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# The Concise Guide to PHARMACOLOGY 2025/26: Enzymes

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**Abstract**

The Concise Guide to Pharmacology 2025/26 marks the seventh edition in this series of biennial publications in the British Journal of Pharmacology. Presented in landscape format, the guide provides a comparative overview of the pharmacology of drug target families. The concise nature of the Concise Guide refers to the style of presentation, being clear, accessible, and well-structured, rather than the scope of the content, which spans approximately 500 pages. The Concise Guide summarises the key pharmacological properties of around 1900 human drug targets, and nearly 7000 interactions, involving around 4400 ligands. While the content is a substantially condensed version of the more detailed information and links available at the www.guidetopharmacology.org website, the printed guide serves as a permanent, citable, point-in-time record, that remains stable despite ongoing updates to the online database. The full contents of this publication can be found at https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bph.70234.

The Concise Guides provide expert-curated recommendations of 'Gold Standard' selective pharmacological tools, available either commercially or as donations, which enable the identification of individual drug targets or families of drug targets. While the Concise Guide offers a more streamlined overview, more comprehensive information, including detailed pharmacological profiles and links to multiple online databases, is available through the Guide to Pharmacology website. The 2025/26 edition of the Concise Guide is based on material current as of mid-2025, and supersedes all previous editions, including the 2023/24 Guide, and earlier Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR), and as such provides official IUPHAR classification and nomenclature for human drug targets, where applicable.

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. Each section includes nomenclature guidance, concise summaries, information of the best available pharmacological tools, key references, and suggestions for further reading.

**Conflict of interest**

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

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**Introduction**: 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 [567, 612], which is not to say that they are of modest importance.

The majority of drugs which act on enzymes act as inhibitors; one exception is ingenol mebutate, which is a non-selective protein kinase C activator approved for the topical treatment of actinic keratoses. Kinetic assays allow discrimination of competitive, non-competitive, and un-competitive inhibitors. The majority of inhibitors are competitive (acting at the enzyme's ligand recognition site), non-competitive (acting at a distinct site; potentially interfering with co-factor or co-enzyme binding) or of mixed type. One rare example of an uncompetitive inhibitor is lithium ions, which are effective inhibitors at inositol monophosphatase only in the presence of high substrate concentrations. Some inhibitors are irreversible, including a group known as suicide substrates, which bind to the ligand recognition site and then couple covalently to the enzyme. It is beyond the scope of the Guide to give mechanistic information about the inhibitors described, although generally this information is available from the indicated literature.

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


S312 AAA ATPases
S312 Acetylcholine turnover
– Acyl-CoA synthetases
S313 Adenosine turnover
S314 ADP-ribosyltransferases (ARTs)
S314 Mono-ADP-ribosylating PARPs
S315 Poly ADP-ribosylating PARPs
S316 Amino acid hydroxylases
S317 L-Arginine turnover
S317 2.1.1.- Protein arginine N-methyltransferases
S317 Arginase
S318 Arginine:glycine amidinotransferase
S318 Dimethylarginine dimethylaminohydrolases
S318 Nitric oxide synthases
S320 Carbonic anhydrases
S320 Carboxylases and decarboxylases
S320 Carboxylases
S322 Decarboxylases
– Carnitine palmitoyltransferases
S324 Catecholamine turnover
S326 Ceramide turnover
S326 Serine palmitoyltransferase
– 3-ketodihydrosphingosine reductase
S327 Ceramide synthase
S327 Sphingolipid $\Delta^4$-desaturase
S328 Sphingomyelin synthase
S328 Sphingomyelin phosphodiesterase
S329 Neutral sphingomyelinase coupling factors
S329 Ceramide glucosyltransferase
S329 Acid ceramidase
S330 Neutral ceramidases
S330 Alkaline ceramidases
S330 Ceramide kinase
– Chitinases
– Cholesterol biosynthesis pathway
S331 Chromatin modifying enzymes
– 1.14.11.- Histone demethylases
S331 2.1.1.- Protein arginine N-methyltransferases
– 2.1.1.43 Histone methyltransferases (HMTs)
– 2.3.1.48 Histone acetyltransferases (HATs)
S332 3.5.1.- Histone deacetylases (HDACs)
– 3.6.1.3 ATPases
– Enzymatic bromodomain-containing proteins
– Bromodomain kinase (BRDK) family
– TAF1 family
– TIF1 family
– Citrate metabolism
S333 Cyclic nucleotide turnover/signalling
S333 Adenylyl cyclases (ACs)
– Cyclic GMP-AMP turnover
S334 Exchange proteins activated by cyclic AMP (EPACs)
S335 Phosphodiesterases, 3′,5′-cyclic nucleotide (PDEs)
S338 Cytochrome P450
S338 CYP1 family
S339 CYP2 family: drug metabolising subset
S340 CYP2 family: physiological enzymes subset
S341 CYP3 family
S341 CYP4 family
S343 CYP5, CYP7 and CYP8 families
S344 CYP11, CYP17, CYP19, CYP20 and CYP21 families
S345 CYP24, CYP26 and CYP27 families
S346 CYP39, CYP46 and CYP51 families
– DNA glycosylases
– DNA polymerases
S346 DNA topoisomerases
– E2 ubiquitin-conjugating enzymes
S347 E3 ubiquitin ligase components
S347 Endocannabinoid turnover
S348 *N*-Acylethanolamine turnover
S349 2-Acylglycerol ester turnover
S350 Eicosanoid turnover
S350 Cyclooxygenase
S351 Prostaglandin synthases
S352 Lipoxygenases
S354 Leukotriene and lipoxin metabolism




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- G-alpha family G(q) subfamily
- S355 GABA turnover
- S356 Glycerophospholipid turnover
- S356 Phosphoinositide-specific phospholipase C
- S358 Phospholipase $A_2$
- S359 Phosphatidylcholine-specific phospholipase D
- S360 Lipid phosphate phosphatases
- S360 Phosphatidylinositol kinases
- S362 Phosphatidylinositol phosphate kinases
- Glycine recycling
- S363 Haem oxygenase
- S364 Hydrogen sulphide synthesis
- S365 Hydrolases & Lipases
- S366 Inositol phosphate turnover
- S366 Inositol 1,4,5-trisphosphate 3-kinases
- S367 Inositol polyphosphate phosphatases
- S367 Inositol monophosphatase
- Itaconate biosynthesis
- S368 Kinases (EC 2.7.x.x)
- AGC: Containing PKA, PKG, PKC families
- DMPK family
- GEK subfamily
- Other DMPK family kinases
- S368 Rho kinase
- G protein-coupled receptor kinases (GRKs)
- Beta-adrenergic receptor kinases (βARKs)
- Opsin/rhodopsin kinases
- GRK4 subfamily
- MAST family
- NDR family
- PDK1 family
- Protein kinase A (PKA) family
- Akt (Protein kinase B, PKB) family
- S369 Protein kinase C (PKC) family
- S369 Alpha subfamily
- S369 Delta subfamily
- S370 Eta subfamily
- S370 Iota subfamily
- Protein kinase G (PKG) family
- Protein kinase N (PKN) family
- RSK family
- MSK subfamily
- p70 subfamily
- RSK subfamily
- RSKR subfamily
- RSKL family
- SGK family
- YANK family
- Atypical
- ABC1 family
- ABC1-A subfamily
- ABC1-B subfamily
- Alpha kinase family
- ChaK subfamily
- eEF2 K subfamily
- Other alpha kinase family kinases
- BCR family
- Bromodomain kinase (BRDK) family
- G11 family
- Phosphatidyl inositol 3′ kinase-related kinases (PIKK) family
- ATR subfamily
- S371 FRAP subfamily
- SMG1 subfamily
- TRRAP subfamily
- Other PIKK family kinases
- RIO family
- RIO1 subfamily
- RIO2 subfamily
- RIO3 subfamily
- PDHK family
- Pyruvate dehydrogenase kinase (PDHK) family
- TAF1 family
- TIF1 family
- S371 CAMK: Calcium/calmodulin-dependent protein kinases
- CAMK1 family
- CAMK2 family
- CAMK-like (CAMKL) family
- AMPK subfamily
- BRSK subfamily
- CHK1 subfamily
- HUNK subfamily
- LKB subfamily
- MARK subfamily
- MELK subfamily
- NIM1 subfamily
- NuaK subfamily
- PASK subfamily
- QIK subfamily
- SNRK subfamily
- CAMK-unique family
- CASK family
- DCAMKL family
- Death-associated kinase (DAPK) family
- MAPK-Activated Protein Kinase (MAPKAPK) family
- MAPKAPK subfamily
- MKN subfamily
- Myosin Light Chain Kinase (MLCK) family
- Phosphorylase kinase (PHK) family
- PIM family
- Protein kinase D (PKD) family
- PSK family
- RAD53 family
- Testis specific kinase (TSSK) family
- Trbl family
- Trio family
- CK1: Casein kinase 1
- Casein kinase 1 (CK1) family
- Tau tubulin kinase (TTBK) family
- Vaccina related kinase (VRK) family
- CMGC: Containing CDK, MAPK, GSK3, CLK families
- CLK family
- S372 Cyclin-dependent kinase (CDK) family
- CCRK subfamily
- CDK1 subfamily
- S372 CDK4 subfamily
- CDK5 subfamily
- CDK7 subfamily
- CDK8 subfamily
- CDK9 subfamily
- CDK10 subfamily
- CRK7 subfamily
- PITSLRE subfamily
- TAIRE subfamily
- Cyclin-dependent kinase-like (CDKL) family
- Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase (DYRK) family
- Dyrk1 subfamily
- Dyrk2 subfamily
- HIPK subfamily
- PRP4 subfamily
- Glycogen synthase kinase (GSK) family
- S372 GSK subfamily
- Mitogen-activated protein kinases (MAP kinases)
- ERK subfamily
- Erk7 subfamily
- JNK subfamily
- p38 subfamily
- nmo subfamily
- RCK family
- SRPK family
- Lipid modifying kinases
- 1-phosphatidylinositol 4-kinase family



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- Phosphatidylinositol-4-phosphate 3-kinase family
- Phosphatidylinositol 3-kinase family
- Phosphatidylinositol-4,5-bisphosphate 3-kinase family
- 1-phosphatidylinositol-3-phosphate 5-kinase family
- Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)
- Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)
- Other protein kinases
  - CAMKK family
    - Meta subfamily
  - Aurora kinase (Aur) family
  - Bub family
  - Bud32 family
  - Casein kinase 2 (CK2) family
  - CDC7 family
  - Haspin family
  - IKK family
  - IRE family
  - MOS family
  - NAK family
  - NIMA (never in mitosis gene a)- related kinase (NEK) family
  - NKF1 family
  - NKF2 family
  - NKF4 family
  - NKF5 family
  - NRBP family
  - Numb-associated kinase (NAK) family
  - Other-unique family
  - S373 Polo-like kinase (PLK) family
  - PEK family
    - GCN2 subfamily
    - PEK subfamily
    - Other PEK family kinases
  - SgK493 family
  - Slob family
  - TBCK family
  - TOPK family
  - Tousled-like kinase (TLK) family
  - TTK family
  - Unc-51-like kinase (ULK) family
  - VPS15 family
  - WEE family
  - Wnk family
- Miscellaneous protein kinases
  - actin-binding proteins ADF family
    - Twinfilin subfamily
  - SCY1 family
  - Hexokinases
- STE: Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases
  - S374 STE7 family
  - STE11 family
  - STE20 family
    - FRAY subfamily
    - KHS subfamily
    - MSN subfamily
    - MST subfamily
    - NinaC subfamily
    - PAKA subfamily
    - PAKB subfamily
    - SLK subfamily
    - STE20 subfamily
    - STLK subfamily
    - TAO subfamily
    - YSK subfamily
  - STE-unique family
- TK: Tyrosine kinase
  - Non-receptor tyrosine kinases (nRTKs)
    - S374 Abl family
    - S375 Ack family
    - Csk family
    - Fak family
    - Fer family
    - S375 Janus kinase (JakA) family
    - S376 Src family
    - Syk family
    - S376 Tec family
- TKL: Tyrosine kinase-like
  - Interleukin-1 receptor-associated kinase (IRAK) family
  - Leucine-rich repeat kinase (LRRK) family
  - LIM domain kinase (LISK) family
    - LIMK subfamily
    - TESK subfamily
  - Mixed Lineage Kinase (MLK) family
    - HH498 subfamily
    - ILK subfamily
    - LZK subfamily
    - MLK subfamily
    - TAK1 subfamily
  - S377 RAF family
  - Receptor interacting protein kinase (RIPK) family
  - TKL-unique family
- Diacylglycerol kinases
  - Pyruvate kinases (EC 2.7.1.40)
  - Sugar kinases
- S377 Lanosterol biosynthesis pathway
  - LPA synthesis
  - Membrane bound O-acyltransferases
  - Methionine turnover
  - Mitofusin proteins
  - NADPH oxidases
- S379 Nucleoside synthesis and metabolism
  - Nucleotide salvage
    - Pyrimidine salvage
  - Nucleotide turnover
  - N-myristoyltransferases
- S381 Paraoxonase (PON) family
- S381 Peptidases and proteinases
  - S382 Blood coagulation components
  - AA: Aspartic (A) Peptidases
    - S384 A1: Pepsin
  - AD: Aspartic (A) Peptidases
    - S384 A22: Presenilin
  - CA: Cysteine (C) Peptidases
    - C1: Papain
    - C2: Calpain
    - C12: Ubiquitin C-terminal hydrolase
    - C19: Ubiquitin-specific protease
    - C54: Aut2 peptidase
    - C65: Otubains
    - C101: OTULIN peptidase
  - CD: Cysteine (C) Peptidases
    - C13: Legumain
    - S384 C14: Caspase
  - CE: Cysteine (C) Peptidases
    - C48: Ulp1 endopeptidase
  - M-: Metallo (M) Peptidases
    - M79: Prenyl protease 2
  - MA: Metallo (M) Peptidases
    - S385 M1: Aminopeptidase N
    - S385 M2: Angiotensin-converting enzymes (ACE and ACE2)
    - S386 M10: Matrix metallopeptidase
    - S386 M12: Astacin/Adamalysin
    - M13: Neprilysin
    - M49: Dipeptidyl-peptidase III
  - MC: Metallo (M) Peptidases
    - M14: Carboxypeptidase A
  - ME: Metallo (M) Peptidases
    - M16: Pitrilysin
  - MF: Metallo (M) Peptidases
    - M17: Leucyl aminopeptidase
  - MG: Metallo (M) Peptidases



