC ₅₀ 4.5) [649]
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
Common abbreviation	PDE4A	PDE4B	PDE4C	PDE4D	PDE5A
HGNC, UniProt	PDE4A , P27815	PDE4B , Q07343	PDE4C , Q08493	PDE4D , Q08499	PDE5A , O76074
EC number	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17
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
Activators	–	–	–	PKA-mediated phosphorylation [309]	Protein kinase A, protein kinase G [126]
Inhibitors	ibudilast (pIC ₅₀ 7.3) [366], RS-25344 (pIC ₅₀ 7.2) [590]	roflumilast (pIC ₅₀ 9.4) [431], ibudilast (pIC ₅₀ 7.2) [366], RS-25344 (pIC ₅₀ 6.5) [590], roflupram (Knocking down the expression of PDE4B in primary microglial cells led to enhanced level of LC-3 II and decreased activation of inflammasome.) [760]	RS-25344 (pIC ₅₀ 8.1) [590], ibudilast (pIC ₅₀ 6.6) [366]	RS-25344 (pIC ₅₀ 8.4) [590], difamilast (pIC ₅₀ > 7.3) [515], CBS-3595 (pIC ₅₀ 6.1) [16]	gisadenafil (pIC ₅₀ 8.9) [568], milrinone (pIC ₅₀ 7.3), icariside II [223]
Sub/family-selective inhibitors	rolipram (pIC ₅₀ 9) [710], CDP840 (pK _i 8) [538], Ro20-1724 (pIC ₅₀ 6.5) [710]	rolipram (pIC ₅₀ 9) [710], Ro20-1724 (pIC ₅₀ 6.4) [710]	CDP840 (pK _i 7.7) [538], rolipram (pIC ₅₀ 6.5) [710], Ro20-1724 (pIC ₅₀ 5.4) [710]	CDP840 (pK _i 8.1) [538], rolipram (pIC ₅₀ 7.2) [710], Ro20-1724 (pIC ₅₀ 6.2) [710]	–
Selective inhibitors	YM976 (pIC ₅₀ 8.3) [22], apremilast (pIC ₅₀ 7.8) [597]	–	apremilast (pIC ₅₀ 6.9) [597]	apremilast (pIC ₅₀ 7.5) [597]	vardenafil (pIC ₅₀ 9.7) [68], T0156 (pIC ₅₀ 9.5) [477], sildenafil (pIC ₅₀ 8.4–9) [687, 708], tadalafil (pIC ₅₀ 8.5) [479], SCH51866 (pIC ₅₀ 7.2) [695], zaprinast (pIC ₅₀ 6.8) [687]

Nomenclature	phosphodiesterase 6A	phosphodiesterase 6B	phosphodiesterase 6C	phosphodiesterase 6D	phosphodiesterase 6G	phosphodiesterase 6H
Common abbreviation	PDE6A	PDE6B	PDE6C	PDE6D	PDE6G	PDE6H
HGNC, UniProt	PDE6A , P16499	PDE6B , P35913	PDE6C , P51160	PDE6D , O43924	PDE6G , P18545	PDE6H , Q13956
EC number	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17
Inhibitors	compound 53 (pIC ₅₀ 8) [315]	–	sildenafil (pIC ₅₀ 7.4) [708], PDE4 inhibitor 16 (pIC ₅₀ 5.5) [770]	–	–	–

Nomenclature	phosphodiesterase 7A	phosphodiesterase 7B	phosphodiesterase 8A	phosphodiesterase 8B
Common abbreviation	PDE7A	PDE7B	PDE8A	PDE8B
HGNC, UniProt	PDE7A , Q13946	PDE7B , Q9NP56	PDE8A , O60658	PDE8B , O95263
EC number	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic AMP \gg cyclic GMP [466]	cyclic AMP \gg cyclic GMP [229]	cyclic AMP \gg cyclic GMP [197]	cyclic AMP \gg cyclic GMP [289]
Inhibitors	crisaborole (pIC ₅₀ 6.1) [13]	BRL50481 (pIC ₅₀ 4.9) [14]	–	–

Selective inhibitors	BRL50481 (pIC ₅₀ 6.7–6.8) [14, 631]	dipyridamole (pIC ₅₀ 5.7–6) [229, 595], SCH51866 (pIC ₅₀ 5.8) [595]	PF-04957325 (pIC ₅₀ 7.4) [453], dipyridamole (pIC ₅₀ 5.1) [197]	dipyridamole (pIC ₅₀ 4.3) [289]
Comments	PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively	–	–	–

Nomenclature	phosphodiesterase 9A	phosphodiesterase 10A	phosphodiesterase 11A
Common abbreviation	PDE9A	PDE10A	PDE11A
HGNC, UniProt	PDE9A , O76083	PDE10A , Q9Y233	PDE11A , Q9HCR9
EC number	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic GMP ≫ cyclic AMP [198]	cyclic AMP , cyclic GMP [212]	cyclic AMP , cyclic GMP [192]
Inhibitors	SCH51866 (pIC ₅₀ 5.8) [198], zaprinast (pIC ₅₀ 4.5) [198]	–	tadalafil (pIC ₅₀ 6.5) [479], BC11-38 (pIC ₅₀ 6.5) [92]
Selective inhibitors	–	mardepodect (pIC ₅₀ 9.4) [699]	–

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 [303, 304]. PDE4A–D splice variants can be membrane-bound or cytosolic [309]. PDE4 isoforms may be labelled with [³H]rolipram. PDE6 is a membrane-bound tetramer composed of two catalytic chains (PDE6A or PDE6C and PDE6B), an inhibitory chain

(PDE6G or PDE6H) and the PDE6D chain. The enzyme is essentially [cyclic GMP](#) specific and is activated by the α -subunit of transducin ($G\alpha_t$) and inhibited by [sildenafil](#), [zaprinast](#) and [dipyridamole](#) with potencies lower than those observed for PDE5A. Defects in PDE6B are a cause of retinitis pigmentosa and congenital stationary night blindness.

Further reading on Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs)

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- Bolger GB. (2021) The PDE-Opathies: Diverse Phenotypes Produced by a Functionally Related Multigene Family. *Trends Genet* **37**: 669-681 [PMID:33832760]
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- Peng T *et al.* (2020) Advances in the Development of Phosphodiesterase-4 Inhibitors. *J Med Chem* **63**: 10594-10617 [PMID:32255344]

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- Samidurai A *et al.* (2021) Role of phosphodiesterase 1 in the pathophysiology of diseases and potential therapeutic opportunities. *Pharmacol Ther* **226**: 107858 [PMID:33895190]
- Turner MJ *et al.* (2021) Cyclic nucleotide phosphodiesterase inhibitors as therapeutic interventions for cystic fibrosis. *Pharmacol Ther* **224**: 107826 [PMID:33662448]

Cytochrome P450

Enzymes → Cytochrome P450

Overview: The cytochrome P450 enzyme superfamily (CYP), E.C. 1.14.-.-, are haem-containing monooxygenases with a vast range of both endogenous and exogenous substrates. These include sterols, fatty acids, eicosanoids, fat-soluble vitamins, hormones, pesticides and carcinogens as well as drugs. Listed below are the human enzymes, their relationship with rodent CYP enzyme activities is obscure in that the species orthologue

may not metabolise the same substrates. Some of the CYP enzymes located in the liver are particularly important for drug metabolism, both hepatic and extrahepatic CYP enzymes also contribute to patho/physiological processes. Genetic variation of CYP isoforms is widespread and likely underlies a proportion of individual variation in drug disposition. The superfamily has the root symbol CYP, followed by a number to indicate the family, a

capital letter for the subfamily with a numeral for the individual enzyme. Some CYP are able to metabolise multiple substrates, others are oligo- or mono- specific. CYP also catalyse diverse oxidation and reduction reactions. These include ring hydroxylation, N-oxidation, sulfoxidation, epoxidation, the dealkylation of N-, S- and O- moieties, desulfation, deamination, as well as reduction of azo, nitro and N-oxide groups.

CYP1 family

Enzymes → Cytochrome P450 → CYP1 family

Overview: CYP1 enzymes catalyse the generation of highly mutagenic compounds *via* activation of procarcinogens (such as polycyclic aromatic hydrocarbons and aromatic amines) that are present in combustion products. They can also deactivate many anticancer agents [459].

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
Inhibitors	65PF (pIC ₅₀ 6.8) [413]	5H78PF (pIC ₅₀ 7.8) [413]	stilbenes [174]
Comments	CYP1A1 is an extra-hepatic enzyme. It shows a preference for linear planar aromatic molecules [640].	CYP1A2 is constitutively expressed in liver. It shows a preference for triangular planar aromatic molecules [640].	Mainly expressed in extra-hepatic tissues such as breast, prostate and uterus. Can metabolise 17β-estradiol into a mutagen [174], as well as leukotrienes and eicosanoids [162]. Gene variants have been associated with primary congenital glaucoma [694].

Comments: Targeting these enzymes for inhibition is a possible cancer prevention strategy and possible therapeutic target due to over-expression of the CYP1 family in many cancers.

CYP2 family: drug metabolising subset

Enzymes → Cytochrome P450 → CYP2 family: drug metabolising subset

Overview: CYP1, 2 and 3 family enzymes are involved in the biotransformation of xenobiotics, including clinically used drugs. Polymorphisms, particularly in the CYP2 family, impact upon an individual's response to drugs [764], including the risk of adverse drug reactions, drug efficacy and dose requirement.

Nomenclature	CYP2A6	CYP2A7	CYP2A13	CYP2B6	CYP2C8	CYP2C9
HGNC, UniProt	CYP2A6, P11509	CYP2A7, P20853	CYP2A13, Q16696	CYP2B6, P20813	CYP2C8, P10632	CYP2C9, P11712
EC number	1.14.14.1	1.14.14.1	1.14.14.1	1.14.14.1	1.14.14.1	1.14.14.51(S)-limonene + [reduced NADPH-hemoprotein reductase] + O(2) <=> (-)-trans-carveol + [oxidized NADPH-hemoprotein reductase] + H(2)O
Competitive inhibitor	–	–	–	–	–	sulfaphenazole [471]
Substrates	nicotine, tegafur	–	–	–	–	sulfaphenazole
Inhibitors	esculetin (pIC ₅₀ 6.4) [554]	–	kaempferol (pK _i 6.9) [65]	ticlopidine (pIC ₅₀ 6.7) [201], sibutramine (pIC ₅₀ 5.8) [32], thiotepa (pK _i 5.3) [707]	phenelzine (pK _i 5.1) [201]	–

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CYP2 family: drug metabolising subset S317

Comments	Metabolises coumarin [536].	CYP2A7 is functionally inactive [213].	Metabolises tobacco carcinogen, 4-methyl-nitrosoamino-1-(3-pyridyl)-1-butanone [648]. Expressed specifically in the respiratory tract.	Drug substrates include efavirenz, bupropion, cyclophosphamide, ketamine, propofol [688].	Converts arachidonic acid to 11(R)-12(S)-epoxyeicosatrienoic acid or 14(R)-15(S)-epoxyeicosatrienoic acid [766]. Drug substrates include amodiaquine and paclitaxel [30].	Drug substrates include tolbutamide, losartan, phenytoin, warfarin [140, 471, 654].
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Nomenclature	CYP2C19	CYP2D6	CYP2E1	CYP2F1	CYP2J2
HGNC, UniProt	CYP2C19, P33261	CYP2D6, P10635	CYP2E1, P05181	CYP2F1, P24903	CYP2J2, P51589
EC number	1.14.14.51	1.14.14.1	1.14.14.1	1.14.14.1	1.14.14.1
Inhibitors	compound 30 (pK _i 7.7) [204], compound 51 (pI _{C₅₀} 7.3) [132], UE2343 (pI _{C₅₀} 5.8) [721]	berberine (pI _{C₅₀} 5.4) [357]	compound 23 (pK _i 7.4) [753], 12-Imidazolyl-1-dodecanol (pK _i 6.2) [158]	–	compound 4 (pI _{C₅₀} 6.8) [383], terfenadine (pI _{C₅₀} 5.1) [383]
Comments	Drug substrates include omeprazole, proguanil, mephenytoin, diazepam [53, 152, 295]. Common genetic polymorphism for null function.	Substrates include: debrisoquine, metoprolol, codeine [419]. Highly polymorphic enzyme.	Substrates: Ethanol, p-nitrophenol [439].	Substrate: naphthalene [398].	Converts arachidonic acid to 14(R)-15(S)-epoxyeicosatrienoic acid [737]. Hydroxylates albendazole [740]. Expressed in cardiomyocytes [634].

CYP2 family: physiological enzymes subset

Enzymes → Cytochrome P450 → CYP2 family: physiological enzymes subset

Overview: Compared to the other CYP2 family enzymes, this subset have physiological rather than drug metabolising enzyme activities.

Nomenclature	CYP2R1	CYP2S1	CYP2U1	CYP2W1
HGNC, UniProt	CYP2R1, Q6VVX0	CYP2S1, Q96SQ9	CYP2U1, Q7Z449	CYP2W1, Q8TAV3
EC number	1.14.13.15	1.14.14.1	1.14.14.1	1.14.14.-
Comments	Converts vitamin D3 to calcifediol [104]. Expressed in CD34 ⁺ human cord blood hematopoietic stem and early progenitor cells [745].	Considered an orphan CYP [750]. Possibly involved in polyunsaturated fatty acid ω-1 hydroxylation [193].	Thymus and brain specific catalysis of ω- and (ω-1)-hydroxylation of fatty acids [114]. Oxidation of N-arachidonylserotonin [619]. Mutations have been associated with hereditary spastic paraplegia [154].	Appears to have cancer specific expression [526]. Potential drug target in colorectal cancer [115].

CYP3 family

Enzymes → Cytochrome P450 → CYP3 family

Overview: CYP1, 2 and 3 family enzymes are involved in the biotransformation of xenobiotics, including clinically used drugs. CYP3A4 is the major enzyme involved in drug metabolism by the liver.

Nomenclature	CYP3A4	CYP3A5	CYP3A7	CYP3A43
HGNC, UniProt	CYP3A4, P08684	CYP3A5, P20815	CYP3A7, P24462	CYP3A43, Q9HB55
EC number	1.14.14.551.14.14.56	1.14.14.1	1.14.14.1	1.14.14.1
Substrates	midazolam [728], nifedipine [262]	–	–	–
Inhibitors	troleandomycin (pK _i 7.8) [611], ketoconazole (pK _i 7) [252], ritonavir (pK _i >7) [356]	ritonavir (pK _i 6.9) [201]	–	–
Comments	Metabolises a vast range of xenobiotics, including antidepressants, benzodiazepines, calcium channel blockers, and chemotherapeutic agents [772]. The active site is plastic, with both homotropic and heterotropic cooperativity observed with some substrates [611]. CYP3A4 catalyses the 25-hydroxylation of trihydroxycholestane [218].	CYP3A5 is expressed extrahepatically, including in the small intestine. It has overlapping substrate specificity with CYP3A4 [139, 728].	Fetal form, rarely expressed in adults. Has overlapping substrate specificity with CYP3A4 [139, 728].	Fetal expression only and considered an orphan CYP [261]. Testosterone may be a substrate [256].

CYP4 family

Enzymes → Cytochrome P450 → CYP4 family

Overview: CYP4 family enzymes catalyse the ω -oxidation of endogenous fatty acids and eicosanoids [178]. They have been proposed as molecular targets for the treatment of fatty acid-linked orphan diseases.

Nomenclature	CYP4A11	CYP4A22	CYP4B1	CYP4F2	CYP4F3	CYP4F8
HGNC, UniProt	CYP4A11, Q02928	CYP4A22, Q5TCH4	CYP4B1, P13584	CYP4F2, P78329	CYP4F3, Q08477	CYP4F8, P98187
EC number	1.14.14.80	1.14.14.80	1.14.14.1	1.14.14.781.14.14.791.14.14.94	1.14.14.781.14.14.791.14.14.94	1.14.14.1
Inhibitors	epalrestat (pIC ₅₀ 5.7) [749]	–	–	sesamin (pIC ₅₀ 6.4) [716], 17-octadecynoic acid (pK _i 5.9) [614]	–	–
Comments	Converts lauric acid to 12-hydroxylauric acid. Catalyses luciferin-4A O-demethylation [749].	Appears to be an orphan CYP [173].	Converts 4-ipomeanol into a toxicant, and is also important in oxidation of endobiotic fatty acids and fatty alcohols [677].	Responsible for ω -hydroxylation of LTB ₄ , LXB ₄ [474], and tocopherols, including vitamin E [638]. Associated with the warfarin response [769].	Responsible for ω -hydroxylation of LTB ₄ , LXB ₄ [474] and polyunsaturated fatty acids [195, 281], and ω -hydroxylation of fatty acid epoxides [390]. Possible role in Crohn's disease [127].	Converts PGH ₂ to 19-hydroxyPGH ₂ [77] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [501].

