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THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Enzymes

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Abstract

The Concise Guide to PHARMACOLOGY 2019/20 is the fourth in this series of biennial publications. The Concise Guide provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to the open access knowledgebase source of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at <http://onlinelibrary.wiley.com/doi/10.1111/bph.14752>. 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-2019, and supersedes data presented in the 2017/18, 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (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 [454, 492], which is not to say that they are of modest importance.

The majority of drugs which act on enzymes act as inhibitors; one exception is metformin, which appears to stimulate activity of AMP-activated protein kinase, albeit through an imprecisely-

defined mechanism. Kinetic assays allow discrimination of competitive, non-competitive, and un-competitive inhibitors. The majority of inhibitors are competitive (acting at the enzyme's ligand recognition site), non-competitive (acting at a distinct site; potentially interfering with co-factor or co-enzyme binding) or of mixed type. One rare example of an uncompetitive inhibitor is lithium ions, which are effective inhibitors at inositol monophosphatase only in the presence of high substrate concentrations. Some inhibitors are irreversible, including a group known as suicide substrates, which bind to the ligand recognition site and then

Searchable database: <http://www.guidetopharmacology.org/index.jsp>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.14752/full>

Enzymes S297

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

| | | | | | |
|------|---|------|---|------|---|
| – | AAA ATPases | S321 | Adenylyl cyclases (ACs) | S358 | Hydrogen sulphide synthesis |
| S301 | Acetylcholine turnover | S323 | Exchange protein activated by cyclic AMP (EPACs) | S358 | Hydrolases |
| S302 | Adenosine turnover | S323 | Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs) | S360 | Inositol phosphate turnover |
| S303 | Amino acid hydroxylases | S327 | Cytochrome P450 | S360 | Inositol 1,4,5-trisphosphate 3-kinases |
| S304 | L-Arginine turnover | S327 | CYP1 family | S360 | Inositol polyphosphate phosphatases |
| S304 | 2.1.1.- Protein arginine N-methyltransferases | S328 | CYP2 family | S361 | Inositol monophosphatase |
| S305 | Arginase | S329 | CYP3 family | – | Itaconate biosynthesis |
| S305 | Arginine:glycine amidinotransferase | S330 | CYP4 family | S361 | Kinases (EC 2.7.x.x) |
| S305 | Dimethylarginine dimethylaminohydrolases | S331 | CYP5, CYP7 and CYP8 families | – | AGC: Containing PKA, PKG, PKC families |
| S306 | Nitric oxide synthases | S332 | CYP11, CYP17, CYP19, CYP20 and CYP21 families | – | DMPK family |
| S307 | Carbonic anhydrases | S333 | CYP24, CYP26 and CYP27 families | – | GEK subfamily |
| S308 | Carboxylases and decarboxylases | S333 | CYP39, CYP46 and CYP51 families | – | Other DMPK family kinases |
| S308 | Carboxylases | – | DNA glycosylases | S362 | Rho kinase |
| S309 | Decarboxylases | S334 | DNA topoisomerases | – | G protein-coupled receptor kinases (GRKs) |
| S311 | Catecholamine turnover | S335 | Endocannabinoid turnover | – | Beta-adrenergic receptor kinases (BARs) |
| S313 | Ceramide turnover | S336 | N-Acylethanolamine turnover | – | Opsin/rhodopsin kinases |
| S313 | Serine palmitoyltransferase | S337 | 2-Acylglycerol ester turnover | – | GRK4 subfamily |
| – | 3-ketodihydrosphingosine reductase | S338 | Eicosanoid turnover | – | MAST family |
| S314 | Ceramide synthase | S338 | Cyclooxygenase | – | NDR family |
| S314 | Sphingolipid Δ^4 -desaturase | S339 | Prostaglandin synthases | – | PDK1 family |
| S315 | Sphingomyelin synthase | S341 | Lipoxygenases | – | Protein kinase A (PKA) family |
| S315 | Sphingomyelin phosphodiesterase | S342 | Leukotriene and lipoxin metabolism | – | Akt (Protein kinase B, PKB) family |
| S316 | Neutral sphingomyelinase coupling factors | S343 | GABA turnover | – | Protein kinase C (PKC) family |
| S316 | Ceramide glucosyltransferase | S344 | Glycerophospholipid turnover | S362 | Alpha subfamily |
| S316 | Acid ceramidase | S344 | Phosphoinositide-specific phospholipase C | S363 | Delta subfamily |
| S317 | Neutral ceramidases | S346 | Phospholipase A ₂ | S363 | Eta subfamily |
| S317 | Alkaline ceramidases | S348 | Phosphatidylcholine-specific phospholipase D | S364 | Iota subfamily |
| S318 | Ceramide kinase | S349 | Lipid phosphate phosphatases | – | Protein kinase G (PKG) family |
| – | Chitinases | S349 | Phosphatidylinositol kinases | – | Protein kinase N (PKN) family |
| S319 | Chromatin modifying enzymes | S350 | 1-phosphatidylinositol 4-kinase family | – | RSK family |
| – | 1.14.11.- Histone demethylases | S351 | Phosphatidylinositol-4-phosphate 3-kinase family | – | MSK subfamily |
| S319 | 2.1.1.- Protein arginine N-methyltransferases | S351 | Phosphatidylinositol 3-kinase family | – | p70 subfamily |
| – | 2.1.1.43 Histone methyltransferases (HMTs) | S351 | Phosphatidylinositol-4,5-bisphosphate 3-kinase family | – | RSK subfamily |
| – | 2.3.1.48 Histone acetyltransferases (HATs) | S352 | 1-phosphatidylinositol-3-phosphate 5-kinase family | – | RSKR subfamily |
| S320 | 3.5.1.- Histone deacetylases (HDACs) | S353 | Type I PIP kinases | – | RSKL family |
| – | 3.6.1.3 ATPases | S353 | (1-phosphatidylinositol-4-phosphate 5-kinase family) | – | SGK family |
| – | Enzymatic bromodomain-containing proteins | S353 | Type II PIP kinases | – | YANK family |
| – | Bromodomain kinase (BRDK) family | S353 | (1-phosphatidylinositol-5-phosphate 4-kinase family) | – | Atypical |
| – | TAF1 family | S354 | Sphingosine kinase | – | ABC1 family |
| – | TIF1 family | S356 | Phosphatidylinositol phosphate kinases | | |
| S321 | Cyclic nucleotide turnover/signalling | S356 | Haem oxygenase | | |

| | | | | | |
|------|--|------|--|------|--|
| - | ABC1-A subfamily | - | PSK family | - | IRE family |
| - | ABC1-B subfamily | - | RAD53 family | - | MOS family |
| - | Alpha kinase family | - | Testis specific kinase (TSSK) family | - | NAK family |
| - | ChaK subfamily | - | Trbl family | - | NIMA (never in mitosis gene a)-related kinase (NEK) family |
| - | eEF2K subfamily | - | Trio family | - | NKF1 family |
| - | Other alpha kinase family kinases | - | CK1: Casein kinase 1 | - | NKF2 family |
| - | BCR family | - | Casein kinase 1 (CK1) family | - | NKF4 family |
| - | Bromodomain kinase (BRDK) family | - | Tau tubulin kinase (TTBK) family | - | NKF5 family |
| - | G11 family | - | Vaccina related kinase (VRK) family | - | NRBP family |
| - | Phosphatidylinositol 3' kinase-related kinases | - | CMGC: Containing CDK, MAPK, GSK3, CLK families | - | Numb-associated kinase (NAK) family |
| - | (PIKK) family | - | CLK family | - | Other-unique family |
| - | ATR subfamily | S365 | Cyclin-dependent kinase (CDK) family | - | Polo-like kinase (PLK) family |
| S364 | FRAP subfamily | - | CCRK subfamily | S367 | PEK family |
| - | SMG1 subfamily | - | CDK1 subfamily | - | GCN2 subfamily |
| - | TRRAP subfamily | S365 | CDK4 subfamily | - | PEK subfamily |
| - | Other PIKK family kinases | - | CDK5 subfamily | - | Other PEK family kinases |
| - | RIO family | - | CDK7 subfamily | - | Sgk493 family |
| - | RIO1 subfamily | - | CDK8 subfamily | - | Slob family |
| - | RIO2 subfamily | - | CDK9 subfamily | - | TBCK family |
| - | RIO3 subfamily | - | CDK10 subfamily | - | TOPK family |
| - | PDHK family | - | CRK7 subfamily | - | Tousled-like kinase (TLK) family |
| - | Pyruvate dehydrogenase kinase (PDHK) family | - | PITSLRE subfamily | - | TTK family |
| - | TAF1 family | - | TAIRE subfamily | - | Unc-51-like kinase (ULK) family |
| - | TIF1 family | - | Cyclin-dependent kinase-like (CDKL) family | - | VPS15 family |
| - | CAMK: Calcium/calmodulin-dependent protein kinases | - | Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase (DYRK) family | - | WEE family |
| - | CAMK1 family | - | Dyrk1 subfamily | - | Wnk family |
| - | CAMK2 family | - | Dyrk2 subfamily | - | Miscellaneous protein kinases |
| - | CAMK-like (CAMKL) family | - | HIPK subfamily | - | actin-binding proteins ADF family |
| - | AMPK subfamily | - | PRP4 subfamily | - | Twinfilin subfamily |
| - | BRSK subfamily | - | Glycogen synthase kinase (GSK) family | - | SCY1 family |
| - | CHK1 subfamily | S366 | GSK subfamily | - | Hexokinases |
| - | HUNK subfamily | - | Mitogen-activated protein kinases (MAP kinases) | - | STE: Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases |
| - | LKB subfamily | - | ERK subfamily | - | S367 STE7 family |
| - | MARK subfamily | - | Erk7 subfamily | - | STE11 family |
| - | MELK subfamily | - | JNK subfamily | - | STE20 family |
| - | NIM1 subfamily | - | p38 subfamily | - | FRAY subfamily |
| - | NuaK subfamily | - | nmo subfamily | - | KHS subfamily |
| - | PASK subfamily | - | RCK family | - | MSN subfamily |
| - | QIK subfamily | - | SRPK family | - | MST subfamily |
| - | SNRK subfamily | - | Lipid modifying kinases | - | NinaC subfamily |
| - | CAMK-unique family | - | Other protein kinases | - | PAKA subfamily |
| - | CASK family | - | CAMKK family | - | PAKB subfamily |
| - | DCAMKL family | - | Meta subfamily | - | SLK subfamily |
| - | Death-associated kinase (DAPK) family | - | Aurora kinase (Aur) family | - | STE20 subfamily |
| - | MAPK-Activated Protein Kinase (MAPKAPK) family | - | Bub family | - | STLK subfamily |
| - | MAPKAPK subfamily | - | Bud32 family | - | TAO subfamily |
| - | MKN subfamily | - | Casein kinase 2 (CK2) family | - | YSK subfamily |
| - | Myosin Light Chain Kinase (MLCK) family | - | CDC7 family | - | STE-unique family |
| - | Phosphorylase kinase (PHK) family | - | Haspin family | - | TK: Tyrosine kinase |
| - | PIM family | - | IKK family | | |
| - | Protein kinase D (PKD) family | | | | |

| | | | | | |
|------|--|------|--|------|--|
| - | Non-receptor tyrosine kinases (nRTKs) | - | C13: Legumain | - | S33: Prolyl aminopeptidase |
| S368 | Abl family | S378 | C14: Caspase | - | Phosphatases |
| S368 | Ack family | - | CE: Cysteine (C) Peptidases | - | Protein tyrosine phosphatases |
| - | Csk family | - | C48: Ulp1 endopeptidase | - | Sugar phosphatases |
| - | Fak family | - | M-: Metallo (M) Peptidases | S383 | Poly ADP-ribose polymerases |
| - | Fer family | - | M79: Prenyl protease 2 | S384 | Prolyl hydroxylases |
| S369 | Janus kinase (JakA) family | - | MA: Metallo (M) Peptidases | S384 | Sphingosine 1-phosphate turnover |
| S369 | Src family | S378 | M1: Aminopeptidase N | S385 | Sphingosine kinase |
| - | Syk family | S379 | M2: Angiotensin-converting (ACE and ACE2) | S386 | Sphingosine 1-phosphate phosphatase |
| S370 | Tec family | S379 | M10: Matrix metallopeptidase | S387 | Sphingosine 1-phosphate lyase |
| - | TKL: Tyrosine kinase-like | S380 | M12: Astacin/Adamalysin | S387 | Thyroid hormone turnover |
| - | Interleukin-1 receptor-associated kinase (IRAK) family | - | M13: Neprilysin | - | UDP glucuronosyltransferases (UGT) |
| - | Leucine-rich repeat kinase (LRRK) family | - | M49: Dipeptidyl-peptidase III | - | 1.-.- Oxidoreductases |
| - | LIM domain kinase (LISK) family | - | MC: Metallo (M) Peptidases | - | 1.1.1.42 Isocitrate dehydrogenases |
| - | LIMK subfamily | - | M14: Carboxypeptidase A | - | 1.4.3.13 Lysyl oxidases |
| - | TESK subfamily | - | ME: Metallo (M) Peptidases | - | 1.13.11.- Dioxygenases |
| - | Mixed Lineage Kinase (MLK) family | - | M16: Pitrilysin | S388 | 1.14.13.9 Kynurenine 3-monooxygenase |
| - | HH498 subfamily | - | MF: Metallo (M) Peptidases | - | 1.17.4.1 Ribonucleoside-diphosphate reductases |
| - | ILK subfamily | - | M17: Leucyl aminopeptidase | - | 2.1.1.- Methyltransferases |
| - | LZK subfamily | - | MG: Metallo (M) Peptidases | - | 2.1.2.- Hydroxymethyl-, formyl- and related transferases |
| - | MLK subfamily | - | M24: Methionyl aminopeptidase | - | 2.3.1.- Acyltransferases |
| - | TAK1 subfamily | - | MH: Metallo (M) Peptidases | - | 2.3.2.- Aminoacyltransferases |
| S371 | RAF family | - | M18: Aminopeptidase I | - | 2.3.2.13 Transglutaminases |
| - | Receptor interacting protein kinase (RIPK) family | - | M20: Carnosine dipeptidase | - | 2.3.2.27 RING-type E3 ubiquitin transferase |
| - | TKL-unique family | S380 | M28: Aminopeptidase Y | - | 2.4.2.1 Purine-nucleoside phosphorylase |
| S372 | Lanosterol biosynthesis pathway | - | MJ: Metallo (M) Peptidases | S389 | 2.5.1.58 Protein farnesyltransferase |
| - | LPA synthesis | S381 | M19: Membrane dipeptidase | - | 2.6.1.42 Branched-chain-amino-acid transaminase |
| - | NADPH oxidases | - | MP: Metallo (M) Peptidases | - | 2.7.1.40 Pyruvate kinases |
| S374 | Nucleoside synthesis and metabolism | - | M67: PSMD14 peptidase | - | 3.1.- Ester bond enzymes |
| S376 | Paraoxonase (PON) family | - | PA: Serine (S) Peptidases | - | 3.1.1.- Carboxylic Ester Hydrolases |
| S377 | Peptidases and proteinases | S381 | S1: Chymotrypsin | - | 3.2.1.- Glycosidases |
| - | AA: Aspartic (A) Peptidases | - | PB: Threonine (T) Peptidases | - | 3.4.21.46 Complement factor D |
| S377 | A1: Pepsin | - | C44: Phosphoribosyl pyrophosphate amidotransferase | S390 | 3.5.1.- Histone deacetylases (HDACs) |
| - | AD: Aspartic (A) Peptidases | S382 | T1: Proteasome | - | 3.5.1.2 Glutaminases |
| S377 | A22: Presenilin | - | T2: Glycosylasparaginase precursor | S391 | 3.5.3.15 Peptidyl arginine deiminases (PADI) |
| - | CA: Cysteine (C) Peptidases | - | PC: Cysteine (C) Peptidases | S391 | 3.6.5.2 Small monomeric GTPases |
| - | C1: Papain | - | C26: Gamma-glutamyl hydrolase | S391 | RAS subfamily |
| - | C2: Calpain | - | SB: Serine (S) Peptidases | S392 | RAB subfamily |
| - | C12: Ubiquitin C-terminal hydrolase | S382 | S8: Subtilisin | - | 5.-.- Isomerases |
| - | C19: Ubiquitin-specific protease | - | SC: Serine (S) Peptidases | - | 5.2.- Cis-trans-isomerases |
| - | C54: Aut2 peptidase | S383 | S9: Prolyl oligopeptidase | - | 6.3.3.- Cyclo-ligases |
| - | C101: OTULIN peptidase | - | S10: Carboxypeptidase Y | | |
| - | CD: Cysteine (C) Peptidases | - | S28: Lysosomal Pro-Xaa carboxypeptidase | | |

Acetylcholine turnover

Enzymes → Acetylcholine turnover

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

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

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

| | | | |
|---------------------------------|--|---|--|
| Nomenclature | choline O-acetyltransferase | acetylcholinesterase (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 | compound 2 (pIC ₅₀ 6.5) [216] – Mouse | tacrine (pK _i 7.5) [67], galantamine (pIC ₅₀ 6.3) [108], rivastigmine (pIC ₅₀ 5.4) [380] | rivastigmine (pIC ₅₀ 7.4) [380], tacrine (pK _i 7.2) [67] |
| Sub/family-selective inhibitors | – | physostigmine (pIC ₅₀ 7.6–7.8) [380] | physostigmine (pIC ₅₀ 7.6–7.8) [380] |
| Selective inhibitors | – | donepezil (pIC ₅₀ 7.7–8.3) [78 , 193 , 380], BW284C51 (pIC ₅₀ 7.7) [205] | bambuterol (pIC ₅₀ 8.5) [205] |
| Comments | Splice variants of choline O-acetyltransferase are suggested to be differentially distributed in the periphery and CNS (see [40]). | – | – |

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 [[644](#)].