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- M24: Methionyl aminopeptidase
- MH: Metallo (M) Peptidases
- M18: Aminopeptidase I
- M20: Carnosine dipeptidase
- S387 M28: Aminopeptidase Y
- MJ: Metallo (M) Peptidases
- S387 M19: Membrane dipeptidase
- MP: Metallo (M) Peptidases
- M67: PSMD14 peptidase
- PA: Serine (S) Peptidases
- S388 S1: Chymotrypsin
- PB: Threonine (T) Peptidases
- C44: Phosphoribosyl pyrophosphate amidotransferase
- S389 T1: Proteasome
- T2: Glycosylasparaginase precursor
- PC: Cysteine (C) Peptidases
- C26: Gamma-glutamyl hydrolase
- SB: Serine (S) Peptidases
- S389 S8: Subtilisin
- SC: Serine (S) Peptidases
- S389 S9: Prolyl oligopeptidase
- S10: Carboxypeptidase Y
- S28: Lysosomal Pro-Xaa carboxypeptidase
- S33: Prolyl aminopeptidase
- S390 Peptidyl-prolyl cis/trans isomerases
- Phosphatases
- Class I classical (Cys-based) phosphatases
- Dual specificity phosphatases
- Protein tyrosine phosphatases non-receptor type (PTPN)
- Metal-dependent protein phosphatase (PPM) family
- Sugar phosphatases
- Protein phosphatase catalytic subunits
- Phosphodiesterases (other)
- Phospholipid scramblases (PLSCR)
- S391 Prolyl hydroxylases
- Selenoenzymes
- S392 Sphingosine 1-phosphate turnover
- S392 Sphingosine kinase
- S393 Sphingosine 1-phosphate phosphatase
- S394 Sphingosine 1-phosphate lyase
- Thioredoxin (Trx) system proteins
- S395 Thyroid hormone turnover
- UDP glucuronosyltransferases (UGT)
- 1.-.-.- Oxidoreductases
- 1.1.1.42 Isocitrate dehydrogenases
- 1.2.3.1 Aldehyde oxidase
- 1.4.3.13 Lysyl oxidases
- 1.13.11.- Dioxygenases
- S396 1.14.13.9 Kynurenine 3-monooxygenase
- 1.17.4.1 Ribonucleoside-diphosphate reductases
- 2.1.1.- Methyltransferases
- 2.1.2.- Hydroxymethyl-, formyl- and related transferases
- 2.3.1.- Acyltransferases
- 2.3.2.- Aminoacyltransferases
- 2.3.2.13 Transglutaminases
- 2.3.2.27 RING-type E3 ubiquitin transferase
- 2.4.2.1 Purine-nucleoside phosphorylase
- 2.5.1.18 Glutathione transferases
- S396 2.5.1.58 Protein farnesyltransferase
- 2.6.1.42 Branched-chain-amino-acid transaminase
- 3.1.-.- Ester bond enzymes
- 3.1.1.- Carboxylic Ester Hydrolases
- 3.2.1.- Glycosidases
- 3.4.21.46 Complement factor D
- S397 3.5.1.- Histone deacetylases (HDACs)
- 3.5.1.2 Glutaminases
- S397 3.5.3.15 Peptidyl arginine deiminases (PADI)
- 3.6.4.12 RecQ helicases family
- S398 3.6.5.2 Small monomeric GTPases
- S398 RAS subfamily
- S398 RAB subfamily
- 5.-.-.- Isomerases
- 6.3.3.- Cyclo-ligases



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# AAA ATPases

Enzymes → AAA ATPases

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

Information on members of this family may be found in the online database.

# Acetylcholine turnover

Enzymes → Acetylcholine turnover

**Overview**: Acetylcholine is familiar as a neurotransmitter in the central nervous system and in the periphery. In the somatic nervous system, it activates nicotinic acetylcholine receptors at the skeletal neuromuscular junction. It is also employed in the autonomic nervous system, in both parasympathetic and sympathetic branches; in the former, at the smooth muscle neuromuscular junction, activating muscarinic acetylcholine receptors. In the latter, acetylcholine is involved as a neurotransmitter at the ganglion, activating nicotinic acetylcholine receptors. Acetylcholine is synthesised in neurones through the action of choline O-acetyltransferase and metabolised after release through the extracellular action of acetylcholinesterase and cholinesterase. Choline is accumulated from the extracellular medium by selective transporters (see SLC5A7 and the SLC44 family). Acetylcholine is accumulated in synaptic vesicles through the action of the vesicular acetylcholine transporter SLC18A3.

| | | | |
|---|---|---|---|
| Nomenclature | choline O-acetyltransferase | acetylcholinesterase (Yt blood group) | butyrylcholinesterase |
| Common abbreviation | ChAT | AChE | BChE |
| HGNC, UniProt | *CHAT*, P28329 | *ACHE*, P22303 | *BCHE*, P06276 |
| EC number | 2.3.1.6: acetyl CoA + choline = acetylcholine + coenzyme A | 3.1.1.7: acetylcholine + $H_2O$ = acetic acid + choline + $H^+$ | 3.1.1.7: acetylcholine + $H_2O$ = acetic acid + choline + $H^+$ |
| Inhibitors | naphthylvinylmethylpyridine ($pIC_{50}$ 6.5) [265] – Mouse | tacrine ($pK_i$ 7.5) [79], galantamine ($pIC_{50}$ 6.3) [124], rivastigmine ($pIC_{50}$ 5.4) [471] | rivastigmine ($pIC_{50}$ 7.4) [471], tacrine ($pK_i$ 7.2) [79] |
| Sub/family-selective inhibitors | – | physostigmine ($pIC_{50}$ 7.6–7.8) [471] | physostigmine ($pIC_{50}$ 7.6–7.8) [471] |
| Selective inhibitors | – | donepezil ($pIC_{50}$ 7.7–8.3) [89, 232, 471], BW284C51 ($pIC_{50}$ 7.7) [247] | bambuterol ($pIC_{50}$ 8.5) [247] |
| Comments | Splice variants of choline O-acetyltransferase are suggested to be differentially distributed in the periphery and CNS (see [48]). | – | – |

**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 [794].



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# Adenosine turnover

Enzymes → Adenosine turnover

**Overview**: A multifunctional, ubiquitous molecule, adenosine acts at cell-surface G protein-coupled receptors, as well as numerous enzymes, including protein kinases and adenylyl cyclase. Extracellular adenosine is thought to be produced either by export or by metabolism, predominantly through ecto-5′-nucleotidase activity (also producing inorganic phosphate). It is inactivated either by extracellular metabolism *via*adenosine deaminase (also producing ammonia) or, following uptake by nucleoside transporters, *via*adenosine deaminase or adenosine kinase (requiring ATP as co-substrate). Intracellular adenosine may be produced by cytosolic 5′-nucleotidases or through S-adenosylhomocysteine hydrolase (also producing L-homocysteine).

| Nomenclature | Adenosine deaminase | Adenosine kinase | Ecto-5′-Nucleotidase | S-Adenosylhomocysteine hydrolase |
|---|---|---|---|---|
| Systematic nomenclature | – | – | CD73 | – |
| Common abbreviation | ADA | ADK | NT5E | SAHH |
| HGNC, UniProt | *ADA*, P00813 | *ADK*, P55263 | *NT5E*, P21589 | *AHCY*, P23526 |
| EC number | 3.5.4.4: adenosine + $H_2O$ = 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 | adenosine, guanine, inosine, uridine | adenosine |
| Inhibitors | – | – | – | DZNep (p$K_i$ 12.3) [252] – Hamster |
| Selective inhibitors | pentostatin (p$IC_{50}$ 10.8) [8], EHNA (p$K_i$ 8.8) [8] | A134974 (p$IC_{50}$ 10.2) [498], ABT702 (p$IC_{50}$ 8.8) [354] | αβ-methyleneADP (p$IC_{50}$ 8.7) [77] | 3-deazaadenosine (p$IC_{50}$ 8.5) [280] |
| 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 [67, 792]. | Pharmacological inhibition of CD73 is being investigated as a novel cancer immunotherapy strategy [768]. | – |



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**Comments**: An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, *CECR1*, Q9NZK5) has been identified [134, 476], which is insensitive to EHNA [836]. Other forms of adenosine deaminase act on ribonucleic acids and may be divided into two families: *ADAT1* (Q9BUB4) deaminates transfer RNA; *ADAR* (EC 3.5.4.37, also known as 136 kDa double-stranded RNA-binding protein, P136, K88DSRBP, Interferon-inducible protein 4); *ADARB1* (EC 3.5.-.-, , also known as dsRNA adenosine deaminase) and *ADARB2* (EC 3.5.-.-, also known as dsRNA adenosine deaminase B2, RNA-dependent adenosine deaminase 3) act on double-stranded RNA. Particular polymorphisms of the ADA gene result in loss-of-function and severe combined immunodeficiency syndrome. Adenosine deaminase is able to complex with dipeptidyl peptidase IV (EC 3.4.14.5, *DPP4*, also known as T-cell activation antigen CD26, TP103, adenosine deaminase complexing protein 2) to form a cell-surface activity [371].

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# ADP-ribosyltransferases (ARTs)

Enzymes → ADP-ribosyltransferases (ARTs)

**Overview**: ADP-ribosylation is a post-translational modification that is catalysed by ADP-ribosyltransferases (ARTs). This modification affects the functions of proteins across a diverse range of cellular pathways and processes. ADP-ribosylhydrolases act in opposition, to remove the modifications.
Nomenclature for the ADP-ribosyltransferases follows the recommendations from Lüscher *et al.* (2022) [412]. This nomenclature subclassifies the enzymes as:

**Poly-ADP-ribosylating (PARylating) ARTs**
The PARylating subfamily contains the well known poly-ADP-ribose polymerases (the 'original' PARPs) PARP1 and PARP2 and the tankyrases TNKS and TNKS2. These enzymes share a conserved H-Y-E catalytic motif, and they all reside in the nucleus.
**Mono-ADP-ribosylating (MARylating) ARTs**
The MARylating subfamily is larger with 11 human genes encoding the enzymes PARP3, -4, -6, -7 (*TIPARP*), -8, -10, -11, -12, -14, -15, -16). The catalytic triad for the MARylating enzymes retains the H-Y residues with the third position being a variable hydrophobic amino acid (E, I, L or Y). Subcellularly the MARylating enzymes are found in the nucleus and/or the cytosol.
ADP-ribosyltransferases are therapeutic targets, with several PARP1/2 inhibitors already in clinical use as antineoplastic agents. Atamparib (RBN2397) is the first clinical candidate that selectively inhibits MARylating PARP7.