Nomenclature	CYP4F11	CYP4F12	CYP4F22	CYP4V2	CYP4X1	CYP4Z1
HGNC, UniProt	CYP4F11, Q9HB16	CYP4F12, Q9HCS2	CYP4F22, Q6NT55	CYP4V2, Q6ZWL3	CYP4X1, Q8N118	CYP4Z1, Q86W10
EC number	1.14.14.11.14.14.78	1.14.14.1	1.14.14.-	1.14.14.79	1.14.14.1	1.14.14.1

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16181/full>

CYP5, CYP7 and CYP8 families S319

Inhibitors	–	HET0016 (pIC ₅₀ 7.9) [749]	–	–	–	compound 7 (pIC ₅₀ 5.2) [374]
Comments	Associated with the warfarin response [769].	AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12	Converts arachidonic acid to 16-HETE and 18-HETE [501]. Involved in production of acylceramide and skin barrier integrity [514]. Variants may influence ichthyosis [185, 194, 504].	Converts myristic acid to 14-hydroxymyristic acid [494]. Variants are associated with ocular disease [637].	Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [645]. May influence age of onset of sporadic Creutzfeldt-Jakob diseases [546].	Converts lauric acid to 12-hydroxylauric acid. Only expressed in mammary tissue.

CYP5, CYP7 and CYP8 families

Enzymes → Cytochrome P450 → CYP5, CYP7 and CYP8 families

Overview: Members of this enzyme family catalyse reactions in the pathways that synthesise or catabolise important lipid mediators, steroids and cholesterol.

Nomenclature	CYP5A1	CYP7A1	CYP7B1	CYP8A1	CYP8B1
Common abbreviation	Thromboxane-A synthase	Cholesterol 7 alpha-hydroxylase	–	Prostacyclin synthase	–
HGNC, UniProt	TBXAS1 , P24557	CYP7A1 , P22680	CYP7B1 , O75881	PTGIS , Q16647	CYP8B1 , Q9UNU6
EC number	5.3.99.5: PGH ₂ = thromboxane A ₂	1.14.14.23	1.14.14.29	5.3.99.4	1.14.14.1391.14.18.8
Inhibitors	dazoxiben (pIC ₅₀ 8.5) [562], ozagrel (pIC ₅₀ 8.4) [301], furegrelate sodium (pIC ₅₀ 7.8) [247], picotamide (pIC ₅₀ 3.8) [254], camonagrel [259]	(2S,4S)-ketoconazole (pIC ₅₀ 9.7) [585]	–	compound 7p (pIC ₅₀ >6) [191], tranylcypromine [258]	–
Comments	–	Converts cholesterol to 7α-hydroxycholesterol [505].	Converts dehydroepiandrosterone to 7α-DHEA [583].	Converts prostaglandin H ₂ (PGH ₂) to thromboxane A ₂ (thromboxane A ₂) [285].	Converts 7α-hydroxycholest-4-en-3-one to 7-α,12α-dihydroxycholest-4-en-3-one (in rabbit) [322] in the biosynthesis of bile acids.

CYP11, CYP17, CYP19, CYP20 and CYP21 families

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

Overview: The reactions catalysed by this family of cytochrome P450 monooxygenases are required for steroid biosynthesis.

Nomenclature	CYP11A1	CYP11B1	CYP11B2	CYP17A1	CYP19A1	CYP20A1	CYP21A2
Common abbreviation	Cholesterol side-chain cleavage enzyme	Steroid 11β-hydroxylase	Aldosterone synthase	–	Aromatase	–	Steroid 21-hydroxylase

HGNC, UniProt	CYP11A1 , P05108	CYP11B1 , P15538	CYP11B2 , P19099	CYP17A1 , P05093	CYP19A1 , P11511	CYP20A1 , Q6UW02	CYP21A2 , P08686
EC number	1.14.15.6	1.14.15.4	1.14.15.41.14.15.5	1.14.14.191.14.14.32	1.14.14.14	1.14.-.-	1.14.14.16
Inhibitors	(2S,4S)-ketoconazole (pIC ₅₀ 5.9) [585], mitotane [394, 407]	osilodrostat (pIC ₅₀ 8.5) [754], metyrapone (pIC ₅₀ 7.8) [776], (2S,4S)-ketoconazole (pIC ₅₀ 6.9) [585]	osilodrostat (pIC ₅₀ 9.7) [754], metyrapone (pIC ₅₀ 7.1) [776]	abiraterone (pIC ₅₀ 7.1–7.3) [270, 550]	anastrozole (pIC ₅₀ 7.8) [171], (2S,4S)-ketoconazole (pIC ₅₀ 5.4) [585], aminoglutethimide [535]	–	(2S,4S)-ketoconazole (pIC ₅₀ 5.4) [585] – Rat
Selective inhibitors	–	–	–	galeterone (pIC ₅₀ 6.5) [278]	letrozole (pK _i 10.7) [455], letrozole (pIC ₅₀ 7.9) [55], exemestane (pK _i 7.6) [238], exemestane (pIC ₅₀ 7.4) [238], testolactone (pK _i 4.5) [129]	–	–
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.	Converts corticosterone to aldosterone	Converts pregnenolone and progesterone to 17 α -hydroxypregnenolone and 17 α -hydroxyprogesterone, respectively. Converts 17 α -hydroxypregnenolone and 17 α -hydroxyprogesterone to dehydroepiandrosterone and androstenedione, respectively. Converts corticosterone to cortisol.	Converts androstenedione and testosterone to estrone and 17 β -estradiol, respectively.	Unknown function.	Converts progesterone and 17 α -hydroxyprogesterone to deoxycortisone and 11-deoxycortisol, respectively

CYP24, CYP26 and CYP27 families

Enzymes → Cytochrome P450 → CYP24, CYP26 and CYP27 families

Overview: CYP24s deactivate vitamin D metabolites and CYP27s are required for the biosynthesis of vitamin D from cholesterol. CYP26 enzymes metabolise excess all-trans-retinol to limit toxicity.

Nomenclature	CYP24A1	CYP26A1	CYP26B1	CYP26C1	CYP27A1	CYP27B1	CYP27C1
Common abbreviation	Vitamin D3 24-hydroxylase	–	–	–	Sterol 27-hydroxylase	25-Hydroxyvitamin D 1-alpha-hydroxylase	–
HGNC, UniProt	CYP24A1 , Q07973	CYP26A1 , O43174	CYP26B1 , Q9NR63	CYP26C1 , Q6V0L0	CYP27A1 , Q02318	CYP27B1 , O15528	CYP27C1 , Q4G0S4
EC number	1.14.15.16	1.14.-.-	1.14.-.-	1.14.-.-	1.14.15.15	1.14.15.18	1.14.19.53
Inhibitors	CTA091 (pIC ₅₀ 8.2) [549], lunacalcipol (pIC ₅₀ 7.6) [549], compound 4d (pIC ₅₀ 4.8) [3]	R116010 (pIC ₅₀ 8.4) [676], liarozole (pIC ₅₀ 5.7) [676], talarozole [676]	–	–	compound 4d (pIC ₅₀ 7.2) [3], CTA091 (pIC ₅₀ <6) [343]	CTA091 (pIC ₅₀ 6.3) [343]	–

Selective inhibitors	–	compound 5 (pIC ₅₀ 9.5) [244]	–	–	–	–	–
Comments	Converts 1,25-dihydroxyvitamin D3 (calcitriol) to 1 α ,24R,25-trihydroxyvitamin D ₃ .	Converts retinoic acid to 4-hydroxyretinoic acid. Inhibited by liarozole	Converts retinoic acid to 4-hydroxyretinoic acid.	Converts retinoic acid to 4-hydroxyretinoic acid [657].	Converts cholesterol to 27-hydroxycholesterol .	Converts 25-hydroxyvitamin D ₃ to 1,25-dihydroxyvitamin D3 (calcitriol)	Converts retinol (vitamin A1) to 3,4-didehydroretinol (vitamin A2) [376].

CYP39, CYP46 and CYP51 families

Enzymes → Cytochrome P450 → CYP39, CYP46 and CYP51 families

Overview: Enzymes in this family are involved in cholesterol turnover and the biosynthesis of the crucial steroid precursor, lanosterol.

Nomenclature	CYP39A1	CYP46A1	CYP51A1
Common abbreviation	–	Cholesterol 24-hydroxylase	Lanosterol 14- α -demethylase
HGNC, UniProt	CYP39A1 , Q9NYLS	CYP46A1 , Q9Y6A2	CYP51A1 , Q16850
EC number	1.14.14.26	1.14.14.25	1.14.14.1541.14.15.36
Inhibitors	–	soticlestat (pIC ₅₀ 8.4) [503]	azalanstat (pK _i 9.1) [704], compound 10 (Irreversible inhibition) (pIC ₅₀ >6) [209]
Comments	Converts 24-hydroxycholesterol to 7 α ,24-dihydroxycholesterol [405].	Converts cholesterol to 24(S)-hydroxycholesterol .	Converts lanosterol to 4,4-dimethylcholesta-8.14.24-trienol. Proteins within the cholesterol pathway are being investigated as potential oncology targets. Small molecule inhibitors of human CYP51A1 have been reported to exhibit anti-proliferative activity in various cancer cells [209].

Further reading on Cytochrome P450

Angle ED *et al.* (2023) Multidisciplinary Insights into the Structure-Function Relationship of the CYP2B6 Active Site. *Drug Metab Dispos* **51**: 369-384 [PMID:36418184]
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 Jones G *et al.* (2014) Cytochrome P450-mediated metabolism of vitamin D. *J Lipid Res* **55**: 13-31 [PMID:23564710]

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 Lorbek G *et al.* (2012) Cytochrome P450s in the synthesis of cholesterol and bile acids—from mouse models to human diseases. *FEBS J* **279**: 1516-33 [PMID:22111624]
 Röder A *et al.* (2023) Spotlight on CYP4B1. *Int J Mol Sci* **24**: 2038 [PMID:36768362]

DNA topoisomerases

Enzymes → 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	DNA topoisomerase I	DNA topoisomerase II alpha
HGNC, UniProt	TOP1 , P11387	TOP2A , P11388
EC number	5.99.1.2	5.99.1.2
Inhibitors	irinotecan [164 , 667] – Bovine	etoposide (pIC ₅₀ 7.3), teniposide [168] – Mouse

Further reading on DNA topoisomerases

- Baglini E *et al.* (2021) Multiple Topoisomerase I (TopoI), Topoisomerase II (TopoII) and Tyrosyl-DNA Phosphodiesterase (TDP) inhibitors in the development of anticancer drugs. *Eur J Pharm Sci* **156**: 105594 [[PMID:33059042](#)]
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- Riccio AA *et al.* (2020) Molecular mechanisms of topoisomerase 2 DNA-protein crosslink resolution. *Cell Mol Life Sci* **77**: 81-91 [[PMID:31728578](#)]

E3 ubiquitin ligase components

Enzymes → E3 ubiquitin ligase components

Overview: Ubiquitination (a.k.a. ubiquitylation) is a protein post-translational modification that typically requires the sequential action of three enzymes: E1 (ubiquitin-activating enzymes), E2 (ubiquitin-conjugating enzymes), and E3 (ubiquitin ligases) [[484](#)]. Ubiquitination of proteins can target them for proteasomal degradation, or modulate cellular processes including cell cycle progression, transcriptional regulation, DNA repair and signal transduction.

E3 ubiquitin ligases, of which there are >600 in humans, are a family of highly heterogeneous proteins and protein complexes that recruit ubiquitin-loaded E2 enzymes to mediate transfer of the ubiquitin molecule from the E2 to protein substrates. Target substrate specificity is determined by a substrate recognition subunit within the E3 complex.

E3 ligases are being exploited as pharmacological targets to facilitate targeted protein degradation (TPD), as an alternative to small molecule inhibitors [[46](#)], through the development of proteolysis targeting chimeras (PROTACs) and molecular glue.

Nomenclature	cereblon
HGNC, UniProt	CRBN , Q96SW2
Ligands	thalidomide (Binding) (pK _d 8.1) [325]
Comments	Cereblon is the substrate-recognition module of the cullin-RING type E3 ubiquitin ligase CRL4

Further reading on E3 ubiquitin ligase components

Asatsuma-Okumura T *et al.* (2019) Molecular mechanisms of cereblon-based drugs. *Pharmacol Ther* **202**: 132-139 [PMID:31202702] Chamberlain PP *et al.* (2019) Development of targeted protein degradation therapeutics *Nat Chem Biol* **15**: 937-944 [PMID:31527835]

Endocannabinoid turnover

Enzymes → Endocannabinoid turnover

Overview: The principle endocannabinoids are 2-acylglycerol esters, such as 2-arachidonoylglycerol (2-AG), and *N*-acylethanolamines, such as anandamide (*N*-arachidonoylethanolamine, AEA). The glycerol esters and ethanolamides are synthesised and hydrolysed by parallel, independent pathways. Mechanisms for release and re-uptake of endocannabinoids are unclear, although potent and selective inhibitors of facilitated diffusion of

endocannabinoids across cell membranes have been developed [271]. FABP5 (Q01469) has been suggested to act as a canonical intracellular endocannabinoid transporter *in vivo* [107]. For the generation of 2-arachidonoylglycerol, the key enzyme involved is diacylglycerol lipase (DAGL), whilst several routes for anandamide synthesis have been described, the best characterized of which involves *N*-acylphosphatidylethanolamine-phospholipase

D (NAPE-PLD, [623]). A transacylation enzyme which forms *N*-acylphosphatidylethanolamines has been identified as a cytosolic enzyme, PLA2G4E (Q3MJ16) [511]. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism *via* cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [17, 205, 633].

N-Acylethanolamine turnover

Enzymes → Endocannabinoid turnover → N-Acylethanolamine turnover

Overview: *N*-acylethanolamine (NAE) is fatty acid amide that is required for the biosynthesis of bioactive lipid amide mediators of the endocannabinoid system.

Nomenclature	N-Acylphosphatidylethanolamine-phospholipase D	Fatty acid amide hydrolase	Fatty acid amide hydrolase-2	N-Acylethanolamine acid amidase
Common abbreviation	NAPE-PLD	FAAH	FAAH2	NAAA
HGNC, UniProt	NAPEPLD, Q6IQ20	FAAH, O00519	FAAH2, Q6GMR7	NAAA, Q02083
EC number	3.1.4.54	3.5.1.99: 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	3.5.1.-
		The enzyme is responsible for the catabolism of neuro-modulatory fatty acid amides, including anandamide and oleamide: anandamide + H ₂ O ⇌ arachidonic acid + ethanolamine oleamide + H ₂ O ⇌ oleic acid + NH ₃	The enzyme is responsible for the catabolism of neuro-modulatory fatty acid amides, including anandamide and oleamide: anandamide + H ₂ O ⇌ arachidonic acid + ethanolamine oleamide + H ₂ O ⇌ oleic acid + NH ₃	
Rank order of affinity	–	anandamide > oleamide > N-oleoylethanolamide > N-palmitoylethanolamine [722]	oleamide > N-oleoylethanolamide > anandamide > N-palmitoylethanolamine [722]	N-palmitoylethanolamine > MEA > SEA ≥ N-oleoylethanolamide > anandamide [689]
Inhibitors	hexachlorophene (pIC ₅₀ 5) [9], bithionol (pIC ₅₀ 5) [9], ARN19874 (pIC ₅₀ 4.5) [90]	–	–	–

Selective inhibitors	LEI-401 (pK _i 7.6) [478]	ASP8477 (pIC ₅₀ 8.4) [715], JNJ1661010 (pIC ₅₀ 7.8) [354], PF750 (pIC ₅₀ 6.3–7.8) [10], OL135 (pIC ₅₀ 7.4) [722], MM-433593 (pIC ₅₀ 7), URB597 (pIC ₅₀ 6.3–7) [722], PF3845 (pIC ₅₀ 6.6) [11]	OL135 (pIC ₅₀ 7.9–8.4) [351, 722], URB597 (pIC ₅₀ 7.5–8.3) [351, 722], ASP8477 (pIC ₅₀ 7.2) [715]	F215 (pIC ₅₀ 8.1) [402, 403], ARN726 (Irreversible inhibition) (pIC ₅₀ 7.6) [572], S-OOPP (pIC ₅₀ 6.4) [635] – Rat, CCP (pIC ₅₀ 5.3) [684]
Comments	NAPE-PLD activity appears to be enhanced by polyamines in the physiological range [416], but fails to transphosphatidylate with alcohols [539] unlike phosphatidylcholine-specific phospholipase D.	Microdeletion in a FAAH pseudogene that is expressed in dorsal root ganglia and brain (FAAH-OUT), and a functional single-nucleotide polymorphism in FAAH conferring reduced expression and activity, have been identified in a patient with high anandamide concentrations and pain insensitivity, a discovery that points to a new mechanistic target for developing FAAH-based analgesic therapeutics [267].	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 [722].	–

Comments: Routes for *N*-acylethanolamine biosynthesis other than through NAPE-PLD activity have been identified [685].