Further reading on Acetylcholine turnover

- Li Q *et al.* (2017) Recent progress in the identification of selective butyrylcholinesterase inhibitors for Alzheimer's disease. *Eur J Med Chem* **132**: 294-309 [[PMID:28371641](#)]
- 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](#)]
- Masson P *et al.* (2016) Slow-binding inhibition of cholinesterases, pharmacological and toxicological relevance. *Arch Biochem Biophys* **593**: 60-8 [[PMID:26874196](#)]
- Rotundo RL. (2017) Biogenesis, assembly and trafficking of acetylcholinesterase. *J Neurochem* **142 Suppl 2**: 52-58 [[PMID:28326552](#)]
- Silman I *et al.* (2017) Recent developments in structural studies on acetylcholinesterase. *J Neurochem* **142 Suppl 2**: 19-25 [[PMID:28503857](#)]

Adenosine turnover

Enzymes → Adenosine turnover

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

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

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

| Nomenclature | Adenosine deaminase | Adenosine kinase | Ecto-5'-Nucleotidase | S-Adenosylhomocysteine hydrolase |
|-------------------------|--|---|--|--|
| Systematic nomenclature | – | – | CD73 | – |
| Common abbreviation | ADA | ADK | NT5E | SAHH |
| HGNC, UniProt | ADA , P00813 | ADK , P55263 | NT5E , P21589 | AHCY , P23526 |
| EC number | 3.5.4.4 : adenosine + H ₂ O = inosine + NH ₃ | 2.7.1.20 | 3.1.3.5 | 3.3.1.1 |
| Rank order of affinity | 2'-deoxyadenosine > adenosine | adenosine | adenosine 5'-monophosphate, 5'-GMP, 5'-inosine monophosphate, 5'-UMP > 5'-dAMP, 5'-dGMP | – |
| Endogenous substrates | – | – | – | S-adenosylhomocysteine |
| Products | 2'-deoxyinosine, inosine | adenosine 5'-monophosphate | uridine, inosine, guanine, adenosine | adenosine |
| Inhibitors | – | – | – | DZNep (pK _i 12.3) [208] – Hamster |
| Selective inhibitors | pentostatin (pIC ₅₀ 10.8) [6], EHNA (pK _i 8.8) [6] | A134974 (pIC ₅₀ 10.2) [403], ABT702 (pIC ₅₀ 8.8) [287] | $\alpha\beta$ -methyleneADP (pIC ₅₀ 8.7) [65] | 3-deazaadenosine (pIC ₅₀ 8.5) [227] |
| 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 [57, 642]. | Pharmacological inhibition of CD73 is being investigated as a novel cancer immunotherapy strategy [622]. | – |

Comments: An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, [CECR1](#), [Q9NZK5](#)) has been identified [117, 387], which is insensitive to EHNA [671]. Other forms of adenosine deaminase act on ribonucleic acids and may be divided into two families: [ADATI](#) ([Q9BUB4](#)) deaminates transfer RNA; [ADAR](#) ([EC 3.5.4.37](#), also

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

vere combined immunodeficiency syndrome. Adenosine deaminase is able to complex with dipeptidyl peptidase IV ([EC 3.4.14.5](#), [DPP4](#), also known as T-cell activation antigen CD26, TP103, adenosine deaminase complexing protein 2) to form a cell-surface activity [301].

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 | PAH , P00439 | TH , P07101 | TPH1 , P17752 | TPH2 , Q8IWU9 |
| EC number | 1.14.16.1: L-phenylalanine + O ₂ -> L-tyrosine | 1.14.16.2: L-tyrosine + O ₂ -> levodopa | 1.14.16.4 | 1.14.16.4 |
| Endogenous substrates | L-phenylalanine | L-tyrosine | L-tryptophan | L-tryptophan |
| Products | L-tyrosine | levodopa | 5-hydroxy-L-tryptophan | 5-hydroxy-L-tryptophan |
| Cofactors | sapropterin | sapropterin, Fe ²⁺ | – | – |
| Endogenous activators | Protein kinase A-mediated phosphorylation (Rat) [2] | Protein kinase A-mediated phosphorylation [290] | Protein kinase A-mediated phosphorylation [291] | Protein kinase A-mediated phosphorylation [291] |
| Inhibitors | – | – | telotristat ethyl [311] | – |
| Selective inhibitors | α -methylphenylalanine [218] – Rat, fenclonine | α -propylidopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine | α -propylidopacetamide, 6-fluorotryptophan [434], fenclonine, fenfluramine | α -propylidopacetamide, 6-fluorotryptophan [434], 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 [127]. | – | – |

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 mod-

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

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 dimethylated products; these may be symmetric ([SDMA](#)) or asym-

metric (N^G,N^G -dimethyl-L-arginine) versions, where both guanidino 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 [592], *S*-(2-boronoethyl)-L-cysteine [111, 312] and 2(*S*)-amino-6-boronoheptanoic acid [32, 111].

Arginine:glycine amidinotransferase

Enzymes → L-Arginine turnover → Arginine:glycine amidinotransferase

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

Dimethylarginine dimethylaminohydrolases

Enzymes → L-Arginine turnover → Dimethylarginine dimethylaminohydrolases

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

| | | |
|---------------------|--|--|
| Nomenclature | <i>N^G</i> , <i>N^G</i> -Dimethylarginine dimethylaminohydrolase 1 | <i>N^G</i> , <i>N^G</i> -Dimethylarginine dimethylaminohydrolase 2 |
| Common abbreviation | DDAH1 | DDAH2 |
| HGNC, UniProt | <i>DDAH1</i> , O94760 | <i>DDAH2</i> , O95865 |
| EC number | 3.5.3.18 | 3.5.3.18 |
| Cofactors | Zn ²⁺ | – |
| Inhibitors | compound 2e (p <i>K</i> _i 5.7) [324] | – |

Nitric oxide synthases

Enzymes → L-Arginine turnover → Nitric oxide synthases

Overview: Nitric oxide synthases (NOS, **E.C. 1.14.13.39**) are a family of oxidoreductases that synthesize nitric oxide (NO) via the NADPH and oxygen-dependent consumption of **L-arginine** with the resultant by-product, **L-citrulline**. There are 3 NOS isoforms and they are related by their capacity to produce NO, highly conserved organization of functional domains and significant homology at the amino acid level. NOS isoforms are functionally distinguished by the cell type where they are expressed, intracellular targeting and transcriptional and post-translation mechanisms regulating enzyme activity. The nomenclature suggested by **NC-IUPHAR** of NOS I, II and III [420] 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 | L-citrulline, NO |
| Cofactors | oxygen, BH ₄ , Zn ²⁺ , flavin mononucleotide, NADPH, heme, flavin adenine dinucleotide | heme, flavin mononucleotide, flavin adenine dinucleotide, oxygen, NADPH, Zn²⁺, BH₄ | flavin adenine dinucleotide, heme, oxygen, BH₄, flavin mononucleotide, NADPH, Zn²⁺ |
| Selective inhibitors | – | 1400W (pIC ₅₀ 8.2) [201], 2-amino-4-methylpyridine (pIC ₅₀ 7.4) [164], PIBTU (pIC ₅₀ 7.3) [202], NIL (pIC ₅₀ 5.5) [421], aminoguanidine [115] | 3-bromo-7NI (pIC ₅₀ 6.1–6.5) [52], 7NI (pIC ₅₀ 5.3) [24] |

Comments: The reductase domain of NOS catalyses the reduction of cytochrome c and other redox-active dyes [400]. 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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Searchable database: <http://www.guidetopharmacology.org/index.jsp>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.14752/full>

Nitric oxide synthases S306

Further reading on L-Arginine turnover

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Carbonic anhydrases

Enzymes → Carbonic anhydrases

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

| | | | | | |
|---------------------|--|--|--|---------------------------------------|---------------------------------------|
| Nomenclature | carbonic anhydrase 1 | carbonic anhydrase 7 | carbonic anhydrase 12 | 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 (p <i>K</i> _i 6.5) | methazolamide (p <i>K</i> _i 8.7) [533], acetazolamide (p <i>K</i> _i 8.6) [23], brinzolamide (p <i>K</i> _i 8.6) [533], chlorthalidone (p <i>K</i> _i 8.6) [591] | SLC-0111 (p <i>K</i> _i 8.4) [112] | – | – |

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 | Pyruvate carboxylase | Acetyl-CoA carboxylase 1 | Acetyl-CoA carboxylase 2 | Propionyl-CoA carboxylase | γ -Glutamyl carboxylase |
| Common abbreviation | PC | ACC1 | ACC2 | PCCA,PCCB | GGCX |
| HGNC, UniProt | PC , P11498 | ACACA , Q13085 | ACACB , O00763 | – | GGCX , P38435 |
| Subunits | – | – | – | Propionyl-CoA carboxylase β subunit, Propionyl-CoA carboxylase α subunit | – |
| EC number | 6.4.1.1 | 6.4.1.2 | 6.4.1.2 | 6.4.1.3 | 4.1.1.90 |
| Endogenous substrates | ATP, pyruvic acid | ATP, acetyl CoA | acetyl CoA, ATP | propionyl-CoA, ATP | glutamyl peptides |
| Products | P_i , ADP, oxalacetic acid | P_i , ADP, malonyl-CoA | P_i , ADP, malonyl-CoA | ADP, methylmalonyl-CoA, P_i | carboxyglutamyl peptides |
| Cofactors | biotin | biotin | biotin | biotin | vitamin K hydroquinone, NADPH |
| Inhibitors | – | – | – | – | anisindione |
| Selective inhibitors | – | compound 21 (pIC_{50} 8) [219], TOFA (pIC_{50} 4.9) [676] | compound 21 (pIC_{50} 8.4) [219], TOFA (pIC_{50} 4.9) [676] | – | – |
| 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. | Propionyl-CoA carboxylase is able to function in both forward and reverse activity modes, as a ligase (carboxylase) or lyase (decarboxylase), respectively. | Loss-of-function mutations in γ -glutamyl carboxylase are associated with clotting disorders . |

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

Decarboxylases

Enzymes → Carboxylases and decarboxylases → Decarboxylases

Overview: The decarboxylases generate CO₂ and the indicated products from acidic substrates, requiring [pyridoxal 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 + CO₂ | 4.1.1.15: L-glutamic acid + H⁺ -> GABA + CO₂ | 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 [198] |
| Comments | L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [650]. 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 This enzyme also catalyses the following reaction: L-tryptophan -> tryptamine + CO ₂ | 4.1.1.9 | 4.1.1.17 | 4.1.1.65 | 4.1.1.50 |
| Endogenous substrates | L-arginine | levodopa, 5-hydroxy-L-tryptophan, L-tryptophan | malonyl-CoA | L-ornithine | phosphatidylserine | S-adenosyl methionine |
| Products | agmatine [678] | 5-hydroxytryptamine, dopamine | acetyl CoA | putrescine | phosphatidylethanolamine | S-adenosyl-L-methioninamine |
| Cofactors | pyridoxal 5-phosphate | pyridoxal 5-phosphate | pyridoxal 5-phosphate | pyridoxal 5-phosphate | pyruvic acid | pyruvic acid |
| Selective inhibitors | – | 3-hydroxybenzylhydrazine, L- α -methyl-dopa, benserazide [125], carbidopa | – | APA (pI _{C50} 7.5) [563], eflornithine (pK _d 4.9) [482] | – | sardomozide (pI _{C50} 8) [562] |
| Comments | The presence of a functional ADC activity in human tissues has been questioned [110]. | AADC is a homodimer. | Inhibited by AMP-activated protein kinase-evoked phosphorylation [515] | 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 [455]. | S-allylglycine is also an inhibitor of SAMDC [455]. |

Further reading on Carboxylases and decarboxylases

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Catecholamine turnover

Enzymes → Catecholamine turnover

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

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

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

| | | | | |
|-----------------------|---|--|---|--|
| Nomenclature | L-Phenylalanine hydroxylase | Tyrosine aminotransferase | L-Tyrosine hydroxylase | Dopamine beta-hydroxylase (dopamine beta-monoxygenase) |
| Common abbreviation | – | TAT | – | DBH |
| HGNC, UniProt | PAH, P00439 | TAT, P17735 | TH, P07101 | DBH, P09172 |
| EC number | 1.14.16.1: L-phenylalanine + O₂ -> L-tyrosine | 2.6.1.5: L-tyrosine + α-ketoglutaric acid -> 4-hydroxyphenylpyruvic acid + L-glutamic acid | 1.14.16.2: L-tyrosine + O₂ -> levodopa | 1.14.17.1: dopamine + O₂ = (-)-noradrenaline + H₂O |
| Endogenous substrates | L-phenylalanine | – | L-tyrosine | – |
| Products | L-tyrosine | – | levodopa | – |
| Cofactors | sapropterin | pyridoxal 5-phosphate | sapropterin, Fe²⁺ | Cu²⁺, L-ascorbic acid |
| Endogenous activators | Protein kinase A-mediated phosphorylation (Rat) [2] | – | Protein kinase A-mediated phosphorylation [290] | – |
| Selective inhibitors | α-methylphenylalanine [218] – Rat, fenclonine | – | α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine | nepicastat (pIC₅₀ 8) [565] |
| 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 [128]. | 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 [87]. |

| | | | |
|-----------------------|--|--|---|
| 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 + CO₂ 5-hydroxy-L-tryptophan -> 5-hydroxytryptamine + CO₂ This enzyme also catalyses the following reaction:: L-tryptophan -> tryptamine + CO₂ | 2.1.1.28: (-)-noradrenaline -> (-)-adrenaline | 2.1.1.6: S-adenosyl-L-methionine + a catechol = S-adenosyl-L-homocysteine + a guaiacol (-)-noradrenaline -> normetanephrine dopamine -> 3-methoxytyramine 3,4-dihydroxymandelic acid -> vanillylmandelic acid (-)-adrenaline -> metanephrine S-adenosyl methionine |
| Endogenous substrates | levodopa, 5-hydroxy-L-tryptophan, L-tryptophan | – | tolcapone (soluble enzyme) (pK_i 9.6) [370], tolcapone (membrane-bound enzyme) (pK_i 9.5) [370], entacapone (soluble enzyme) (pK_i 9.5) [370], entacapone (membrane-bound enzyme) (pK_i 8.7) [370] |
| Products | 5-hydroxytryptamine, dopamine | – | tolcapone (soluble enzyme) (pK_i 9.6) [370], tolcapone (membrane-bound enzyme) (pK_i 9.5) [370], entacapone (soluble enzyme) (pK_i 9.5) [370], entacapone (membrane-bound enzyme) (pK_i 8.7) [370] |
| Cofactors | pyridoxal 5-phosphate | S-adenosyl methionine | – |
| Inhibitors | – | LY134046 (pK_i 7.6) [186] | COMT appears to exist in both membrane-bound and soluble forms. COMT has also been described to methylate steroids, particularly hydroxyestradiols |
| Selective inhibitors | 3-hydroxybenzylhydrazine, L-α-methyl dopa, benserazide [125], carbidopa | – | – |
| Comments | AADC is a homodimer. | – | – |

| | | |
|----------------------|--|---|
| Nomenclature | Monoamine oxidase A | Monoamine oxidase B |
| Common abbreviation | MAO-A | MAO-B |
| HGNC, UniProt | MAOA, P21397 | MAOB, P27338 |
| EC number | 1.4.3.4 (-)-adrenaline -> 3,4-dihydroxymandelic acid + NH₃ (-)-noradrenaline -> 3,4-dihydroxymandelic acid + NH₃ tyramine -> 4-hydroxyphenyl acetaldehyde + NH₃ dopamine -> 3,4-dihydroxyphenylacetaldehyde + NH₃ 5-hydroxytryptamine -> 5-hydroxyindole acetaldehyde + NH₃ | 1.4.3.4 |
| Cofactors | – | flavin adenine dinucleotide + |
| Inhibitors | – | rasagiline (pI_{C50} 7.8) [668], phenelzine (Irreversible inhibition) (pK_i 7.8) [49], lazabemide (pK_i 7.1) [230, 599], selegiline (pK_i 5.7–6) [141, 413], tranlycypromine (pI_{C50} 4.7) [664] |
| Selective inhibitors | flavin adenine dinucleotide | safinamide (pK_i 6.3) [48] |
| Comments | moclobemide (pK_i 8.3) [284], phenelzine (Irreversible inhibition) (pK_i 7.3) [49], tranlycypromine (pI_{C50} 4.7) [664], selegiline (pK_i 4.2) [413], bexloxtone [124], clorgiline, pirlindole [406] | – |

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Ceramide turnover

Enzymes → Ceramide turnover

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

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

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

Serine palmitoyltransferase

Enzymes → Ceramide turnover → Serine palmitoyltransferase

Overview: The functional enzyme is a heterodimer of SPT1 (LCB1) with either SPT2 (LCB2) or SPT3 (LCB2B); the small subunits of SPT (ssSPTa or ssSPTb) bind to the heterodimer to enhance enzymatic activity. The complexes of SPT1/SPT2/ssSPTa and SPT1/SPT2/ssSPTb were most active with palmitoylCoA as substrate, with the latter complex also showing some activity with stearoylCoA [234]. Complexes involving SPT3 appeared more broad in substrate selectivity, with incorporation of myristoylCoA prominent for SPT1/SPT3/ssSPTa complexes, while SP1/SPT3/ssSPTb complexes had similar activity with C16, C18 and C20 acylCoAs [234].

| 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 | – | – |
| Selective inhibitors | myriocin (pK _i 9.6) [414] – Mouse | myriocin [414] | myriocin [414] | – | – |

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 , Q8N5B7 | CERS6 , Q6ZMG9 |
| EC number | 2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A | 2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A | 2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A | 2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A | 2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A | 2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A |
| Substrates | C18-CoA [611] | C24- and C26-CoA [338] | C26-CoA and longer [417, 484] | C18-, C20- and C22-CoA [501] | C16-CoA [334, 501] | C14- and C16-CoA [416] |

Sphingolipid Δ^4 -desaturase

Enzymes → Ceramide turnover → Sphingolipid Δ^4 -desaturase

Overview: DEGS1 and DEGS2 are 4TM proteins.

| | | |
|---------------|---|--|
| Nomenclature | delta 4-desaturase, sphingolipid 1 | delta 4-desaturase, sphingolipid 2 |
| HGNC, UniProt | DEGS1 , O15121 | DEGS2 , Q6QHC5 |
| EC number | 1.14.-.- | 1.14.-.- |
| Cofactors | NAD | NAD |
| Inhibitors | SKI II (p <i>K</i> _i 6.5) [107], RBM2-1B (p <i>C</i> ₅₀ 4.7) [73] | – |
| Comments | Myristoylation of DEGS1 enhances its activity and targets it to the mitochondria [37]. | – |

Comments: DEGS1 activity is inhibited by a number of natural products, including [curcumin](#) and Δ^9 -tetrahydrocannabinol [163].