# Mono-ADP-ribosylating PARPs

Enzymes → ADP-ribosyltransferases (ARTs) → Mono-ADP-ribosylating PARPs

**Overview**: The enzymes in this subfamily of mono-ADP-ribosylating (MARylating) PARPs are encoded by 11 genes in humans. In published literature these enzymes may be referred to as 'mono-ARTs'. We have included here those enzymes for which small molecule modulators have been reported. Of note is the PARP7 (*TIPARP*) inhibitor atamparib (RBN2397) that is in clinical trial as an antineoplastic for solid tumours.



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| | | |
|---|---|---|
| Nomenclature | poly (ADP-ribose) polymerase 3 | TCDD inducible poly(ADP-ribose) polymerase |
| Common abbreviation | PARP3 | PARP7 |
| HGNC, UniProt | *PARP3*, Q9Y6F1 | *TIPARP*, Q7Z3E1 |
| EC number | 2.4.2.30 | 2.4.2.30 |
| Inhibitors | olaparib ($pK_d$ 8.2) [361], KU0058948 ($pK_d$ 7.2) [425] | atamparib ($pK_d$ 9.7) [546], atamparib ($pIC_{50}$ 8.5) [547], (S)-XY-05 ($pIC_{50}$ 8.4) [275] |
| Selective inhibitors | ME0328 ($pIC_{50}$ 6.1) [441] | – |
| Comments | Located in the nucleus; primarily involved in DNA damage repair | Located in the nucleus and/or cytosol; primarily involved in gene regulation and immune responses. Being investigated as a therapeutic target, with inhibitors proposed to promote immunomodulatory and antineoplastic actions [275, 546]. |

# Poly ADP-ribosylating PARPs

Enzymes → ADP-ribosyltransferases (ARTs) → Poly ADP-ribosylating PARPs

**Overview**: This subfamily of four enzymes (the PARylating PARPs) catalyse the addition of poly-ADP-ribose chains as post-translational protein modifications . The best characterised members are the nuclear enzymes PARP1, PARP2 and the tankyrases (TNKSs). PARPs 1 and 2 appear 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, that are subsequently degraded by a glycohydrolase (*PARG*, Q86W56). The most well defined function of the tankyrases (TNKSs) is their regulatory action on Wnt/β-catenin signalling [482]. PARPs 1 and 2 are targets of PARP inhibitor class anti-cancer drugs which are designed to disrupt the DNA damage response pathways to induce cancer cell death.

| | | |
|---|---|---|
| Nomenclature | poly(ADP-ribose) polymerase 1 | poly(ADP-ribose) polymerase 2 |
| Common abbreviation | PARP1 | PARP2 |
| HGNC, UniProt | *PARP1*, P09874 | *PARP2*, Q9UGN5 |
| EC number | 2.4.2.30 | 2.4.2.30 |
| Selective inhibitors | MC2050 ($pIC_{50}$ 6.9) [525] | – |
| Comments | PARP1 is a molecular target of PARP inhibitor class drugs. These drugs are used to modulate the DNA damage response pathways in susceptible cancers [271]. | PARP2 function is modulated by non-selective PARP inhibitor class drugs. These drugs are used to modulate the DNA damage response pathways in susceptible cancers [271]. |



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**Further reading on Poly ADP-ribosylating PARPs**

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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 [360] | Protein kinase A-mediated phosphorylation [362] | Protein kinase A-mediated phosphorylation [362] |
| Inhibitors | – | – | TPT-004 ($pK_d$ 8.5) [692], rodatristat ($pIC_{50}$ 7.5) [255], compound 23a ($pIC_{50}$ 7.4) [32], telotristat ethyl ($pIC_{50}$ 7.2) [32, 386], TPT-004 ($pIC_{50}$ 7.1) [692], LP533401 ($pIC_{50}$ 6.2) [32] | rodatristat ($pIC_{50}$ 8.1) [255], TPT-004 ($pIC_{50}$ 7.8) [692] |
| Selective inhibitors | α-methylphenylalanine [267] – Rat, fenclonine | α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine | α-propyldopacetamide, 6-fluorotryptophan [540], fenclonine, fenfluramine | α-propyldopacetamide, 6-fluorotryptophan [540], 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 [148]. | – | – |



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**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 creatine synthesis pathway under the influence of arginine:glycine amidinotransferase with L-ornithine as a byproduct. Nitric oxide synthase uses L-arginine to generate nitric oxide, with L-citrulline also as a byproduct.
L-Arginine in proteins may be subject to post-translational modification through methylation, catalysed by protein arginine methyltransferases. Subsequent proteolysis can liberate asymmetric $N^G$,$N^G$-dimethyl-L-arginine (ADMA), which is an endogenous inhibitor of nitric oxide synthase activities. ADMA is hydrolysed by dimethylarginine dimethylhydrolase activities to generate L-citrulline and dimethylamine.

# 2.1.1.- Protein arginine N-methyltransferases

Enzymes → L-Arginine turnover → 2.1.1.- Protein arginine N-methyltransferases

**Overview**: Protein arginine N-methyltransferases (PRMT, EC 2.1.1.-) encompass histone arginine *N*-methyltransferases (PRMT4, PRMT7, EC 2.1.1.125) and myelin basic protein *N*-methyltransferases (PRMT7, EC 2.1.1.126). They are dimeric or tetrameric enzymes which use S-adenosyl methionine as a methyl donor, generating S-adenosylhomocysteine as a by-product. They generate both monomethylated and di-methylated products; these may be symmetric (SDMA) or asymmetric ($N^G$,$N^G$-dimethyl-L-arginine) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.

Information on members of this family may be found in the online database.

# Arginase

Enzymes → L-Arginine turnover → Arginase

**Overview**: Arginase (EC 3.5.3.1) are manganese-containing isoforms, which appear to show differential distribution, where the ARG1 isoform predominates in the liver and erythrocytes, while ARG2 is associated more with the kidney.
Information on members of this family may be found in the online database.

**Comments**: $N^{\omega}$-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 $N^{\omega}$-hydroxy-nor-L-arginine [730], S-(2-boronoethyl)-L-cysteine [127, 387] and 2(*S*)-amino-6-boronohexanoic acid [38, 127].



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# Arginine:glycine amidinotransferase

Enzymes → L-Arginine turnover → Arginine:glycine amidinotransferase

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

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

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

# Dimethylarginine dimethylaminohydrolases

Enzymes → L-Arginine turnover → Dimethylarginine dimethylaminohydrolases

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

| | | |
|---|---|---|
| Nomenclature | $N^G$,$N^G$-Dimethylarginine dimethylaminohydrolase 1 | $N^G$,$N^G$-Dimethylarginine dimethylaminohydrolase 2 |
| Common abbreviation | DDAH1 | DDAH2 |
| HGNC, UniProt | *DDAH1*, O94760 | *DDAH2*, O95865 |
| EC number | 3.5.3.18 | 3.5.3.18 |
| Cofactors | $Zn^{2+}$ | – |
| Inhibitors | compound 2e (p$K_i$ 5.7) [400] | – |

# 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 [519] 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 en-



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zymes 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 $Ca^{2+}$/calmodulin (*CALM1*CALM2CALM3, 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 $IC_{50}$ values in the micromolar range.

| Nomenclature | Endothelial NOS | Inducible NOS | Neuronal NOS |
|---|---|---|---|
| Common abbreviation | eNOS | iNOS | nNOS |
| HGNC, UniProt | *NOS3*, P29474 | *NOS2*, P35228 | *NOS1*, P29475 |
| EC number | 1.14.13.39 | 1.14.13.39 | 1.14.13.39 |
| Endogenous Substrate | L-arginine | L-arginine | L-arginine |
| Products | NO, L-citrulline | NO, L-citrulline | NO, L-citrulline |
| Cofactors | heme, flavin adenine dinucleotide, flavin mononucleotide, NADPH, oxygen, BH4, $Zn^{2+}$ | heme, flavin adenine dinucleotide, flavin mononucleotide, NADPH, oxygen, BH4, $Zn^{2+}$ | heme, flavin adenine dinucleotide, flavin mononucleotide, NADPH, oxygen, BH4, $Zn^{2+}$ |
| Inhibitors | – | – | NANT |
| Selective inhibitors | – | 1400W ($pIC_{50}$ 8.2) [242], 2-amino-4-methylpyridine ($pIC_{50}$ 7.4) [199], PIBTU ($pIC_{50}$ 7.3) [243], NIL ($pIC_{50}$ 5.5) [521], aminoguanidine [131] | 3-bromo-7NI ($pIC_{50}$ 6.1–6.5) [63], 7NI ($pIC_{50}$ 5.3) [29] |

**Comments**: The reductase domain of NOS catalyses the reduction of cytochrome c and other redox-active dyes [492]. NADPH:$O_2$ oxidoreductase catalyses the formation of superoxide anion/$H_2O_2$ in the absence of L-arginine and sapropterin.

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# Carbonic anhydrases

Enzymes → Carbonic anhydrases

**Overview**: Carbonic anhydrases facilitate the interconversion of water and carbon dioxide to bicarbonate ions and protons (EC 4.2.1.1), with over a dozen gene products identified in man. The enzymes function in acid-base balance and the movement of carbon dioxide and water. They are targetted 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$K_i$ 6.5) | methazolamide (p$K_i$ 8.7) [662], acetazolamide (p$K_i$ 8.6) [28], brinzolamide (p$K_i$ 8.6) [662], chlorthalidone (p$K_i$ 8.6) [729] | SLC-0111 (p$K_i$ 8.4) [128] | – | – |

**Further reading on Carbonic anhydrases**


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Kumar S *et al.* (2021) Recent advances in the medicinal chemistry of carbonic anhydrase inhibitors. *Eur J Med Chem* **209**: 112923 [PMID:33121862]

Mishra CB *et al.* (2020) Progress in the development of human carbonic anhydrase inhibitors and their pharmacological applications: Where are we today? *Med Res Rev* **40**: 2485-2565 [PMID:32691504]

Supuran CT. (2020) Exploring the multiple binding modes of inhibitors to carbonic anhydrases for novel drug discovery. *Expert Opin Drug Discov* **15**: 671-686 [PMID:32208982]


# 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.-).



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### Complexes

| | |
|---|---|
| Nomenclature | Propionyl-CoA carboxylase |
| Common abbreviation | PCCA,PCCB |
| Subunits | Propionyl-CoA carboxylase α subunit, Propionyl-CoA carboxylase β subunit |
| EC number | 6.4.1.3 |
| Endogenous substrates | ATP, propionyl-CoA |
| Products | ADP, methylmalonyl-CoA, $P_i$ |
| Cofactors | biotin |
| Comments | Propionyl-CoA carboxylase is able to function in both forward and reverse activity modes, as a ligase (carboxylase) or lyase (decarboxylase), respectively. A mRNA-nanoparticle (mRNA-3927) that encodes both the PCCA and PCCB subunits is in clinical development to replace the defective proteins in patients with the ultra-rare metabolic disease propionic acidaemia [395]. |

### Subunits

| | | | | |
|---|---|---|---|---|
| Nomenclature | Pyruvate carboxylase | Acetyl-CoA carboxylase 1 | Acetyl-CoA carboxylase 2 | γ-Glutamyl carboxylase |
| Common abbreviation | PC | ACC1 | ACC2 | GGCX |
| HGNC, UniProt | *PC*, P11498 | *ACACA*, Q13085 | *ACACB*, O00763 | *GGCX*, P38435 |
| EC number | 6.4.1.1 | 6.4.1.2 | 6.4.1.2 | 4.1.1.90 |
| Endogenous substrates | ATP, pyruvic acid | ATP, acetyl CoA | ATP, acetyl CoA | glutamyl peptides |
| Products | ADP, oxalacetic acid, $P_i$ | malonyl-CoA, ADP, $P_i$ | malonyl-CoA, ADP, $P_i$ | carboxyglutamyl peptides |
| Cofactors | biotin | biotin | biotin | NADPH, vitamin K hydroquinone |
| Inhibitors | – | – | compound 2e ($pIC_{50}$ 8.7) [714], A-908292 ($pIC_{50}$ 7.6) [772] | anisindione |
| Selective inhibitors | – | compound 21 ($pIC_{50}$ 8) [269], TOFA ($pIC_{50}$ 4.9) [844] | compound 21 ($pIC_{50}$ 8.4) [269], TOFA ($pIC_{50}$ 4.9) [844] | – |
| Selective allosteric modulators | – | firsocostat (Negative) ($pIC_{50}$ 8.7) [298] | firsocostat (Negative) ($pIC_{50}$ 8.2) [298] | – |
| Comments | – | Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase. | Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase. | Loss-of-function mutations in γ-glutamyl carboxylase are associated with clotting disorders. |