2-Acylglycerol ester turnover

Enzymes → Endocannabinoid turnover → 2-Acylglycerol ester turnover

Nomenclature	Diacylglycerol lipase α	Diacylglycerol lipase β	Monoacylglycerol lipase	$\alpha\beta$-Hydrolase 6	$\alpha\beta$-Hydrolase 12
Common abbreviation	DAGL α	DAGL β	MAGL	ABHD6	ABHD12
HGNC, UniProt	DAGLA , Q9Y4D2	DAGLB , Q8NCG7	MGLL , Q99685	ABHD6 , Q9BV23	ABHD12 , Q8N2K0
EC number	3.1.1.-	3.1.1.-	3.1.1.23	3.1.1.23	3.1.1.23
Endogenous substrates	diacylglycerol	diacylglycerol	2-oleoyl glycerol = 2-arachidonoylglycerol \gg anandamide [233]	1-arachidonoylglycerol > 2-arachidonoylglycerol > 1-oleoylglycerol > 2-oleoyl glycerol [498]	–
Inhibitors	LEI105 (pIC ₅₀ 8.5) [35], DH376 (pIC ₅₀ 8.2) [509], DO34 (pIC ₅₀ 8.2) [509], KT-109 (pIC ₅₀ 5.6) [312]	DH376 (pIC ₅₀ 8.6) [509], DO34 (pIC ₅₀ 8.1) [509], LEI105 (pIC ₅₀ 8.1) [35], KT-109 (pIC ₅₀ 7.1) [312]	MJN110 (pIC ₅₀ 8) [502]	–	–
Selective inhibitors	–	–	JJKK 048 (pIC ₅₀ 9.3) [1], JNJ-42226314 (pIC ₅₀ 8.9) [742], KML29 (pIC ₅₀ 8.5) [96], JZL184 (pIC ₅₀ 8.1) [422]	WWL70 (pIC ₅₀ 7.2) [400], WWL123 (pIC ₅₀ 6.4) [29]	DO264 (pIC ₅₀ 8) [510]
Comments	–	–	–	ABHD6 has also been shown to accept diacylglycerol as a substrate, thereby producing 2-acylglycerols [692]. WWL70 has been suggested to have activity at oxidative metabolic pathways independent of ABHD6 [663].	–

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 [722] and only 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 [36], including **ABHD2** (P08910) [470], **ABHD12** (Q8N2K0) [61] and carboxylesterase 1 (**CES1**, P23141 [743]). **ABHD2** (P08910) has also been described as a triacylglycerol lipase and ester hydrolase [437], while **ABHD12** (Q8N2K0)

is also able to hydrolyse lysophosphatidylserine [681]. **ABHD12** (Q8N2K0) has been described to be inhibited selectively by pentacyclic triterpenoids, such as oleanolic acid [531].

Further reading on Endocannabinoid turnover

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deRoos-Cassini TA *et al.* (2020) Meet Your Stress Management Professionals: The Endocannabinoids. *Trends Mol Med* **26**: 953-968 [PMID:32868170]

Di Marzo V. (2018) New approaches and challenges to targeting the endocannabinoid system. *Nat Rev Drug Discov* **17**: 623-639 [PMID:30116049]

Fowler CJ *et al.* (2017) Endocannabinoid Turnover. *Adv Pharmacol* **80**: 31-66 [PMID:28826539]

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Maccarrone M. (2017) Metabolism of the Endocannabinoid Anandamide: Open Questions after 25 Years. *Front Mol Neurosci* **10**: 166 [PMID:28611591]

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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 oxygenases, 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	PTGS1 , P23219	PTGS2 , P35354
EC number	1.14.99.1: Hydrogen donor + arachidonic acid + 2O ₂ = hydrogen acceptor + H ₂ O + PGH₂ arachidonic acid ⇒ PGG₂ ⇒ PGH₂ This enzyme is also associated with the following reaction: docosahexaenoic acid ⇒ PGH₃	1.14.99.1: Hydrogen donor + arachidonic acid + 2O ₂ = hydrogen acceptor + H ₂ O + PGH₂ arachidonic acid ⇒ PGG₂ ⇒ PGH₂ This enzyme is also associated with the following reaction: docosahexaenoic acid ⇒ PGH₃
Inhibitors	bromfenac (pIC ₅₀ 8.1) [26], diclofenac (pIC ₅₀ 7.9) [779], meclufenamic acid (pIC ₅₀ 7.3) [344], flurbiprofen (pIC ₅₀ 7.1) [714], fenoprofen (pIC ₅₀ 6.8) [26], ketoprofen (pIC ₅₀ 6.5) [54], suprofen (pIC ₅₀ 6.2) [54]	benzquinamide (pIC ₅₀ 8.3) [26], flurbiprofen (pIC ₅₀ 8) [42], meclufenamic acid (pIC ₅₀ 7.4) [344], carprofen (pIC ₅₀ 7) [299], ketorolac (pIC ₅₀ 6.9) [701], nimesulide (pIC ₅₀ 6.2) [522], ketoprofen (pIC ₅₀ 6.2) [54]
Selective inhibitors	ketorolac (pIC ₅₀ 9.7) [714], FK-881 (pIC ₅₀ 8.3) [320], SC-560 (pIC ₅₀ 8.1) [629], FR122047 (pIC ₅₀ 7.5) [508]	celecoxib (pIC ₅₀ 8.7) [59], SC-236 (pIC ₅₀ 8–8.3) [235, 537], valdecoxib (pIC ₅₀ 8.3) [662], SC-58125 (pIC ₅₀ 7.4) [235], rofecoxib (pIC ₅₀ 6.1–6.5) [714], lumiracoxib (pK _i 6.5) [62]

Further reading on Cyclooxygenase

Mitchell JA *et al.* (2021) Cyclooxygenases and the cardiovascular system. *Pharmacol Ther* **217**: 107624 [PMID:32640277]

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. 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 CB1. Conversion of the 15-hydroxyecosanoids, including prostaglandins, lipoxins and leukotrienes to their keto derivatives by the NAD-dependent enzyme HPGD leads to a reduction in their biological activity.

Nomenclature	CYP5A1	CYP8A1	mPGES1	mPGES2	cPGES
Common abbreviation	Thromboxane-A synthase	Prostacyclin synthase	–	–	–
HGNC, UniProt	<i>TBXAS1</i> , P24557	<i>PTGIS</i> , Q16647	<i>PTGES</i> , O14684	<i>PTGES2</i> , Q9H7Z7	<i>PTGES3</i> , Q15185
EC number	5.3.99.5: PGH ₂ = thromboxane A ₂	5.3.99.4	5.3.99.3: PGH ₂ = PGE ₂	5.3.99.3: PGH ₂ = PGE ₂	5.3.99.3: PGH ₂ = PGE ₂
Cofactors	–	–	glutathione	dihydrolipoic acid	–
Inhibitors	dazoxiben (pIC ₅₀ 8.5) [562], ozagrel (pIC ₅₀ 8.4) [301], furegrelate sodium (pIC ₅₀ 7.8) [247], picotamide (pIC ₅₀ 3.8) [254], camonagrel [259]	compound 7p (pIC ₅₀ > 6) [191], tranlycypromine [258]	compound 44 (pIC ₅₀ 9) [237]	compound 30 (pIC ₅₀ <6) [575]	–
Selective inhibitors	–	–	compound 39 (pIC ₅₀ 8.4) [618], compound III (pIC ₅₀ 7.1) [391]	–	–
Comments	–	Converts prostaglandin H ₂ (PGH ₂) to thromboxane A ₂ (thromboxane A ₂) [285].	–	–	Phosphorylated and activated by casein kinase 2 (CK2) [364]. Appears to regulate steroid hormone function by interaction with dimeric hsp90 [93, 338].

Nomenclature	L-PGDS	H-PGDS	AKR1C3	CB1	HPGD
HGNC, UniProt	<i>PTGDS</i> , P41222	<i>HPGDS</i> , O60760	<i>AKR1C3</i> , P42330	<i>CB1</i> , P16152	<i>HPGD</i> , P15428
EC number	5.3.99.2: PGH ₂ = PGD ₂	5.3.99.2: PGH ₂ = PGD ₂	1.1.1.188: PGD ₂ + NADP ⁺ = PGF _{2α} + NADPH + H ⁺ 1.3.1.201.1.1.2131.1.1.2391.1.1.64	1.1.1.1971.1.1.1841.1.1.189: PGE ₂ + NADP ⁺ = PGF _{2α} + NADPH + H ⁺	1.1.1.14115-hydroxyprostaglandins => 15-ketoprostaglandins LXA ₄ => 15-keto-lipoxin A ₄
Cofactors	–	–	NADP ⁺	NADP ⁺	–
Inhibitors	–	TFC007 (pIC ₅₀ 7.1) [490], HQL-79 (pIC ₅₀ 5.3–5.5) [24]	tolfenamic acid (pK _i 8.1) [555], flufenamic acid, indomethacin, flavonoids such as 2'-hydroxyflavanone (pIC ₅₀ 6.5) [452, 628]	wedelolactone (pIC ₅₀ 5.4) [778]	compound 3 (pIC ₅₀ 8.1) [738]
Selective inhibitors	AT-56 (pK _i 4.1) [321]	–	–	–	–
Comments	–	–	AKR1C3 also exhibits an hydroxysteroid dehydrogenase activity.	–	–

Comments: [YS121](#) has been reported to inhibit mPGES1 and 5-LOX with a pIC_{50} value of 5.5 [367].

Further reading on Prostaglandin synthases

Liu Y *et al.* (2020) Overview of AKR1C3: Inhibitor Achievements and Disease Insights. *J Med Chem* **63**: 11305-11329 [PMID:32463235]

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-HPETElinoleic acid + O ₂ => 13S-HPODE	1.13.11.33: arachidonic acid + O ₂ = 15S-HPETE	1.13.11.-
Substrates	–	methyl arachidonate	–	–	–	–
Endogenous substrates	arachidonic acid	–	–	–	–	12R-HPETE
Endogenous activators	5-LOX activating protein (ALOX-5AP) , P20292)	–	–	–	–	–
Endogenous inhibitors	Protein kinase A-mediated phosphorylation [434]	–	–	–	–	–
Inhibitors	BW B70C (pIC_{50} 6.7) [534]	–	–	ML351 (pIC_{50} 6.7) [559], PD-146176 (pK_i 6.7) [609]	compound 21n (pIC_{50} 7.3) [724]	–
Selective inhibitors	CJ13610 (pIC_{50} 7.2) [196], PF-04191834 (pIC_{50} 6.6) [450], zileuton (pIC_{50} 6.4) [88]	–	ML355 (pIC_{50} 6.5) [429]	compound 34 (pK_i >8) [560]	–	–
Comments	FLAP activity can be inhibited by MK-886 [163] and BAY-X1005 [286] leading to a selective inhibition of 5-LOX activity	–	–	–	Inhibited by MLS000536924 (pK_i 5.6) [331].	E-LOX metabolises the product from the 12R-lipoxygenase (12R-HPETE) to a specific epoxy-alcohol compound [762].

Comments: An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 [217]. 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 [587]. [2-TEDC](#) is used as 5-, 12- and 15-LOX inhibitor [110].

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 [564].

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 [512].

Nomenclature	Leukotriene C ₄ synthase	γ-Glutamyltransferase	Dipeptidase 1	Dipeptidase 2	Leukotriene A ₄ hydrolase
HGNC, UniProt	LTC4S, Q16873	GGCT, O75223	DPEP1, P16444	DPEP2, Q9H4A9	LTA4H, P09960
EC number	4.4.1.20: LTC ₄ = glutathione + LTA ₄	2.3.2.2: (S-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	3.3.2.6
Inhibitors	AZD9898 (pIC ₅₀ 9.5) [488, 581], example 36 (pIC ₅₀ 8.1) [581]	acivicin (pIC ₅₀ 6.2) [18], GGsTop (pK _i 3.8) [275]	cilastatin (pK _i 6) [250]	–	bestatin (pK _i 5.4) [519]

Comments: LTA4H is a member of a family of arginyl aminopeptidases (ENFSM00250000001675), 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.

Further reading on Eicosanoid turnover

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- Haeggström JZ. (2018) Leukotriene biosynthetic enzymes as therapeutic targets. *J Clin Invest* **128**: 2680-2690 [PMID:30108195]
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- Orafiya A *et al.* (2020) An overview of lipoxygenase inhibitors with approach of in vivo studies. *Prostaglandins Other Lipid Mediat* **148**: 106411 [PMID:31953016]
- Seo MJ *et al.* (2017) Prostaglandin synthases: Molecular characterization and involvement in prostaglandin biosynthesis. *Prog Lipid Res* **66**: 50-68 [PMID:28392405]
- Thulasingam M *et al.* (2020) Integral Membrane Enzymes in Eicosanoid Metabolism: Structures, Mechanisms and Inhibitor Design. *J Mol Biol* **432**: 4999-5022 [PMID:32745470]
- Xu D *et al.* (2021) Pathophysiological role of prostaglandin E synthases in liver diseases. *Prostaglandins Other Lipid Mediat* **154**: 106552 [PMID:33930567]

GABA turnover

Enzymes → GABA turnover

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

with nerve terminals [183] where GABA is principally accumulated in vesicles through the action of the vesicular inhibitory amino acid transporter **SLC32A1**. The role of γ -aminobutyraldehyde dehydrogenase (ALDH9A1) in neurotransmitter GABA synthesis is less clear. Following release from neurons, GABA may interact with either GABA_A or GABA_B receptors and may

be accumulated 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
Common abbreviation	GAD1	GAD2
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
Endogenous substrates	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid
Products	GABA	GABA
Cofactors	pyridoxal 5-phosphate	pyridoxal 5-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 [735]. 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
Common abbreviation	–	GABA-T	SSADH
HGNC, UniProt	ALDH9A1, P49189	ABAT, P80404	ALDH5A1, P51649
EC number	1.2.1.47: 4-trimethylammoniumbutanal + NAD + H ₂ O = 4-trimethylammoniumbutanoate + NADPH + 2H ⁺ 1.2.1.3: an aldehyde + H ₂ O + NAD = a carboxylate + 2H ⁺ + NADH 1.2.1.19: 4-aminobutanal + NAD + H ₂ O = GABA + NADH + H ⁺	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-nonenol + NADH + 2H ⁺
Cofactors	NAD	pyridoxal 5-phosphate	NAD [613]
Inhibitors	–	vigabatrin (Irreversible inhibition) (pK _i 3.1) [410, 620]	4-acryloylphenol (pIC ₅₀ 6.5) [668]

Further reading on GABA turnover

Graus F *et al.* (2020) GAD antibodies in neurological disorders - insights and challenges *Nat Rev Neurol* **16**: 353-365 [PMID:32457440]
Koenig MK *et al.* (2017) Phenotype of GABA-transaminase deficiency. *Neurology* **88**: 1919-1924 [PMID:28411234]

Lee H *et al.* (2015) Ornithine aminotransferase versus GABA aminotransferase: implications for the design of new anticancer drugs. *Med Res Rev* **35**: 286-305 [PMID:25145640]

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 PIP₂ to IP₃ and 1,2-diacylglycerol, each of which have major second messenger functions. Two domains, X and Y, essential for catalytic activity, are conserved in the different forms of PLC. Isoforms of PLC- β 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. Ca²⁺ ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC- Δ activity.

PLC has been suggested to be activated non-selectively by the small molecule **m3M3FBS** [34], although this mechanism of action has been questioned [378]. The aminosteroid **U73122** has been described as an inhibitor of phosphoinositide-specific PLC [630], although its selectivity among the isoforms is untested and it has been reported to occupy the H₁ histamine receptor [316].