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) [350] | compound D24 (pIC ₅₀ 4.9) [134] | – |
| Comments | – | Palmitoylation of sphingomyelin synthase 2 may allow targeting to the plasma membrane [585]. | – |

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> , Q9NYS9 | <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 | – | inhibitor A (pK _i 5.8) [663] – Bovine | – | – | – | – |

Neutral sphingomyelinase coupling factors

Enzymes → Ceramide turnover → Neutral sphingomyelinase coupling factors

Overview: Protein FAN [4] and polycomb protein EED [469] allow coupling between TNF receptors and neutral sphingomyelinase phosphodiesterases.

| | | |
|----------------------|---|---|
| Nomenclature | embryonic ectoderm development | neutral sphingomyelinase activation associated factor |
| HGNC, UniProt | EED, O75530 | NSMAF, Q92636 |
| Selective inhibitors | A-395 (Binding) (pK _i 9.4) [252] | – |

Ceramide glucosyltransferase

Enzymes → Ceramide turnover → Ceramide glucosyltransferase

| | |
|---------------|--|
| Nomenclature | UDP-glucose ceramide glucosyltransferase |
| HGNC, UniProt | UGCG, Q16739 |
| EC number | 2.4.1.80: UDP-glucose + ceramide = uridine diphosphate + glucosylceramide |
| Inhibitors | miglustat (pK _i 5.1) [68] |
| Comments | Glycoceramides are an extended family of sphingolipids, differing in the content and organization of the sugar moieties, as well as the acyl sidechains. |

Acid ceramidase

Enzymes → Ceramide turnover → Acid ceramidase

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

| | |
|---------------|---|
| Nomenclature | N-acylsphingosine amidohydrolase 1 |
| HGNC, UniProt | ASAHT, 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 [318]. |

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 [584]. | – |

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 [572]. | ACER2 is associated with the Golgi apparatus [657]. | ACER3 is associated with the ER and Golgi apparatus [391]. |

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) [214] |

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

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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 [325]. 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) [325].

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 [161], where a wide variety of cellular and pro-

tein aberrations are known to perturb chromatin structure, gene transcription and ultimately cellular pathways [35, 544]. 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 [199, 637]) and erasers (*e.g.* the HDAC inhibitors **vorinostat**, **romidepsin** and **belinostat** for the treatment of T-cell lymphomas [177, 309]) 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 [71]. Current progress in this field is reviewed by Simó-Riudalbas and Esteller (2015) [545].

2.1.1.- Protein arginine N-methyltransferases

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

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

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

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

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

3.5.1.- Histone deacetylases (HDACs)

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

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

The histone deacetylase family has been classified into five subfamilies based on phylogenetic comparison with yeast homologues:

Class I contains HDACs 1, 2, 3 and 8

Class IIa contains HDACs 4, 5, 7 and 9

Class IIb contains HDACs 6 and 10

Class III contains the sirtuins (SIRT1-7)

Class IV contains only HDAC11.

Classes I, II and IV use 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 [521].

HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [104] such as microtubules [270], the hsp90 chaperone [326] and the tumour suppressor p53 [377].

Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [355, 509], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [639]. 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) [545].

| | |
|----------------------|---|
| Nomenclature | histone deacetylase 6 |
| HGNC, UniProt | HDAC6 , Q9UBN7 |
| EC number | 3.5.1.98 |
| Inhibitors | trichostatin A (p <i>K</i> _i 9) [61], vorinostat (p <i>K</i> _i 8.8) [61], romidepsin (p <i>K</i> _i 8) [61] |
| Selective inhibitors | ricolinostat (pIC ₅₀ 8.3) [518] |

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).

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 [137]) 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, [479]). Adenosine and its derivatives (e.g. 2',5'-dideoxyadenosine), acting through the P-site, are inhibitors of adenylyl cyclase activity [594]. Four families of membranous adenylyl cyclase are distinguishable: calmodulin (CALM1 CALM2 CALM3, P62158)-stimulated (AC1, AC3 and AC8), Ca^{2+} - and $G\beta\gamma$ -inhibitable (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 [93].

| 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 |
| Endogenous activators | calmodulin (CALM1 CALM2 CALM3, P62158), PKC-evoked phosphorylation [283, 583] | $G\beta\gamma$, PKC-evoked phosphorylation, Raf-evoked phosphorylation [91, 145, 381, 588] | calmodulin (CALM1 CALM2 CALM3, P62158), PKC-evoked phosphorylation [102, 283] | $G\beta\gamma$ [195] | PKC-evoked phosphorylation, $G\beta\gamma$, Raf-evoked phosphorylation [145, 197, 306] |
| Activators | compound 45 (pIC ₅₀ 7.7) [506] – Bovine | FD1 [449] | – | – | FD6 [449] |
| Endogenous inhibitors | $G\alpha_i$, $G\alpha_o$, $G\beta\gamma$ [588, 589] | – | RGS2, $G\beta\gamma$, CaM kinase II-evoked phosphorylation [142, 546, 633] | PKC-evoked phosphorylation [680] | $G\alpha_i$, Ca^{2+} , PKA-evoked phosphorylation, $G\beta\gamma$, NO [197, 258, 279, 282, 589] |
| Inhibitors | – | SKF-83566 [114] | – | – | NKY80 (pIC ₅₀ 5.2) [62, 449] |
| Selective inhibitors | ST034307 (pIC ₅₀ 5.6) [64] | – | – | – | – |

| 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 | Gβγ, Raf-evoked phosphorylation [145, 197] | Gβγ, PKC-evoked phosphorylation [39, 632] | calmodulin (<i>CALM1 CALM2 CALM3</i> , P62158) [72] | – | Bicarbonate, Ca ²⁺ [93, 357] |
| Endogenous inhibitors | Gα _i , Ca ²⁺ , PKA-evoked phosphorylation, PKC-evoked phosphorylation, NO [94, 258, 335, 589, 667] | – | PKA-evoked phosphorylation [643] | Ca ²⁺ /calcineurin [461] | – |
| Inhibitors | NKY80 (pIC ₅₀ 4.8) [62] | – | – | – | KH7 (pIC ₅₀ 5–5.5) [256], LRE1 (pIC ₅₀ 5) [488] |

Comments: Many of the activators and inhibitors listed are only somewhat selective or have not been tested against all AC isoforms [62, 114]. AC3 shows only modest *in vitro* activation by Ca²⁺/CaM.

Further reading on Adenylyl cyclases (ACs)

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Exchange protein activated by cyclic AMP (EPACs)

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

Overview: Epacs are members of a family of guanine nucleotide exchange factors (ENSM00250000000899), 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 [158]. 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 [524].

| | | |
|---------------------|--|--|
| Nomenclature | Rap guanine nucleotide exchange factor 3 | Rap guanine nucleotide exchange factor 4 |
| Common abbreviation | Epac1 | Epac2 |
| HGNC, UniProt | <i>RAPGEF3</i> , O95398 | <i>RAPGEF4</i> , Q8WZA2 |
| Inhibitors | ESI-09 (pIC ₅₀ 5.5) [15] | HJC 0350 (pIC ₅₀ 6.5) [89], ESI-09 (pIC ₅₀ 4.4–5.2) [15, 90] |

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

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 Robichaux WG and Cheng X. (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 |
| Common abbreviation | PDE1A | PDE1B | PDE1C |
| HGNC, UniProt | PDE1A , P54750 | PDE1B , Q01064 | PDE1C , Q14123 |
| EC number | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 |
| Rank order of affinity | cyclic GMP > cyclic AMP | cyclic GMP > cyclic AMP | cyclic GMP = cyclic AMP |
| Endogenous activators | calmodulin (CALM1 CALM2 CALM3 , P62158) | calmodulin (CALM1 CALM2 CALM3 , P62158) | calmodulin (CALM1 CALM2 CALM3 , P62158) |
| Endogenous inhibitors | – | – | – |
| Inhibitors | crisaborole (pIC ₅₀ 5.2) [10] | – | – |
| Sub/family-selective inhibitors | – | – | – |
| Selective inhibitors | SCH51866 (pIC ₅₀ 7.2) [609], vinpocetine (pIC ₅₀ 5.1) [372] | SCH51866 (pIC ₅₀ 7.2) [609] | SCH51866 (pIC ₅₀ 7.2) [609], vinpocetine (pIC ₅₀ 4.3) [372] |
| Comments | – | – | – |

| | | | |
|---------------------------------|--|--|--|
| Nomenclature | phosphodiesterase 2A | phosphodiesterase 3A | phosphodiesterase 3B |
| Common abbreviation | PDE2A | PDE3A | PDE3B |
| HGNC, UniProt | PDE2A , O00408 | PDE3A , Q14432 | PDE3B , Q13370 |
| EC number | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 |
| Rank order of affinity | cyclic AMP ≫ cyclic GMP | – | – |
| Endogenous activators | cyclic GMP | – | – |
| Endogenous inhibitors | – | cyclic GMP | cyclic GMP |
| Inhibitors | milrinone (pIC ₅₀ <6.5) [571] | cilostazol (pIC ₅₀ 6.7) [571], inamrinone (pIC ₅₀ 4.8) [547] | – |
| Sub/family-selective inhibitors | – | – | – |
| Selective inhibitors | BAY607550 (pIC ₅₀ 8.3–8.8) [56], EHNA (pIC ₅₀ 5.3) [411] | cilostamide (pIC ₅₀ 7.5) [571], anagrelide (pIC ₅₀ 7.1–7.3) [295 , 395 , 405], milrinone (pIC ₅₀ 6.3–6.4) [156 , 571] | cilostamide (pIC ₅₀ 7.3) [571], cilostazol (pIC ₅₀ 6.4) [571], milrinone (pIC ₅₀ 6) [571], inamrinone (pIC ₅₀ 4.5) [571] |
| 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 » cyclic GMP | cyclic AMP » cyclic GMP | cyclic AMP » cyclic GMP | cyclic AMP » cyclic GMP | cyclic GMP > cyclic AMP |
| Activators | – | – | – | PKA-mediated phosphorylation [265] | Protein kinase A, protein kinase C [116] |
| Inhibitors | ibudilast (pIC ₅₀ 7.3) [319], RS-25344 (pIC ₅₀ 7.2) [517] | roflumilast (pIC ₅₀ 9.4) [376], ibudilast (pIC ₅₀ 7.2) [319], RS-25344 (pIC ₅₀ 6.5) [517] | RS-25344 (pIC ₅₀ 8.1) [517], ibudilast (pIC ₅₀ 6.6) [319] | RS-25344 (pIC ₅₀ 8.4) [517], difamilast (pIC ₅₀ >7.3) [446], CBS-3595 (pIC ₅₀ 6.1) [13] | gisadenafil (pIC ₅₀ 8.9) [495], milrinone (pIC ₅₀ 7.3) |
| Sub/family-selective inhibitors | rolipram (pIC ₅₀ 9) [623], CDP840 (pK _i 8) [465], Ro20-1724 (pIC ₅₀ 6.5) [623] | rolipram (pIC ₅₀ 9) [623], Ro20-1724 (pIC ₅₀ 6.4) [623] | CDP840 (pK _i 7.7) [465], rolipram (pIC ₅₀ 6.5) [623], Ro20-1724 (pIC ₅₀ 5.4) [623] | CDP840 (pK _i 8.1) [465], rolipram (pIC ₅₀ 7.2) [623], Ro20-1724 (pIC ₅₀ 6.2) [623] | – |
| Selective inhibitors | YM976 (pIC ₅₀ 8.3) [17], apremilast (pIC ₅₀ 7.8) [522] | – | apremilast (pIC ₅₀ 6.9) [522] | apremilast (pIC ₅₀ 7.5) [522] | vardenafil (pIC ₅₀ 9.7) [60], T0156 (pIC ₅₀ 9.5) [418], sildenafil (pIC ₅₀ 8.4–9) [604, 621], tadalafil (pIC ₅₀ 8.5) [419], SCH51866 (pIC ₅₀ 7.2) [609], zaprinast (pIC ₅₀ 6.8) [604] |

| | | | | | | |
|---------------------|---|--------------------------------------|--|--------------------------------------|--------------------------------------|--------------------------------------|
| 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) [271] | – | sildenafil (pIC ₅₀ 7.4) [621] | – | – | – |

| | | | | |
|------------------------|--|--|--|---|
| 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 » cyclic GMP [409] | cyclic AMP » cyclic GMP [200] | cyclic AMP » cyclic GMP [171] | cyclic AMP » cyclic GMP [249] |
| Inhibitors | crisaborole (pIC ₅₀ 6.1) [10] | BRL50481 (pIC ₅₀ 4.9) [11] | – | – |
| Selective inhibitors | BRL50481 (pIC ₅₀ 6.7–6.8) [11, 553] | dipyridamole (pIC ₅₀ 5.7–6) [200, 520], SCH51866 (pIC ₅₀ 5.8) [520] | PF-04957325 (pIC ₅₀ 7.4) [399], dipyridamole (pIC ₅₀ 5.1) [171] | dipyridamole (pIC ₅₀ 4.3) [249] |
| 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 [170] | cyclic AMP , cyclic GMP [184] | cyclic AMP , cyclic GMP [167] |
| Inhibitors | SCH51866 (pIC ₅₀ 5.8) [170], zaprinast (pIC ₅₀ 4.5) [170] | – | tadalafil (pIC ₅₀ 6.5) [419], BC11-38 (pIC ₅₀ 6.5) [84] |
| Selective inhibitors | – | mardepodect (pIC ₅₀ 9.4) [613] | – |

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 [260, 261]. PDE4A–D splice variants can be membrane-bound or cytosolic [265]. 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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Cytochrome P450

Enzymes → Cytochrome P450

Overview: The cytochrome P450 enzyme family (CYP450), E.C. 1.14.-.-, were originally defined by their strong absorbance at 450 nm due to the reduced carbon monoxide-complexed haem component of the cytochromes. They are an extensive family of haem-containing monooxygenases with a huge range of both endogenous and exogenous substrates. These include sterols, fat-soluble

vitamins, pesticides and carcinogens as well as drugs. The substrates of some orphan CYP are not known. Listed below are the human enzymes; their relationship with rodent CYP450 enzyme activities is obscure in that the species orthologue may not catalyse the metabolism of the same substrates. Although the majority of CYP450 enzyme activities are concentrated in the liver, the extra-

hepatic enzyme activities also contribute to patho/physiological processes. Genetic variation of CYP450 isoforms is widespread and likely underlies a significant proportion of the individual variation to drug administration.

CYP1 family

Enzymes → Cytochrome P450 → CYP1 family

| | | | |
|---------------|--|--|--|
| Nomenclature | CYP1A1 | CYP1A2 | CYP1B1 |
| HGNC, UniProt | CYP1A1, P04798 | CYP1A2, P05177 | CYP1B1, Q16678 |
| EC number | 1.14.1.1 | 1.14.1.1 | 1.14.1.1 |
| Inhibitors | 5H3'FPE (pIC ₅₀ 7.4) [359] | 5H3'FPE (pIC ₅₀ 6.4) [359] | stilbenes [154] |
| Comments | CYP1A1 is an extra-hepatic enzyme. It shows a preference for linear planar aromatic molecules [561]. | CYP1A2 is constitutively expressed in liver. It shows a preference for triangular planar aromatic molecules [561]. | Mainly expressed in extra-hepatic tissues. Can metabolise 17β-estradiol [154], leukotrienes and eicosanoids [146]. Mutations have been associated with primary congenital glaucoma [569] |

CYP2 family

Enzymes → Cytochrome P450 → CYP2 family

| | | | | | |
|---------------|---|---|--|---|--|
| Nomenclature | CYP2A6 | CYP2A7 | CYP2A13 | CYP2B6 | CYP2C8 |
| HGNC, UniProt | CYP2A6, P11509 | CYP2A7, P20853 | CYP2A13, Q16696 | CYP2B6, P20813 | CYP2C8, P10632 |
| EC number | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 |
| Substrates | nicotine | – | – | – | – |
| Inhibitors | – | – | – | ticlopidine (pIC ₅₀ 6.7) [175], sibutramine (pIC ₅₀ 5.8) [27], thiotepa (pK _i 5.3) [620] | phenelzine (pK _i 5.1) [175] |
| Comments | Metabolises coumarin [660]. | CYP2A7 does not incorporate haem and is functionally inactive [185] | Metabolises tobacco carcinogen, 4-methylnitrosoamino-1-(3-pyridyl)-1-butanone [570]. | Substrates include: efavirenz, bupropion, cyclophosphamide, ketamine, propofol [605]. | Converts arachidonic acid to 11(R)-12(S)-epoxyeicosatrienoic acid or 14(R)-15(S)-epoxyeicosatrienoic acid [672]. Drug substrates include amodiaquine [26]. |

| | | | | | | |
|----------------------|---|--|---|---|---|--|
| Nomenclature | CYP2C19 | CYP2D6 | CYP2E1 | CYP2F1 | CYP2J2 | CYP2R1 |
| HGNC, UniProt | CYP2C19, P33261 | CYP2D6, P10635 | CYP2E1, P05181 | CYP2F1, P24903 | CYP2J2, P51589 | CYP2R1, Q6VWX0 |
| EC number | 1.14.14.51 | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 | 1.14.13.15 |
| | (S)-limonene + [reduced NADPH–hemoprotein reductase] + O(2) <=> (-)-trans-carveol + [oxidized NADPH–hemoprotein reductase] + H(2)O | | | | | |
| Inhibitors | compound 51 (pIC ₅₀ 7.3) [120] | – | compound 23 (pK _i 7.4) [661] | – | compound 4 (pIC ₅₀ 6.8) [333], terfenadine (pIC ₅₀ 5.1) [333] | – |
| Selective inhibitors | compound 30 (pK _i 7.7) [178] | – | – | – | – | – |
| Comments | Substrates include: omeprazole, proguanil, mephentoin, diazepam [45 , 138 , 254]. | Substrates include: debrisoquine, metoprolol, codeine [365]. | Substrates: Ethanol, p-nitrophenol [386]. | Substrate: naphthalene [345]. | Converts arachidonic acid to 14(R)-15(S)-epoxyeicosatrienoic acid [652]. Hydroxylates albandazole [654]. Expressed in cardiomyocytes [556]. | Converts vitamin D3 to calcifediol [96]. |

CYP3 family

Enzymes → Cytochrome P450 → CYP3 family

| | CYP3A4 | CYP3A5 | CYP3A7 | CYP3A43 |
|---------------|--|--|---|---|
| Nomenclature | CYP3A4 | CYP3A5 | CYP3A7 | CYP3A43 |
| HGNC, UniProt | CYP3A4, P08684 | CYP3A5, P20815 | CYP3A7, P24462 | CYP3A43, Q9HB55 |
| EC number | 1.14.14.56: 1,8-cineole + NADPH + O ₂ = 2-exo-hydroxy-1,8-cineole + NADP ⁺ + H ₂ O 1.14.13.97: Taurochenodeoxycholate + NADPH + O ₂ = taurohyocholate + NADP ⁺ + H ₂ O Lithocholate + NADPH + O ₂ = hyodeoxycholate + NADP ⁺ + H ₂ O 1.14.14.55: quinine + NADPH + O ₂ = 3-hydroxyquinine + NADP ⁺ + H ₂ O ₂ | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 |
| Substrates | nifedipine [225], midazolam [641] | – | – | – |
| Inhibitors | troleandomycin (pK _i 7.8) [534], ketoconazole (pK _i 7) [217], ritonavir (pK _i > 7) [310] | ritonavir (pK _i 6.9) [175] | – | – |
| Comments | Metabolises a vast range of xenobiotics, including antidepressants, benzodiazepines, calcium channel blockers, and chemotherapeutic agents [675]. The active site is plastic, with both homotropic and heterotropic cooperativity observed with some substrates [534]. CYP3A4 catalyses the 25-hydroxylation of trihydroxycholestane in liver microsomes [189]. | CYP3A5 is expressed extrahepatically, including in the small intestine. It has overlapping substrate specificity with CYP3A4 [126, 641]. | Fetal form, rarely expressed in adults. Has overlapping substrate specificity with CYP3A4 [126, 641]. | Fetal expression only and considered an orphan fCYP [224]. Testosterone may be a substrate [220]. |