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

### Further reading on Carboxylases

Tong L. (2005) Acetyl-coenzyme A carboxylase: crucial metabolic enzyme and attractive target for drug discovery. *Cell Mol Life Sci* **62**: 1784-803 [PMID:15968460]
Wang Y *et al*. (2022) Acetyl-CoA Carboxylases and Diseases. *Front Oncol* **12**: 836058 [PMID:35359351]



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# Decarboxylases

Enzymes → Carboxylases and decarboxylases → Decarboxylases

**Overview**: The decarboxylases generate $CO_2$ and the indicated products from acidic substrates, requiring pyridoxal 5-phosphate or pyruvic acid as a co-factor.

| Nomenclature | Glutamic acid decarboxylase 1 | Glutamic acid decarboxylase 2 | Histidine decarboxylase |
|---|---|---|---|
| Common abbreviation | GAD1 | GAD2 | HDC |
| HGNC, UniProt | *GAD1*, Q99259 | *GAD2*, Q05329 | *HDC*, P19113 |
| EC number | 4.1.1.15: L-glutamic acid + $H^+$ -> GABA + $CO_2$ | 4.1.1.15: L-glutamic acid + $H^+$ -> GABA + $CO_2$ | 4.1.1.22 |
| Endogenous substrates | L-glutamic acid, L-aspartic acid | L-glutamic acid, L-aspartic acid | L-histidine |
| Products | GABA | GABA | histamine |
| Cofactors | pyridoxal 5-phosphate | pyridoxal 5-phosphate | pyridoxal 5-phosphate |
| Selective inhibitors | s-allylglycine | s-allylglycine | AMA, FMH [238] |
| Comments | L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [800]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading). | | – |



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| 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 | 5-hydroxy-L-tryptophan, L-tryptophan, levodopa | malonyl-CoA | L-ornithine | phosphatidylserine | S-adenosyl methionine |
| Products | agmatine [846] | 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-methyldopa, benserazide [145], carbidopa | – | APA ($pIC_{50}$ 7.5) [696], eflornithine ($pK_d$ 4.9) [603] | – | sardomozide ($pIC_{50}$ 8) [695] |
| Comments | The presence of a functional ADC activity in human tissues has been questioned [126]. | AADC is a homodimer. | Inhibited by AMP-activated protein kinase-evoked phosphorylation [637] | 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 [568]. | S-allylglycine is also an inhibitor of SAMDC [568]. |

**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 catacholamines in mammalian biology are the neurotransmitter/hormones dopamine, (-)-noradrenaline (norepinephrine) and (-)-adrenaline (epinephrine). These hormone/transmitters are synthesized by sequential metabolism from L-phenylalanine via L-tyrosine. Hydroxylation of L-tyrosine generates levodopa, which is decarboxylated to form dopamine. Hydroxylation of the ethylamine sidechain generates (-)-noradrenaline (norepinephrine), which can be methylated to form (-)-adrenaline (epinephrine). In particular neuronal and adrenal chromaffin cells, the catecholamines dopamine, (-)-noradrenaline and (-)-adrenaline are accumulated into vesicles under the influence of the vesicular monoamine transporters (VMAT1/SLC18A1 and VMAT2/SLC18A2). After release into the synapse or the bloodstream, catecholamines are accumulated through the action cell-surface transporters, primarily the dopamine (DAT/SLC6A3) and norepinephrine transporter (NET/SLC6A2). The primary routes of metabolism of these catecholamines are oxidation via monoamine oxidase activities of methylation via catechol O-methyltransferase.

| Nomenclature | L-Phenylalanine hydroxylase | Tyrosine aminotransferase | L-Tyrosine hydroxylase | Dopamine beta-hydroxylase (dopamine beta-monooxygenase) |
|---|---|---|---|---|
| Common abbreviation | – | TAT | – | DBH |
| HGNC, UniProt | *PAH*, P00439 | *TAT*, P17735 | *TH*, P07101 | *DBH*, P09172 |
| EC number | 1.14.16.1: L-phenylalanine + $O_2$ -> L-tyrosine | 2.6.1.5: L-tyrosine + α-ketoglutaric acid -> 4-hydroxyphenylpyruvic acid + L-glutamic acid | 1.14.16.2: L-tyrosine + $O_2$ -> levodopa | 1.14.17.1: dopamine + $O_2$ = (-)-noradrenaline + $H_2O$ |
| Endogenous substrates | L-phenylalanine | – | L-tyrosine | – |
| Products | L-tyrosine | – | levodopa | – |
| Cofactors | sapropterin | pyridoxal 5-phosphate | sapropterin, $Fe^{2+}$ | L-ascorbic acid, $Cu^{2+}$ |
| Endogenous activators | Protein kinase A-mediated phosphorylation (Rat) [2] | – | Protein kinase A-mediated phosphorylation [360] | – |
| Selective inhibitors | α-methylphenylalanine [267] – Rat, fenclonine | – | α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine | nepicastat ($pIC_{50}$ 8) [698] |
| Comments | PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monooxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria | Tyrosine may also be metabolized in the liver by tyrosine transaminase to generate 4-hydroxyphenylpyruvic acid, which can be further metabolized to homogentisic acid. TAT is a homodimer, where loss-of-function mutations are associated with type II tyrosinemia. | TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [148]. | 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 [99]. |



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| Nomenclature | L-Aromatic amino-acid decarboxylase | Phenylethanolamine N-methyltransferase | Catechol-O-methyltransferase |
|---|---|---|---|
| Common abbreviation | AADC | PNMT | COMT |
| HGNC, UniProt | *DDC*, P20711 | *PNMT*, P11086 | *COMT*, P21964 |
| EC number | 4.1.1.28: levodopa -> dopamine + $CO_2$5-hydroxy-L-tryptophan -> 5-hydroxytryptamine + $CO_2$ This enzyme also catalyses the following reaction:: L-tryptophan -> tryptamine + $CO_2$ | 2.1.1.28: (-)-noradrenaline -> (-)-adrenaline | 2.1.1.6: S-adenosyl-L-methionine + a catechol = S-adenosyl-L-homocysteine + a guaiacol<br>(-)-noradrenaline -> normetanephrine<br>(-)-adrenaline -> metanephrine<br>3,4-dihydroxymandelic acid -> vanillylmandelic acid<br>dopamine -> 3-methoxytyramine |
| Endogenous substrates | 5-hydroxy-L-tryptophan, L-tryptophan, levodopa | – | – |
| Products | 5-hydroxytryptamine, dopamine | – | – |
| Cofactors | pyridoxal 5-phosphate | S-adenosyl methionine | S-adenosyl methionine |
| Inhibitors | – | LY134046 (p$K_i$ 7.6) [225] | tolcapone (soluble enzyme) (p$K_i$ 9.6) [461], tolcapone (membrane-bound enzyme) (p$K_i$ 9.5) [461], entacapone (soluble enzyme) (p$K_i$ 9.5) [461], entacapone (membrane-bound enzyme) (p$K_i$ 8.7) [461] |
| Selective inhibitors | 3-hydroxybenzylhydrazine, L-α-methyldopa, benserazide [145], carbidopa | – | – |
| Comments | AADC is a homodimer. | – | COMT appears to exist in both membrane-bound and soluble forms. COMT has also been described to methylate steroids, particularly hydroxyestradiols |

| 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 dopamine -> 3,4-dihydroxyphenylacetaldehyde + $NH_3$<br>(-)-noradrenaline -> 3,4-dihydroxymandelic acid + $NH_3$<br>(-)-adrenaline -> 3,4-dihydroxymandelic acid + $NH_3$<br>5-hydroxytryptamine -> 5-hydroxyindole acetaldehyde + $NH_3$<br>tyramine -> 4-hydroxyphenyl acetaldehyde + $NH_3$ | 1.4.3.4 |
| Cofactors | flavin adenine dinucleotide | flavin adenine dinucleotide |
| Inhibitors | moclobemide (p$K_i$ 8.3) [351], phenelzine (Irreversible inhibition) (p$K_i$ 7.3) [61], tranylcypromine (p$IC_{50}$ 4.7) [825], selegiline (p$K_i$ 4.2) [511], befloxatone [143], clorgiline, pirlindole [502] | rasagiline (p$IC_{50}$ 7.8) [830], phenelzine (Irreversible inhibition) (p$K_i$ 7.8) [61], lazabemide (p$K_i$ 7.1) [283, 740], selegiline (p$K_i$ 5.7–6) [164, 511], tranylcypromine (p$IC_{50}$ 4.7) [825] |
| Selective inhibitors | – | safinamide (p$K_i$ 6.3) [60] |



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**Further reading on Catecholamine turnover**

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Deshwal S *et al*. (2017) Emerging role of monoamine oxidase as a therapeutic target for cardiovascular disease. *Curr Opin Pharmacol* **33**: 64-69 [PMID:28528298]

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Manzoor S *et al*. (2020) A comprehensive review of monoamine oxidase inhibitors as Anti-Alzheimer's disease agents: A review. *Eur J Med Chem* **206**: 112787 [PMID:32942081]

Silva TB *et al*. (2020) Liver says no: the ongoing search for safe catechol O-methyltransferase inhibitors to replace tolcapone. *Drug Discov Today* **25**: 1846-1854 [PMID:32687872]

Waløen K *et al*. (2017) Tyrosine and tryptophan hydroxylases as therapeutic targets in human disease. *Expert Opin Ther Targets* **21**: 167-180 [PMID:27973928]

# Ceramide turnover

Enzymes → Ceramide turnover

**Overview**: Ceramides are a family of sphingophospholipids synthesized in the endoplasmic reticulum, which mediate cell stress responses, including apoptosis, autophagy and senescence, Serine palmitoyltransferase generates 3-ketosphinganine, which is reduced to dihydrosphingosine. N-Acylation allows the formation of dihydroceramides, which are subsequently reduced to form ceramides. Once synthesized, ceramides are trafficked from the ER to the Golgi bound to the ceramide transfer protein, CERT (*COL4A3BP*, Q9Y5P4). Ceramide can be metabolized via multiple routes, ensuring tight regulation of its cellular levels. Addition of phosphocholine generates sphingomyelin while carbohydrate is added to form glucosyl- or galactosylceramides. Ceramidase re-forms sphingosine or sphinganine from ceramide or dihydroceramide. Phosphorylation of ceramide generates ceramide phosphate. The determination of accurate kinetic parameters for many of the enzymes in the sphingolipid metabolic pathway is complicated by the lipophilic nature of the substrates.