Nomenclature	PLC β 1	PLC β 2	PLC β 3	PLC β 4
HGNC, UniProt	PLCB1, Q9NQ66	PLCB2, Q00722	PLCB3, Q01970	PLCB4, Q15147
EC number	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol
Endogenous activators	G α q, G α 11, G β γ [296, 530, 632]	G α 16, G β γ , Rac2 (RAC2, P15153) [82, 318, 319, 392, 530]	G α q, G β γ [87, 392, 530]	G α q [333]

Nomenclature	PLC γ 1	PLC γ 2	PLC δ 1	PLC δ 3	PLC δ 4
HGNC, UniProt	PLCG1, P19174	PLCG2, P16885	PLCD1, P51178	PLCD3, Q8N3E9	PLCD4, Q9BRC7
EC number	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol
Endogenous activators	PIP ₃ [33]	PIP ₃ , Rac1 (RAC1, P63000), Rac2 (RAC2, P15153), Rac3 (RAC3, P60763) [33, 542, 705]	Transglutaminase II, p122-RhoGAP {Rat}, spermine, G β γ [266, 306, 489, 530]	–	–
Endogenous inhibitors	–	–	Sphingomyelin [533]	–	–
Inhibitors	–	CCT129957 (pLC ₅₀ 5.5) [571]	–	–	–

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16181/full>

Phospholipase A₂ S331

Nomenclature	PLC ϵ 1	PLC ζ 1	PLC η 1	PLC η 2
HGNC, UniProt	PLCE1, Q9P212	PLCZ1, Q86YW0	PLCH1, Q4KWH8	PLCH2, O75038
EC number	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol	3.1.4.11: 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate + H ₂ O = 1D-myo-inositol 1,4,5-trisphosphate + diacylglycerol
Endogenous activators	Ras, rho [636, 732]	–	–	G β γ [774]

Comments: A series of PLC-like proteins (*PLCL1*, *Q15111*; *PLCL2*, *Q9UPRO* 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 [464].

Further reading on Phosphoinositide-specific phospholipase C

Filkin SY *et al.* (2020) Phospholipase Superfamily: Structure, Functions, and Biotechnological Applications. *Biochemistry (Mosc)* **85**: S177-S195 [PMID:32087059]

Katan M *et al.* (2020) Phospholipase C families: Common themes and versatility in physiology and pathology. *Prog Lipid Res* **80**: 101065 [PMID:32966869]

Nakamura Y *et al.* (2017) Regulation and physiological functions of mammalian phospholipase C. *J Biochem* **161**: 315-321 [PMID:28130414]

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.* bromoenol lactone, arachidonyl trifluoromethyl ketone or methyl arachidonyl fluorophosphate) are either non-selective within the family of phospholi-

pase A₂ enzymes or have activity against other eicosanoid-metabolising enzymes.

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

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

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

Nomenclature	sPLA ₂ -1B	sPLA ₂ -2D	sPLA ₂ -2E	sPLA ₂ -2F	sPLA ₂ -3	cPLA ₂ -4A
HGNC, UniProt	PLA2G1B, P04054	PLA2G2D, Q9UNK4	PLA2G2E, Q9NZK7	PLA2G2F, Q9BZM2	PLA2G3, Q9NZ20	PLA2G4A, P47712
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 28xvii (pIC ₅₀ 8.9) [269]	compound 12e (pIC ₅₀ 8.1) [521]	compound 12e (pIC ₅₀ 8.1) [521]	compound 12e (pIC ₅₀ 7.3) [521]	–	compound 57 (pIC ₅₀ 8.4) [430]
Comments	–	–	–	–	–	cPLA ₂ -4A also expresses lysophospholipase (EC 3.1.1.5) activity [616].

Nomenclature	cPLA ₂ -4B	cPLA ₂ -4C	cPLA ₂ -4D	cPLA ₂ -4E	cPLA ₂ -4F	PLA ₂ -G5
HGNC, UniProt	PLA2G4B, P0C869	PLA2G4C, Q9UP65	PLA2G4D, Q86XP0	PLA2G4E, Q3MJ16	PLA2G4F, Q68DD2	PLA2G5, P39877
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 12e (pIC ₅₀ 7.5) [521]

Nomenclature	iPLA ₂ -G6	sPLA ₂ -10	sPLA ₂ -12A	platelet activating factor acetylhydrolase 2
HGNC, UniProt	PLA2G6, O60733	PLA2G10, O15496	PLA2G12A, Q9BZM1	PAFAH2, Q99487
EC number	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.47
Inhibitors	–	compound 12e (pIC ₅₀ 7.7) [521]	–	–
Comments	–	–	–	PAFAH2 also expresses PAF hydrolase activity (EC 3.1.1.47)

Comments: The sequence of PLA₂-2C suggests a lack of catalytic activity, while PLA₂-12B (GXIIIB, GXIII sPLA₂-like) appears to be catalytically inactive [586]. A further fragment has been identified with sequence similarities to Group II PLA₂ members. Otoconin 90 (OC90) shows sequence homology to PLA₂-G10.

A binding protein for secretory phospholipase A₂ has been identified which shows modest selectivity for sPLA₂-1B over sPLA₂-2A, and also binds snake toxin phospholipase A₂ [20]. 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 [44]. PLA₂-G7 and PAFAH2 also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47).

Further reading on Phospholipase A2

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Khan MI *et al.* (2020) Human Secretary Phospholipase A2 Mutations and Their Clinical Implications *J Inflamm Res* **13**: 551-561 [PMID:32982370]

Kita Y *et al.* (2019) Cytosolic phospholipase A2 and lysophospholipid acyltransferases. *Biochim Biophys Acta Mol Cell Biol Lipids* **1864**: 838-845 [PMID:30905348]

Mouchlis VD *et al.* (2019) Phospholipase A2 catalysis and lipid mediator lipidomics. *Biochim Biophys Acta Mol Cell Biol Lipids* **1864**: 766-771 [PMID:30905345]

Murakami M *et al.* (2019) Group IID, IIE, IIF and III secreted phospholipase A2s. *Biochim Biophys Acta Mol Cell Biol Lipids* **1864**: 803-818 [PMID:30905347]

Samuchiwal SK *et al.* (2019) Harmful and protective roles of group V phospholipase A2: Current perspectives and future directions. *Biochim Biophys Acta Mol Cell Biol Lipids* **1864**: 819-826 [PMID:30308324]

Shayman JA *et al.* (2019) Lysosomal phospholipase A2. *Biochim Biophys Acta Mol Cell Biol Lipids* **1864**: 932-940 [PMID:30077006]

van Hensbergen VP *et al.* (2020) Type IIA Secreted Phospholipase A2 in Host Defense against Bacterial Infections *Trends Immunol* **41**: 313-326 [PMID:32151494]

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 [563].

Nomenclature	PLD1	PLD2
HGNC, UniProt	PLD1, Q13393	PLD2, O14939
EC number	3.1.4.4	3.1.4.4A phosphatidylcholine + H ₂ O ⇌ choline + a phosphatidate
Endogenous activators	ADP-ribosylation factor 1 (ARF1, P84077), PIP ₂ , RhoA, PKC evoked phosphorylation, RaIA [273, 433]	ADP-ribosylation factor 1 (ARF1, P84077), PIP ₂ [424], oleic acid [594]

Endogenous inhibitors	Gβγ [551]	Gβγ [551]
Inhibitors	FIPI (pIC ₅₀ 8) [606]	–
Selective inhibitors	compound 69 (pIC ₅₀ 7.3) [606]	VU0364739 (pIC ₅₀ 7.7) [389]

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 [240]). Additionally, an N-acyl ethanolamine-specific phospholipase D (*NAPEPLD*, Q61Q20) has been characterized, which appears to

have a role in the generation of endocannabinoids/endovanilloids, including anandamide [517]. This enzyme activity appears to be enhanced by polyamines in the physiological range [416] and fails to transphosphatidylate with alcohols [539].

Three further, less well-characterised isoforms are PLD3 (*PLD3*, Q81V08, 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 [520]. PLD4 is described not to have phospholipase D catalytic activity [757], but has been associated with inflammatory disorders [516, 653, 674]. Sequence analysis suggests that PLD5 is catalytically inactive.

Further reading on Phosphatidylcholine-specific 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]

McDermott MI *et al.* (2020) Mammalian phospholipase D: Function, and therapeutics. *Prog Lipid Res* **78**: 101018 [PMID:31830503]

Onono FO *et al.* (2020) Phospholipase D and Choline Metabolism. *Handb Exp Pharmacol* **259**: 205-218 [PMID:32086667]

Yao Y *et al.* (2021) Structural insights into phospholipase D function. *Prog Lipid Res* **81**: 101070 [PMID:33181180]

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
Common abbreviation	–	–	–	–	–	–	PTEN
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	3.1.3.163.1.3.483.1.3.67
Substrates	–	phosphatidic acid	–	–	phosphatidic acid	–	phosphatidylinositol (3,4,5)-trisphosphate

Further reading on Lipid phosphate phosphatases

Csolle MP *et al.* (2020) PTEN and Other PtdIns(3,4,5)P₃ Lipid Phosphatases in Breast Cancer. *Int J Mol Sci* **21**: [PMID:33276499]

Dey P *et al.* (2020) A review of phosphatidate phosphatase assays. *J Lipid Res* **61**: 1556-1564 [PMID:32963036]

Knafo S *et al.* (2017) PTEN: Local and Global Modulation of Neuronal Function in Health and Disease. *Trends Neurosci* **40**: 83-91 [PMID:28081942]

Lee YR *et al.* (2018) The functions and regulation of the PTEN tumour suppressor: new modes and prospects. *Nat Rev Mol Cell Biol* **19**: 547-562 [PMID:29858604]

Yehia L *et al.* (2020) The Clinical Spectrum of *PTEN* Mutations. *Annu Rev Med* **71**: 103-116 [PMID:31433956]

Yehia L *et al.* (2019) PTEN-opathies: from biological insights to evidence-based precision medicine. *J Clin Invest* **129**: 452-464 [PMID:30614812]

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 C2 domains.

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

Phosphatidylinositol 4-kinases

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

Nomenclature	phosphatidylinositol 4-kinase alpha	phosphatidylinositol 4-kinase beta	phosphatidylinositol 4-kinase type 2 alpha	phosphatidylinositol 4-kinase type 2 beta
Common abbreviation	PI4KIII α /PIK4CA	PI4KIII β /PIK4CB	PI4KII α /PI4K2A	PI4KII β /PI4K2B
HGNC, UniProt	PI4KA , P42356	PI4KB , Q9UBF8	PI4K2A , Q9BTU6	PI4K2B , Q8TCG2
EC number	2.7.1.67	2.7.1.67	2.7.1.67	2.7.1.67
Endogenous activation	–	PKD-mediated phosphorylation [287]	–	–
Sub/family-selective inhibitors	wortmannin (pIC ₅₀ 6.7–6.8) [232, 465]	wortmannin (pIC ₅₀ 6.7–6.8) [232, 465]	adenosine (pIC ₅₀ 4.5–5) [656]	adenosine (pIC ₅₀ 4.5–5) [656]
Selective inhibitors	–	PIK-93 (pIC ₅₀ 7.7) [39, 363]	–	–

Nomenclature	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 alpha	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 beta	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 gamma
Common abbreviation	C2 α /PIK3C2A	C2 β /PIK3C2B	C2 γ /PIK3C2G
HGNC, UniProt	PIK3C2A , O00443	PIK3C2B , O00750	PIK3C2G , O75747
EC number	2.7.1.154	2.7.1.154	2.7.1.154
Inhibitors	torin 2 (pIC ₅₀ 7.6) [417]	PI-103 (pIC ₅₀ 8) [288]	–

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

Nomenclature	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
Common abbreviation	PI3K α	PI3K β	PI3K γ	PI3K δ
HGNC, UniProt	PIK3CA , P42336	PIK3CB , P42338	PIK3CG , P48736	PIK3CD , O00329
EC number	2.7.1.1532.7.11.1	2.7.1.153	2.7.1.153	2.7.1.153
Inhibitors	PIK-75 (pIC ₅₀ 9.5) [288], gedatolisib (pIC ₅₀ 9.4) [698], PF-04691502 (pK _i 9.2) [414], PI-103 (pIC ₅₀ 8.7) [570], BGT-226 (pIC ₅₀ 8.4) [446], KU-0060648 (pIC ₅₀ 8.4) [83], dactolisib (pIC ₅₀ 8.4) [441], apitolisib (pIC ₅₀ 8.3) [652], PIK-75 (pIC ₅₀ 8.2) [363]	KU-0060648 (pIC ₅₀ 9.3) [83], PI-103 (pIC ₅₀ 8.5) [570], AZD6482 (pIC ₅₀ 8) [506], ZSTK474 (pIC ₅₀ 7.4–7.8) [736, 746], apitolisib (pIC ₅₀ 7.6) [652], BGT-226 (pIC ₅₀ 7.2) [446]	dactolisib (pIC ₅₀ 8.3) [441], apitolisib (pIC ₅₀ 7.8) [652], PI-103 (pIC ₅₀ 7.8) [570], BGT-226 (pIC ₅₀ 7.4) [446], ZSTK474 (pIC ₅₀ 7.3–7.3) [736, 746], TG-100-115 (pIC ₅₀ 7.1) [525], alpelisib (pIC ₅₀ 6.6) [215], KU-0060648 (pIC ₅₀ 6.2) [83]	KU-0060648 (pIC ₅₀ >10) [83], idelalisib (in vitro activity against recombinant enzyme) (pIC ₅₀ 8.6) [386], PI-103 (pIC ₅₀ 8.5) [570], ZSTK474 (pIC ₅₀ 8.2–8.3) [736, 746], apitolisib (pIC ₅₀ 8.2) [652], dactolisib (pIC ₅₀ 8.1) [441], alpelisib (pIC ₅₀ 6.5) [215]
Sub/family-selective inhibitors	pictilisib (pIC ₅₀ 8.5) [200]	pictilisib (pIC ₅₀ 7.5) [200]	pictilisib (pIC ₅₀ 7.1) [200]	pictilisib (pIC ₅₀ 8.5) [200]
Selective inhibitors	GSK1059615 (pIC ₅₀ 8.7) [362]	–	CZC 24832 (pIC ₅₀ 7.6) [50]	–

Comments: [Wortmannin](#) also inhibits type III phosphatidylinositol 4-kinases and polo-like kinase [418]. PIK93 also inhibits PI 3-kinases [363]. Adenosine activates [adenosine receptors](#).

Further reading on Phosphatidylinositol kinases

Goncalves MD *et al.* (2018) Phosphatidylinositol 3-Kinase, Growth Disorders, and Cancer. *N Engl J Med* **379**: 2052-2062 [PMID:30462943]

Raphael J *et al.* (2018) Phosphoinositide 3-kinase inhibitors in advanced breast cancer: A systematic review and meta-analysis. *Eur J Cancer* **91**: 38-46 [PMID:29331750]

Wang D *et al.* (2019) Upstream regulators of phosphoinositide 3-kinase and their role in diseases. *J Cell Physiol* [PMID:30710358]

Phosphatidylinositol phosphate kinases

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.

Nomenclature	phosphatidylinositol-4-phosphate 5-kinase type 1 alpha	phosphatidylinositol-4-phosphate 5-kinase type 1 beta	phosphatidylinositol-4-phosphate 5-kinase type 1 gamma
Common abbreviation	PIPSK1A	PIPSK1B	PIPSK1C
HGNC, UniProt	PIPSK1A , Q99755	PIPSK1B , O14986	PIPSK1C , O60331
EC number	2.7.1.68	2.7.1.68	2.7.1.68
Inhibitors	ISA-2011B [608]	–	–

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16181/full>

Phosphatidylinositol phosphate kinases S336

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
Common abbreviation	PIP4K2A	PIP4K2B	PIP4K2C
HGNC, UniProt	PIP4K2A , P48426	PIP4K2B , P78356	PIP4K2C , Q8TBX8
EC number	2.7.1.149 ATP + 1-phosphatidyl-1D-myo-inositol 5-phosphate \rightleftharpoons ADP + 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate	2.7.1.149	2.7.1.149

Further reading on Glycerophospholipid turnover

Cauvin C *et al.* (2015) Phosphoinositides: Lipids with informative heads and mastermind functions in cell division. *Biochim Biophys Acta* **1851**: 832-43 [[PMID:25449648](#)]
 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
Common abbreviation	HO1	HO2
HGNC, UniProt	HMOX1 , P09601	HMOX2 , P30519
EC number	1.14.14.18 Protoheme + 3 [reduced NADPH-hemoprotein reductase] + 3 O(2) \rightleftharpoons 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) \rightleftharpoons biliverdin + Fe(2+) + CO + 3 [oxidized NADPH-hemoprotein reductase] + 3 H(2)O
Inhibitors	–	compound 1 (pIC ₅₀ 3.5) [702] – Rat

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 [[290](#)]. The chemical [tin protoporphyrin IX](#) acts as a haem oxygenase inhibitor in rat liver with an IC₅₀ value of 11 nM [[169](#)].