CYP4 family

Enzymes → Cytochrome P450 → CYP4 family

| | | | | | |
|---------------|--|--|---|--|--|
| Nomenclature | CYP4A11 | CYP4A22 | CYP4B1 | CYP4F2 | CYP4F3 |
| HGNC, UniProt | CYP4A11 , Q02928 | CYP4A22 , Q5TCH4 | CYP4B1 , P13584 | CYP4F2 , P78329 | CYP4F3 , Q08477 |
| EC number | 1.14.14.80 | 1.14.14.80 | 1.14.14.1 | 1.14.14.78 1.14.14.79 1.14.14.94 | 1.14.14.78 1.14.14.79 1.14.14.94 |
| Inhibitors | – | – | – | 17-octadecynoic acid (p <i>K</i> _i 5.9) [537] | – |
| Comments | Converts lauric acid to 12-hydroxylauric acid. | Reported to be enzymatically inactive [191]. | – | Responsible for ω-hydroxylation of LTB ₄ , LXB ₄ [415], and tocopherols, including vitamin E [559] | Responsible for ω-hydroxylation of LTB ₄ , LXB ₄ [415], and polyunsaturated fatty acids [168, 241] |

| | | | | | | | |
|---------------|--|--|--|---|--|--|---|
| Nomenclature | CYP4F8 | CYP4F11 | CYP4F12 | CYP4F22 | CYP4V2 | CYP4X1 | CYP4Z1 |
| HGNC, UniProt | CYP4F8 , P98187 | CYP4F11 , Q9HBI6 | CYP4F12 , Q9HCS2 | CYP4F22 , Q6NT55 | CYP4V2 , Q6ZWL3 | CYP4X1 , Q8N118 | CYP4Z1 , Q86W10 |
| EC number | 1.14.14.1 | 1.14.14.1 1.14.14.78 | 1.14.14.1 | 1.14.14.- | 1.14.14.79 | 1.14.14.1 | 1.14.14.1 |
| Comments | Converts PGH ₂ to 19-hydroxyPGH ₂ [69] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [435]. | – | AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12 | Converts arachidonic acid to 16-HETE and 18-HETE [435]. | Converts myristic acid to 14-hydroxymyristic acid [429]. | Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [566]. | Converts lauric acid to 12-hydroxylauric acid. |

CYP5, CYP7 and CYP8 families

Enzymes → Cytochrome P450 → CYP5, CYP7 and CYP8 families

| Nomenclature | CYP5A1 | CYP7A1 | CYP7B1 | CYP8A1 | CYP8B1 |
|---------------------|--|--|---|--|---|
| Common abbreviation | Thromboxane synthase | – | – | 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 | 1.14.14.139 1.14.18.8 |
| Inhibitors | ozagrel (pIC ₅₀ 8.4) [259] | – | – | compound 7p (pIC ₅₀ >6) [166] | – |
| Comments | Inhibited by dazoxiben [489], camonagrel [222] and furegrelate sodium (U-63557A: PubChem CID 23663954) [213]. | Converts cholesterol to 7α-hydroxycholesterol [437]. | Converts dehydroepiandrosterone to 7α-DHEA [510]. | Converts PGH ₂ to PGI₂ [244]. Inhibited by tranilcypromine [221] | Converts 7α-hydroxycholest-4-en-3-one to 7-α,12α-dihydroxycholest-4-en-3-one (in rabbit) [278] in the biosynthesis of bile acids. |

CYP11, CYP17, CYP19, CYP20 and CYP21 families

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

| Nomenclature | CYP11A1 | CYP11B1 | CYP11B2 | CYP17A1 | CYP19A1 | CYP20A1 | CYP21A2 |
|----------------------|---|--|--|--|--|----------------------------------|---|
| Common abbreviation | – | – | Aldosterone synthase | – | Aromatase | – | – |
| 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 | 1.14.15.4 1.14.15.5 | 1.14.14.19 1.14.14.32 | 1.14.14.14 | 1.14.-.- | 1.14.14.16 |
| Inhibitors | mitotane [343, 353] | metyrapone (pIC ₅₀ 7.8) [679], mitotane | osilodrostat (pIC ₅₀ 9.7) [662] | abiraterone (pIC ₅₀ 7.1–8.4) [472, 477] | anastrozole (pIC ₅₀ 7.8) [424], aminoglutethimide [463] | – | (2S,4S)- ketoconazole (pIC ₅₀ 5.3) [512] – Rat |
| Selective inhibitors | – | – | – | galeterone (pIC ₅₀ 6.5) [238] | letrozole (pK _i 10.7) [401], exemestane (pIC ₅₀ 7.3) [105], testolactone (pK _i 4.5) [118] | – | – |
| Comments | Converts cholesterol to pregnenolone plus 4-methylpentanal. | Converts deoxycortisone and 11-deoxycortisol to cortisone and cortisol , respectively. Loss-of-function mutations are associated with familial adrenal hyperplasia and hypertension. Inhibited by metyrapone [629] | Converts corticosterone to aldosterone | Converts pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone , respectively. Converts 17α-hydroxypregnenolone and 17α-hydroxyprogesterone to dehydroepiandrosterone and androstenedione , respectively. Converts corticosterone to cortisol . | Converts androstenedione and testosterone to estrone and 17β-estradiol , respectively. Inhibited by anastrozole [475], and letrozole [46] | – | Converts progesterone and 17α-hydroxyprogesterone to deoxycortisone and 11-deoxycortisol , respectively |

CYP24, CYP26 and CYP27 families

Enzymes → Cytochrome P450 → CYP24, CYP26 and CYP27 families

| Nomenclature | CYP24A1 | CYP26A1 | CYP26B1 | CYP26C1 | CYP27A1 | CYP27B1 | CYP27C1 |
|----------------------|---|--|---|---|---|---|---|
| Common abbreviation | – | – | – | – | Sterol 27-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 | MK-24 (pIC ₅₀ 8.1) [298], compound 3a (pIC ₅₀ 8.1) [298], compound 4d (pIC ₅₀ 4.8) [3] | – | – | – | compound 4d (pIC ₅₀ 7.2) [3], MK-24 (pIC ₅₀ <6) [298] | MK-24 (pIC ₅₀ 6.3) [298] | – |
| Selective inhibitors | – | compound 5 (pIC ₅₀ 9.5) [212] | – | – | – | – | – |
| 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 [578]. | 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) [328]. |

CYP39, CYP46 and CYP51 families

Enzymes → Cytochrome P450 → CYP39, CYP46 and CYP51 families

| Nomenclature | CYP39A1 | CYP46A1 | CYP51A1 |
|---------------------|--|--|--|
| Common abbreviation | – | Cholesterol 24-hydroxylase | Lanosterol 14- α -demethylase |
| HGNC, UniProt | CYP39A1 , Q9NYL5 | CYP46A1 , Q9Y6A2 | CYP51A1 , Q16850 |
| EC number | 1.14.14.26 | 1.14.14.25 | – |
| Inhibitors | – | – | azalanstat (pK _i 9.1) [618] |
| Comments | Converts 24-hydroxycholesterol to 7 α ,24-dihydroxycholesterol [351]. | Converts cholesterol to 24(S)-hydroxycholesterol . | Converts lanosterol to 4,4-dimethylcholesta-8.14.24-trienol. |

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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 [148, 586] – Bovine | etoposide (pIC ₅₀ 7.3), teniposide [151] – Mouse |

Further reading on DNA topoisomerases

- Bansal S *et al.* (2017) Topoisomerases: Resistance versus Sensitivity, How Far We Can Go? *Med Res Rev* **37**: 404-438 [PMID:27687257]
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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*-arachidonylethanolamine, 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 [232]. [FABP5 \(Q01469\)](#) has been suggested to act as a canonical intracellular endocannabinoid transporter *in vivo* [99]. 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, [543]). A transacylation enzyme which forms *N*-acylphosphatidylethanolamines has been identified as a cytosolic enzyme, [PLA2G4E \(Q3MJ16\)](#) [443]. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism *via* cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [14, 179, 555].

N-Acylethanolamine turnover

Enzymes → Endocannabinoid turnover → N-Acylethanolamine turnover

| | | | | |
|------------------------|---|--|--|--|
| Nomenclature | N-Acylphosphatidylethanolamine-phospholipase D | Fatty acid amide hydrolase | Fatty acid amide hydrolase-2 | N-Acylethanolamine acid amidase |
| Common abbreviation | NAPE-PLD | FAAH | FAAH2 | NAAA |
| HGNC, UniProt | NAPEPLD , Q6IQ20 | FAAH , O00519 | FAAH2 , Q6GMR7 | NAAA , Q02083 |
| EC number | – | 3.5.1.99 : anandamide + H ₂ O ⇌ arachidonic acid + ethanolamine oleamide + H ₂ O ⇌ oleic acid + NH ₃ | 3.5.1.99 : anandamide + H ₂ O ⇌ arachidonic acid + ethanolamine oleamide + H ₂ O ⇌ oleic acid + NH ₃ | 3.5.1.- |
| Rank order of affinity | – | anandamide > oleamide > N-oleoylethanolamide > N-palmitoylethanolamine [634] | oleamide > N-oleoylethanolamide > anandamide > N-palmitoylethanolamine [634] | N-palmitoylethanolamine > MEA > SEA ≥ N-oleoylethanolamide > anandamide [606] |
| Selective inhibitors | – | ASP8477 (pIC ₅₀ 8.4) [628], JNJ1661010 (pIC ₅₀ 7.8) [308], PF750 (pIC ₅₀ 6.3–7.8) [7], OL135 (pIC ₅₀ 7.4) [634], MM-433593 (pIC ₅₀ 7), URB597 (pIC ₅₀ 6.3–7) [634], PF3845 (pIC ₅₀ 6.6) [8] | OL135 (pIC ₅₀ 7.9–8.4) [305, 634], URB597 (pIC ₅₀ 7.5–8.3) [305, 634], ASP8477 (pIC ₅₀ 7.2) [628] | F215 (pIC ₅₀ 8.1) [348, 349], ARN726 (Irreversible inhibition) (pIC ₅₀ 7.6) [499], S-OOPP (pIC ₅₀ 6.4) [557] – Rat, CCP (pIC ₅₀ 5.3) [601] |
| Comments | NAPE-PLD activity appears to be enhanced by polyamines in the physiological range [362], but fails to transphosphatidylate with alcohols [467] unlike phosphatidylcholine-specific phospholipase D. | – | The FAAH2 gene is found in many primate genomes, marsupials, and other distantly related vertebrates, but not a variety of lower placental mammals, including mouse and rat [634]. | – |

Comments: Routes for N-acylethanolamine biosynthesis other than through NAPE-PLD activity have been identified [602].

2-Acylglycerol ester turnover

Enzymes → Endocannabinoid turnover → 2-Acylglycerol ester turnover

Overview: ABHD12 is a 398-aa protein, with serine hydrolase activity. It has a molecular weight of 45 kDa. A single TM is predicted at 75-95, with an extracellular catalytic domain. ABHD12 is a monoacylglycerol hydrolase [432], but may also regulate lysophosphatidylserine levels [300]. Loss-of-function mutations in ABHD12 are associated with a disorder known as PHARC (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataracts) [172].

| 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 | – |
| 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 [204] | 1-arachidonoylglycerol > 2-arachidonoylglycerol > 1-oleoylglycerol > 2-oleoyl glycerol [432] | – |
| Inhibitors | LEI105 (pIC ₅₀ 8.5) [30], DH376 (pIC ₅₀ 8.2) [441], DO34 (pIC ₅₀ 8.2) [441], KT-109 (pIC ₅₀ 5.6) [268] | DH376 (pIC ₅₀ 8.6) [441], DO34 (pIC ₅₀ 8.1) [441], LEI105 (pIC ₅₀ 8.1) [30], KT-109 (pIC ₅₀ 7.1) [268] | MJN110 (pIC ₅₀ 8) [436] | – | – |
| Selective inhibitors | – | – | JJKK 048 (pIC ₅₀ 9.3) [1], KML29 (pIC ₅₀ 8.5) [88], JZL184 (pIC ₅₀ 8.1) [367] | WWL70 (pIC ₅₀ 7.2) [346], WWL123 (pIC ₅₀ 6.4) [25] | DO264 (pIC ₅₀ 8) [442] |
| Comments | – | – | – | WWL70 has also been suggested to have activity at oxidative metabolic pathways independent of ABHD6 [582]. | – |

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 [634] and a limited range of inhibitors have been assessed at this enzyme activity. 2-arachidonoylglycerol has been

reported to be hydrolysed by multiple enzyme activities from neural preparations [31], including *ABHD2* (P08910) [412] and carboxylesterase 1 (*CEST1*, P23141 [656]). *ABHD2* (P08910) has also been described as a triacylglycerol lipase and ester hydrolase [384], while *ABHD12* (Q8N2K0) is also able to hydrolyse lysophos-

phatidylserine [598]. *ABHD12* (Q8N2K0) has been described to be inhibited selectively by pentacyclic triterpenoids, such as oleanolic acid [460].

Further reading on Endocannabinoid turnover

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Eicosanoid turnover

Enzymes → Eicosanoid turnover

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

jugation with **coenzyme A** and subsequently glycerol derivatives. Oxidative metabolism of arachidonic acid is conducted through three major enzymatic routes: cyclooxygenases; lipoxygenases and cytochrome P450-like epoxygenases, particularly **CYP2J2**. Iso-prostanates 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.

| | COX-1 | COX-2 |
|----------------------|---|--|
| 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 |
| Selective activators | – | SC-236 (Inhibition) (pIC ₅₀ 8) [464] |
| Inhibitors | bromfenac (pIC ₅₀ 8.1) [22], diclofenac (pIC ₅₀ 7.9) [697], meclofenamic acid (pIC ₅₀ 7.3) [299], flurbiprofen (pIC ₅₀ 7.1) [627], fenoprofen (pIC ₅₀ 6.8) [22], ketoprofen (pIC ₅₀ 6.5) [70], suprofen (pIC ₅₀ 6.2) [70] | benzquinamide (pIC ₅₀ 8.3) [22], flurbiprofen (pIC ₅₀ 8) [36], meclofenamic acid (pIC ₅₀ 7.4) [299], carprofen (pIC ₅₀ 7) [257], ketorolac (pIC ₅₀ 6.9) [615], nimesulide (pIC ₅₀ 6.2) [453], ketoprofen (pIC ₅₀ 6.2) [70] |
| Selective inhibitors | ketorolac (pIC ₅₀ 9.7) [627], FK-881 (pIC ₅₀ 8.3) [275], SC-560 (pIC ₅₀ 8.1) [551], FR122047 (pIC ₅₀ 7.5) [440] | celecoxib (pIC ₅₀ 8.7) [50], valdecoxib (pIC ₅₀ 8.3) [581], diclofenac (pIC ₅₀ 7.7) [54], rofecoxib (pIC ₅₀ 6.1–6.5) [627], lumiracoxib (pK _i 6.5) [55], meloxicam (pIC ₅₀ 6.3) [340], etoricoxib (pIC ₅₀ 6) [503] |

Prostaglandin synthases

Enzymes → Eicosanoid turnover → Prostaglandin synthases

Overview: Subsequent to the formation of PGH_2 , the cytochrome P450 activities thromboxane synthase (CYP5A1, *TBXAS1*, P24557, EC 5.3.99.5) and prostacyclin synthase (CYP8A1, *PTGIS*, Q16647, EC 5.3.99.4) generate thromboxane A_2 and prostacyclin (PGI_2), respectively. Additionally, multiple en-

zyme activities are able to generate prostaglandin E_2 (PGE_2), prostaglandin D_2 (PGD_2) and prostaglandin $\text{F}_{2\alpha}$ ($\text{PGF}_{2\alpha}$). PGD_2 can be metabolised to $9\alpha,11\beta$ -prostacyclin $\text{F}_{2\alpha}$ through the multi-functional enzyme activity of AKR1C3. PGE_2 can be metabolised to $9\alpha,11\beta$ -prostaglandin $\text{F}_{2\alpha}$ through the 9-ketoreductase activity

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

| Nomenclature | CYP5A1 | CYP8A1 | mPGES1 | mPGES2 | cPGES | L-PGDS |
|----------------------|---|---|--|---|--|---|
| Common abbreviation | Thromboxane 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 | <i>PTGDS</i> , P41222 |
| EC number | 5.3.99.5: $\text{PGH}_2 = \text{thromboxane A}_2$ | 5.3.99.4 | 5.3.99.3: $\text{PGH}_2 = \text{PGE}_2$ | 5.3.99.3: $\text{PGH}_2 = \text{PGE}_2$ | 5.3.99.3: $\text{PGH}_2 = \text{PGE}_2$ | 5.3.99.2: $\text{PGH}_2 = \text{PGD}_2$ |
| Cofactors | – | – | glutathione | dihydrolipoic acid | – | – |
| Inhibitors | ozagrel (pIC_{50} 8.4) [259] | compound 7p ($\text{pIC}_{50} > 6$) [166] | compound 44 (pIC_{50} 9) [207] | compound 30 ($\text{pIC}_{50} < 6$) [502] | – | – |
| Selective inhibitors | – | – | compound 39 (pIC_{50} 8.4) [541] | – | – | AT-56 (pK_i 4.1) [277] |
| Comments | Inhibited by dazoxiben [489], camonagrel [222] and furegrelate sodium (U-63557A: PubChem CID 23663954) [213]. | Converts PGH_2 to PGI_2 [244]. Inhibited by tranilcypromine [221] | – | – | Phosphorylated and activated by casein kinase 2 (CK2) [317]. Appears to regulate steroid hormone function by interaction with dimeric hsp90 [85, 292]. | – |

| | | | | |
|---------------|---|--|--|---|
| Nomenclature | H-PGDS | AKR1C3 | CBR1 | HPGD |
| HGNC, UniProt | HPGDS , O60760 | AKR1C3 , P42330 | CBR1 , P16152 | HPGD , P15428 |
| EC number | 5.3.99.2: PGH ₂ = PGD ₂ | 1.3.1.20 1.1.1.188: PGD ₂ + NADP ⁺ = PGF _{2α} + NADPH + H ⁺ 1.1.1.64 1.1.1.239 1.1.1.213 | 1.1.1.184 1.1.1.189: PGE ₂ + NADP ⁺ = PGF _{2α} + NADPH + H ⁺ 1.1.1.197 | 1.1.1.141 15-hydroxyprostaglandins => 15-ketoprostaglandins LXA ₄ => 15-keto-lipoxin A ₄ |
| Cofactors | – | NADP ⁺ | NADP ⁺ | – |
| Inhibitors | HQL-79 (pIC ₅₀ 5.3–5.5) [19] | tolfenamic acid (pK _i 8.1) [481] flufenamic acid , indomethacin , flavonoids such as 2'-Hydroxyflavanone (pIC ₅₀ 6.5) [398 , 550] | wedelolactone (pIC ₅₀ 5.4) [681] | compound 3 (pIC ₅₀ 8.1) [653] |
| Comments | – | AKR1C3 also exhibits an hydroxysteroid dehydrogenase activity. | – | – |

Comments: [YS121](#) has been reported to inhibit mPGES1 and 5-LOX with a pIC₅₀ value of 5.5 [[320](#)].