# Serine palmitoyltransferase

Enzymes → Ceramide turnover → Serine palmitoyltransferase

**Overview**: The functional enzyme is a heterodimer of SPT1 (LCB1) with either SPT2 (LCB2) or SPT3 (LCB2B); the small subunits of SPT (ssSPTa or ssSPTb) bind to the heterodimer to enhance enzymatic activity. The complexes of SPT1/SPT2/ssSPTa and SPT1/SPT2/ssSPTb were most active with palmitoylCoA as substrate, with the latter complex also showing some activity with stearoylCoA [289]. 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 [289].

| Nomenclature | serine palmitoyltransferase long chain base subunit 1 | serine palmitoyltransferase long chain base subunit 2 | serine palmitoyltransferase long chain base subunit 3 | serine palmitoyltransferase small subunit A | serine palmitoyltransferase small subunit B |
|---|---|---|---|---|---|
| Common abbreviation | SPT1 | SPT2 | SPT3 | SPTSSA | SPTSSB |
| HGNC, UniProt | *SPTLC1*, O15269 | *SPTLC2*, O15270 | *SPTLC3*, Q9NUV7 | *SPTSSA*, Q969W0 | *SPTSSB*, Q8NFR3 |
| EC number | 2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A + $CO_2$ | 2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A + $CO_2$ | 2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A + $CO_2$ | – | – |
| Cofactors | pyridoxal 5-phosphate | pyridoxal 5-phosphate | pyridoxal 5-phosphate | – | – |
| Inhibitors | – | – | – | – | compound 18 (p$K_i$ 5.8) [320] |
| Selective inhibitors | myriocin (p$K_i$ 9.6) [512] – Mouse | myriocin [512] | myriocin [512] | – | – |



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# 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 + dihydrosphingosine -> dihydroceramide + coenzyme Asphingosine + acylCoA -> ceramide + coenzyme A | | | | | |
| Substrates | C18-CoA [755] | C24- and C26-CoA [418] | C26-CoA and longer [515, 605] | C18-, C20- and C22-CoA [622] | C16-CoA [414, 622] | C14- and C16-CoA [514] |

# Sphingolipid $\Delta^4$-desaturase

Enzymes → Ceramide turnover → Sphingolipid $\Delta^4$-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 ($pK_i$ 6.5) [123], RBM2-1B ($pIC_{50}$ 4.7) [84] | – |
| Comments | Myristoylation of DEGS1 enhances its activity and targets it to the mitochondria [44]. | – |

**Comments**: DEGS1 activity is inhibited by a number of natural products, including curcumin and $\Delta^9$-tetrahydrocannabinol [198].



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# Sphingomyelin synthase

Enzymes → Ceramide turnover → Sphingomyelin synthase

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

| Nomenclature | sphingomyelin synthase 1 | sphingomyelin synthase 2 | sterile alpha motif domain containing 8 |
|---|---|---|---|
| HGNC, UniProt | *SGMS1*, Q86VZ5 | *SGMS2*, Q8NHU3 | *SAMD8*, Q96LT4 |
| EC number | 2.7.8.27: ceramide + phosphatidylcholine -> sphingomyelin + diacylglycerol | 2.7.8.27: ceramide + phosphatidylcholine -> sphingomyelin + diacylglycerol | 2.7.8.-: ceramide + phosphatidylethanolamine -> ceramide phosphoethanolamine |
| Inhibitors | compound 1j ($pIC_{50}$ 5.7) [435] | compound D24 ($pIC_{50}$ 4.9) [156] | – |
| Comments | – | Palmitoylation of sphingomyelin synthase 2 may allow targeting to the plasma membrane [723]. | – |

# 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 | *SMPD1*, P17405 | *SMPD2*, O60906 | *SMPD3*, Q9NY59 | *SMPD4*, Q9NXE4 | *SMPDL3A*, Q92484 | *SMPDL3B*, Q92485 |
| EC number | 3.1.4.12: sphingomyelin -> ceramide + phosphocholine | | | | | |
| Inhibitors | compound 21b ($pIC_{50}$ 6.5) [820], WJYK50 ($pIC_{50}$ 6.3) [819], WJYK50 ($pIC_{50}$ 6.1) [820] | inhibitor A ($pK_i$ 5.8) [824] – Bovine | – | – | – | – |



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# Neutral sphingomyelinase coupling factors

Enzymes → Ceramide turnover → Neutral sphingomyelinase coupling factors

**Overview**: Protein FAN [4] and polycomb protein EED [586] 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) (p$K_i$ 9.4) [310] | – |

# 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 = UDP + glucosylceramide |
| Inhibitors | miglustat (p$K_i$ 5.1) [80] |
| 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 optimae into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

| | |
|---|---|
| Nomenclature | N-acylsphingosine amidohydrolase 1 |
| HGNC, UniProt | *ASAH1*, Q13510 |
| EC number | 3.5.1.23: ceramide -> sphingosine + a fatty acid |
| Comments | This lysosomal enzyme is proteolysed to form the mature protein made up of two chains from the same gene product [393]. |



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# Neutral ceramidases

Enzymes → Ceramide turnover → Neutral ceramidases

**Overview**: The six human ceramidases may be divided on the basis of pH optimae 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 [722]. | – |

**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 optimae 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 [707]. | ACER2 is associated with the Golgi apparatus [810]. | ACER3 is associated with the ER and Golgi apparatus [481]. |

# 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) [262] |

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



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**Further reading on Ceramide turnover**

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Iqbal J *et al*. (2017) Sphingolipids and Lipoproteins in Health and Metabolic Disorders. *Trends Endocrinol Metab* **28**: 506-518 [PMID:28462811]
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Parashuraman S *et al*. (2019) Visualizing sphingolipid biosynthesis in cells. *Chem Phys Lipids* **218**: 103-111 [PMID:30476485]
Presa N *et al*. (2020) Novel signaling aspects of ceramide 1-phosphate. *Biochim Biophys Acta Mol Cell Biol Lipids* **1865**: 158630 [PMID:31958571]
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Snider JM *et al*. (2019) Approaches for probing and evaluating mammalian sphingolipid metabolism. *Anal Biochem* **575**: 70-86 [PMID:30917945]

# 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 [401]. 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) [401].
**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 [196], where a wide variety of cellular and protein abberations are known to perturb chromatin structure, gene transcription and ultimately cellular pathways [42, 675]. 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 [239, 787]) and erasers (*e.g.* the HDAC inhibitors vorinostat, romidepsin and belinostat for the treatment of T-cell lymphomas [214, 382]) 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 [82]. Current progress in this field is reviewed by Simó-Riudalbas and Esteller (2015) [676].

# 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 monomethylated and di-methylated products; these may be symmetric (SDMA) or asymmetric ($N^G$,$N^G$-dimethyl-L-arginine) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.
Information on members of this family may be found in the online database.



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# 3.5.1.- Histone deacetylases (HDACs)

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

**Overview**: Histone deacetylases act as erasers of epigenetic acetylation marks on lysine residues in histones. Removal of the acetyl groups facilitates tighter packing of chromatin (heterochromatin formation) leading to transcriptional repression.
The histone deacetylase family has been classified in to five subfamilies based on phylogenetic comparison with yeast homologues:
Class I contains HDACs 1, 2, 3 and 8
Class IIa contains HDACs 4, 5, 7 and 9
Class IIb contains HDACs 6 and 10
Class III contains the sirtuins (SIRT1-7)
Class IV contains only HDAC11.
Classes I, II and IV use $Zn^+$ as a co-factor, whereas catalysis by Class III enzymes requires $NAD^+$ as a co-factor, and members of this subfamily have ADP-ribosylase activity in addition to protein deacetylase function [646].
HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [119] such as microtubules [332], the hsp90 chaperone [402] and the tumour suppressor p53 [468].
Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [440, 630], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [789]. 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 anticancer therapeutics are reviewed by Simó-Riudalbas and Esteller (2015) [676].

| | |
|---|---|
| Nomenclature | histone deacetylase 6 |
| HGNC, UniProt | *HDAC6*, Q9UBN7 |
| EC number | 3.5.1.98 |
| Inhibitors | trichostatin A ($pK_i$ 9) [72], vorinostat ($pK_i$ 8.8) [72], romidepsin ($pK_i$ 8) [72] |
| Selective inhibitors | ricolinostat ($pIC_{50}$ 8.3) [643] |

### Further reading on 3.5.1.- Histone deacetylases (HDACs)


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Fiorentino F *et al.* (2021) Emerging Therapeutic Potential of SIRT6 Modulators. *J Med Chem* **64**: 9732-9758 [PMID:34213345]
Ho TCS *et al.* (2020) Thirty Years of HDAC Inhibitors: 2020 Insight and Hindsight. *J Med Chem* **63**: 12460-12484 [PMID:32608981]
Kunadis E *et al.* (2021) Targeting post-translational histone modifying enzymes in glioblastoma. *Pharmacol Ther* **220**: 107721 [PMID:33144118]
Liu T *et al.* (2020) Dual-Target Inhibitors Based on HDACs: Novel Antitumor Agents for Cancer Therapy. *J Med Chem* **63**: 8977-9002 [PMID:32320239]
Zhang XH *et al.* (2021) A Review of Progress in Histone Deacetylase 6 Inhibitors Research: Structural Specificity and Functional Diversity. *J Med Chem* **64**: 1362-1391 [PMID:33523672]


### Further reading on Chromatin modifying enzymes


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Beyer JN *et al.* (2021) Advances and Opportunities in Epigenetic Chemical Biology. *Chembiochem* **22**: 17-42 [PMID:32786101]
Carter B *et al.* (2021) The epigenetic basis of cellular heterogeneity. *Nat Rev Genet* **22**: 235-250 [PMID:33244170]
Hogg SJ *et al.* (2020) Targeting the epigenetic regulation of antitumour immunity. *Nat Rev Drug Discov***19**: 776-800 [PMID:32929243]
Oh ES *et al.* (2021) Origins of human disease: the chrono-epigenetic perspective. *Nat Rev Genet* **22**: 533-546 [PMID:33903745]
Tsai K *et al.* (2020) Epigenetic and epitranscriptomic regulation of viral replication. *Nat Rev Microbiol***18**: 559-570 [PMID:32533130]




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# Cyclic nucleotide turnover/signalling

Enzymes → Cyclic nucleotide turnover/signalling

**Overview**: Cyclic nucleotides are second messengers generated by cyclase enzymes from precursor triphosphates and hydrolysed by phosphodiesterases. The cellular actions of these cyclic nucleotides are mediated through activation of protein kinases (cAMP- and cGMP-dependent protein kinases), ion channels (cyclic nucleotide-gated, CNG, and hyperpolarization and cyclic nucleotide-gated, HCN) and guanine nucleotide exchange factors (GEFs, Epac).
For details of the enzymes involved in cGMP synthesis see the Receptor Guanylyl Cyclase (RGC) family, in the Catalytic receptors section.

# Adenylyl cyclases (ACs)

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

**Overview**: Adenylyl cyclase, E.C. 4.6.1.1, converts ATP to cyclic AMP and pyrophosphate. Mammalian membrane-delimited adenylyl cyclases (**nomenclature as approved by the NC-IUPHAR Subcommittee on Adenylyl cyclases** [159]) 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, [599]). Adenosine and its derivatives (*e.g.* 2′,5′-dideoxyadenosine), acting through the P-site,are inhibitors of adenylyl cyclase activity [732]. Four families of membranous adenylyl cyclase are distinguishable: calmodulin (*CALM1*CALM2CALM3, P62158)-stimulated (AC1, AC3 and AC8), $Ca^{2+}$- and Gβγ-inhibitable (AC5, AC6 and AC9), Gβγ-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 [105].

| Nomenclature | adenylyl cyclase 1 | adenylyl cyclase 2 | adenylyl cyclase 3 | adenylyl cyclase 4 | adenylyl cyclase 5 | adenylyl cyclase 6 |
|---|---|---|---|---|---|---|
| Common abbreviation | AC1 | AC2 | AC3 | AC4 | AC5 | AC6 |
| HGNC, UniProt | *ADCY1*, Q08828 | *ADCY2*, Q08462 | *ADCY3*, O60266 | *ADCY4*, Q8NFM4 | *ADCY5*, O95622 | *ADCY6*, O43306 |
| EC number | 4.6.1.1 | 4.6.1.1 | 4.6.1.1 | 4.6.1.1 | 4.6.1.1 | 4.6.1.1 |
| Endogenous activators | calmodulin (*CALM1*CALM2CALM3, P62158), PKC-evoked phosphorylation [349, 721] | Gβγ, PKC-evoked phosphorylation, Raf-evoked phosphorylation [103, 170, 472, 726] | calmodulin (*CALM1*CALM2CALM3, P62158), PKC-evoked phosphorylation [117, 349] | Gβγ [234] | PKC-evoked phophorylation, Gβγ, Raf-evoked phophorylation [170, 237, 378] | Gβγ, Raf-evoked phosphorylation [170, 237] |
| Activators | compound 45 ($pIC_{50}$ 7.7) [627] – Bovine | FD1 [562] | – | – | FD6 [562] | – |
| Endogenous inhibitors | $G\alpha_i$, $G\alpha_o$, Gβγ [726, 727] | – | RGS2, Gβγ, CaM kinase II-evoked phosphorylation [165, 678, 781] | PKC-evoked phophorylation [848] | $G\alpha_i$, $Ca^{2+}$, PKA-evoked phosphorylation, Gβγ, NO [237, 318, 343, 348, 727] | $G\alpha_i$, $Ca^{2+}$, PKA-evoked phosphorylation, PKC-evoked phosphorylation, NO [106, 318, 415, 727, 828] |
| Inhibitors | – | SKF-83566 [130] | – | – | NKY80 ($pIC_{50}$ 5.2) [73, 562] | NKY80 ($pIC_{50}$ 4.8) [73] |
| Selective inhibitors | ST034307 ($pIC_{50}$ 5.6) [76] | – | – | – | – | – |