Further reading on Haem oxygenase

Campbell NK *et al.* (2021) Regulation of inflammation by the antioxidant haem oxygenase 1. *Nat Rev Immunol* [[PMID:33514947](#)]
 Drummond GS *et al.* (2019) HO-1 overexpression and underexpression: Clinical implications. *Arch Biochem Biophys* **673**: 108073 [[PMID:31425676](#)]
 Ryter SW. (2019) Heme oxygenase-1/carbon monoxide as modulators of autophagy and inflammation. *Arch Biochem Biophys* **678**: 108186 [[PMID:31704095](#)]

Sasson A *et al.* (2021) The pivotal role of heme Oxygenase-1 in reversing the pathophysiology and systemic complications of NAFLD. *Arch Biochem Biophys* **697**: 108679 [[PMID:33248947](#)]
 Szade A *et al.* (2021) The role of heme oxygenase-1 in hematopoietic system and its microenvironment. *Cell Mol Life Sci* [[PMID:33787980](#)]

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. For an authoritative review on the pharmacological modulation of H₂S levels, see Szabo and Papapetropoulos, 2017 [655].

Nomenclature	Cystathionine β -synthase	Cystathionine γ -lyase	L-Cysteine:2-oxoglutarate aminotransferase	3-Mercaptopyruvate sulfurtransferase
Common abbreviation	CBS	CSE	CAT	MPST
HGNC, UniProt	CBS , P35520	CTH , P32929	KYAT1 , Q16773	MPST , P25325
EC number	4.2.1.22	4.4.1.1	4.4.1.13	2.8.1.2
Endogenous substrates	L-homocysteine [100], L-cysteine (K _m 6×10 ⁻³ M) [100]	L-cysteine	L-cysteine	3-mercaptopyruvic acid (K _m 1.2×10 ⁻³ M) [491]
Products	cystathionine	pyruvic acid, NH ₃	pyruvic acid, NH ₃	pyruvic acid
Cofactors	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyridoxal 5-phosphate	Zn ²⁺
Inhibitors	aminoxyacetic acid (pI _{C₅₀} 5.1) [25], benserazide (pI _{C₅₀} ~4.5) [170]	aminoethoxyvinylglycine (pI _{C₅₀} 6) [25], aminoxyacetic acid (pI _{C₅₀} 6) [25], β -Cyano-L-alanine (pI _{C₅₀} 5.8) [25], propargylglycine (pI _{C₅₀} 4.4) [25]	–	13MT-3 (pI _{C₅₀} 5.6) [277]
Comments	A copper-containing metabolite of disulfiram acts as a direct inhibitor of CBS and H ₂ S scavenger [780].	–	–	Pioglitazone and rosiglitazone inhibit bacterial 3-MST [131], but have not been shown to inhibit the mammalian orthologue.

Further reading on Hydrogen sulphide synthesis

Asimakopoulou A *et al.* (2013) Selectivity of commonly used pharmacological inhibitors for cystathionine β synthase (CBS) and cystathionine γ lyase (CSE). *Br J Pharmacol* **169**: 922-32 [PMID:23488457]

Szabo C *et al.* (2017) International Union of Basic and Clinical Pharmacology. CII: Pharmacological Modulation of H₂S Levels: H₂S Donors and H₂S Biosynthesis Inhibitors. *Pharmacol Rev* **69**: 497-564 [PMID:28978633]

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. Hor

mone-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.

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16181/full>

Hydrolases S338

Nomenclature	carboxylesterase 1	ectonucleoside triphosphate diphosphohydrolase 1
Systematic nomenclature	–	CD39
Common abbreviation	CES1	NTPDase-1
HGNC, UniProt	CES1, P23141	ENTPD1, P49961
EC number	3.1.1.1	3.6.1.5 Hydrolyzes NTPs to nucleotide monophosphates (NMPs): A nucleoside 5'-triphosphate + 2 H ₂ O \rightleftharpoons a nucleoside 5'-phosphate + 2 phosphate
Inhibitors	–	–
Selective inhibitors	–	–
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.

Nomenclature	ectonucleoside triphosphate diphosphohydrolase 2	lipase E, hormone sensitive type	lipase G, endothelial type
Systematic nomenclature	CD39L1	–	–
Common abbreviation	NTPDase-2	LIPE	LIPG
HGNC, UniProt	ENTPD2, Q9Y5L3	LIPE, Q05469	LIPG, Q9Y5X9
EC number	3.6.1.- Hydrolyzes extracellular nucleotide 5'-triphosphates: NTP>NMP + 2 phosphate	3.1.1.79	3.1.1.3
Rank order of affinity	–	–	–
Inhibitors	–	–	–
Selective inhibitors	PSB-6426 (pK _i 5.1) [71]	–	–
Comments	–	–	Endothelial lipase (EL) activity is implicated in HDL metabolism and in atherosclerotic plaque development. Small molecule EL inhibitors are being investigated as a potential therapeutic intervention for the treatment of dyslipidemia related cardiovascular disease [245, 334, 650]

Nomenclature	pancreatic lipase	PLD2
Common abbreviation	PNLIP	–
HGNC, UniProt	PNLIP, P16233	PLD2, O14939
EC number	3.1.1.3	3.1.4.4A phosphatidylcholine + H ₂ O \rightleftharpoons choline + a phosphatidate
Endogenous substrates	–	–
Endogenous activators	–	ADP-ribosylation factor 1 (ARF1, P84077) , PIP2 [424], oleic acid [594]
Endogenous inhibitors	–	Gβγ [551]
Inhibitors	orlistat (pIC ₅₀ 8.9) [74], cetilistat (pIC ₅₀ 8.2) [747]	–
Selective inhibitors	–	VU0364739 (pIC ₅₀ 7.7) [389]

Further reading on Hydrolases

- Coleman RA. (2020) The "discovery" of lipid droplets: A brief history of organelles hidden in plain sight *Biochim Biophys Acta Mol Cell Biol Lipids* **1865**: 158762 [PMID:32622088]
- Haas CB *et al.* (2021) Ectonucleotidases in Inflammation, Immunity, and Cancer. *J Immunol* **206**: 1983-1990 [PMID:33879578]
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- Lan L *et al.* (2020) Detection techniques of carboxylesterase activity: An update review. *Bioorg Chem* **94**: 103388 [PMID:31676115]
- Zimmermann H. (2021) Ectonucleoside triphosphate diphosphohydrolases and ecto-5'-nucleotidase in purinergic signaling: how the field developed and where we are now. *Purinergic Signal* **17**: 117-125 [PMID:33336318]
- Zou LW *et al.* (2018) Carboxylesterase Inhibitors: An Update. *Curr Med Chem* **25**: 1627-1649 [PMID:29210644]

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) [123].

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, ENSFM00250000001432) 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 [598].

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, [456]; pIC_{50} 3.2, [513]) than IMPase 2 (pIC_{50} 1.8-2.1, [513]). IMPase activity may be inhibited competitively by

L690330 (pK_i 5.5, [456]), although the enzyme selectivity is not yet established.

Nomenclature	IMPase 1	IMPase 2
HGNC, UniProt	<i>IMPA1</i> , P29218	<i>IMPA2</i> , O14732
EC number	3.1.3.25	3.1.3.25
Rank order of affinity	inositol 4-phosphate > inositol 3-phosphate > inositol 1-phosphate [456]	–
Inhibitors	Li ⁺ (pK_i 3.5) [456]	–

Comments: Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder [626, 627, 758]. Disruption of the gene encoding IMPase 1, but not IMPase 2, appears to mimic the effects of **Li⁺** in mice [133, 134].

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]

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 [443]. 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 selectivity

in intact cell assays. In particular, ambient **ATP** concentrations may be influential in responses to inhibitors, since the majority are directed at the ATP binding site [142].

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 [375].

Nomenclature	Rho associated coiled-coil containing protein kinase 1	Rho associated coiled-coil containing protein kinase 2
Systematic nomenclature	ROCK1	ROCK2
Common abbreviation	Rho kinase 1	Rho kinase 2
HGNC, UniProt	ROCK1 , Q13464	ROCK2 , O75116
EC number	2.7.11.1	2.7.11.1
Inhibitors	RKI-1447 (pIC ₅₀ >9) [544], Y27632 (pIC ₅₀ 5.9–7.3) [421, 733], fasudil (pK _i 7) [569], Y27632 (pK _i 6.8) [690], fasudil (pIC ₅₀ 5.5–5.6) [421, 569]	RKI-1447 (pIC ₅₀ >9) [544], compound 11d [DOI: 10.1039/c0md00194e] (pIC ₅₀ >9) [103], GS-K269962A (pIC ₅₀ 8.4) [165], compound 32 (pIC ₅₀ 8.4) [66], compound 22 (pIC ₅₀ 7.7) [733], Y27632 (pIC ₅₀ 6.3–7.2) [421, 733], Y27632 (pK _i 6.8–6.9) [421, 690], fasudil (pIC ₅₀ 5.9–5.9) [421, 569]
Selective inhibitors	GSK269962A (pIC ₅₀ 8.8) [165]	–

Further reading on Rho kinase

Abedi F *et al.* (2020) Acute lung injury: The therapeutic role of Rho kinase inhibitors. *Pharmacol Res* **155**: 104736 [PMID:32135249]

Sharma P *et al.* (2020) ROCK-2-selective targeting and its therapeutic outcomes. *Drug Discov Today* **25**: 446-455 [PMID:31837997]

Protein kinase C (PKC) family

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

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](#)). Subfamilies of protein kinase C are identified on the basis of sequence similarities, although functional division into the groups of **classical protein kinase C isoforms** (PKC α , PKC β , and PKC γ) activated by Ca²⁺ and diacylglycerol, **novel protein kinase C isoforms** (PKC δ , PKC ϵ , PKC η , and PKC θ) activated by diacylglycerol and **atypical protein kinase C isoforms** (PKC ζ and PKC ξ) are useful.

Alpha subfamily

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

Overview: These two classical PKC isoforms are Ser/Thr kinases. They are activated by Ca²⁺ and diacylglycerol, and may be inhibited by [GF109203X](#), [calphostin C](#), [Gö 6983](#), [chelerythrine](#) and [Ro31-8220](#).

Nomenclature	protein kinase C beta	protein kinase C gamma
Common abbreviation	PKC β	PKC γ

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16181/full>

Kinases (EC 2.7.x.x) S342

HGNC, UniProt	PRKCB , P05771	PRKCG , P05129
EC number	2.7.11.13	2.7.11.13
Inhibitors	sotrastaurin (pIC ₅₀ 8.7) [703], Gö 6983 (pIC ₅₀ 8.1) [260], GF109203X (pIC ₅₀ 7.8) [683] – Bovine, 7-hydroxystaurosporine (pIC ₅₀ 7.5) [612]	Gö 6983 (pIC ₅₀ 8.2) [260], 7-hydroxystaurosporine (pIC ₅₀ 7.5) [612]
Selective inhibitors	ruboxistaurin (pIC ₅₀ 8.2) [335], enzastaurin (pIC ₅₀ 7.5) [190], CGP53353 (pIC ₅₀ 6.4) [94]	–

Delta subfamily

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

Overview: PKC δ and PKC θ are PKC isoforms that are activated by diacylglycerol and may be inhibited by [calphostin C](#), [Gö 6983](#) and [chelerythrine](#).

Nomenclature	protein kinase C alpha	protein kinase C delta	protein kinase C theta
Common abbreviation	PKC α	PKC δ	PKC θ
HGNC, UniProt	PRKCA , P17252	PRKCD , Q05655	PRKCT , Q04759
EC number	2.7.11.13	2.7.11.13	2.7.11.13
Activators	–	ingenol mebutate (pK _i 9.4) [353]	–
Inhibitors	sotrastaurin (pIC ₅₀ 8.7) [703], Gö 6983 (pIC ₅₀ 8.1) [260], 7-hydroxystaurosporine (pIC ₅₀ 7.5) [612]	sotrastaurin (pIC ₅₀ 8.9) [703], Gö 6983 (pIC ₅₀ 8) [260]	sotrastaurin (pIC ₅₀ 9) [703]

Eta subfamily

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

Overview: PKC ϵ and PKC η are PKC isoforms that are activated by diacylglycerol and may be inhibited by [calphostin C](#), [Gö 6983](#) and [chelerythrine](#).

Nomenclature	protein kinase C epsilon	protein kinase C eta
Common abbreviation	PKC ϵ	PKC η
HGNC, UniProt	PRKCE , Q02156	PRKCH , P24723
EC number	2.7.11.13	2.7.11.13
Inhibitors	sotrastaurin (pIC ₅₀ 8.2) [703]	balanol (pIC ₅₀ 8.5) [145], sotrastaurin (pIC ₅₀ 8.2) [703]

Iota subfamily

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

Overview: PKC_ι, PKC_ζ are atypical serine/threonine protein kinase C isoforms. In contrast to other PKC enzymes these are not activated by phorbol esters or diacylglycerol.

Nomenclature	protein kinase C iota	protein kinase C zeta
Common abbreviation	PKC _ι	PKC _ζ
HGNC, UniProt	PRKCI , P41743	PRKCZ , Q05513
EC number	2.7.11.13	2.7.11.13
Endogenous activators	–	arachidonic acid [487]
Inhibitors	–	Gö 6983 (pIC ₅₀ 7.2) [260]
Comments	Known as PKC _λ in rodents	–

Further reading on Protein kinase C (PKC) family

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]

Reina-Campos M *et al.* (2019) The Dual Roles of the Atypical Protein Kinase Cs in Cancer *Cancer Cell* **36**: 218-235 [PMID:31474570]

Salzer E *et al.* (2016) Protein Kinase C δ : 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

Overview: The protein product of the *MTOR* gene (previously been known as FK506-binding protein 12-rapamycin-associated protein 1; FRAP1) is the only member of this kinase subfamily. mTOR is the key enzymatic component of the TORC1 and TORC2 protein complexes. It can act as a Ser/Thr kinase (in both complexes) or a Tyr kinase (in TORC2). The clinically used drugs [temsirolimus](#) and [everolimus](#) inhibit mTOR kinase activity.

Nomenclature	mechanistic target of rapamycin kinase
Common abbreviation	mTOR
HGNC, UniProt	MTOR , P42345
EC number	2.7.11.1
Inhibitors	ridaforolimus (pIC ₅₀ 9.7) [578], torin 1 (pIC ₅₀ 9.5) [415], sapanisertib (pIC ₅₀ 9) [311], sapanisertib (pK _i 8.9) [311], gedatolisib (pIC ₅₀ 8.8) [698], dactolisib (pIC ₅₀ 8.2) [441], PP121 (pIC ₅₀ 8) [23], XL388 (pIC ₅₀ 8) [660], PF-04691502 (pK _i 7.8) [414], apitolisib (pK _i 7.8) [652]
Selective inhibitors	everolimus (pIC ₅₀ 8.7) [607], PP-242 (pIC ₅₀ 8.1) [23], temsirolimus (pIC ₅₀ 5.8) [370]

Further reading on FRAP subfamily

Chen Y *et al.* (2020) Research progress of mTOR inhibitors. *Eur J Med Chem* **208**: 112820 [PMID:32966896]

Liu GY *et al.* (2020) mTOR at the nexus of nutrition, growth, ageing and disease. *Nat Rev Mol Cell Biol* **21**: 183-203 [PMID:31937935]

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

Xu T *et al.* (2020) Targeting mTOR for fighting diseases: A revisited review of mTOR inhibitors. *Eur J Med Chem* **199**: 112391 [PMID:32416459]

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: Five of the cyclin-dependent kinases (CDKs: 7, 8, 9, 12, and 13) are involved in the phosphorylation of serine residues in the C-terminal domain of RNA polymerase II, the enzyme that is responsible for the transcription of protein-coding genes into mRNA in eukaryotes. Phosphorylation of RNA polymerase II at Ser5 is essential for transcriptional initiation, and phosphorylation of Ser 2 contributes to transcriptional elongation and termination. All five of the C-terminal domain kinases can phosphorylate Ser5, but only CDK9, CDK12, and CDK13 can phosphorylate at Ser2 [67, 368, 406].