Lipoxygenases

Enzymes → Eicosanoid turnover → Lipoxygenases

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

| Nomenclature | 5-LOX | 12R-LOX | 12S-LOX | 15-LOX-1 | 15-LOX-2 | E-LOX |
|-----------------------|---|---|---|--|--|--|
| HGNC, UniProt | ALOX5 , P09917 | ALOX12B , O75342 | ALOX12 , P18054 | ALOX15 , P16050 | ALOX15B , O15296 | ALOXE3 , Q9BYJ1 |
| EC number | 1.13.11.34: arachidonic acid + O ₂ = LTA ₄ + H ₂ O | 1.13.11.31 arachidonic acid + O ₂ => 12R-HPETE | 1.13.11.31 arachidonic acid + O ₂ => 12S-HPETE | 1.13.11.33: arachidonic acid + O ₂ = 15S-HPETE linoleic acid + O ₂ => 13S-HPODE | 1.13.11.33: arachidonic acid + O ₂ = 15S-HPETE | 1.13.11.- |
| Substrates | – | methyl arachidonate | – | – | – | – |
| Endogenous substrates | arachidonic acid | – | – | – | – | 12R-HPETE |
| Endogenous activators | 5-LOX activating protein (ALOX5AP, P20292) | – | – | – | – | – |
| Endogenous inhibitors | Protein kinase A-mediated phosphorylation [379] | – | – | – | – | – |
| Inhibitors | – | – | – | ML351 (pIC ₅₀ 6.7) [485] | compound 21n (pIC ₅₀ 7.3) [636] | – |
| Selective inhibitors | CJ13610 (pIC ₅₀ 7.2) [169], PF-04191834 (pIC ₅₀ 6.6) [396], zileuton (pIC ₅₀ 6.4) [81] | – | ML355 (pIC ₅₀ 6.5) [374] | compound 34 (pK _i > 8) [486] | – | – |
| Comments | FLAP activity can be inhibited by MK-886 [147] and BAY-X1005 [245] leading to a selective inhibition of 5-LOX activity | – | – | – | Inhibited by MLS000536924 (pK _i 5.6) [286]. | E-LOX metabolises the product from the 12R-lipoxygenase (12R-HPETE) to a specific epoxyalcohol compound [669]. |

Comments: An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 [[190](#)]. 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 [[514](#)].

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 [491]. 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 [444].

| | | | | | |
|---------------|--|--|---|---|--------------------------------------|
| 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: (5-L-glutamyl)-peptide + an amino acid = a peptide + a 5-L-glutamyl amino acid LTC ₄ + H ₂ O => LTD ₄ + L-glutamate | 3.4.13.19: LTD ₄ + H ₂ O = LTE ₄ + glycine | 3.4.13.19: LTD ₄ + H ₂ O = LTE ₄ + glycine | 3.3.2.6 |
| Inhibitors | example 36 (pIC ₅₀ 8.1) [508], compound 39 (pIC ₅₀ <5.5) [541] | GGsTop (pK _i 3.8) [235] | cilastatin (pK _i 6) [215] | – | bestatin (pK _i 5.4) [450] |

Comments: LTA4H is a member of a family of arginyl aminopeptidases (ENSM0025000001675), which also includes aminopep-

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

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

Further reading on Eicosanoid turnover

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GABA turnover

Enzymes → GABA turnover

Overview: The inhibitory neurotransmitter γ -aminobutyrate (GABA, 4-aminobutyrate) is generated in neurones by glutamic acid decarboxylase. GAD1 and GAD2 are differentially expressed during development, where GAD2 is thought to 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 [160] where GABA is principally accumulated in vesicles through the action of the vesicular inhibitory amino acid transporter *SLC32A1*. The role of γ -aminobutyraldehyde dehydrogenase (ALDH9A1) in neurotransmitter GABA synthesis is less clear. Following release from neurons, GABA may interact with either GABA_A or GABA_B receptors and may be accumu-

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

| | | |
|-----------------------|--|---|
| Nomenclature | Glutamic acid decarboxylase 1 | Glutamic acid decarboxylase 2 |
| Common abbreviation | GAD1 | GAD2 |
| HGNC, UniProt | <i>GAD1</i> , Q99259 | <i>GAD2</i> , 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 [65]. 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 | <i>ALDH9A1</i> , P49189 | <i>ABAT</i> , P80404 | <i>ALDH5A1</i> , P51649 |
| EC number | 1.2.1.19: 4-aminobutanal + NAD + H ₂ O = GABA + NADH + H ⁺ 1.2.1.47: 4-trimethylammoniumbutanal + NAD + H ₂ O = 4-trimethylammoniumbutanoate + NADPH + 2H ⁺ 1.2.1.3: an aldehyde + H ₂ O + NAD = a carboxylate + 2H ⁺ + NADH | 2.6.1.19: GABA + α -ketoglutaric acid = L-glutamic acid + 4-oxobutanoate 2.6.1.22: (S)-3-amino-2-methylpropanoate + α -ketoglutaric acid = 2-methyl-3-oxopropanoate + L-glutamic acid | 1.2.1.24: 4-oxobutanoate + NAD + H ₂ O = succinic acid + NADH + 2H ⁺ 4-hydroxy-trans-2-nonenal + NAD + H ₂ O = 4-hydroxy-trans-2-nonenate + NADH + 2H ⁺ |
| Cofactors | NAD | pyridoxal 5-phosphate | NAD [536] |
| Inhibitors | – | vigabatrin (Irreversible inhibition) (p <i>K</i> _i 3.1) [356, 542] | 4-acryloylphenol (p <i>C</i> ₅₀ 6.5) [587] |

Further reading on GABA turnover

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Glycerophospholipid turnover

Enzymes → Glycerophospholipid turnover

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

Phosphoinositide-specific phospholipase C

Enzymes → Glycerophospholipid turnover → Phosphoinositide-specific phospholipase C

Overview: Phosphoinositide-specific phospholipase C (PLC, EC 3.1.4.11), catalyses the hydrolysis of 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-ε1 may represent a point of convergence of signalling via both G protein-coupled and catalytic receptors. Ca²⁺ ions are required for catalytic activity of PLC isoforms and have been suggested to be

the major physiological form of regulation of PLC-δ activity. PLC has been suggested to be activated non-selectively by the small molecule m3M3FBS [29], although this mechanism of action has been questioned [330]. The aminosteroid U73122 has been described as an inhibitor of phosphoinositide-specific PLC [552], although its selectivity among the isoforms is untested and it has been reported to occupy the H1 histamine receptor [272].

| | | | | |
|-----------------------|---|---|-------------------------|---------------|
| Nomenclature | PLCβ1 | PLCβ2 | PLCβ3 | PLCβ4 |
| 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 | | | |
| Endogenous activators | Gαq, Gα11, Gβγ [255, 459, 554] | Gα16, Gβγ, Rac2 (RAC2, P15153) [75, 273, 274, 341, 459] | Gαq, Gβγ [80, 341, 459] | Gαq [288] |

| | | | | | |
|-----------------------|---|--|--|--|--|
| 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- <i>myo</i> -inositol 4,5-bisphosphate + H ₂ O = 1D- <i>myo</i> -inositol 1,4,5-trisphosphate + diacylglycerol | | | | |
| Endogenous activators | PIP ₃ [28] | PIP ₃ , Rac1 (RAC1 , P63000), Rac2 (RAC2 , P15153), Rac3 (RAC3 , P60763) [28, 470, 619] | Transglutaminase II, p122-RhoGAP {Rat}, spermine, G $\beta\gamma$ [229, 262, 425, 459] | – | – |
| Endogenous inhibitors | – | – | Sphingomyelin [462] | – | – |
| Inhibitors | – | CCT129957 (pIC ₅₀ 5.5) [498] | – | – | – |

| | | | | |
|-----------------------|---|--|--|--|
| Nomenclature | PLC ϵ 1 | PLC ζ 1 | PLC η 1 | PLC η 2 |
| HGNC, UniProt | PLCE1 , Q9P212 | PLCZ1 , Q86YWO | PLCH1 , Q4KWH8 | PLCH2 , O75038 |
| EC number | 3.1.4.11: 1-phosphatidyl-1D- <i>myo</i> -inositol 4,5-bisphosphate + H ₂ O = 1D- <i>myo</i> -inositol 1,4,5-trisphosphate + diacylglycerol | | | |
| Endogenous activators | Ras, rho [558, 645] | – | – | G $\beta\gamma$ [677] |

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 [407].

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Phospholipase A₂

Enzymes → Glycerophospholipid turnover → Phospholipase A₂

Overview: Phospholipase A₂ (PLA₂, EC 3.1.1.4) cleaves the *sn*-2 fatty acid of phospholipids, primarily phosphatidylcholine, to generate **lysophosphatidylcholine** and **arachidonic acid**. Most commonly-used inhibitors (*e.g.* **bromo-enol lactone**, **arachidonyl trifluoromethyl ketone** or

methyl arachidonyl fluorophosphonate) are either non-selective within the family of phospholipase A₂ enzymes or have activity against other eicosanoid-metabolising enzymes.

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

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

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

| | | | | | | |
|---------------|---|-----------------------|--|--|--|----------------------|
| Nomenclature | sPLA ₂ -1B | sPLA ₂ -2A | sPLA ₂ -2D | sPLA ₂ -2E | sPLA ₂ -2F | sPLA ₂ -3 |
| HGNC, UniProt | PLA2G1B, P04054 | PLA2G2A, P14555 | PLA2G2D, Q9UNK4 | PLA2G2E, Q9NZK7 | PLA2G2F, Q9BZM2 | PLA2G3, Q9NZ20 |
| 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) [231] | – | compound 12e (pIC ₅₀ 8.1) [452] | compound 12e (pIC ₅₀ 8.1) [452] | compound 12e (pIC ₅₀ 7.3) [452] | – |
| Comments | – | – | – | – | – | – |

| | | | | | | |
|---------------|---|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Nomenclature | cPLA ₂ -4A | cPLA ₂ -4B | cPLA ₂ -4C | cPLA ₂ -4D | cPLA ₂ -4E | cPLA ₂ -4F |
| HGNC, UniProt | PLA2G4A, P47712 | PLA2G4B, P0C869 | PLA2G4C, Q9UP65 | PLA2G4D, Q86XP0 | PLA2G4E, Q3MJ16 | PLA2G4F, Q68DD2 |
| EC number | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 |
| Inhibitors | compound 57 (pIC ₅₀ 8.4) [375] | – | – | – | – | – |
| Comments | cPLA ₂ -4A also expresses lysophospholipase (EC 3.1.1.5) activity [539]. | – | – | – | – | – |

| | | | | | | |
|----------------------|--|-----------------------|--|--|------------------------|--|
| Nomenclature | PLA ₂ -G5 | iPLA ₂ -G6 | PLA ₂ -G7 | sPLA ₂ -10 | sPLA ₂ -12A | platelet activating factor acetylhydrolase 2 |
| HGNC, UniProt | PLA2G5, P39877 | PLA2G6, O60733 | PLA2G7, Q13093 | PLA2G10, O15496 | PLA2G12A, Q9BZM1 | PAFAH2, Q99487 |
| EC number | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.47 |
| Inhibitors | compound 12e (pIC ₅₀ 7.5) [452] | – | darapladib (pIC ₅₀ 10) [51] | compound 12e (pIC ₅₀ 7.7) [452] | – | – |
| Selective inhibitors | – | – | rilapladib (Competitive) (pIC ₅₀ 9.6) [640] | – | – | – |
| 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 [513]. 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 [16]. 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 [38].

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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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 [490].

| | | |
|-----------------------|---|--|
| Nomenclature | PLD1 | PLD2 |
| HGNC, UniProt | PLD1 , Q13393 | PLD2 , O14939 |
| EC number | 3.1.4.4 | 3.1.4.4 A phosphatidylcholine + H ₂ O ⇌ choline + a phosphatidate |
| Endogenous activators | ADP-ribosylation factor 1 (ARF1 , P84077), PIP₂ , RhoA, PKC evoked phosphorylation, RalA [233 , 378] | ADP-ribosylation factor 1 (ARF1 , P84077), PIP₂ [369], oleic acid [519] |
| Endogenous inhibitors | Gβγ [478] | Gβγ [478] |
| Inhibitors | FIPI (pIC ₅₀ 8) [530] | – |
| Selective inhibitors | compound 69 (pIC ₅₀ 7.3) [530] | VU0364739 (pIC ₅₀ 7.7) [339] |

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

acterized, which appears to have a role in the generation of [endocannabinoids](#)/endovanilloids, including [anandamide](#) [[448](#)]. This enzyme activity appears to be enhanced by polyamines in the physiological range [[362](#)] and fails to transphosphatidylate with alcohols [[467](#)].

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

phosphatase 4, Phosphatidylcholine-hydrolyzing phospholipase, D4C14orf175 UNQ2488/PRO5775) and PLD5 ([PLD5](#), [Q8N7P1](#)). PLD3 has been reported to be involved in myogenesis [[451](#)]. PLD4 is described not to have phospholipase D catalytic activity [[665](#)], but has been associated with inflammatory disorders [[447](#), [574](#), [593](#)]. 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](#)]
Frohman MA. (2015) The phospholipase D superfamily as therapeutic targets. *Trends Pharmacol. Sci.* **36**: 137-44 [[PMID:25661257](#)]

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

Lipid phosphate phosphatases

Enzymes → Glycerophospholipid turnover → Lipid phosphate phosphatases

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

| | | | | | | | |
|---------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|--|
| Nomenclature | Lipin1 | Lipin2 | Lipin3 | PPA2A | PPA2B | PPA3A | phosphatase and tensin homolog |
| Common abbreviation | – | – | – | – | – | – | PTEN |
| HGNC, UniProt | LPIN1, Q14693 | LPIN2, Q92539 | LPIN3, Q9BQK8 | PLPP1, O14494 | PLPP3, O14495 | PLPP2, O43688 | PTEN, P60484 |
| EC number | 3.1.3.4 | 3.1.3.4 | 3.1.3.4 | 3.1.3.4 | 3.1.3.4 | 3.1.3.4 | 3.1.3.67 3.1.3.48 3.1.3.16 |
| Substrates | – | phosphatidic acid | – | – | phosphatidic acid | – | phosphatidylinositol (3,4,5)-trisphosphate |

Further reading on Lipid phosphate phosphatases

- Knafo S and Esteban JA. (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.* (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

C2domains.

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

Phosphatidylinositol 4-kinases

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

1-phosphatidylinositol 4-kinase family

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

| | | |
|---------------------------------|--|--|
| Nomenclature | phosphatidylinositol 4-kinase alpha | phosphatidylinositol 4-kinase beta |
| Common abbreviation | PI4KIII α /PIK4CA | PI4KIII β /PIK4CB |
| HGNC, UniProt | PI4KA , P42356 | PI4KB , Q9UBF8 |
| EC number | 2.7.1.67 | 2.7.1.67 |
| Endogenous activation | – | PKD-mediated phosphorylation [247] |
| Sub/family-selective inhibitors | wortmannin (pIC ₅₀ 6.7–6.8) [203 , 408] | wortmannin (pIC ₅₀ 6.7–6.8) [203 , 408] |
| Selective inhibitors | – | PIK-93 (pIC ₅₀ 7.7) [34 , 316] |

Phosphatidylinositol-4-phosphate 3-kinase family

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

| | | | |
|---------------------|--|---|--|
| Nomenclature | phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 alpha | phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 beta | phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 gamma |
| Common abbreviation | C2 α /PIK3C2A | C2 β /PIK3C2B | C2 γ /PIK3C2G |
| HGNC, UniProt | 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) [363] | PI-103 (pIC ₅₀ 8) [248] | – |

Phosphatidylinositol 3-kinase family

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

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

Phosphatidylinositol-4,5-bisphosphate 3-kinase family

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

Overview: PI3K activation is one of the most important signal transduction pathways used to transmit signals from cell-surface receptors to regulate intracellular processes (cell growth, survival, proliferation and movement). PI3K catalytic (and regulatory) subunits play vital roles in normal cell function and in disease. Progress made in developing PI3K-targeted agents as potential therapeutics for treating cancer and other diseases is reviewed by Fruman *et al.* (2017) [182].

| | | |
|---------------------------------|--|---|
| Nomenclature | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta |
| Common abbreviation | PI3K α | PI3K β |
| HGNC, UniProt | PIK3CA , P42336 | PIK3CB , P42338 |
| EC number | 2.7.1.153 2.7.11.1 | 2.7.1.153 |
| Inhibitors | PIK-75 (pIC ₅₀ 9.5) [248], gedatolisib (pIC ₅₀ 9.4) [612], PF-04691502 (pK _i 9.2) [360], PI-103 (pIC ₅₀ 8.7) [497], BGT-226 (pIC ₅₀ 8.4) [392], KU-0060648 (pIC ₅₀ 8.4) [76], dactolisib (pIC ₅₀ 8.4) [388], apitolisib (pIC ₅₀ 8.3) [573], PIK-75 (pIC ₅₀ 8.2) [316] | KU-0060648 (pIC ₅₀ 9.3) [76], PI-103 (pIC ₅₀ 8.5) [497], AZD6482 (pIC ₅₀ 8) [438], ZSTK474 (pIC ₅₀ 7.4–7.8) [651, 658], apitolisib (pIC ₅₀ 7.6) [573], BGT-226 (pIC ₅₀ 7.2) [392] |
| Sub/family-selective inhibitors | pictilisib (pIC ₅₀ 8.5) [174] | pictilisib (pIC ₅₀ 7.5) [174] |
| Selective inhibitors | GSK1059615 (pIC ₅₀ 8.7) [315] | – |

| | | |
|---------------------------------|---|--|
| Nomenclature | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta |
| Common abbreviation | PI3K γ | PI3K δ |
| HGNC, UniProt | PIK3CG , P48736 | PIK3CD , O00329 |
| EC number | 2.7.1.153 | 2.7.1.153 |
| Inhibitors | dactolisib (pIC ₅₀ 8.3) [388], apitolisib (pIC ₅₀ 7.8) [573], PI-103 (pIC ₅₀ 7.8) [497], BGT-226 (pIC ₅₀ 7.4) [392], ZSTK474 (pIC ₅₀ 7.3–7.3) [651, 658], TG-100-115 (pIC ₅₀ 7.1) [456], alpelisib (pIC ₅₀ 6.6) [187], KU-0060648 (pIC ₅₀ 6.2) [76] | KU-0060648 (pIC ₅₀ > 10) [76], idelalisib (<i>in vitro</i> activity against recombinant enzyme) (pIC ₅₀ 8.6) [336], PI-103 (pIC ₅₀ 8.5) [497], ZSTK474 (pIC ₅₀ 8.2–8.3) [651, 658], apitolisib (pIC ₅₀ 8.2) [573], dactolisib (pIC ₅₀ 8.1) [388], alpelisib (pIC ₅₀ 6.5) [187] |
| Sub/family-selective inhibitors | pictilisib (pIC ₅₀ 7.1) [174] | pictilisib (pIC ₅₀ 8.5) [174] |
| Selective inhibitors | CZC 24832 (pIC ₅₀ 7.6) [42] | – |