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| Nomenclature | adenylyl cyclase 7 | adenylyl cyclase 8 | adenylyl cyclase 9 | adenylyl cyclase 10 |
|---|---|---|---|---|
| Common abbreviation | AC7 | AC8 | AC9 | AC10 |
| HGNC, UniProt | *ADCY7*, P51828 | *ADCY8*, P40145 | *ADCY9*, O60503 | *ADCY10*, Q96PN6 |
| EC number | 4.6.1.1 | 4.6.1.1 | 4.6.1.1 | – |
| Endogenous activators | Gβγ, PKC-evoked phosphorylation [46, 779] | calmodulin (*CALM1*CALM2CALM3, P62158) [83] | – | Bicarbonate, $Ca^{2+}$ [105, 443] |
| Endogenous inhibitors | – | PKA-evoked phosphorylation [793] | $Ca^{2+}$/calcineurin [576] | – |
| Inhibitors | – | – | – | TDI-11861 (Binding) (p$K_d$ 8.9) [508], TDI-11861 (p$IC_{50}$ 8.3) [508], KH7 (p$IC_{50}$ 5–5.5) [316], LRE1 (p$IC_{50}$ 5) [608] |
| Comments | ADCY7 is required for NLRP3 inflammasome activation. It catalyses formation of both cyclic-AMP (c-AMP) and dimeric c-AMP (c-di-AMP) the latter of which binds directly to the NLRP3 inflammasome and promotes its assembly into an active complex [449]. | – | – | – |

**Comments**: Many of the activators and inhibitors listed are only somewhat selective or have not been tested against all AC isoforms [73, 130]. AC3 shows only modest *in vitro* activation by $Ca^{2+}$/CaM.

### Further reading on Adenylyl cyclases (ACs)

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Halls ML *et al.* (2017) Adenylyl cyclase signalling complexes - Pharmacological challenges and opportunities. *Pharmacol Ther* **172**: 171-180 [PMID:28132906]

Wiggins SV *et al.* (2018) Pharmacological modulation of the $CO_2$/$HCO_3^-$/pH-, calcium-, and ATP-sensing soluble adenylyl cyclase. *Pharmacol Ther* **190**: 173-186 [PMID:29807057]

# Exchange proteins activated by cyclic AMP (EPACs)

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

**Overview**: Epacs are members of a family of guanine nucleotide exchange factors (ENSFM00250000000899), 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 [189]. 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 [650].



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| | | |
|---|---|---|
| Nomenclature | Rap guanine nucleotide exchange factor 3 | Rap guanine nucleotide exchange factor 4 |
| Common abbreviation | Epac1 | Epac2 |
| HGNC, UniProt | *RAPGEF3*, O95398 | *RAPGEF4*, Q8WZA2 |
| Inhibitors | ESI-09 ($pIC_{50}$ 5.5) [19], CE3F4 | HJC 0350 ($pIC_{50}$ 6.5) [101], ESI-09 ($pIC_{50}$ 4.4–5.2) [19, 102] |
| Comments | EPAC1 enhances growth of brown adipose tissue, and is suggested as a molecular target to combat metabolic diseases [618]. | – |

**Further reading on Exchange proteins activated by cyclic AMP (EPACs)**

Bouvet M *et al*. (2019) The Epac1 Protein: Pharmacological Modulators, Cardiac Signalosome and Pathophysiology *Cells* **8**: 1543 [PMID:31795450]
Fujita T *et al*. (2017) The role of Epac in the heart. *Cell Mol Life Sci* **74**: 591-606 [PMID:27549789]
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Robichaux 3rd WG *et al*. (2018) Intracellular cAMP Sensor EPAC: Physiology, Pathophysiology, and Therapeutics Development. *Physiol Rev* **98**: 919-1053 [PMID:29537337]
Wang P *et al*. (2017) Exchange proteins directly activated by cAMP (EPACs): Emerging therapeutic targets. *Bioorg Med Chem Lett* **27**: 1633-1639 [PMID:28283242]

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

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

**Overview**: 3',5'-Cyclic nucleotide phosphodiesterases (PDEs, 3',5'-cyclic-nucleotide 5'-nucleotidohydrolase), E.C. 3.1.4.17, catalyse the hydrolysis of a 3',5'-cyclic nucleotide (usually cyclic AMP or cyclic GMP). Isobutylmethylxanthine is a nonselective inhibitor with an $IC_{50}$ value in the millimolar range for all isoforms except PDE 8A, 8B and 9A. A 2',3'-cyclic nucleotide 3'-phosphodiesterase (E.C. 3.1.4.37 CNPase) activity is associated with myelin formation in the development of the CNS.

| | | | | | | |
|---|---|---|---|---|---|---|
| Nomenclature | phosphodiesterase 1A | phosphodiesterase 1B | phosphodiesterase 1C | phosphodiesterase 2A | phosphodiesterase 3A | phosphodiesterase 3B |
| Common abbreviation | PDE1A | PDE1B | PDE1C | PDE2A | PDE3A | PDE3B |
| HGNC, UniProt | *PDE1A*, P54750 | *PDE1B*, Q01064 | *PDE1C*, Q14123 | *PDE2A*, O00408 | *PDE3A*, Q14432 | *PDE3B*, Q13370 |
| EC number | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 |
| Rank order of affinity | cyclic GMP > cyclic AMP | cyclic GMP > cyclic AMP | cyclic GMP = cyclic AMP | cyclic AMP≫ cyclic GMP | – | – |
| Endogenous activators | calmodulin (*CALM-1*CALM2CALM3, P62158) | calmodulin (*CALM-1*CALM2CALM3, P62158) | calmodulin (*CALM-1*CALM2CALM3, P62158) | cyclic GMP | – | – |
| Endogenous inhibitors | – | – | – | – | cyclic GMP | cyclic GMP |
| Inhibitors | Lu AF64196 ($pK_i$ 7.2) [381], crisaborole ($pIC_{50}$ 5.2) [13] | Lu AF64196 ($pK_i$ 7.9) [381] | Lu AF64196 ($pK_i$ 7.3) [381] | PF-05180999 ($pIC_{50}$ 8.8) [312], milrinone ($pIC_{50}$<6.5) [705] | cilostazol ($pIC_{50}$ 6.7) [705], inamrinone ($pIC_{50}$ 4.8) [679] | – |



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| | | | | | | |
|---|---|---|---|---|---|---|
| Selective inhibitors | SCH51866 ($pIC_{50}$ 7.2) [753], vinpocetine ($pIC_{50}$ 5.1) [463] | lenrispodun ($pIC_{50}$ 10.2) [430], SCH51866 ($pIC_{50}$ 7.2) [753] | compound 3m ($pIC_{50}$ 8.5) [804], SCH51866 ($pIC_{50}$ 7.2) [753], vinpocetine ($pIC_{50}$ 4.3) [463] | BAY607550 ($pIC_{50}$ 8.3–8.8) [66], EHNA ($pIC_{50}$ 5.3) [507] | cilostamide ($pIC_{50}$ 7.5) [705], anagrelide ($pIC_{50}$ 7.1–7.3) [366, 487, 500], milrinone ($pIC_{50}$ 6.3–6.4) [186, 705] | cilostamide ($pIC_{50}$ 7.3) [705], cilostazol ($pIC_{50}$ 6.4) [705], milrinone ($pIC_{50}$ 6) [705], inamrinone ($pIC_{50}$ 4.5) [705] |
| 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 [327] | Protein kinase A, protein kinase G [132] |
| Inhibitors | ibudilast ($pIC_{50}$ 7.3) [394], RS-25344 ($pIC_{50}$ 7.2) [639] | roflumilast ($pIC_{50}$ 9.4) [467], ibudilast ($pIC_{50}$ 7.2) [394], RS-25344 ($pIC_{50}$ 6.5) [639], roflupram (Knocking down the expression of PDE4B in primary microglial cells led to enhanced level of LC-3 II and decreased activation of inflammasome.) [829] | RS-25344 ($pIC_{50}$ 8.1) [639], ibudilast ($pIC_{50}$ 6.6) [394] | RS-25344 ($pIC_{50}$ 8.4) [639], difamilast ($pIC_{50}$>7.3) [559], CBS-3595 ($pIC_{50}$ 6.1) [16] | gisadenafil ($pIC_{50}$ 8.9) [615], milrinone ($pIC_{50}$ 7.3), icariside II [235] |
| Sub/family-selective inhibitors | rolipram ($pIC_{50}$ 9) [769], CDP840 ($pK_i$ 8) [582], Ro20-1724 ($pIC_{50}$ 6.5) [769] | rolipram ($pIC_{50}$ 9) [769], Ro20-1724 ($pIC_{50}$ 6.4) [769] | CDP840 ($pK_i$ 7.7) [582], rolipram ($pIC_{50}$ 6.5) [769], Ro20-1724 ($pIC_{50}$ 5.4) [769] | CDP840 ($pK_i$ 8.1) [582], rolipram ($pIC_{50}$ 7.2) [769], Ro20-1724 ($pIC_{50}$ 6.2) [769] | – |
| Selective inhibitors | YM976 ($pIC_{50}$ 8.3) [22], apremilast ($pIC_{50}$ 7.8) [648] | – | apremilast ($pIC_{50}$ 6.9) [648] | apremilast ($pIC_{50}$ 7.5) [648] | vardenafil ($pIC_{50}$ 9.7) [71], T0156 ($pIC_{50}$ 9.5) [516], sildenafil ($pIC_{50}$ 8.4–9) [745, 767], tadalafil ($pIC_{50}$ 8.5) [518], SCH51866 ($pIC_{50}$ 7.2) [753], zaprinast ($pIC_{50}$ 6.8) [745] |



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| 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) [333] | – | sildenafil ($pIC_{50}$ 7.4) [767], PDE4 inhibitor 16 ($pIC_{50}$ 5.5) [841] | – | – | – |

| 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 [505] | cyclic AMP≫ cyclic GMP [241] | cyclic AMP≫ cyclic GMP [208] | cyclic AMP≫ cyclic GMP [307] |
| Inhibitors | crisaborole ($pIC_{50}$ 6.1) [13] | BRL50481 ($pIC_{50}$ 4.9) [14] | – | – |
| Selective inhibitors | BRL50481 ($pIC_{50}$ 6.7–6.8) [14, 685] | dipyridamole ($pIC_{50}$ 5.7–6) [241, 645], SCH51866 ($pIC_{50}$ 5.8) [645] | PF-04957325 ($pIC_{50}$ 7.4) [491], dipyridamole ($pIC_{50}$ 5.1) [208] | dipyridamole ($pIC_{50}$ 4.3) [307] |
| 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 [209] | cyclic AMP, cyclic GMP [223] | cyclic AMP, cyclic GMP [202] |
| Inhibitors | SCH51866 ($pIC_{50}$ 5.8) [209], zaprinast ($pIC_{50}$ 4.5) [209] | – | tadalafil ($pIC_{50}$ 6.5) [518], BC11-38 ($pIC_{50}$ 6.5) [96] |
| Selective inhibitors | – | mardepodect ($pIC_{50}$ 9.4) [757] | – |

**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 [321, 322]. PDE4A-D splice variants can be membrane-bound or cytosolic [327]. PDE4 isoforms may be labelled with [$^3$H]rolipram.
PDE6 is a membrane-bound tetramer composed of two catalytic chains (PDE6A or PDE6C and PDE6B), an inhibitory chain (PDE6G or PDE6H) and the PDE6D chain. The enzyme is essentially cyclic GMP specific and is activated by the α-subunit of transducin ($G\alpha_t$) and inhibited by sildenafil, zaprinast and dipyridamole with potencies lower than those observed for PDE5A. Defects in PDE6B are a cause of retinitis pigmentosa and congenital stationary night blindness.