CDK4 subfamily

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

Overview: CDK4 and CDK6 are Ser/Thr protein kinases that are components of protein complexes that regulate progression through the G1 phase of the cell cycle. These kinases are important integrators of mitogenic and antimitogenic signals, and are oncology drug targets. CDK4/6 inhibitors are in clinical use (*e.g.* [abemaciclib](#), [ribociclib](#) and [palbociclib](#)).

Nomenclature	cyclin dependent kinase 4	cyclin dependent kinase 6
Common abbreviation	CDK4	CDK6
HGNC, UniProt	CDK4 , P11802	CDK6 , Q00534
EC number	2.7.11.22	2.7.11.22
Inhibitors	R547 (pK _i 9) [149], palbociclib (pIC ₅₀ 8) [211], Ro-0505124 (pIC ₅₀ 7.7) [160], riviciclib (pIC ₅₀ 7.2) [342], alvocidib (pK _i 7.2) [86]	palbociclib (pIC ₅₀ 7.8) [211]

Comments on Cyclin-dependent kinase (CDK) family: The development of CDK inhibitors as anticancer drugs is reviewed in [592], with detailed content covering CDK4 and CDK6 inhibitors that are under clinical evaluation. Data produced by Jorda *et al.* (2018) highlights the caution that must be used when deploying commercially available CDK inhibitors as pharmacological probes [341], as most of them are more promiscuous in their selectivity than indicated. To make their findings easily accessible the Jorda data is hosted on the [cyclin-dependent kinase inhibitor database \(CDKiDB\)](#).

GSK subfamily

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

Overview: GSK3A and GSK3B are protein Ser/Thr kinases that are involved in the regulation of glycogen synthesis. GSK3B (GSK-3 β) has been associated with the pathogenesis and progression of diseases including obesity, diabetes, cancer and Alzheimer's, and as a result pharmacological inhibition of this enzyme is an attractive therapeutic mechanism.

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16181/full>

FRAP subfamily S345

Nomenclature	glycogen synthase kinase 3 beta
Common abbreviation	GSK3B
HGNC, UniProt	GSK3B , P49841
EC number	2.7.11.26
Inhibitors	CHIR-98014 (pIC ₅₀ 9.2) [576], LY2090314 (pIC ₅₀ 9) [179], laduviglusib (pIC ₅₀ 8.2) [576], SB 216763 (pIC ₅₀ ~8.1) [119], 1-azakenpaullone (pIC ₅₀ 7.7) [380], SB-415286 (pIC ₅₀ ~7.4) [119], IM-12 (pIC ₅₀ 7.3) [600]
Selective inhibitors	AZD2858 (pK _i 8.3) [49]
Comments	Due to its Tau phosphorylating activity, small molecule inhibitors of GSK-3β are being investigated as potential treatments for Alzheimer's disease (AD) [49]. 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 [447].

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-3β 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](#)]

Lauretti E *et al.* (2020) Glycogen synthase kinase-3 signaling in Alzheimer's disease. *Biochim Biophys Acta Mol Cell Res* **1867**: 118664 [[PMID:32006534](#)]

Polo-like kinase (PLK) family

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

Overview: The Polo-like kinases (PLK) are Ser/Thr kinases of the cell cycle that are involved in regulating mitotic entry, mitotic exit, spindle formation, cytokinesis, and meiosis [[40](#), [591](#)]. PLK inhibitors are predicted to offer anti-proliferative potential for application in oncology [[603](#), [771](#)].

Nomenclature	polo like kinase 4
Common abbreviation	PLK4
HGNC, UniProt	PLK4 , O00444
EC number	2.7.11.21
Inhibitors	ocifisertib (pIC ₅₀ 8.6) [451]

STE7 family

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

Overview: STE7 (also known as MAPKK, MAP 2K or MEK) kinases are part of the MAPK signalling cascades. They are activated by phosphorylation by upstream STE11 (MAP 3K, MAPKKK) kinases and phosphorylate downstream MAPK kinases. Small molecule pharmacological inhibitors, including negative allosteric modulators, of MEKs are used to disrupt signalling *via* the RAS-RAF-MEK-ERK pathway that drives proliferation in certain cancers.

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16181/full>

Cyclin-dependent kinase (CDK) family S346

Nomenclature	mitogen-activated protein kinase kinase 1	mitogen-activated protein kinase kinase 2
Common abbreviation	MEK1	MEK2
HGNC, UniProt	MAP2K1 , Q02750	MAP2K2 , P36507
EC number	2.7.12.2	2.7.12.2
Inhibitors	trametinib (pIC ₅₀ 9–9.1) [236 , 748], mirdametinib (pIC ₅₀ 8.1) [284]	trametinib (pIC ₅₀ 8.7) [748]
Allosteric modulators (Negative)	binimetinib (pIC ₅₀ 7.9) [540], refametinib (pIC ₅₀ 7.7) [326], CI-1040 (pK _d 6.9) [144]	binimetinib (pIC ₅₀ 7.9) [540], refametinib (pIC ₅₀ 7.3) [326]
Selective allosteric modulators	cobimetinib (Negative) (pIC ₅₀ 9.1) [573]	–

Further reading on STE7 family

Wang C *et al.* (2021) Research progress of MEK1/2 inhibitors and degraders in the treatment of cancer *Eur J Med Chem* 218: 113386 [[PMID:33774345](#)]

Abi family

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

Overview: ABL1 is a tyrosine kinase. Deletion of the kinase's inhibitory SH3 domain converts it into an oncogene. A fusion protein caused by a gene translocation, t(9;22), that generates a BCR-ABL fusion is present in many cases of chronic myelogenous leukemia (CML). The clinically approved drug [imatinib](#), was the first kinase inhibitor to target ABL1 activity to treat CML.

Nomenclature	ABL proto-oncogene 1, non-receptor tyrosine kinase
Common abbreviation	Abl
HGNC, UniProt	ABL1 , P00519
EC number	2.7.10.2
Inhibitors	compound 8h (pIC ₅₀ 9.7) [679], dasatinib (pIC ₅₀ 9.6) [361], compound 24 (pIC ₅₀ 9.3) [150], PD-173955 (pK _d 9.2) [144], bosutinib (pIC ₅₀ 9) [241], PD-173955 (pIC ₅₀ ~8.3) [492], bafetinib (pIC ₅₀ 7.6–8.2) [308 , 360], ponatinib (pIC ₅₀ 8.1) [313], nilotinib (pIC ₅₀ 7.8) [507], PP121 (pIC ₅₀ 7.7) [23], imatinib (pIC ₅₀ 6.7) [308], GNF-5 (pIC ₅₀ 6.7) [767]

Ack family

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

Overview: TNK2 (ACK1) is a tyrosine kinase that induces cell survival mechanisms. Substrates include receptor tyrosine kinases (EGFR, MERTK, AXL, HER2 and insulin receptor), AKT, FYN, the androgen receptor and the GTPase Cdc42Hs. TNK2 is associated with tumour cell survival, proliferation and hormone-resistance, and hence TNK2 is considered to be a novel cancer target, although no inhibitors have entered clinical trials.

Nomenclature	tyrosine kinase non receptor 2
Common abbreviation	Ack
HGNC, UniProt	TNK2, Q07912
EC number	2.7.10.2
Inhibitors	compound 30 (pIC ₅₀ 9) [159]

Janus kinase (JakA) family

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

Overview: Janus kinases (JAKs) are a family of four enzymes; JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). They are essential for cytokine signalling and are strongly linked to both cancer and inflammatory diseases.

Nomenclature	Janus kinase 1	Janus kinase 2	Janus kinase 3	tyrosine kinase 2
Common abbreviation	JAK1	JAK2	JAK3	Tyk2
HGNC, UniProt	JAK1, P23458	JAK2, O60674	JAK3, P52333	TYK2, P29597
EC number	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2
Inhibitors	ruxolitinib (pIC ₅₀ 8.5–10.1) [276, 557], filgotinib (pIC ₅₀ 8) [693]	ilginatinib (pIC ₅₀ 9.1) [497], BMS-911543 (pIC ₅₀ 9) [553], AT-9283 (pIC ₅₀ 8.9) [310], XL019 (pIC ₅₀ 8.7) [202], fedratinib (pIC ₅₀ 8.5) [442, 726], gandotinib (pIC ₅₀ 8.4) [438]	AT-9283 (pIC ₅₀ 9) [310]	–
Selective inhibitors	–	compound 1d (pIC ₅₀ >9) [711]	–	–
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 [81, 147]. Small molecule compounds which inhibit aberrant JAK2 activity are being developed as novel anti-cancer pharmaceuticals.	–	–

Further reading on Janus kinase (JakA) family

Bharadwaj U *et al.* (2020) Targeting Janus Kinases and Signal Transducer and Activator of Transcription 3 to Treat Inflammation, Fibrosis, and Cancer: Rationale, Progress, and Caution. *Pharmacol Rev* 72: 486-526 [PMID:32198236]

Src family

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

Overview: Activation of Src-family kinases leads to both stimulatory and inhibitory signaling responses, with cell-specific and signaling pathway-specific outcomes and redundancy of kinase function.

Immune system:

In immune cells Src kinases are involved in many signalling pathways, including ITAM- and ITIM-domain-containing

receptor signaling, integrin signaling, and responses to chemokines/chemoattractants, cytokines, innate immune stimuli and a large variety of non-immune cell specific stimuli (UV irradiation, heat, osmotic shock *etc.*). In many cases Src kinases signal to MAP kinase or NF- κ B pathways, but they can also modulate other pathways through less well characterized mechanisms.

The primary T cell Src kinases are Lck and Fyn; the main B cell Srcs are Lyn, Fyn and Blk. Mast cells express Fyn and Lyn, with low expression of Src.

Nomenclature	BLK proto-oncogene, Src family tyrosine kinase	fyn related Src family tyrosine kinase	FYN proto-oncogene, Src family tyrosine kinase	LYN proto-oncogene, Src family tyrosine kinase	SRC proto-oncogene, non-receptor tyrosine kinase
Common abbreviation	Blk	FRK	Fyn	Lyn	Src
HGNC, UniProt	BLK , P51451	FRK , P42685	FYN , P06241	LYN , P07948	SRC , P12931
EC number	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2
Inhibitors	–	–	PP1 (pIC ₅₀ 8.2) [279]	bafetinib (pIC ₅₀ 8) [308]	WH-4-023 (pIC ₅₀ 8.2) [448], PD166285 (pK _i 8.1) [528], PP121 (pIC ₅₀ 7.8) [23], ENMD-2076 (pIC ₅₀ 7.7) [547]

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
Common abbreviation	Etk	Btk	TXK
HGNC, UniProt	BMX , P51813	BTK , Q06187	TXK , P42681
EC number	2.7.10.2	2.7.10.2	2.7.10.2
Inhibitors	compound 38 (pIC ₅₀ 9.1) [401], ibrutinib (pIC ₅₀ 9.1) [426], compound 31 (pIC ₅₀ 8.7) [401]	ibrutinib (pIC ₅₀ 9.3) [527], compound 31 (pIC ₅₀ 8.4) [401], compound 38 (pIC ₅₀ >8.4) [401]	–
Selective inhibitors	BMX-IN-1 (pIC ₅₀ 8.1) [412]	CGI1746 (pIC ₅₀ 8.7) [155], CHMFL-BTK-11 (Irreversible inhibition) (pIC ₅₀ 7.6) [734]	–

RAF family

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

Overview: The RAF (acronym for rapidly accelerated fibrosarcoma) kinases are a family of related Ser/Thr kinases that are important for normal cellular and physiological processes, but are also associated with oncogenesis [395]. They are components of the Ras-Raf-MAPK signalling pathway.

Nomenclature	B-Raf proto-oncogene, serine/threonine kinase	Raf-1 proto-oncogene, serine/threonine kinase
Common abbreviation	B-Raf	c-Raf
HGNC, UniProt	BRAF , P15056	RAF1 , P04049
EC number	2.7.11.1	2.7.11.1
Inhibitors	GDC-0879 (pIC ₅₀ 9.7–9.9) [144 , 280], dabrafenib (pIC ₅₀ 8.5) [387], regorafenib (pIC ₅₀ 7.6) [763], vemurafenib (pIC ₅₀ 7) [712], PLX-4720 (pK _d 6.5) [144], compound 2 (pK _d 6.3) [307], CHIR-265 (pK _d 5.9) [144]	–
Selective inhibitors	–	GW5074 (pIC ₅₀ 8.1) [109]

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

Attwood MM *et al.* (2021) Trends in kinase drug discovery: targets, indications and inhibitor design *Nature Reviews Drug Discovery*

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

Martin KJ *et al.* (2012) Selective kinase inhibitors as tools for neuroscience research. *Neuropharmacology* **63**: 1227-37 [PMID:22846224]

Saha D *et al.* (2020) The Exploration of Chirality for Improved Druggability within the Human Kinome. *J Med Chem* **63**: 441-469 [PMID:31550151]

Zarrin AA *et al.* (2021) Kinase inhibition in autoimmunity and inflammation. *Nat Rev Drug Discov* **20**: 39-63 [PMID:33077936]

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
HGNC, UniProt	ACAT1 , P24752	ACAT2 , Q9BWD1
EC number	2.3.1.9 : 2acetyl CoA = acetoacetyl CoA + coenzyme A	2.3.1.9 : 2acetyl CoA = acetoacetyl CoA + coenzyme A

Nomenclature	hydroxymethylglutaryl-CoA synthase 1	hydroxymethylglutaryl-CoA synthase 2
HGNC, UniProt	HMGCS1 , Q01581	HMGCS2 , P54868
EC number	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)-mesvalonate synthesis and the latter with ketogenesis.

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16181/full>

Janus kinase (JakA) family S350

Nomenclature	hydroxymethylglutaryl-CoA reductase			
HGNC, UniProt	HMGR , P04035			
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 ⁺			
Inhibitors	lovastatin (Competitive) (pK _i 9.2) [15], rosuvastatin (Competitive) (pIC ₅₀ 8.3) [324], cerivastatin (Competitive) (pK _i 8.2) [84], atorvastatin (Competitive) (pIC ₅₀ 8.1) [324], cerivastatin (Competitive) (pIC ₅₀ 8) [678], simvastatin (Competitive) (pIC ₅₀ 8) [324], fluvastatin (Competitive) (pIC ₅₀ 7.6) [324]			
Comments	HMGR 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.			
Nomenclature	mevalonate kinase	phosphomevalonate kinase	diphosphomevalonate decarboxylase	
HGNC, UniProt	MVK , Q03426	PMVK , Q15126	MVD , P53602	
EC number	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⁻	
Comments	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	IDI1 , Q13907	IDI2 , Q9BXS1	GGPS1 , O95749	
EC number	5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate	5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate	2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate → trans,trans-farnesyl diphosphate + diphosphate 2.5.1.29: trans,trans-farnesyl diphosphate + isopentenyl diphosphate → geranylgeranyl diphosphate + diphosphate	
Nomenclature	farnesyl diphosphate synthase	squalene synthase	squalene monooxygenase	lanosterol synthase
HGNC, UniProt	FDPS , P14324	FDFT1 , P37268	SQLE , Q14534	LSS , P48449
EC number	2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate → trans,trans-farnesyl diphosphate + diphosphate	2.5.1.21: 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) [51], zoledronic acid (pK _i 7.1) [172], alendronate (pIC ₅₀ 6.3) [51]	zaragozic acid A (pK _i 10.1) [52] – Rat, zaragozic acid A (pIC ₅₀ 9.2) [680]	–	–
Selective inhibitors	ibandronic acid (pK _i 6.7) [172], pamidronic acid (pIC ₅₀ 6.7) [172]	–	–	–

Further reading on Lanosterol biosynthesis pathway

Göbel A *et al.* (2020) Cholesterol and beyond - The role of the mevalonate pathway in cancer biology. *Biochim Biophys Acta Rev Cancer* **1873**: 188351 [PMID:32007596]

Juarez D *et al.* (2021) Targeting the Mevalonate Pathway in Cancer. *Trends Cancer* **7**: 525-540 [PMID:33358111]

Moutinho M *et al.* (2017) The mevalonate pathway in neurons: It's not just about cholesterol. *Exp Cell Res* **360**: 55-60 [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]

Proto MC *et al.* (2021) Lipid homeostasis and mevalonate pathway in COVID-19: Basic concepts and potential therapeutic targets. *Prog Lipid Res* **82**: 101099 [PMID:33915202]