1-phosphatidylinositol-3-phosphate 5-kinase family

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

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

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

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

Overview: Type I PIP kinases are required for the production of the second messenger phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P₂) by phosphorylating PtdIns(4)P [487]. This enzyme family is also known as type I PIP(5)Ks.

| | | |
|---------------------|--|--|
| Nomenclature | phosphatidylinositol-4-phosphate 5-kinase type 1 alpha | phosphatidylinositol-4-phosphate 5-kinase type 1 gamma |
| Common abbreviation | PIP5K1A | PIP5K1C |
| HGNC, UniProt | <i>PIP5K1A</i> , Q99755 | <i>PIP5K1C</i> , O60331 |
| EC number | 2.7.1.68 | 2.7.1.68 |
| Inhibitors | ISA-2011B [532] | – |

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

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

Overview: Type II PIP kinases are essential for the production of the second messenger phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P₂) by phosphorylating PtdIns(5)P [487]. This enzyme family is also known as type II PIP(5)Ks.

| | | | |
|---------------------|--|---|--|
| Nomenclature | phosphatidylinositol-5-phosphate 4-kinase type 2 alpha | phosphatidylinositol-5-phosphate 4-kinase type 2 beta | phosphatidylinositol-5-phosphate 4-kinase type 2 gamma |
| Common abbreviation | PIP4K2A | PIP4K2B | PIP4K2C |
| HGNC, UniProt | <i>PIP4K2A</i> , P48426 | <i>PIP4K2B</i> , P78356 | <i>PIP4K2C</i> , Q8TBX8 |
| EC number | 2.7.1.149 | 2.7.1.149 | 2.7.1.149 |
| | ATP + 1-phosphatidyl-1D- <i>myo</i> -inositol 5-phosphate <=> ADP + 1-phosphatidyl-1D- <i>myo</i> -inositol 4,5-bisphosphate | | |

Sphingosine kinase

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Sphingosine 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 phos-

phorylation. Intracellular targets of nuclear S1P include the catalytic subunit of telomerase (TERT) 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 therapeutic potential in many diseases.

| | | |
|----------------------|---|--|
| 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 = sphingosine 1-phosphate + ADP | 2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP dihydrosphingosine + ATP = sphingosine 1-phosphate + ADP |
| Cofactors | Mg ²⁺ [536] | Mg ²⁺ |
| Inhibitors | SKI II (pK _i 4.8) [181], MP-A08 (pIC ₅₀ 4.6) [474] | MP-A08 (pK _i 5.2) [474], SKI II (pK _i 5.1) [196] |
| Selective inhibitors | PF-543 (pK _i 8.4) [527] | SLC4101431 (pK _i 7.1) [100], compound 27d (pIC ₅₀ 6.8) [526], opaganib (pK _i 5) [181], ROME (pK _i 4.8) [354] |
| Comments | SK1 inhibitors induce its proteasomal degradation [373, 404]. SK1 crystal structures confirm that it is dimeric [5]; there is no crystal structure available for SK2. | There is no crystal structure available for SK2. |

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*) [404, 610]) and induces proteasomal degradation of SK1 [404]. ABC294640 is in clinical trials for advanced cholangiocarcinoma, advanced hepatocellular carcinoma and refractory/relapsed multiple myeloma (to view ClinicalTrials.gov list click [here](#)).

Further reading on Sphingosine kinase

- Adams DR *et al.* (2016) Sphingosine Kinases: Emerging Structure-Function Insights. *Trends Biochem. Sci.* **41**: 395–409 [PMID:27021309]
- Lynch KR *et al.* (2016) Sphingosine kinase inhibitors: a review of patent literature (2006–2015). *Expert Opin Ther Pat* **26**: 1409–1416 [PMID:27539678]
- Pitman MR *et al.* (2016) Recent advances in the development of sphingosine kinase inhibitors. *Cell. Signal.* **28**: 1349–63 [PMID:27297359]
- Pulkoski-Gross MJ *et al.* (2018) An intrinsic lipid-binding interface controls sphingosine kinase 1 function. *J. Lipid Res.* **59**: 462–474 [PMID:29326159]
- Pyne NJ *et al.* (2017) Sphingosine Kinase 2 in Autoimmune/Inflammatory Disease and the Development of Sphingosine Kinase 2 Inhibitors. *Trends Pharmacol. Sci.* **38**: 581–591 [PMID:28606480]
- Pyne S *et al.* (2018) Sphingosine Kinases as Druggable Targets. *Handb Exp Pharmacol* [PMID:29460151]

| | | | | | | | |
|---------------------------------|--|---|---|--|---|--|--|
| Nomenclature | phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit gamma | phosphatidylinositol 4-kinase type 2 beta | phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit delta | 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 | phosphatidylinositol 3-kinase catalytic subunit type 3 |
| Common abbreviation | PI3K γ | PI4KII β /PI4K2B | PI3K δ | C2 α /PIK3C2A | C2 β /PIK3C2B | C2 γ /PIK3C2G | VPS34 |
| HGNC, UniProt | PIK3CC , P48736 | PI4K2B , Q8TCG2 | PIK3CD , O00329 | PIK3C2A , O00443 | PIK3C2B , O00750 | PIK3C2G , O75747 | PIK3C3 , Q8NEB9 |
| EC number | 2.7.1.153 | 2.7.1.67 | 2.7.1.153 | 2.7.1.154 | 2.7.1.154 | 2.7.1.154 | 2.7.1.137 |
| Inhibitors | dactolisib (pIC ₅₀ 8.3) [388], apitolisib (pIC ₅₀ 7.8) [573], PI-103 (pIC ₅₀ 7.8) [497], BGT-226 (pIC ₅₀ 7.4) [392], ZSTK474 (pIC ₅₀ 7.3–7.3) [651 , 658], TG-100-115 (pIC ₅₀ 7.1) [456], alpelisib (pIC ₅₀ 6.6) [187], KU-0060648 (pIC ₅₀ 6.2) [76] | – | KU-0060648 (pIC ₅₀ > 10) [76], idelalisib (<i>in vitro</i> activity against recombinant enzyme) (pIC ₅₀ 8.6) [336], PI-103 (pIC ₅₀ 8.5) [497], ZSTK474 (pIC ₅₀ 8.2–8.3) [651 , 658], apitolisib (pIC ₅₀ 8.2) [573], dactolisib (pIC ₅₀ 8.1) [388], alpelisib (pIC ₅₀ 6.5) [187] | torin 2 (pIC ₅₀ 7.6) [363] | PI-103 (pIC ₅₀ 8) [248] | – | – |
| Sub/family-selective inhibitors | pictilisib (pIC ₅₀ 7.1) [174] | adenosine (pIC ₅₀ 4.5–5) [577] | pictilisib (pIC ₅₀ 8.5) [174] | – | – | – | – |
| Selective inhibitors | CZC 24832 (pIC ₅₀ 7.6) [42] | – | – | – | – | – | – |

Comments: [Wortmannin](#) also inhibits type III phosphatidylinositol 4-kinases and polo-like kinase [[364](#)]. PIK93 also inhibits PI 3-kinases [[316](#)]. Adenosine activates [adenosine receptors](#).

Further reading on Phosphatidylinositol kinases

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](#)]

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

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 | 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 | PIP5K1A | PIP5K1B | PIP5K1C | PIP4K2A | PIP4K2B | PIP4K2C |
| HGNC, UniProt | PIP5K1A , Q99755 | PIP5K1B , O14986 | PIP5K1C , O60331 | PIP4K2A , P48426 | PIP4K2B , P78356 | PIP4K2C , Q8TBX8 |
| EC number | 2.7.1.68 | 2.7.1.68 | 2.7.1.68 | 2.7.1.149 ATP + 1-phosphatidyl-1D- <i>myo</i> -inositol 5-phosphate <=> ADP + 1-phosphatidyl-1D- <i>myo</i> -inositol 4,5-bisphosphate | 2.7.1.149 | 2.7.1.149 |
| Inhibitors | ISA-2011B [532] | – | – | – | – | – |

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) <=> biliverdin + Fe(2+) + CO + 3 [oxidized NADPH-hemoprotein reductase] + 3 H(2)O | 1.14.14.18 Protoheme + 3 [reduced NADPH-hemoprotein reductase] + 3 O(2) <=> biliverdin + Fe(2+) + CO + 3 [oxidized NADPH-hemoprotein reductase] + 3 H(2)O |
| Inhibitors | – | compound 1 (pIC ₅₀ 3.5) [616] – 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 [[250](#)]. The chemical [tin protoporphyrin IX](#) acts as a haem oxygenase inhibitor in rat liver with an IC₅₀ value of 11 nM [[152](#)].

Further reading on Haem oxygenase

- Magierowska K *et al.* (2018) Emerging role of carbon monoxide in regulation of cellular pathways and in the maintenance of gastric mucosal integrity. *Pharmacol Res* **129**: 56-64 [[PMID:29360501](#)]
- Rochette L *et al.* (2018) Redox Functions of Heme Oxygenase-1 and Biliverdin Reductase in Diabetes Trends. *Endocrinol Metab.* **29**: 74-85 [[PMID:29249571](#)]
- Salerno L *et al.* (2017) Heme oxygenase-1: A new druggable target in the management of chronic and acute myeloid leukemia. *Eur J Med Chem.* **142**: 163-178 [[PMID:28756878](#)]
- Sebastian VP *et al.* (2018) Heme Oxygenase-1 as a Modulator of Intestinal Inflammation Development and Progression. *Front Immunol.* **9**: 1956 [[PMID:30258436](#)]
- Tomczyk M *et al.* (2019) Modulation of the monocyte/macrophage system in heart failure by targeting heme oxygenase-1. *Vascul Pharmacol.* **112**: 79-90 [[PMID:30213580](#)]
- Vijayan V *et al.* (2018) The macrophage heme-heme oxygenase-1 system and its role in inflammation. *Biochem Pharmacol.* **153**: 159-167 [[PMID:29452096](#)]

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. Cystathion-

ine 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 predomi-

nantly 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 Papatropoulos, 2017 [575].

| | | | | |
|-----------------------|---|---|--|--|
| 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-cysteine (K_m 6×10^{-3} M) [92], L-homocysteine [92] | L-cysteine | L-cysteine | 3-mercaptopyruvic acid (K_m 1.2×10^{-3} M) [426] |
| Products | cystathionine | NH ₃ , pyruvic acid | NH ₃ , pyruvic acid | pyruvic acid |
| Cofactors | pyridoxal 5-phosphate | pyridoxal 5-phosphate | pyridoxal 5-phosphate | Zn ²⁺ |
| Inhibitors | aminoxyacetic acid (pIC ₅₀ 5.1) [20] | aminoethoxyvinylglycine (pIC ₅₀ 6) [20], aminoxyacetic acid (pIC ₅₀ 6) [20], β-Cyano-L-alanine (pIC ₅₀ 5.8) [20], propargylglycine (pIC ₅₀ 4.4) [20] | – | I3MT-3 (pIC ₅₀ 5.6) [237] |

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. Hormone-sensitive lipase is also a relatively non-selective esterase associated with steroid ester hydrolysis and triglyceride metabolism, particularly

in adipose tissue. Endothelial lipase is secreted from endothelial cells and regulates circulating cholesterol in high density lipoproteins.

Searchable database: <http://www.guidetopharmacology.org/index.jsp>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.14752/full>

Hydrolases S358

| | | | | | | |
|-------------------------|---|--|--|------------------------------------|---|--|
| Nomenclature | pancreatic lipase | lipase E, hormone sensitive type | lipase G, endothelial type | carboxylesterase 1 | ectonucleoside triphosphate diphosphohydrolase 1 | ectonucleoside triphosphate diphosphohydrolase 2 |
| Systematic nomenclature | – | – | – | – | CD39 | CD39L1 |
| Common abbreviation | PNLIP | LIPE | LIPG | CES1 | NTPDase-1 | NTPDase-2 |
| HGNC, UniProt | PNLIP, P16233 | LIPE, Q05469 | LIPG, Q9Y5X9 | CES1, P23141 | ENTPD1, P49961 | ENTPD2, Q9Y5L3 |
| EC number | 3.1.1.3 | 3.1.1.79 | 3.1.1.3 | 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 | 3.6.1.- Hydrolyzes extracellular nucleotide 5'-triphosphates: NTP > NMP + 2 phosphate |
| Inhibitors | orlistat (pIC ₅₀ 8.9) [66] | – | – | – | – | – |
| Selective inhibitors | – | – | – | – | – | PSB-6426 (pK _i 5.1) [63] |
| Comments | – | – | – | – | ENTPD1 sequentially converts extracellular purine nucleotides (ATP and ADP) to the monophosphate form. Adenosine is then generated by the action of Ecto-5'-Nucleotidase (CD73). ENTPD1 is the rate-limiting step. Extracellular ATP acts as a damage-associated molecular pattern (DAMP) that activates innate immune cells through adenosine-induced activation of P2X and P2Y purinogenic receptors. | – |

Further reading on Hydrolases

- Allard B *et al.*. (2017) The ectonucleotidases CD39 and CD73: Novel checkpoint inhibitor targets. *Immunol Rev.* **276**: 121-144 [PMID:28258700]
- Kishore BK *et al.* (2018) CD39-adenosinergic axis in renal pathophysiology and therapeutics. *Purinergic Signal* **14**: 109-120 [PMID:29332180]
- Rasmussen HB *et al.* (2018) Carboxylesterase 1 genes: systematic review and evaluation of existing genotyping procedures. *Drug Metab Pers Ther* **33**: 3-14 [PMID:29427553]
- 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, IP_3 , which acts at intracellular ligand-gated ion channels, IP_3 receptors to elevate intracellular calcium. IP_3 is recycled to inositol by phosphatases or phosphorylated to form other active inositol polyphosphates. Inositol produced from dephosphorylation of IP_3 is recycled into membrane phospholipid under the influence of phosphatidylinositol synthase activity (CDP-diacylglycerol-inositol 3-phosphatidyltransferase [EC 2.7.8.11]).

Inositol 1,4,5-trisphosphate 3-kinases

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

Overview: Inositol 1,4,5-trisphosphate 3-kinases (E.C. 2.7.1.127, ENSFM00250000001260) catalyse the generation of inositol 1,3,4,5-tetrakisphosphate (IP_4) from IP_3 . IP_3 kinase activity is enhanced in the presence of calcium/calmodulin (*CALM1 CALM2 CALM3*, P62158) [113].

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 IP_3 , as well as towards other inositol derivatives, including the phospholipids PIP_2 and PIP_3 . With IP_3 as substrate, 1-phosphatase (EC 3.1.3.57) generates 4,5- IP_2 , 4-phosphatases (EC 3.1.3.66, ENSFM00250000001432) generate 1,5- IP_2 and 5-phosphatases (E.C. 3.1.3.36 or 3.1.3.56) generate 1,4- IP_2 .

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

Comments: *In vitro* analysis suggested IP_3 and IP_4 were poor substrates for SKIP, synaptojanin 1 and synaptojanin 2, but suggested that PIP_2 and PIP_3 were more efficiently hydrolysed [523].

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 non-selective un-competitive inhibitor more potent at IMPase 1 (pK_i ca. 3.5, [402]; pIC_{50} 3.2, [445]) than IMPase 2 (pIC_{50} 1.8–2.1, [445]). IMPase activity may be inhibited competitively by L690330 (pK_i 5.5, [402]), although the enzyme selectivity is not yet established.

| | | |
|------------------------|--|--|
| Nomenclature | IMPase 1 | IMPase 2 |
| HGNC, UniProt | IMPA1 , P29218 | IMPA2 , O14732 |
| EC number | 3.1.3.25 | 3.1.3.25 |
| Rank order of affinity | inositol 4-phosphate > inositol 3-phosphate > inositol 1-phosphate [402] | – |
| Inhibitors | Li^+ (pK_i 3.5) [402] | – |

Comments: Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder [548, 549, 666]. Disruption of the gene encoding IMPase 1, but not IMPase 2, appears to mimic the effects of Li^+ in mice [121, 122].

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 [390]. 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 [128].

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 [[327](#)].

| | | |
|-------------------------|---|--|
| 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) [473], Y27632 (pIC ₅₀ 5.9–7.3) [383 , 648], fasudil (pK _i 7) [496], Y27632 (pK _i 6.8) [607], fasudil (pIC ₅₀ 5.5–5.6) [383 , 496] | RKI-1447 (pIC ₅₀ >9) [473], compound 11 d [DOI: 10.1039/c0md00194e] (pIC ₅₀ >9) [95], GSK269962A (pIC ₅₀ 8.4) [149], compound 32 (pIC ₅₀ 8.4) [58], compound 22 (pIC ₅₀ 7.7) [648], Y27632 (pIC ₅₀ 6.3–7.2) [383 , 648], Y27632 (pK _i 6.8–6.9) [383 , 607], fasudil (pIC ₅₀ 5.9–5.9) [383 , 496] |
| Selective inhibitors | GSK269962A (pIC ₅₀ 8.8) [149] | – |

Further reading on Rho kinase

- Feng Y *et al.* (2016) Rho Kinase (ROCK) Inhibitors and Their Therapeutic Potential. *J. Med. Chem.* **59**: 2269–300 [[PMID:26486225](#)]
- Nishioka T *et al.* (2015) Developing novel methods to search for substrates of protein kinases such as Rho-kinase. *Biochim. Biophys. Acta* **1854**: 1663–6 [[PMID:25770685](#)]
- Shimokawa H *et al.* (2016) RhoA/Rho-Kinase in the Cardiovascular System. *Circ. Res.* **118**: 352–66 [[PMID:26838319](#)]

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](#)). Classical protein kinase C isoforms: **PKC α** , **PKC β** , and **PKC γ** are activated by Ca²⁺ and diacylglycerol, and may be inhibited by [GF109203X](#), [calphostin C](#), [Gö 6983](#), [chelerythrine](#) and [Ro31-8220](#). **PKC μ** are activated by diacylglycerol and may be inhibited by [calphostin C](#), [Gö 6983](#) and [chelerythrine](#). Novel protein kinase C isoforms: **PKC δ** , **PKC ϵ** , **PKC η** , **PKC θ** and **PKC ζ** . Atypical protein kinase C isoforms: **PKC ι** , **PKC ξ** .