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

Baillie GS *et al*. (2019) Therapeutic targeting of 3′,5′-cyclic nucleotide phosphodiesterases: inhibition and beyond. *Nat Rev Drug Discov* **18**: 770-796 [PMID:31388135]

Bolger GB. (2021) The PDE-Opathies: Diverse Phenotypes Produced by a Functionally Related Multigene Family. *Trends Genet* **37**: 669-681 [PMID:33832760]

Lugnier C *et al*. (2020) Cyclic nucleotide phosphodiesterases: New targets in the metabolic syndrome? *Pharmacol Ther* **208**: 107475 [PMID:31926200]

Peng T *et al*. (2020) Advances in the Development of Phosphodiesterase-4 Inhibitors. *J Med Chem* **63**: 10594-10617 [PMID:32255344]

Piazza GA *et al*. (2020) PDE5 and PDE10 inhibition activates cGMP/PKG signaling to block Wnt/β-catenin transcription, cancer cell growth, and tumor immunity. *Drug Discov Today* **25**: 1521-1527 [PMID:32562844]

Samidurai A *et al*. (2021) Role of phosphodiesterase 1 in the pathophysiology of diseases and potential therapeutic opportunities. *Pharmacol Ther* **226**: 107858 [PMID:33895190]

Turner MJ *et al*. (2021) Cyclic nucleotide phosphodiesterase inhibitors as therapeutic interventions for cystic fibrosis. *Pharmacol Ther* **224**: 107826 [PMID:33662448]

# Cytochrome P450

Enzymes → Cytochrome P450

**Overview**: The cytochrome P450 enzyme superfamily (CYP), E.C. 1.14.-.-, are haem-containing monooxygenases with a vast range of both endogenous and exogenous substrates. These include sterols, fatty acids, eicosanoids, fat-soluble vitamins, hormones, pesticides and carcinogens as well as drugs. Listed below are the human enzymes, their relationship with rodent CYP enzyme activities is obscure in that the species orthologue may not metabolise the same substrates. Some of the CYP enzymes located in the liver are particularly important for drug metabolism, both hepatic and extrahepatic CYP enzymes also contribute to patho/physiological processes. Genetic variation of CYP isoforms is widespread and likely underlies a proportion of individual variation in drug disposition. The superfamily has the root symbol CYP, followed by a number to indicate the family, a capital letter for the subfamily with a numeral for the individual enzyme. Some CYP are able to metabolise multiple substrates, others are oligo- or mono- specific. CYP also catalyse diverse oxidation and reduction reactions. These include ring hydroxylation, N-oxidation, sulfoxidation, epoxidation, the dealkylation of N-, S- and O- moieties, desulfation, deamination, as well as reduction of azo, nitro and N-oxide groups.

# CYP1 family

Enzymes → Cytochrome P450 → CYP1 family

**Overview**: CYP1 enzymes catalyse the generation of highly mutagenic compounds *via* activation of procarcinogens (such as polycyclic aromatic hydrocarbons and aromatic amines) that are present in combustion products. They can also deactivate many anticancer agents [497].

| Nomenclature | CYP1A1 | CYP1A2 | CYP1B1 |
|---|---|---|---|
| HGNC, UniProt | *CYP1A1*, P04798 | *CYP1A2*, P05177 | *CYP1B1*, Q16678 |
| EC number | 1.14.1.1 | 1.14.1.1 | 1.14.1.1 |
| Inhibitors | 65PF ($pIC_{50}$ 6.8) [446] | 5H78PF ($pIC_{50}$ 7.8) [446] | stilbenes [183] |
| Comments | CYP1A1 is an extra-hepatic enzyme. It shows a preference for linear planar aromatic molecules [694]. | CYP1A2 is constitutively expressed in liver. It shows a preference for triangular planar aromatic molecules [694]. | Mainly expressed in extra-hepatic tissues such as breast, prostate and uterus. Can metabolise 17β-estradiol into a mutagen [183], as well as leukotrienes and eicosanoids [171]. Gene variants have been associated with primary congenitial glaucoma [752]. |

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



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# CYP2 family: drug metabolising subset

Enzymes → Cytochrome P450 → CYP2 family: drug metabolising subset

**Overview**: CYP1, 2 and 3 family enzymes are involved in the biotransformation of xenobiotics, including clinically used drugs. Polymorphisms, particularly in the CYP2 family, impact upon an individual's response to drugs [835], including the risk of adverse drug reactions, drug efficacy and dose requirement.

| Nomenclature | CYP2A6 | CYP2A7 | CYP2A13 | CYP2B6 | CYP2C8 | CYP2C9 |
|---|---|---|---|---|---|---|
| HGNC, UniProt | *CYP2A6*, P11509 | *CYP2A7*, P20853 | *CYP2A13*, Q16696 | *CYP2B6*, P20813 | *CYP2C8*, P10632 | *CYP2C9*, P11712 |
| EC number | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 | 1.14.14.51 (S)-limonene + [reduced NADPH–hemoprotein reductase] + O(2) <=> (-)-trans-carveol + [oxidized NADPH–hemoprotein reductase] + H(2)O |
| Competitive inhibitor | – | – | – | – | – | sulphaphenazole [510] |
| Substrates | nicotine, tegafur | – | – | – | – | sulfaphenazole |
| Inhibitors | esculetin ($pIC_{50}$ 6.4) [601] | – | kaempferol ($pK_i$ 6.9) [68] | ticlopidine ($pIC_{50}$ 6.7) [212], sibutramine ($pIC_{50}$ 5.8) [33], thiotepa ($pK_i$ 5.3) [766] | phenelzine ($pK_i$ 5.1) [212] | – |
| Comments | Metabolises coumarin [580]. | CYP2A7 is functionally inactive [224]. | Metabolises tobacco carcinogen, 4-methylnitrosamino)-1-(3-pyridyl)-1-butanone [704]. Expressed specifically in the respiratory tract. | Drug substrates include efavirenz, bupropion, cyclophosphamide, ketamine, propofol [746]. | Converts arachidonic acid to 11(R)-12(S)-epoxyeicosatrienoic acid or 14(R)-15(S)-epoxyeicosatrienoic acid [837]. Drug substrates include amodiaquine and paclitaxel [31]. | Drug substrates include tolbutamide, losartan, phenytoin, warfarin [147, 510, 710]. |



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| Nomenclature | CYP2C19 | CYP2D6 | CYP2E1 | CYP2F1 | CYP2J2 |
|---|---|---|---|---|---|
| HGNC, UniProt | *CYP2C19*, P33261 | *CYP2D6*, P10635 | *CYP2E1*, P05181 | *CYP2F1*, P24903 | *CYP2J2*, P51589 |
| EC number | 1.14.14.51 | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 |
| Inhibitors | compound 30 ($pK_i$ 7.7) [215], compound 51 ($pIC_{50}$ 7.3) [138], UE2343 ($pIC_{50}$ 5.8) [782] | berberine ($pIC_{50}$ 5.4) [385] | compound 23 ($pK_i$ 7.4) [821], 12-Imidazolyl-1-dodecanol ($pK_i$ 6.2) [166] | – | compound 4 ($pIC_{50}$ 6.8) [413], terfenadine ($pIC_{50}$ 5.1) [413] |
| Comments | Drug substrates include omeprazole, proguanil, mephenytoin, diazepam [56, 160, 313]. Common genetic polymorphism for null function. | Substrates include: debrisoquine, metoprolol, codeine [454]. Highly polymorphic enzyme. | Substrates: Ethanol, p-nitrophenol [475]. | Substrate: naphthalene [429]. | Converts arachidonic acid to 14(R)-15(S)-epoxyeicosatrienoic acid [802]. Hydroxylates albendazole[805]. Expressed in cardiomyocytes [688]. |

# CYP2 family: physiological enzymes subset

Enzymes → Cytochrome P450 → CYP2 family: physiological enzymes subset

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

| Nomenclature | CYP2R1 | CYP2S1 | CYP2U1 | CYP2W1 |
|---|---|---|---|---|
| HGNC, UniProt | *CYP2R1*, Q6VVX0 | *CYP2S1*, Q96SQ9 | *CYP2U1*, Q7Z449 | *CYP2W1*, Q8TAV3 |
| EC number | 1.14.13.15 | 1.14.14.1 | 1.14.14.1 | 1.14.14.- |
| Comments | Converts vitamin D3 to calcifediol [109]. Expressed in CD34$^+$ human cord blood hematopoietic stem and early progenitor cells [811]. | Considered an orphan CYP [818]. Possibly involved in polyunsaturated fatty acid ω-1 hydroxylation [204]. | Thymus and brain specific catalysis of ω- and (ω-1)-hydroxylation of fatty acids [120]. Oxidation of *N*-arachidonoylserotonin [673]. Mutations have been associated with hereditary spastic paraplegia [162]. | Appears to have cancer specific expression [570]. Potential drug target in colorectal cancer [121]. |



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# CYP3 family

Enzymes → Cytochrome P450 → CYP3 family

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

| Nomenclature | CYP3A4 | CYP3A5 | CYP3A7 | CYP3A43 |
|---|---|---|---|---|
| HGNC, UniProt | *CYP3A4*, P08684 | *CYP3A5*, P20815 | *CYP3A7*, P24462 | *CYP3A43*, Q9HB55 |
| EC number | 1.14.14.55 1.14.14.56 | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 |
| Substrates | midazolam [791], nifedipine [277] | – | – | – |
| Inhibitors | troleandomycin ($pK_i$ 7.8) [663], ketoconazole ($pK_i$ 7) [266], ritonavir ($pK_i$>7) [383] | ritonavir ($pK_i$ 6.9) [212] | – | – |
| Comments | Metabolises a vast range of xenobiotics, including antidepressants, benzodiazepines, calcium channel blockers, and chemotherapeutic agents [843]. The active site is plastic, with both homotropic and heterotropic cooperativity observed with some substrates [663]. CYP3A4 catalyses the 25-hydroxylation of 5β-cholestane-3α,7α,12α-triol (trihydroxycholestane) [229]. | CYP3A5 is expressed extrahepatically, including in the small intestine. It has overlapping substrate specificity with CYP3A4 [146, 791]. | Fetal form, rarely expressed in adults. Has overlapping substrate specificity with CYP3A4 [146, 791]. | Fetal expression only and considered an orphan CYP [276]. Testosterone may be a substrate [270]. |

# CYP4 family

Enzymes → Cytochrome P450 → CYP4 family

**Overview**: CYP4 family enzymes catalyse the ω-oxidation of endogenous fatty acids and eicosanoids [187]. They have been proposed as molecular targets for the treatment of fatty acid-linked orphan diseases.

| Nomenclature | CYP4A11 | CYP4A22 | CYP4B1 | CYP4F2 |
|---|---|---|---|---|
| HGNC, UniProt | *CYP4A11*, Q02928 | *CYP4A22*, Q5TCH4 | *CYP4B1*, P13584 | *CYP4F2*, P78329 |
| 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 |
| Inhibitors | HET0016 ($pIC_{50}$ 7.7) [817], epalrestat ($pIC_{50}$ 5.7) [817] | – | – | HET0016 ($pIC_{50}$ 7.9) [817], sesamin ($pIC_{50}$ 6.4) [776], 17-octadecynoic acid ($pK_i$ 5.9) [667] |
| Comments | Converts lauric acid to 12-hydroxylauric acid and 11-hydroxylauric acid [597]. Catalyses luciferin-4A O-demethylation [817]. | Catalyses lauric acid and myristic acidω-hydroxylation with low activity [182]. Catalyses luciferin-based probe substrate hydroxylation (Luci-ferin-BE>Luciferin-PFBE>Luciferin-CEE) [182] | Converts 4-ipomeanol into a toxicant, and is also important in oxidation of endobiotic fatty acids and fatty alcohols [734]. | Responsible for ω-hydroxylation of $LTB_4$, $LXB_4$ [513], and tocopherols, including vitamin E [691]. Associated with the warfarin response [840]. |