Nucleoside synthesis and metabolism

Enzymes → Nucleoside synthesis and metabolism

Overview: The *de novo* synthesis and salvage of nucleosides have been targetted 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	phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase	dihydroorotate dehydrogenase (quinone)	inosine monophosphate dehydrogenase 1	inosine monophosphate dehydrogenase 2	thymidylate synthetase
Common abbreviation	DHFR	GART	DHODH	IMPDH1	IMPDH2	TYMS
HGNC, UniProt	DHFR , P00374	GART , P22102	DHODH , Q02127	IMPDH1 , P20839	IMPDH2 , P12268	TYMS , P04818
EC number	1.5.1.3	2.1.2.2 6.3.3.1 6.3.4.13	1.3.5.2	1.1.1.205	1.1.1.205	2.1.1.45
Inhibitors	–	pemetrexed (pK _i 5) [617] – Mouse	teriflunomide (pK _i 7.5) [293]	mycophenolic acid (pIC ₅₀ 7.7) [499]	mycophenolic acid (pIC ₅₀ 7.7) [499]	–
Selective inhibitors	methotrexate (pK _i 8.9) [584]	–	–	–	–	raltitrexed (pIC ₅₀ 6.5) [221]

Nomenclature	purine nucleoside phosphorylase	xanthine dehydrogenase	ribonucleotide reductase catalytic subunit M1	ribonucleotide reductase regulatory subunit M2	ribonucleotide reductase regulatory TP53 inducible subunit M2B
Common abbreviation	PNP	XDH	ribonucleotide reductase M1	ribonucleotide reductase M2	ribonucleotide reductase M2B (TP53 inducible)
HGNC, UniProt	PNP , P00491	XDH , P47989	RRM1 , P23921	RRM2 , P31350	RRM2B , Q7LG56
EC number	1.4.2.1 Purine-nucleoside phosphorylase: Purine nucleoside + phosphate <=> purine + alpha-D-ribose 1-phosphate Purine deoxynucleoside + phosphate <=> purine + 2'-deoxy-alpha-D-ribose 1-phosphate	1.1.7.1.4	1.1.7.14.1	1.1.7.4.1	1.1.7.1.4
Inhibitors	–	febuxostat (pIC ₅₀ 8.9) [187], topiroxostat	–	–	–

Comments: TYMS allows the interconversion of dUMP and dTMP, thereby acting as a crucial step in DNA synthesis. PNP allows separation of a nucleoside into the nucleobase and ribose phosphate for nucleotide salvage. XDH generates urate in the purine degradation pathway. Post-translational modifications of XDH convert the enzymatic reaction to a xanthine oxidase, allowing the interconversion of hypoxanthine and xanthine, with the production (or consumption) of reactive oxygen species.

Further reading on Nucleoside synthesis and metabolism

Furuhashi M. (2020) New insights into purine metabolism in metabolic diseases: role of xanthine oxidoreductase activity. *Am J Physiol Endocrinol Metab* **319**: E827-E834 [PMID:32893671]

Okafor ON *et al.* (2017) Allopurinol as a therapeutic option in cardiovascular disease. *Pharmacol Ther* **172**: 139-150 [PMID:27916655]

Paraoxonase (PON) family

Enzymes → Paraoxonase (PON) family

Overview: Paraoxonases (PON) are calcium-dependent esterases, which may be involved in lipoprotein turnover and the conversion of lactone statin prodrugs, as well as being targets of organophosphates, such as the insecticide paraoxon.

Nomenclature	paraoxonase 1	paraoxonase 2	paraoxonase 3
Common abbreviation	PON1	PON2	PON3
HGNC, UniProt	PON1, P27169	PON2, Q15165	PON3, Q15166
EC number	3.1.1.2 A phenyl acetate + H(2)O \rightleftharpoons a phenol + acetate 3.1.1.81 An N-acyl-L-homoserine lactone + H(2)O \rightleftharpoons an N-acyl-L-homoserine 3.1.8.1 An aryl dialkyl phosphate + H(2)O \rightleftharpoons dialkyl phosphate + an aryl alcohol	3.1.1.2 A phenyl acetate + H(2)O \rightleftharpoons a phenol + acetate 3.1.1.81 A N-acyl-L-homoserine lactone + H(2)O \rightleftharpoons a N-acyl-L-homoserine	3.1.1.2 A phenyl acetate + H(2)O \rightleftharpoons a phenol + acetate 3.1.1.81 A N-acyl-L-homoserine lactone + H(2)O \rightleftharpoons a N-acyl-L-homoserine 3.1.8.1 An aryl dialkyl phosphate + H(2)O \rightleftharpoons dialkyl phosphate + an aryl alcohol
Comments	PON1 forms homodimers. Loss-of-function mutations in PON1 are associated with microvascular complications of diabetes [348, 349].	PON2 forms heterotrimers [167].	PON3 likely forms heterodimers in vivo [167].

Further reading on Paraoxonase (PON) family

Dardiotis E *et al.* (2019) Paraoxonase-1 genetic polymorphisms in organophosphate metabolism. *Toxicology* **411**: 24-31 [PMID:30359673]

Taler-Verčič A *et al.* (2020) The Structure and Function of Paraoxonase-1 and Its Comparison to Paraoxonase-2 and -3 *Molecules* **25**: 5980 [PMID:33348669]

Lioudaki S *et al.* (2019) Paraoxonase-1: Characteristics and Role in Atherosclerosis and Carotid Artery Disease. *Curr Vasc Pharmacol* **17**: 141-146 [PMID:29189170]

Peptidases and proteinases

Enzymes → Peptidases and proteinases

Overview: Peptidases and proteinases hydrolyse peptide bonds, and can be simply divided on the basis of whether terminal peptide bonds are cleaved (exopeptidases and exoproteinases) at the amino terminus (aminopeptidases) or carboxy terminus (carboxypeptidases). Non-terminal peptide bonds are cleaved by endopeptidases and endoproteinases, which are divided into serine endopeptidases (EC 3.4.21.-), cysteine endopeptidases

(EC 3.4.22.-), aspartate endopeptidases (EC 3.4.23.-), metallo-endopeptidases (EC 3.4.24.-) and threonine endopeptidases (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 [566] (with whom we collaborate) as an information resource [567].

Blood coagulation components

Enzymes → Peptidases and proteinases → Blood coagulation components

Overview: Coagulation as a process is interpreted as a mechanism for reducing excessive blood loss through the generation of a gel-like clot local to the site of injury. The process involves the activation, adhesion (see [Integrins](#)), degranulation and

aggregation of platelets, as well as proteins circulating in the plasma. The coagulation cascade involves multiple proteins being converted to more active forms from less active precursors (for example, prothrombin [Factor II] is converted to thrombin

[Factor IIa]), typically through proteolysis (see [Proteases](#)). Listed here are the components of the coagulation cascade targeted by agents in current clinical usage or at an advanced level of development.

Nomenclature	coagulation factor V	coagulation factor VIII	serpin family C member 1
Common abbreviation	–	–	antithrombin, antithrombin III
HGNC, UniProt	F5 , P12259	F8 , P00451	SERPINC1 , P01008
Selective activators	–	–	heparin (pK _d 7.8) [248], fondaparinux (pK _d 7.5) [529], dalteparin [305], danaparoid [137, 495], enoxaparin [182], tinzaparin [208]
Selective inhibitors	drotrecogin alfa (Antithrombotic effect thought to occur via inhibition of factors Va and VIIIa) [347, 350]	drotrecogin alfa (Antithrombotic effect thought to occur via inhibition of factors Va and VIIIa) [347, 350]	–

Comments: Antithrombin is an inhibitor of thrombin, Factor Xa and multiple other proteinases. Lepirudin has been withdrawn from market.

Further reading on Blood coagulation components

Beavers CJ *et al.* (2020) Osocimab: A Novel Agent in Preventing Venous Thromboembolism. *J Cardiovasc Pharmacol* **76**: 645-649 [PMID:33105325]

Fredenburgh JC *et al.* (2021) New anticoagulants: Moving beyond the direct oral anticoagulants. *J Thromb Haemost* **19**: 20-29 [PMID:33047462]

Girolami A *et al.* (2017) New clotting disorders that cast new light on blood coagulation and may play a role in clinical practice. *J Thromb Thrombolysis* **44**: 71-75 [PMID:28251495]

Lin L *et al.* (2020) From multi-target anticoagulants to DOACs, and intrinsic coagulation factor inhibitors. *Blood Rev* **39**: 100615 [PMID:31492462]

Rana K *et al.* (2016) Blood flow and mass transfer regulation of coagulation. *Blood Rev* **30**: 357-68 [PMID:27133256]

Wheeler AP *et al.* (2016) The Intrinsic Pathway of Coagulation as a Target for Antithrombotic Therapy. *Hematol Oncol Clin North Am* **30**: 1099-114 [PMID:27637310]

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) [741]

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) [346] in the generation of amyloid beta (A β) [12, 659]. Given that the accumulation and aggregation of A β in the

brain is pivotal in the development of Alzheimer's disease (AD), inhibition of PS activity is one mechanism being investigated as a therapeutic option for AD [243]. 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 [153]. 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

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

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 [671].

Nomenclature	Leukotriene A ₄ hydrolase
HGNC, UniProt	LTA4H, P09960
EC number	3.3.2.6
Inhibitors	bestatin (pK _i 5.4) [519]

M2: Angiotensin-converting enzymes (ACE and ACE2)

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

	Angiotensin-converting enzyme	Angiotensin-converting enzyme 2
Nomenclature	Angiotensin-converting enzyme	Angiotensin-converting enzyme 2
Common abbreviation	ACE	ACE2
HGNC, UniProt	ACE, P12821	ACE2, Q9BYF1
EC number	3.4.15.1	3.4.15.1
Binding dissociation constants for SARS-CoVs (K _d)	–	SARS-CoV-2 (1.2 nM); SARS-CoV (5 nM); Binding of hACE2 ectodomain to immobilised S ^B domains of the viral strains in a biolayer interferometry assay. [706]
Substrates	Ac-SDKP	–
Endogenous substrates	angiotensin I (AGT, P01019) > angiotensin II (AGT, P01019)	angiotensin I (AGT, P01019) > angiotensin-(1-9) (AGT, P01019) [166]
Activators	–	XNT (pEC ₅₀ 4.7) [297]
Inhibitors	zofenoprilat (pK _i 9.4) [377] – Rabbit, captopril (pK _i 8.4) [467], zofenopril	compound 28 (pK _i 9.9) [482]
Selective inhibitors	perindoprilat (pIC ₅₀ 9) [91], cilazaprilat (pIC ₅₀ 8.7) [717] – Rabbit, imidaprilat (pIC ₅₀ 8.7) [580], lisinopril-tryptophan (C-domain assay) (pIC ₅₀ 8.2) [718], RXP-407 (N-domain selective inhibition) (pIC ₅₀ 8.1) [615], fosinoprilat (pIC ₅₀ 8) [146] – Rabbit, enalaprilat (pIC ₅₀ 7.5) [106], benazeprilat (pIC ₅₀ 6.6) [393]	MLN-4760 (pIC ₅₀ 9.4) [482]
Comments	Reports of ACE GPI hydrolase activity [369] have been refuted [396]	–

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.* [700]) 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	TP0556351 (pIC ₅₀ 9.7) [661], ARP100 [686]	–
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
Inhibitors	vipivotide tetraxetan (pK _i 9.4) [48]
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) [250]

S1: Chymotrypsin

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

Nomenclature	complement C1r	elastase, neutrophil expressed	plasminogen	plasminogen activator, tissue type
HGNC, UniProt	<i>C1R</i> , P00736	<i>ELANE</i> , P08246	<i>PLG</i> , P00747	<i>PLAT</i> , P00750
EC number	3.4.21.41	3.4.21.37	3.4.21.7	3.4.21.68
Inhibitors	nafamostat (pIC ₅₀ 4.9) [291]	alvelestat (pK _i 8) [647], sivelestat (pIC ₅₀ 7.4) [130]	aprotinin {Bovine} (Binding) (pIC ₅₀ 6.8) [639], tranexamic acid (Binding) (pIC ₅₀ 3.6) [639]	–
Selective inhibitors	–	–	6-aminocaproic acid (Binding) (pIC ₅₀ 4.4) [105]	–

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M2: Angiotensin-converting enzymes
(ACE and ACE2) S358

Comments	–	Neutrophil elastase (NE) is a destructive serine protease. It is stored in the primary granules of neutrophils and is endogenously inhibited by alpha1-proteinase inhibitor (a.k.a. alpha-1 antitrypsin). NE is a molecular target for neutrophil-mediated inflammatory lung diseases.	–	–
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Nomenclature	serine protease 1	transmembrane serine protease 2	tryptase alpha/beta 1
HGNC, UniProt	PRSS1, P07477	TMPRSS2, O15393	TPSAB1, Q15661
EC number	3.4.21.4	3.4.21.-	3.4.21.59
Inhibitors	nafamostat (pIC ₅₀ 7.8) [291]	–	nafamostat (pIC ₅₀ 10) [483]
Selective inhibitors	–	–	gabexate (pIC ₅₀ 8.5) [181]

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 [116]. This catalytic core enables the degradation of peptides with Arg, Phe, Tyr, Leu, and Glu adjacent to the cleavage site. The $\beta 5$ subunit is the principal target of the approved drug proteasome inhibitor [bortezomib](#).

Nomenclature	proteasome 20S subunit beta 5
HGNC, UniProt	PSMB5, P28074
EC number	3.4.25.1
Inhibitors	bortezomib (pIC ₅₀ 7.7) [493]
Selective inhibitors	ixazomib (pK _i 9) [382]

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 [423, 589, 646]. Therapeutics which inhibit PCSK9 are viewed as potentially lucrative replacements for statins, upon statin patent

expiry. Several monoclonal antibodies including [alirocumab](#), [evolocumab](#), [bococizumab](#), RG-7652 and LY3015014 are under development. One RNAi therapeutic, code named ALN-PCS02, is also in development [135, 199, 206].

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

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M12: Astacin/Adamalysin S359

S9: Prolyl oligopeptidase

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

Nomenclature	dipeptidyl peptidase 4
HGNC, UniProt	<i>DPP4</i> , P27487
EC number	3.4.14.5
Endogenous substrates	glucagon-like peptide 1 (<i>GCG</i> , P01275)
Inhibitors	saxagliptin (pK _i 9.2) [264], linagliptin (pK _i 9) [175], sitagliptin (pI _C ₅₀ 8.1) [143], vildagliptin (pK _i 7.8) [264]
Selective inhibitors	ZY15557 (Competitive) (pK _i 8.3) [330]

Peptidyl-prolyl cis/trans isomerases

Enzymes → Peptidyl-prolyl cis/trans isomerases

Overview: Peptidyl-prolyl cis/trans isomerases (PPIases) are an enzyme family which catalyse the cis/trans isomerisation of proline peptide bonds to promote the folding and re-folding of peptides and proteins. Three subfamilies have been identified: cyclophilins, FK506-binding proteins and parvulins. Individual PPIases are overexpressed in a number of cancers [577], and family members have been targeted for immunosuppressant effects.

Nomenclature	FKBP prolyl isomerase 1A	FKBP prolyl isomerase 8	FKBP prolyl isomerase 5	FKBP prolyl isomerase 4	FKBP prolyl isomerase like
Common abbreviation	FKBP12	FKBP38	FKBP51	FKBP52	–
HGNC, UniProt	<i>FKBP1A</i> , P62942	<i>FKBP8</i> , Q14318	<i>FKBP5</i> , Q13451	<i>FKBP4</i> , Q02790	<i>FKBPL</i> , Q9UIM3
EC number	5.2.1.8	5.2.1.8	5.2.1.8	5.2.1.8	5.2.1.8
Inhibitors	zotarolimus (Binding) (pI _C ₅₀ 8.6) [228]	GPI-1046 (pK _i 7.3) [176]	SLF (pI _C ₅₀ 5.2) [246]	SLF (pI _C ₅₀ 5) [246]	–
Selective inhibitors	tacrolimus (pK _i 9.4) [272], pimecrolimus (pI _C ₅₀ 8.2) [317] – Rat	DM-CHX (pK _i 7.1) [176]	SAFit1 (pK _i 8.4) [219], SAFit2 (pK _i 8.2) [219]	–	–
Comments	–	–	–	–	Peptides based on the non-functional PPIase domain of FKBPL (e.g. AD-01 and <i>ALM201</i>) have potent anti-tumour activity by inhibiting angiogenesis and promoting the differentiation of cancer stem cells [21, 457, 458, 691].