Alpha subfamily

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

| | | |
|----------------------|---|---|
| Nomenclature | protein kinase C beta | protein kinase C gamma |
| Common abbreviation | PKC β | PKC γ |
| HGNC, UniProt | PRKCB , P05771 | PRKCG , P05129 |
| EC number | 2.7.11.13 | 2.7.11.13 |
| Inhibitors | sotrastaurin (pIC ₅₀ 8.7) [617], Gö 6983 (pIC ₅₀ 8.1) [223], GF109203X (pIC ₅₀ 7.8) [600] – Bovine, 7-hydroxystaurosporine (pIC ₅₀ 7.5) [535] | Gö 6983 (pIC ₅₀ 8.2) [223], 7-hydroxystaurosporine (pIC ₅₀ 7.5) [535] |
| Selective inhibitors | ruboxistaurin (pIC ₅₀ 8.2) [289], enzastaurin (pIC ₅₀ 7.5) [165], CGP53353 (pIC ₅₀ 6.4) [86] – | – |

Delta subfamily

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

| | | |
|---------------------|---|---|
| Nomenclature | protein kinase C alpha | protein kinase C delta |
| Common abbreviation | PKC α | PKC δ |
| HGNC, UniProt | PRKCA , P17252 | PRKCD , Q05655 |
| EC number | 2.7.11.13 | 2.7.11.13 |
| Activators | – | ingenol mebutate (pK _i 9.4) [307] |
| Inhibitors | sotrastaurin (pIC ₅₀ 8.7) [617], Gö 6983 (pIC ₅₀ 8.1) [223], 7-hydroxystaurosporine (pIC ₅₀ 7.5) [535] | sotrastaurin (pIC ₅₀ 8.9) [617], Gö 6983 (pIC ₅₀ 8) [223] |

Eta subfamily

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

| | |
|---------------------|--|
| Nomenclature | protein kinase C epsilon |
| Common abbreviation | PKC ϵ |
| HGNC, UniProt | PRKCE , Q02156 |
| EC number | 2.7.11.13 |
| Inhibitors | sotrastaurin (pIC ₅₀ 8.2) [617] |

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](#)]
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

| | |
|----------------------|---|
| 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) [505], torin 1 (pIC ₅₀ 9.5) [361], sapanisertib (pIC ₅₀ 9) [267], sapanisertib (pK _i 8.9) [267], gedatolisib (pIC ₅₀ 8.8) [612], dactolisib (pIC ₅₀ 8.2) [388], PP121 (pIC ₅₀ 8) [18], XL388 (pIC ₅₀ 8) [580], PF-04691502 (pK _i 7.8) [360], apitolisib (pK _i 7.8) [573] |
| Selective inhibitors | everolimus (pIC ₅₀ 8.7) [531], PP-242 (pIC ₅₀ 8.1) [18], temsirolimus (pIC ₅₀ 5.8) [323] |

Further reading on FRAP subfamily

Hukelmann JL *et al.* (2016) The cytotoxic T cell proteome and its shaping by the kinase mTOR. *Nat. Immunol.* **17**: 104-12 [[PMID:26551880](#)]
Saxton RA *et al.* (2017) mTOR Signaling in Growth, Metabolism, and Disease. *Cell* **169**: 361-371 [[PMID:28388417](#)]

Cyclin-dependent kinase (CDK) family

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

Overview: 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 [59, 321, 352].

CDK4 subfamily

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

| | | |
|---------------------|---|---|
| Nomenclature | cyclin dependent kinase 4 | cyclin dependent kinase 6 |
| Common abbreviation | CDK4 | CDK6 |
| HGNC, UniProt | CDK4, P11802 | CDK6, Q00534 |
| EC number | 2.7.11.22 | 2.7.11.22 |
| Inhibitors | R547 (pK _i 9) [135], palbociclib (pIC ₅₀ 8) [183], Ro-0505124 (pIC ₅₀ 7.7) [144], riviciclib (pIC ₅₀ 7.2) [297], alvocidib (pK _i 7.2) [79] | palbociclib (pIC ₅₀ 7.8) [183] |

Comments on Cyclin-dependent kinase (CDK) family: The development of CDK inhibitors as anticancer drugs is reviewed in [576], 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 [296], 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

| | |
|----------------------|--|
| 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) [504], LY2090314 (pIC ₅₀ 9) [157], CHIR-99021 (pIC ₅₀ 8.2) [504], SB 216763 (pIC ₅₀ ~8.1) [109], 1-azakenpaullone (pIC ₅₀ 7.7) [331], SB-415286 (pIC ₅₀ ~7.4) [109], IM-12 (pIC ₅₀ 7.3) [525] |
| Selective inhibitors | AZD2858 (pK _i 8.3) [41] |
| Comments | Due to its Tau phosphorylating activity, small molecule inhibitors of GSK-3β are being investigated as potential treatments for Alzheimer's disease (AD) [41]. 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 [393]. |

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](#)]
- Maqbool M *et al.* (2016) Pivotal role of glycogen synthase kinase-3: A therapeutic target for Alzheimer's disease. *Eur J Med Chem* **107**: 63-81 [[PMID:26562543](#)]

Polo-like kinase (PLK) family

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

| | |
|---------------------|--|
| Nomenclature | polo like kinase 4 |
| Common abbreviation | PLK4 |
| HGNC, UniProt | PLK4 , O00444 |
| EC number | 2.7.11.21 |
| Inhibitors | CFI-400945 (pIC ₅₀ 8.6) [397] |

STE7 family

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

| | | |
|---------------------------------|--|--|
| Nomenclature | mitogen-activated protein kinase kinase 1 | mitogen-activated protein kinase kinase 2 |
| Common abbreviation | MEK1 | MEK2 |
| HGNC, UniProt | MAP2K1 , Q02750 | MAP2K2 , P36507 |
| EC number | 2.7.12.2 | 2.7.12.2 |
| Inhibitors | trametinib (pIC ₅₀ 9–9.1) [206 , 659], PD 0325901 (pIC ₅₀ 8.1) [243] | trametinib (pIC ₅₀ 8.7) [659] |
| Allosteric modulators | binimetinib (Negative) (pIC ₅₀ 7.9) [468], refametinib (Negative) (pIC ₅₀ 7.7) [281], CI-1040 (Negative) (pK _d 6.9) [130] | binimetinib (Negative) (pIC ₅₀ 7.9) [468], refametinib (Negative) (pIC ₅₀ 7.3) [281] |
| Selective allosteric modulators | cobimetinib (Negative) (pIC ₅₀ 9.1) [500] | – |

Abl family

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

| | |
|---------------------|--|
| Nomenclature | ABL proto-oncogene 1, non-receptor tyrosine kinase |
| Common abbreviation | Abl |
| HGNC, UniProt | ABL1, P00519 |
| EC number | 2.7.10.2 |
| Inhibitors | compound 8h (pIC ₅₀ 9.7) [596], dasatinib (pIC ₅₀ 9.6) [314], compound 24 (pIC ₅₀ 9.3) [136], PD-173955 (pK _d 9.2) [130], bosutinib (pIC ₅₀ 9) [210], PD-173955 (pIC ₅₀ ~8.3) [427], bafetinib (pIC ₅₀ 7.6–8.2) [264, 319], ponatinib (pIC ₅₀ 8.1) [269], nilotinib (pIC ₅₀ 7.8) [439], PP121 (pIC ₅₀ 7.7) [18], imatinib (pIC ₅₀ 6.7) [264], GNF-5 (pIC ₅₀ 6.7) [673] |

Ack family

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

| | |
|---------------------|---|
| Nomenclature | tyrosine kinase non receptor 2 |
| Common abbreviation | Ack |
| HGNC, UniProt | TNK2, Q07912 |
| EC number | 2.7.10.2 |
| Inhibitors | compound 30 (pIC ₅₀ 9) [143] |

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) [236 , 483], filgotinib (pIC ₅₀ 8) [608] | ilginatinib (pIC ₅₀ 9.1) [431], BMS-911543 (pIC ₅₀ 9) [480], AT-9283 (pIC ₅₀ 8.9) [266], XL019 (pIC ₅₀ 8.7) [176], fedratinib (pIC ₅₀ 8.5) [389 , 638], gandotinib (pIC ₅₀ 8.4) [385] | AT-9283 (pIC ₅₀ 9) [266] | – |
| Selective inhibitors | – | compound 1d (pIC ₅₀ >9) [624] | – | – |
| 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 [74 , 133]. Small molecule compounds which inhibit aberrant JAK2 activity are being developed as novel anti-cancer pharmaceuticals. | – | – |

Src family

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

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-κB 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) [239] | bafetinib (pIC ₅₀ 8) [264] | WH-4-023 (pIC ₅₀ 8.2) [394], PD166285 (pK _i 8.1) [458], PP121 (pIC ₅₀ 7.8) [18], ENMD-2076 (pIC ₅₀ 7.7) [476] |

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) [347], ibrutinib (pIC ₅₀ 9.1) [371], compound 31 (pIC ₅₀ 8.7) [347] | ibrutinib (pIC ₅₀ 9.3) [457], compound 31 (pIC ₅₀ 8.4) [347], compound 38 (pIC ₅₀ >8.4) [347] | – |
| Selective inhibitors | BMX-IN-1 (pIC ₅₀ 8.1) [358] | CGI1746 (pIC ₅₀ 8.7) [140], CHMFL-BTK-11 (Irreversible inhibition) (pIC ₅₀ 7.6) [649] | – |

RAF family

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

| | | |
|----------------------|---|--|
| Nomenclature | B-Raf proto-oncogene, serine/threonine kinase | Raf-1 proto-oncogene, serine/threonine kinase |
| Common abbreviation | B-Raf | c-Raf |
| HGNC, UniProt | BRAF , P15056 | RAF1 , P04049 |
| EC number | 2.7.11.1 | 2.7.11.1 |
| Inhibitors | GDC-0879 (pIC ₅₀ 9.7–9.9) [130, 240], dabrafenib (pIC ₅₀ 8.5) [337], regorafenib (pIC ₅₀ 7.6) [670], vemurafenib (pIC ₅₀ 7) [625], PLX-4720 (pK _d 6.5) [130], compound 2 (pK _d 6.3) [263], CHIR-265 (pK _d 5.9) [130] | – |
| Selective inhibitors | – | GW5074 (pIC ₅₀ 8.1) [101] |

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

- Eglen R *et al.* (2011) Drug discovery and the human kinome: recent trends. *Pharmacol. Ther.* **130**: 144–56 [PMID:21256157]
- Graves LM *et al.* (2013) The dynamic nature of the kinome. *Biochem. J.* **450**: 1–8 [PMID:23343193]
- Liu Q *et al.* (2013) Developing irreversible inhibitors of the protein kinase cysteinome. *Chem. Biol.* **20**: 146–59 [PMID:23438744]
- Martin KJ *et al.* (2012) Selective kinase inhibitors as tools for neuroscience research. *Neuropharmacology* **63**: 1227–37 [PMID:22846224]
- Tarrant MK *et al.* (2009) The chemical biology of protein phosphorylation. *Annu. Rev. Biochem.* **78**: 797–825 [PMID:19489734]
- Wu-Zhang AX *et al.* (2013) Protein kinase C pharmacology: refining the toolbox. *Biochem. J.* **452**: 195–209 [PMID:23662807]

Lanosterol biosynthesis pathway

Enzymes → Lanosterol biosynthesis pathway

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

| | | | | |
|---------------|---|---|---|--|
| Nomenclature | acetyl-CoA acetyltransferase 1 | acetyl-CoA acetyltransferase 2 | hydroxymethylglutaryl-CoA synthase 1 | hydroxymethylglutaryl-CoA synthase 2 |
| HGNC, UniProt | ACAT1 , P24752 | ACAT2 , Q9BWD1 | HMGS1 , Q01581 | HMGS2 , P54868 |
| EC number | 2.3.1.9: 2acetyl CoA = acetoacetyl CoA + coenzyme A | 2.3.1.9: 2acetyl CoA = acetoacetyl CoA + coenzyme A | 2.3.3.10: acetyl CoA + H ₂ O + acetoacetyl CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A | 2.3.3.10: acetyl CoA + H ₂ O + acetoacetyl CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A |
| Comments | – | – | HMGCoA synthase is found in cytosolic (HMGCoA synthase 1) and mitochondrial (HMGCoA synthase 2) versions; the former associated with (R)-mevalonate synthesis and the latter with ketogenesis. | |

| | |
|---------------|---|
| Nomenclature | hydroxymethylglutaryl-CoA reductase |
| HGNC, UniProt | HMGCR , 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) [12], rosuvastatin (Competitive) (pI _{C₅₀} 8.3) [280], cerivastatin (Competitive) (pK _i 8.2) [77], atorvastatin (Competitive) (pI _{C₅₀} 8.1) [280], cerivastatin (Competitive) (pI _{C₅₀} 8) [595], simvastatin (Competitive) (pI _{C₅₀} 8) [280], fluvastatin (Competitive) (pI _{C₅₀} 7.6) [280] |
| Comments | HMGCoA reductase is associated with intracellular membranes; enzymatic activity is inhibited by phosphorylation by AMP-activated kinase. The enzymatic reaction is a three-step reaction involving the intermediate generation of mevaldehyde-CoA and mevaldehyde. |

| | | | |
|---------------|---|--|--|
| 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 | <i>IDI1</i> , Q13907 | <i>IDI2</i> , Q9BXS1 | <i>GGPS1</i> , O95749 |
| EC number | 5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate | 5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate | 2.5.1.29: trans,trans-farnesyl diphosphate + isopentenyl diphosphate \rightarrow geranylgeranyl diphosphate + diphosphate 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate \rightarrow trans,trans-farnesyl diphosphate + diphosphate 2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate |

| | | | | |
|----------------------|--|--|--|--|
| Nomenclature | farnesyl diphosphate synthase | squalene synthase | squalene monooxygenase | lanosterol synthase |
| HGNC, UniProt | <i>FDPS</i> , P14324 | <i>FDFT1</i> , P37268 | <i>SQLE</i> , Q14534 | <i>LSS</i> , P48449 |
| EC number | 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate \rightarrow trans,trans-farnesyl diphosphate + diphosphate 2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate | 2.5.1.21: 2trans,trans-farnesyl diphosphate \rightarrow presqualene diphosphate + diphosphate presqualene diphosphate + NAD(P)H + H ⁺ \rightarrow 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) [43], zoledronic acid (pK _i 7.1) [153], alendronate (pIC ₅₀ 6.3) [43] | zaragozic acid A (pK _i 10.1) [44] – Rat, zaragozic acid A (pIC ₅₀ 9.2) [597] | – | – |
| Selective inhibitors | ibandronic acid (pK _i 6.7) [153], pamidronic acid (pIC ₅₀ 6.7) [153] | – | – | – |

Further reading on Lanosterol biosynthesis pathway

- Moutinho M *et al.* (2017) The mevalonate pathway in neurons: It's not just about cholesterol. *Exp. Cell Res.* **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]
- Ness GC. (2015) Physiological feedback regulation of cholesterol biosynthesis: Role of translational control of hepatic HMG-CoA reductase and possible involvement of oxysterols. *Biochim. Biophys. Acta* **1851**: 667-73 [PMID:25701719]
- Porter TD. (2015) Electron Transfer Pathways in Cholesterol Synthesis. *Lipids* **50**: 927-36 [PMID:26344922]
- Samaras K *et al.* (2016) Does statin use cause memory decline in the elderly? *Trends Cardiovasc. Med.* **26**: 550-65 [PMID:27177529]

Nucleoside synthesis and metabolism

Enzymes → Nucleoside synthesis and metabolism

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

| | | | | | | |
|----------------------|---|--|--|---|---|---|
| Nomenclature | dihydrofolate reductase | 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 | <i>DHFR</i> , P00374 | <i>GART</i> , P22102 | <i>DHODH</i> , Q02127 | <i>IMPDH1</i> , P20839 | <i>IMPDH2</i> , P12268 | <i>TYMS</i> , 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 (p <i>K_i</i> 5) [540] – Mouse | teriflunomide (p <i>K_i</i> 7.5) [253] | mycophenolic acid (p <i>C₅₀</i> 7.7) [433] | mycophenolic acid (p <i>C₅₀</i> 7.7) [433] | – |
| Selective inhibitors | methotrexate (p <i>K_i</i> 8.9) [511] | – | – | – | – | raltitrexed (p <i>C₅₀</i> 6.5) [194] |

| | | | | | |
|---------------------|--|--|---|--|--|
| 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 \rightleftharpoons purine + alpha-D-ribose 1-phosphate Purine deoxynucleoside + phosphate \rightleftharpoons purine + 2'-deoxy-alpha-D-ribose 1-phosphate | 1.17.1.4 | 1.17.14.1 | 1.17.4.1 | 1.17.1.4 |
| Inhibitors | – | febuxostat (pIC ₅₀ 8.9) [162] | – | – | – |

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

Day RO *et al.* (2016) Xanthine oxidoreductase and its inhibitors: relevance for gout. *Clin Sci (Lond)*. **130**: 2167-2180 [[PMID:27798228](#)]

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

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 | 3.1.8.1 An aryl dialkyl phosphate + H(2)O <=> dialkyl phosphate + an aryl alcohol 3.1.1.2 A phenyl acetate + H(2)O <=> a phenol + acetate 3.1.1.81 An N-acyl-L-homoserine lactone + H(2)O <=> an N-acyl-L-homoserine | 3.1.1.2 A phenyl acetate + H(2)O <=> a phenol + acetate 3.1.1.81 A N-acyl-L-homoserine lactone + H(2)O <=> a N-acyl-L-homoserine | 3.1.8.1 An aryl dialkyl phosphate + H(2)O <=> dialkyl phosphate + an aryl alcohol 3.1.1.2 A phenyl acetate + H(2)O <=> a phenol + acetate 3.1.1.81 A N-acyl-L-homoserine lactone + H(2)O <=> a N-acyl-L-homoserine |
| Comments | PON1 forms homodimers. Loss-of-function mutations in PON1 are associated with microvascular complications of diabetes [303 , 304]. | PON2 forms heterotrimers [150]. | PON3 likely forms heterodimers <i>in vivo</i> [150]. |

Further reading on Paraoxonase

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

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 en-

dopeptidases and endoproteinases, which are divided into serine endopeptidases (EC 3.4.21.-), cysteine endopeptidases (EC 3.4.22.-), aspartate endopeptidases (EC 3.4.23.-), metalloendopeptidases (EC 3.4.24.-) and threonine endopeptidases (EC 3.4.25.-). 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 [493] (with whom we collaborate) as an information resource [494].