Nomenclature	peptidylprolyl cis/trans isomerase, NIMA-interacting 1	peptidylprolyl isomerase A	peptidylprolyl isomerase D
Common abbreviation	–	Cyclophilin A	Cyclophilin D
HGNC, UniProt	<i>PIN1</i> , Q13526	<i>PPIA</i> , P62937	<i>PPID</i> , Q08752
EC number	5.2.1.8	5.2.1.8	5.2.1.8

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S1: Chymotrypsin S360

Inhibitors	BJP-06-005-3 (pK _i 7.8) [543], AG-17724 (pK _i 7.1) [263]	cyclosporin A (Inhibition of the phosphatase activity of calcineurin in Jurkat cells.) (pIC ₅₀ 8.3) [210], voclosporin (Binding) (pK _d 7.8) [379]	cyclosporin A (pIC ₅₀ 8) [381, 548]
Comments	PIN1 isomerises phosphorylated serine/threonine-proline bonds. It plays roles in cell cycle control, neuropathologies and the immune system [184].	–	Cyclosporin A (CsA) is the prototypical cyclophilin D (CyPD) inhibitor, but it also inhibits cyclophilin A and the calcineurin pathway, an effect that has long been used for immunosuppression in humans [548].

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Poly ADP-ribose polymerases

Enzymes → 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](#)). The most well defined function of the tankyrases (TNKSs) is their regulatory action on Wnt/ β -catenin signalling [445]. PARPs

1 and 2 are targets of PARP inhibitor class anti-cancer drugs which are designed to disrupt the DNA damage response pathways to induce cancer cell death.

Nomenclature	poly(ADP-ribose) polymerase 1	poly(ADP-ribose) polymerase 2	poly (ADP-ribose) polymerase 3
Common abbreviation	PARP1	PARP2	PARP3
HGNC, UniProt	PARP1 , P09874	PARP2 , Q9UGN5	PARP3 , Q9Y6F1
EC number	2.4.2.30	2.4.2.30	–
Selective inhibitors	MC2050 (pIC ₅₀ 6.9) [485]	–	–
Comments	PARP1 is a molecular target of PARP inhibitor class drugs. These drugs are used to modulate the DNA damage response pathways in susceptible cancers [257].	PARP2 function is modulated by non-selective PARP inhibitor class drugs. These drugs are used to modulate the DNA damage response pathways in susceptible cancers [257].	–

Further reading on Poly ADP-ribose polymerases

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- Rao PD *et al.* (2020) PARP'ing fibrosis: repurposing poly (ADP ribose) polymerase (PARP) inhibitors. *Drug Discov Today* **25**: 1253-1261 [PMID:32371137]

Prolyl hydroxylases

Enzymes → Prolyl hydroxylases

Overview: Hypoxia-inducible factors (HIFs) are rapidly-responding sensors of reductions in local oxygen tensions, prompting changes in gene transcription. Listed here are the 4-prolyl hydroxylase family, members of which have been iden-

tified to hydroxylate proline residues in HIF1 α (*HIF1A*; [Q16665](#)) leading to an increased degradation through proteasomal hydrolysis. This action requires molecular oxygen and 2-oxoglutarate, and so reduced oxygen tensions prevents HIF1 α hydroxylation,

allowing its translocation to the nucleus and dimerisation with HIF1 β (also known as *ARNT*; [P27540](#)), thereby allowing interaction with the genome as a transcription factor.

Nomenclature	egl-9 family hypoxia inducible factor 2	egl-9 family hypoxia inducible factor 1	egl-9 family hypoxia inducible factor 3
Common abbreviation	PHD1	PHD2	PHD3
HGNC, UniProt	EGLN2, Q96KSO	EGLN1, Q9GZT9	EGLN3, Q9H6Z9
EC number	1.14.11.29	1.14.11.29	1.14.11.29

Further reading on Prolyl hydroxylases

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Spingosine 1-phosphate turnover

Enzymes → Spingosine 1-phosphate turnover

Overview: S1P ([sphingosine 1-phosphate](#)) is a bioactive lipid which, after release from cells via certain transporters, acts as a ligand for a family of five S1P-specific G protein-coupled receptors (S1P1-5). However, it also has a number of intracellular targets. S1P is formed by the ATP-dependent phosphorylation of sphingosine, catalysed by two isoforms of sphingosine kinase (EC 2.7.1.91). It can be dephosphorylated back to sphingosine

by sphingosine 1-phosphate phosphatase (EC 3.1.3) or cleaved into phosphoethanolamine and hexadecenal by sphingosine 1-phosphate lyase (EC 4.1.2.27). Recessive mutations in the S1P lyase (SPL) gene underlie a recently identified sphingolipidosis: SPL Insufficiency Syndrome (SPLIS). In general, S1P promotes cell survival, proliferation, migration, adhesion and inhibition of apoptosis. Intracellular S1P affects epigenetic regulation,

endosomal processing, mitochondrial function and cell proliferation/senescence. S1P has myriad physiological functions, including vascular development, lymphocyte trafficking and neurogenesis. However, S1P is also involved in a number of diseases such as cancer, inflammation and fibrosis. Therefore, its GPCRs and enzymes of synthesis and degradation are a major focus for drug discovery.

Spingosine kinase

Enzymes → Spingosine 1-phosphate turnover → Spingosine kinase

Overview: SPHK1 and SPHK2 are encoded by different genes with some redundancy of function; genetic deletion of both Sphk1 and Sphk2, but not either alone, is embryonic lethal in mice. There are splice variants of each isoform (SphK1a-c and SphK2a, b), distinguished by their N-terminal sequences. SPHK1 and SPHK2 differ in tissue distribution, sub-cellular localisation,

biochemical properties and regulation. They regulate discrete pools of S1P. Receptor stimulation induces SPHK1 translocation from the cytoplasm to the plasma membrane. SPHK1 translocation is regulated by phosphorylation/dephosphorylation, specific protein:protein interactions and interaction with specific lipids at the plasma membrane. SPHK1 is a dimeric protein, as

confirmed by its crystal structure which forms a positive cluster, between protomers, essential for interaction with anionic phospholipids in the plasma membrane. SPHK2 is localised to the ER or associated with mitochondria or shuttles in/out of the nucleus, regulated by phosphorylation. Intracellular targets of nuclear S1P include the catalytic subunit of telomerase (TERT)

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Peptidyl-prolyl cis/trans isomerases **S362**

and regulators of gene expression including histone deacetylases (HDAC 1/2) and peroxisome proliferator-activated receptor gamma (PPAR γ). SPHK2 phosphorylates the pro-drug FTY720

(**fingolimod**, which is used to treat some forms of multiple sclerosis) to a mimic of S1P and that acts as a functional antagonist of S1P₁ receptors. Inhibitors of SPHK1 and SPHK2 have thera-

peutic potential in many diseases. Isoform-selective inhibitors are becoming available; some early inhibitors have recognised off-target effects.

Nomenclature	sphingosine kinase 1	sphingosine kinase 2
Common abbreviation	SPHK1	SPHK2
HGNC, UniProt	SPHK1 , Q9NYA1	SPHK2 , Q9NRA0
EC number	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP dihydrosphingosine + ATP = dihydrosphingosine 1-phosphate + ADP	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP dihydrosphingosine + ATP = dihydrosphingosine 1-phosphate + ADP
Cofactors	Mg ²⁺ [613]	Mg ²⁺
Inhibitors	compound 49 (pIC ₅₀ 7.8) [6], SKI II (pK _i 4.8) [207], MP-A08 (pIC ₅₀ 4.6) [545]	compound 49 (pIC ₅₀ 7.8) [6], MP-A08 (pK _i 5.2) [545], SKI II (pK _i 5.1) [224]
Selective inhibitors	PF-543 (pK _i 8.4) [602]	compound 59 (pIC ₅₀ 7.8) [6], compound 60 (pIC ₅₀ 7.5) [6], compound 55 (pIC ₅₀ 7.4) [6], SLC4101431 (pK _i 7.1) [108], compound 27d (pIC ₅₀ 6.8) [601], opaganib (pK _i 5) [207], ROMe (pK _i 4.8) [408]
Comments	SPHK1 inhibitors induce its proteasomal degradation [428, 461]. SPHK1 crystal structures confirm that it is dimeric [5]; there is no crystal structure available for SPHK2.	There is no crystal structure available for SPHK2.

Comments: [MP-A08](#) is competitive with ATP; other SPHK inhibitors are competitive with sphingosine. ABC294640 ([opaganib](#)) has known off-target effects on dihydroceramide desaturase (*DEGS1*) [461, 696] and induces proteasomal degradation of SPHK1 [461]. ABC294640 is in clinical trials for advanced cholangiocarcinoma, advanced hepatocellular carcinoma and refractory/relapsed multiple myeloma (to view ClinicalTrials.gov list click [here](#)).

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Sphingosine 1-phosphate phosphatase

Enzymes → [Sphingosine 1-phosphate turnover](#) → [Sphingosine 1-phosphate phosphatase](#)

Nomenclature	sphingosine-1-phosphate phosphatase 1	sphingosine-1-phosphate phosphatase 2
Common abbreviation	SGPP1	SGPP2
HGNC, UniProt	SGPP1 , Q9BX95	SGPP2 , Q8IWX5
EC number	3.1.3.-: sphingosine 1-phosphate → sphingosine + inorganic phosphate dihydrosphingosine 1-phosphate → dihydrosphingosine + inorganic phosphate	3.1.3.-: sphingosine 1-phosphate → sphingosine + inorganic phosphate dihydrosphingosine 1-phosphate → dihydrosphingosine + inorganic phosphate

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Poly ADP-ribose polymerases S363

Comments Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [397].

Comments: SGPP1 and SGPP2 are non-redundant endoplasmic reticulum enzymes that dephosphorylate intracellular S1P. The phenotype of *Sgpp1(-/-)* mice differ with genetic background. *Sgpp2(-/-)* mice are also available. No specific SGPP inhibitors available [397].

Further reading on Sphingosine 1-phosphate phosphatase

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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 dihydrosphingosine 1-phosphate → phosphoethanolamine + hexadecanal
Cofactors	pyridoxal 5-phosphate
Inhibitors	compound 31 (pIC ₅₀ 6.7) [283, 420, 604, 723]

Comments: THI (2-Acetyl-5-tetrahydroxybutyl imidazole) inhibits the enzyme activity in intact cell preparations [605]. Recessive mutations in the S1P lyase (*SGPL1*) gene underlie a recently identified sphingolipidosis: SPL Insufficiency Syndrome (SPLIS) [112]. A Phase 2 clinical trial of LX3305 (LX2931) for rheumatoid arthritis has been completed (see NCT00903383). A homozygous point mutation results in mislocalisation of S1P lyase from the endoplasmic reticulum in pediatric alveolar rhabdomyosarcoma [7].

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Thyroid hormone turnover

Enzymes → Thyroid hormone turnover

Overview:

The thyroid hormones triiodothyronine and thyroxine, usually abbreviated as **triiodothyronine** and **T₄**, respectively, are synthesized in the thyroid gland by sequential metabolism of tyrosine residues in the glycosylated homodimeric protein thyroglobulin (**TG**, **P01266**) under the influence of the haem-

containing protein iodide peroxidase. Iodide peroxidase/TPO is a haem-containing enzyme, from the same structural family as eosinophil peroxidase (**EPX**, **P11678**), lactoperoxidase (**LPO**, **P22079**) and myeloperoxidase (**MPO**, **P05164**). Circulating thyroid hormone is bound to thyroxine-binding globulin (**SERPINA7**, **P05543**).

Tissue deiodinases

These are 1 TM selenoproteins that remove an iodine from **T₄** (3,3',5,5'-tetraiodothyronine) to generate **triiodothyronine** (3,3',5-triiodothyronine, a more potent agonist at thyroid hormone receptors) or **rT₃** (rT₃, 3,3',5'-triiodothyronine, a relatively inactive analogue). DIO1 is also able to deiodinate rT₃ to form 3,3'-diiodothyronine (**T₂**). Iodotyrosine deiodinase is a 1TM homodimeric enzyme.

Nomenclature	thyroid peroxidase	iodothyronine deiodinase 1	iodothyronine deiodinase 2	iodothyronine deiodinase 3	iodotyrosine deiodinase
Common abbreviation	TPO	DIO1	DIO2	DIO3	IYD
HGNC, UniProt	TPO , P07202	DIO1 , P49895	DIO2 , Q92813	DIO3 , P55073	IYD , Q6PHW0
EC number	1.11.1.8: [Thyroglobulin]-L-tyrosine + H ₂ O ₂ + H ⁺ + I ⁻ → [Thyroglobulin]-3,5,3'-triiodo-L-tyrosine + [thyroglobulin]-aminoacrylate + H ₂ O	1.97.1.10: T ₄ → triiodothyronine rT ₃ → T ₂	1.97.1.10: T ₄ → triiodothyronine rT ₃ → T ₂	1.97.1.11: T ₄ → triiodothyronine rT ₃ → T ₂	1.22.1.1: 3-iodotyrosine → L-tyrosine + I ⁻ 3,5-diiodo-L-tyrosine → 3-iodotyrosine + I ⁻
Cofactors	Ca ²⁺	–	–	–	flavin adenine dinucleotide, NADPH
Inhibitors	methimazole [496], propylthiouracil [496]	–	–	–	–
Comments	Carbimazole is a pro-drug for methimazole	–	–	–	–

Further reading on Thyroid hormone turnover

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1.14.13.9 Kynurenine 3-monooxygenase

Enzymes → 1.14.13.9 Kynurenine 3-monooxygenase

Nomenclature	kynurenine 3-monooxygenase
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-monooxygenase participates in metabolism of the essential amino acid tryptophan.

Further reading on 1.14.13.9 Kynurenine 3-monooxygenase

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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) [89]. 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) [216]. 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 2.5.1.58 Protein farnesyltransferase

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Sphingosine 1-phosphate lyase S366

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 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 [596].

HDACs have more general protein deacetylase activity, being

able to deacetylate lysine residues in non-histone proteins [113] such as microtubules [314], the hsp90 chaperone [373] and the tumour suppressor p53 [432].

Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [409, 582], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [727]. 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) [622].

Nomenclature	histone deacetylase 6
HGNC, UniProt	HDAC6, Q9UBN7
EC number	3.5.1.98
Inhibitors	trichostatin A (pK _i 9) [69], vorinostat (pK _i 8.8) [69], romidepsin (pK _i 8) [69]
Selective inhibitors	ricolinostat (pIC ₅₀ 8.3) [593]

Further reading on 3.5.1.- Histone deacetylases (HDACs)

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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 biological relevant proteins. The human isozymes exhibit tissue-specific expression patterns [339]. 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 [56]. Pharmacological PADI inhibition reverses protein-hypercitrullination and disease in mouse models of multiple sclerosis [486].

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

Searchable database: <https://www.guidetopharmacology.org/>

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1.14.13.9 Kynurenine 3-monooxygenase S367

Further reading on 3.5.3.15 Peptidyl arginine deiminases (PADI)

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3.6.5.2 Small monomeric GTPases

Enzymes → 3.6.5.2 Small monomeric GTPases

Overview: Small G-proteins, are a family of hydrolase enzymes that can bind and hydrolyze guanosine triphosphate (GTP). They are a type of G-protein found in the cytosol that are homologous to the alpha subunit of heterotrimeric G-proteins, but unlike the alpha subunit of G proteins, a small GTPase can function independently as a hydrolase enzyme to bind to and hydrolyze a guanosine triphosphate (GTP) to form guanosine diphosphate (GDP). The best-known members are the Ras GTPases and hence they are sometimes called Ras subfamily GTPases.

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 kDa. 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 [643], which leads to increased cell proliferation and

decreased apoptosis [768]. Because of their importance in oncogenic transformation these proteins have become the targets of intense drug discovery effort [38].

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

Further reading on RAS subfamily

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RAB subfamily

Enzymes → 3.6.5.2 Small monomeric GTPases → RAB subfamily

Overview: The Rab family of proteins is a member of the Ras superfamily of monomeric G proteins. Rab GTPases regulate many steps of membrane traffic, including vesicle formation, vesicle movement along actin and tubulin networks, and

membrane fusion. These processes make up the route through which cell surface proteins are trafficked from the Golgi to the plasma membrane and are recycled. Surface protein recycling returns proteins to the surface whose function involves carrying

another protein or substance inside the cell, such as the transferrin receptor, or serves as a means of regulating the number of a certain type of protein molecules on the surface (see [HGNC RAB, 65 genes](#)).

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

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3.5.3.15 Peptidyl arginine deiminases (PADI) S369

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