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) [655] |

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) [302] in the generation of amyloid beta (A β) [9, 579]. Given that the accumulation and aggregation of A β in the brain is piv-

otal in the development of Alzheimer's disease (AD), inhibition of PS activity is one mechanism being investigated as a therapeutic option for AD [211]. 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 [139]. 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 [590].

| | |
|---------------|---|
| Nomenclature | Leukotriene A₄ hydrolase |
| HGNC, UniProt | LTA4H, P09960 |
| EC number | 3.3.2.6 |
| Inhibitors | bestatin (pK_i 5.4) [450] |

M2: Angiotensin-converting (ACE and ACE2)

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

| | |
|-----------------------|--|
| Nomenclature | Angiotensin-converting enzyme |
| Common abbreviation | ACE |
| HGNC, UniProt | ACE, P12821 |
| EC number | 3.4.15.1 |
| Substrates | Ac-SDKP |
| Endogenous substrates | angiotensin I (AGT, P01019) > angiotensin II (AGT, P01019) |
| Inhibitors | zofenoprilat (p <i>K</i> _i 9.4) [329] – Rabbit, captopril (p <i>K</i> _i 8.4) [410], zofenopril |
| Selective inhibitors | perindoprilat (p <i>C</i> ₅₀ 9) [83], cilazaprilat (p <i>C</i> ₅₀ 8.7) [630] – Rabbit, imidaprilat (p <i>C</i> ₅₀ 8.7) [507], lisinopril-tryptophan (C-domain assay) (p <i>C</i> ₅₀ 8.2) [631], RXP-407 (N-domain selective inhibition) (p <i>C</i> ₅₀ 8.1) [538], fosinoprilat (p <i>C</i> ₅₀ 8) [131] – Rabbit, enalaprilat (p <i>C</i> ₅₀ 7.5) [98], benazeprilat (p <i>C</i> ₅₀ 6.6) [342] |
| Comments | Reports of ACE GPI hydrolase activity [322] have been refuted [344] |

M10: Matrix metalloproteinase

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

Overview: Matrix metalloproteinases (MMP) are calcium- and zinc-dependent proteinases regulating the extracellular matrix and are often divided (*e.g.* [614]) on functional and structural bases into gelatinases, collagenases, stromelysinases and matrilysins, as well as membrane type-MMP (MT-MMP).

| | | |
|----------------------|--|---------------------------------------|
| Nomenclature | MMP2 | MMP8 |
| HGNC, UniProt | MMP2, P08253 | MMP8, P22894 |
| EC number | 3.4.24.24 | 3.4.24.34 |
| Selective inhibitors | ARP100 [603] | – |
| 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 | FOLH1 , Q04609 |
| EC number | 3.4.17.21 |
| Antibodies | capromab (Binding) |
| Comments | Folate hydrolase is also known as NAALADase as it is responsible for the hydrolysis of N-acetylaspartylglutamate to form N-acetylaspartate and L-glutamate (L-glutamic acid). In the gut, the enzyme assists in the assimilation of folate by hydrolysing dietary poly-gamma-glutamylfolate. The enzyme is highly expressed in the prostate, and its expression is up-regulated in cancerous tissue. A tagged version of the antibody capromab has been used for imaging purposes. |

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

M19: Membrane dipeptidase

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

| | |
|---------------|---|
| Nomenclature | Dipeptidase 1 |
| HGNC, UniProt | <i>DPEP1</i> , P16444 |
| EC number | 3.4.13.19: LTD ₄ + H ₂ O = LTE ₄ + glycine |
| Inhibitors | cilastatin (p <i>K</i> _i 6) [215] |

S1: Chymotrypsin

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

| | | | |
|----------------------|---|--|--|
| Nomenclature | complement C1r | coagulation factor II, thrombin | coagulation factor X |
| HGNC, UniProt | <i>C1R</i> , P00736 | <i>F2</i> , P00734 | <i>F10</i> , P00742 |
| EC number | 3.4.21.41 | 3.4.21.5 | 3.4.21.6 |
| Inhibitors | nafamostat (p <i>C</i> ₅₀ 4.9) [251] | lepirudin (p <i>K</i> _i 13) [626], desirudin (p <i>K</i> _i 12.7) [293], AZ12971554 (p <i>K</i> _i 9.5) [21], melagatran (p <i>K</i> _i 8.7) [228], bivalirudin (p <i>K</i> _i 8.6) [646], dabigatran (p <i>K</i> _i 8.3) [246], argatroban (p <i>K</i> _i 7.7) [276] | apixaban (p <i>K</i> _i 10.1) [647], rivaroxaban (p <i>K</i> _i 9.4) [466], edoxaban (p <i>K</i> _i 9.2) [471] |
| Selective inhibitors | – | Dup-714 (p <i>K</i> _i 10.4) [192], AR-H067637 (p <i>C</i> ₅₀ 8.4) [132] | – |

| | | | | | |
|----------------------|---|---|------------------------------------|---|--|
| Nomenclature | elastase, neutrophil expressed | plasminogen | plasminogen activator, tissue type | serine protease 1 | tryptase alpha/beta 1 |
| HGNC, UniProt | <i>ELANE</i> , P08246 | <i>PLG</i> , P00747 | <i>PLAT</i> , P00750 | <i>PRSS1</i> , P07477 | <i>TPSAB1</i> , Q15661 |
| EC number | 3.4.21.37 | 3.4.21.7 | 3.4.21.68 | 3.4.21.4 | 3.4.21.59 |
| Inhibitors | alvelestat (p <i>K</i> _i 8) [568], sivelestat (p <i>C</i> ₅₀ 7.4) [119] | aprotinin {Bovine} (Binding) (p <i>C</i> ₅₀ 6.8) [560], tranexamic acid (Binding) (p <i>C</i> ₅₀ 3.6) [560] | – | nafamostat (p <i>C</i> ₅₀ 7.8) [251] | nafamostat (p <i>C</i> ₅₀ 10) [422] |
| Selective inhibitors | – | 6-aminocaproic acid (Binding) (p <i>C</i> ₅₀ 4.4) [97] | – | – | gabexate (p <i>C</i> ₅₀ 8.5) [159] |

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 [106]. 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 subunit beta 5 |
| HGNC, UniProt | PSMBS , P28074 |
| EC number | 3.4.25.1 |
| Inhibitors | bortezomib (pIC_{50} 7.7) [428] |
| Selective inhibitors | ixazomib (pK_i 9) [332] |

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 [368, 516, 567]. Therapeutics which inhibit PCSK9 are viewed as potentially lucrative replacements for statins, upon statin patent expiry. Sev-

eral monoclonal antibodies including [alirocumab](#), [evolocumab](#), [bococizumab](#), RG-7652 and LY3015014 are under development. One RNAi therapeutic, code named ALN-PCS02, is also in development [123, 173, 180].

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

S9: Prolyl oligopeptidase

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

| | |
|-----------------------|---|
| Nomenclature | dipeptidyl peptidase 4 |
| HGNC, UniProt | DPP4 , P27487 |
| EC number | 3.4.14.5 |
| Endogenous substrates | glucagon-like peptide 1 (GCG , P01275) |
| Inhibitors | saxagliptin (pK _i 9.2) [226], linagliptin (pK _i 9) [155], sitagliptin (pIC ₅₀ 8.1) [129], vildagliptin (pK _i 7.8) [226] |
| Selective inhibitors | ZY15557 (Competitive) (pK _i 8.3) [285] |

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](#)).

| | | | |
|---------------------|--|--|--|
| 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 | – |

Further reading on Poly ADP-ribose polymerases

- Berger NA *et al.* (2018) Opportunities for the repurposing of PARP inhibitors for the therapy of non-oncological diseases. *Br J Pharmacol.* **175**: 192-222 [[PMID:28213892](#)]
- Faraoni I *et al.* (2019) Targeting ADP-ribosylation by PARP inhibitors in acute myeloid leukaemia and related disorders. *Biochem Pharmacol* [[PMID:31028744](#)]
- Zeniou M *et al.* (2019) Therapeutic considerations of PARP in stem cell biology: Relevance in cancer and beyond. *Biochem Pharmacol* [[PMID:31202733](#)]

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 identified 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

- Joharapurkar AA *et al.* (2018) Prolyl Hydroxylase Inhibitors: A Breakthrough in the Therapy of Anemia Associated with Chronic Diseases. *J Med Chem* **61**: 6964–6982 [[PMID:29712435](#)]
- Lanigan SM and O'Connor JJ. (2019) Prolyl hydroxylase domain inhibitors: can multiple mechanisms be an opportunity for ischemic stroke? *Neuropharmacology* **148**: 117–130 [[PMID:30578795](#)]
- Singh L *et al.* (2018) Prolyl hydroxylase 2: a promising target to inhibit hypoxia-induced cellular metabolism in cancer cells. *Drug Discov Today* **23**: 1873–1882 [[PMID:29772209](#)]
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Sphingosine 1-phosphate turnover

Enzymes → Sphingosine 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 hexadecanal 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.

Sphingosine kinase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine 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 phos-

phorylation. Intracellular targets of nuclear S1P include the catalytic subunit of telomerase (TERT) 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 therapeutic potential in many diseases.

| | | |
|----------------------|---|---|
| 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 = sphingosine 1-phosphate + ADP | 2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP dihydrosphingosine + ATP = sphingosine 1-phosphate + ADP |
| Cofactors | Mg ²⁺ [536] | Mg ²⁺ |
| Inhibitors | SKI II (pK _i 4.8) [181], MP-A08 (pIC ₅₀ 4.6) [474] | MP-A08 (pK _i 5.2) [474], SKI II (pK _i 5.1) [196] |
| Selective inhibitors | PF-543 (pK _i 8.4) [537] | SLC4101431 (pK _i 7.1) [100], compound 27d (pIC ₅₀ 6.8) [526], opaganib (pK _i 5) [181], ROME (pK _i 4.8) [354] |
| Comments | SK1 inhibitors induce its proteasomal degradation [373, 404]. SK1 crystal structures confirm that it is dimeric [5]; there is no crystal structure available for SK2. | There is no crystal structure available for SK2. |

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*) [404, 610]) and induces proteasomal degradation of SK1 [404]. ABC294640 is in clinical trials for advanced cholangiocarcinoma, advanced hepatocellular carcinoma and refractory/relapsed multiple myeloma (to view ClinicalTrials.gov list click [here](#)).

Further reading on Sphingosine kinase

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- Lynch KR *et al.* (2016) Sphingosine kinase inhibitors: a review of patent literature (2006–2015). *Expert Opin Ther Pat* **26**: 1409–1416 [PMID:27539678]
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- Pyne S *et al.* (2018) Sphingosine Kinases as Druggable Targets. *Handb Exp Pharmacol* [PMID:29460151]

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 | 3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate |
| Comments | Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [382]. | – |

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 [[382](#)].

Further reading on Sphingosine 1-phosphate phosphatase

- Allende ML *et al.* (2013) Sphingosine-1-phosphate phosphatase 1 regulates keratinocyte differentiation and epidermal homeostasis. *J. Biol. Chem.* **288**: 18381-91 [[PMID:23637227](#)]
- Huang WC *et al.* (2016) Sphingosine-1-phosphate phosphatase 2 promotes disruption of mucosal integrity, and contributes to ulcerative colitis in mice and humans. *FASEB J.* **30**: 2945-58 [[PMID:27130484](#)]
- Lépine S *et al.* (2011) Sphingosine-1-phosphate phosphohydrolase-1 regulates ER stress-induced autophagy. *Cell Death Differ.* **18**: 350-61 [[PMID:20798685](#)]
- Mandala SM *et al.* (2000) Molecular cloning and characterization of a lipid phosphohydrolase that degrades sphingosine-1-phosphate and induces cell death. *Proc. Natl. Acad. Sci. U.S.A.* **97**: 7859-64 [[PMID:10859351](#)]
- Taguchi Y *et al.* (2016) Sphingosine-1-phosphate Phosphatase 2 Regulates Pancreatic Islet β -Cell Endoplasmic Reticulum Stress and Proliferation. *J. Biol. Chem.* **291**: 12029-38 [[PMID:27059959](#)]

Sphingosine 1-phosphate lyase

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

| | |
|---------------|---|
| Nomenclature | sphingosine-1-phosphate lyase 1 |
| HGNC, UniProt | <i>SGPL1</i> , O95470 |
| EC number | 4.1.2.27: sphingosine 1-phosphate -> phosphoethanolamine + hexadecenal dihydrosphingosine 1-phosphate -> phosphoethanolamine + hexadecanal |
| Cofactors | pyridoxal 5-phosphate |
| Inhibitors | compound 31 (pIC ₅₀ 6.7) [242, 366, 529, 635] |

Comments: THI (2-Acetyl-5-tetrahydroxybutyl imidazole) inhibits the enzyme activity in intact cell preparations [528]. Recessive mutations in the S1P lyase (*SGPL1*) gene underlie a recently identified sphingolipidosis: SPL Insufficiency Syndrome (SPLIS) [103]. A Phase 2 clinical trial of LX3305 (LX2931) for rheumatoid arthritis has been completed (see NCT00903383).

Further reading on Sphingosine 1-phosphate lyase

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- Lovric S *et al.* (2017) Mutations in sphingosine-1-phosphate lyase cause nephrosis with ichthyosis and adrenal insufficiency. *J. Clin. Invest.* **127**: 912-928 [PMID:28165339]
- Prasad R *et al.* (2017) Sphingosine-1-phosphate lyase mutations cause primary adrenal insufficiency and steroid-resistant nephrotic syndrome. *J. Clin. Invest.* **127**: 942-953 [PMID:28165343]

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 + $H_2O_2 + H^+ + I^- \rightarrow$ [Thyroglobulin]-3,5,3'-triiodo-L- thyronine + [thyroglobulin]-aminoacrylate + H_2O | 1.97.1.10: $T_4 \rightarrow$ triiodothyronine $rT_3 \rightarrow T_2$ | 1.97.1.10: $T_4 \rightarrow$ triiodothyronine $rT_3 \rightarrow T_2$ | 1.97.1.11: $T_4 \rightarrow$ triiodothyronine $rT_3 \rightarrow T_2$ | 1.22.1.1: 3-iodotyrosine \rightarrow L-tyrosine + I^- 3,5-diiodo-L-tyrosine \rightarrow 3-iodotyrosine + I^- |
| Cofactors | Ca^{2+} | – | – | – | flavin adenine dinucleotide, NADPH |
| Inhibitors | methimazole [430], propylthiouracil [430] | – | – | – | – |
| Comments | Carbimazole is a pro-drug for methimazole | – | – | – | – |

Further reading on Thyroid hormone turnover

- Darras VM *et al.* (2015) Intracellular thyroid hormone metabolism as a local regulator of nuclear thyroid hormone receptor-mediated impact on vertebrate development. *Biochim. Biophys. Acta* **1849**: 130-41 [PMID:24844179]
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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 L-kynurenine + NADPH + O ₂ <=> 3-hydroxy-L-kynurenine + NADP(+) + H ₂ O |
| Comments | Kynurenine 3-monooxygenase participates in metabolism of the essential amino acid tryptophan. |

Further reading on 1.14.13.9 Kynurenine 3-monooxygenase

- Dounay AB *et al.* (2015) Challenges and Opportunities in the Discovery of New Therapeutics Targeting the Kynurenine Pathway. *J. Med. Chem.* **58**: 8762-82 [PMID:26207924]
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- Song P *et al.* (2017) Abnormal kynurenine pathway of tryptophan catabolism in cardiovascular diseases. *Cell. Mol. Life Sci.* **74**: 2899-2916 [PMID:28314892]

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) [82]. Protein farnesyltransferase catalyses the post-translational formation of a thioether linkage between the C-1 of an isoprenyl group and a cysteine residue fourth from the C-terminus of a protein (*ie* to the CaaX motif, where 'a' is an aliphatic amino acid and 'X' is usually serine, me-

thionine, alanine or glutamine; leucine for EC 2.5.1.59) [188]. 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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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 into five subfamilies based on phylogenetic comparison with yeast homologues:

Class I contains HDACs 1, 2, 3 and 8

Class IIa contains HDACs 4, 5, 7 and 9

Class IIb contains HDACs 6 and 10

Class III contains the sirtuins (SIRT1-7)

Class IV contains only HDAC11.

Classes I, II and IV use 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 [521].

HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [104] such as microtubules [270], the hsp90 chaperone [326] and the tumour suppressor p53 [377].

Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [355, 509], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [639]. 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) [545].

| | |
|----------------------|---|
| Nomenclature | histone deacetylase 6 |
| HGNC, UniProt | HDAC6 , Q9UBN7 |
| EC number | 3.5.1.98 |
| Inhibitors | trichostatin A (p <i>K</i> _i 9) [61], vorinostat (p <i>K</i> _i 8.8) [61], romidepsin (p <i>K</i> _i 8) [61] |
| Selective inhibitors | ricolinostat (p <i>C</i> ₅₀ 8.3) [518] |

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 biologically relevant proteins. The human isozymes exhibit tissue-specific expression patterns [294]. 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 [47]. Pharmacological PADI inhibition reverses protein-hypercitrullination and disease in mouse models of multiple sclerosis [423].

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

Further reading on 3.5.3.15 Peptidyl arginine deiminases (PADI)

Koushik S *et al.* (2017) PAD4: pathophysiology, current therapeutics and future perspective in rheumatoid arthritis. *Expert Opin. Ther. Targets* **21**: 433-447 [[PMID:28281906](#)]
Tu R *et al.* (2016) Peptidyl Arginine Deiminases and Neurodegenerative Diseases. *Curr. Med. Chem.* **23**: 104-14 [[PMID:26577926](#)]
Whiteley CG. (2014) Arginine metabolising enzymes as targets against Alzheimers' disease. *Neurochem. Int.* **67**: 23-31 [[PMID:24508404](#)]

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 kd. They act as an on/off switch linking receptor and non-receptor tyrosine kinase activation to downstream cytoplasmic or nuclear events. Binding of GTP activates the switch, and hydrolysis of the GTP to GDP inactivates the switch. The RAS proto-oncogenes are the most frequently mutated class of proteins in human cancers. Common mutations compromise the GTP-hydrolysing ability of the proteins causing constitutive activation [564], which leads to increased cell proliferation and decreased apoptosis [674]. Because of their importance in oncogenic transformation these proteins have become the targets of intense drug discovery effort [33].

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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