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| Nomenclature | CYP4F3 | CYP4F8 | CYP4F11 | CYP4F12 |
|---|---|---|---|---|
| HGNC, UniProt | *CYP4F3*, Q08477 | *CYP4F8*, P98187 | *CYP4F11*, Q9HBI6 | *CYP4F12*, Q9HCS2 |
| EC number | 1.14.14.78 1.14.14.79 1.14.14.94 | 1.14.14.1 | 1.14.14.1 1.14.14.78 | 1.14.14.1 |
| Inhibitors | HET0016 ($pIC_{50}$ 7) [817] | – | – | HET0016 ($pIC_{50}$ 5.5) [817] |
| Comments | Responsible for ω-hydroxylation of $LTB_4$, $LXB_4$ [513] and polyunsaturated fatty acids [206, 297], and ω-hydroxylation of fatty acid epoxides [420]. Possible role in Crohn's disease [133]. | Converts $PGH_2$ to 19-hydroxy$PGH_2$ [81] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [543]. | Associated with the warfarin response [840]. | AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12 |

| Nomenclature | CYP4F22 | CYP4V2 | CYP4X1 | CYP4Z1 |
|---|---|---|---|---|
| HGNC, UniProt | *CYP4F22*, Q6NT55 | *CYP4V2*, Q6ZWL3 | *CYP4X1*, Q8N118 | *CYP4Z1*, Q86W10 |
| EC number | 1.14.14.- | 1.14.14.79 | 1.14.14.1 | 1.14.14.1 |
| Inhibitors | – | – | – | compound 7c ($pIC_{50}$ 7.4) [832], compound 7 ($pIC_{50}$ 5.2) [403] |
| Comments | Converts arachidonic acid to 16-HETE and 18-HETE [543]. Involved in production of acylceramide and skin barrier integrity [558]. Variants may influence ichthyosis [195, 205, 548]. | Converts myristic acid to 14-hydroxymyristate, lauric acid to 12-hydroxylaurate, and palmitic acid to 16-hydroxypalmitate [534]. | Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [699]. May influence age of onset of sporadic Creutzfeldt-Jakob diseases [592]. | Hydroxylates lauric acid and myristic acid [833]. Hydroxylates arachidonic acid to 20-HETE [703]. Only expressed in mammary tissue. |



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# CYP5, CYP7 and CYP8 families

Enzymes → Cytochrome P450 → CYP5, CYP7 and CYP8 families

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

| Nomenclature | CYP5A1 | CYP7A1 | CYP7B1 | CYP8A1 | CYP8B1 |
|---|---|---|---|---|---|
| Common abbreviation | Thromboxane-A synthase | Cholesterol 7 alpha-hydroxylase | – | Prostacyclin synthase | – |
| HGNC, UniProt | *TBXAS1*, P24557 | *CYP7A1*, P22680 | *CYP7B1*, O75881 | *PTGIS*, Q16647 | *CYP8B1*, Q9UNU6 |
| EC number | 5.3.99.5: $PGH_2$ = thromboxane $A_2$ | 1.14.14.23 | 1.14.14.29 | 5.3.99.4 | 1.14.14.139 1.14.18.8 |
| Inhibitors | dazoxiben ($pIC_{50}$ 8.5) [609], furegrelate sodium ($pIC_{50}$ 7.8) [260], picotamide ($pIC_{50}$ 3.8) [268], camonagrel [273] | (2S,4S)-ketoconazole ($pIC_{50}$ 9.7) [633] | – | compound 7p ($pIC_{50}$>6) [201], tranylcypromine [272] | econazole ($pK_d$ 7.2) [445], miconazole ($pK_d$ 7) [445], tioconazole ($pK_d$ 6.7) [445], miconazole ($pIC_{50}$ 6.3) [445], econazole ($pIC_{50}$ 6.1), tioconazole ($pIC_{50}$ 5.4) [445] |
| Selective inhibitors | ozagrel ($pIC_{50}$ 8.4) [319, 344, 780] | – | – | – | – |
| Comments | Ozagrel has been used in a number of clinical trials across diverse therapeutic areas, including ischemic stroke (NCT00200356) and dry eye syndrome (NCT01211951). | Converts cholesterol to 7α-hydroxycholesterol [549]. | Converts dehydroepiandrosterone to 7α-DHEA [631]. | Converts prostaglandin $H_2$ ($PGH_2$) to thromboxane $A_2$ (thromboxane $A_2$) [301]. | Converts 7α-hydroxycholest-4-en-3-one to 7-alpha,12α-dihydroxycholest-4-en-3-one (in rabbit) [342] in the biosynthesis of bile acids. The azole antifungal drugs miconazole, econazole and tioconazole inhibit the native reaction of human CYP8B1 [445]. CYP8B1 inhibition offers potential in the treatment of metabolic (fatty) liver disease and diabetes [445]. |



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# CYP11, CYP17, CYP19, CYP20 and CYP21 families

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

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

| Nomenclature | CYP11A1 | CYP11B1 | CYP11B2 | CYP17A1 | CYP19A1 | CYP20A1 | CYP21A2 |
|---|---|---|---|---|---|---|---|
| Common abbreviation | Cholesterol side-chain cleavage enzyme | Steroid 11β-hydroxylase | Aldosterone synthase | – | Aromatase | – | Steroid 21-hydroxylase |
| HGNC, UniProt | *CYP11A1*, P05108 | *CYP11B1*, P15538 | *CYP11B2*, P19099 | *CYP17A1*, P05093 | *CYP19A1*, P11511 | *CYP20A1*, Q6UW02 | *CYP21A2*, P08686 |
| EC number | 1.14.15.6 | 1.14.15.4 | 1.14.15.4 1.14.15.5 | 1.14.14.19 1.14.14.32 | 1.14.14.14 | 1.14.-.- | 1.14.14.16 |
| Inhibitors | (2S,4S)-ketoconazole ($pIC_{50}$ 5.9) [633], mitotane [424, 438] | osilodrostat ($pIC_{50}$ 8.5) [823], metyrapone ($pIC_{50}$ 7.8) [847], (2S,4S)-ketoconazole ($pIC_{50}$ 6.9) [633] | osilodrostat ($pIC_{50}$ 9.7) [823], metyrapone ($pIC_{50}$ 7.1) [847] | abiraterone-C6 oxime ($pIC_{50}$ 7.8) [203], abiraterone ($pIC_{50}$ 7.1–7.3) [285, 596] | anastrozole ($pIC_{50}$ 7.8) [180], (2S,4S)-ketoconazole ($pIC_{50}$ 5.4) [633], aminoglutethimide [579] | – | (2S,4S)-ketoconazole ($pIC_{50}$ 5.4) [633] – Rat |
| Selective inhibitors | – | – | – | galeterone ($pIC_{50}$ 6.5) [293] | letrozole ($pK_i$ 10.7) [493], letrozole ($pIC_{50}$ 7.9) [58], exemestane ($pK_i$ 7.6) [251], exemestane ($pIC_{50}$ 7.4) [251], testolactone ($pK_i$ 4.5) [135] | – | – |
| Comments | Converts cholesterol to pregnenolone plus 4-methylpentanal. | Converts deoxycortisone and 11-deoxycortisol to cortisone and cortisol, respectively. Loss-of-function mutations are associated with familial adrenal hyperplasia and hypertension. | Converts corticosterone to aldosterone | Converts pregnenolone and progesterone to 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. | Unknown function. | Converts progesterone and 17α-hydroxyprogesterone to deoxycortisone and 11-deoxycortisol, respectively |



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# CYP24, CYP26 and CYP27 families

Enzymes → Cytochrome P450 → CYP24, CYP26 and CYP27 families

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

| Nomenclature | CYP24A1 | CYP26A1 | CYP26B1 | CYP26C1 | CYP27A1 | CYP27B1 | CYP27C1 |
|---|---|---|---|---|---|---|---|
| Common abbreviation | Vitamin D3 24-hydroxylase | – | – | – | Sterol 27-hydroxylase | 25-Hydroxyvitamin D 1-alpha-hydroxylase | – |
| HGNC, UniProt | *CYP24A1*, Q07973 | *CYP26A1*, O43174 | *CYP26B1*, Q9NR63 | *CYP26C1*, Q6V0L0 | *CYP27A1*, Q02318 | *CYP27B1*, O15528 | *CYP27C1*, Q4G0S4 |
| EC number | 1.14.15.16 | 1.14.-.- | 1.14.-.- | 1.14.-.- | 1.14.15.15 | 1.14.15.18 | 1.14.19.53 |
| Inhibitors | CTA091 ($pIC_{50}$ 8.2) [595], lunacalcipol ($pIC_{50}$ 7.6) [595], compound 4d ($pIC_{50}$ 4.8) [3] | R116010 ($pIC_{50}$ 8.4) [733], liarozole ($pIC_{50}$ 5.7) [733], talarozole [733] | – | – | compound 4d ($pIC_{50}$ 7.2) [3], CTA091 ($pIC_{50}$<6) [369] | CTA091 ($pIC_{50}$ 6.3) [369] | – |
| Selective inhibitors | – | compound 5 ($pIC_{50}$ 9.5) [257] | – | – | – | – | – |
| Comments | Converts 1,25-dihydroxyvitamin D3 (calcitriol) to 1α,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 [713]. | Converts cholesterol to 27-hydroxycholesterol. Autosomal-recessive mutations in *CYP27A1* cause the bile acid metabolism disorder cerebrotendinous xanthomatosis (CTX, cerebral cholesterosis) [25, 542]. An adenovirus vector encoding human *CYP27A1* (VTX-806; Vivet Therapeutics) is being trialled as a gene replacement therapy for CTX. VTX-806 was granted Orphan Drug Designation by the EMA in September 2024 for this rare disease. | Converts 25-hydroxyvitamin $D_3$ to 1,25-dihydroxyvitamin D3 (calcitriol) | Converts retinol (vitamin A1) to 3,4-didehydroretinol (vitamin A2) [405]. |



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# CYP39, CYP46 and CYP51 families

Enzymes → Cytochrome P450 → CYP39, CYP46 and CYP51 families

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

| Nomenclature | CYP39A1 | CYP46A1 | CYP51A1 |
|---|---|---|---|
| Common abbreviation | – | Cholesterol 24-hydroxylase | Lanosterol 14-α-demethylase |
| HGNC, UniProt | *CYP39A1*, Q9NYL5 | *CYP46A1*, Q9Y6A2 | *CYP51A1*, Q16850 |
| EC number | 1.14.14.26 | 1.14.14.25 | 1.14.14.154 1.14.15.36 |
| Inhibitors | – | soticlestat ($pIC_{50}$ 8.4) [545] | azalanstat ($pK_i$ 9.1) [763], compound 10 (Irreversible inhibition) ($pIC_{50}$>6) [220] |
| Comments | Converts 24-hydroxycholesterol to 7α,24-dihydroxycholesterol [436]. | Converts cholesterol to 24(S)-hydroxycholesterol. | Converts lanosterol to 4,4-dimethylcholesta-8.14.24-trienol. Proteins within the cholesterol pathway are being investigated as potential oncology targets. Small molecule inhibitors of human CYP51A1 have been reported to exhibit anti-proliferative activity in various cancer cells [220]. |

**Further reading on Cytochrome P450**


Angle ED *et al.* (2023) Multidisciplinary Insights into the Structure-Function Relationship of the CYP2B6 Active Site. *Drug Metab Dispos* **51**: 369-384 [PMID:36418184]

Durairaj P *et al.* (2025) Brain Cytochrome P450: Navigating Neurological Health and Metabolic Regulation. *J Xenobiot* **15**: [PMID:40126262]

Eccles JA *et al.* (2022) Detoxification Cytochrome P450s (CYPs) in Families 1-3 Produce Functional Oxylipins from Polyunsaturated Fatty Acids. *Cells* **12**: [PMID:36611876]

Jones G *et al.* (2014) Cytochrome P450-mediated metabolism of vitamin D. *J Lipid Res* **55**: 13-31 [PMID:23564710]

Kim JW *et al.* (2025) Heme-thiolate monooxygenase cytochrome P450 1B1, an old dog with many new tricks. *Pharmacol Rev* **77**: 100045 [PMID:40054133]

Klyushova LS *et al.* (2022) The Role of CYP3A in Health and Disease. *Biomedicines* **10**: [PMID:36359206]

Leow JWH *et al.* (2024) CYP2J2-mediated metabolism of arachidonic acid in heart: A review of its kinetics, inhibition and role in heart rhythm control. *Pharmacol Ther* **258**: 108637 [PMID:38521247]

Lorbek G *et al.* (2012) Cytochrome P450s in the synthesis of cholesterol and bile acids–from mouse models to human diseases. *FEBS J* **279**: 1516-33 [PMID:22111624]

Machalz D *et al.* (2021) Structural insights into understudied human cytochrome P450 enzymes. *Drug Discov Today* **26**: 2456-2464 [PMID:34161845]

Röder A *et al.* (2023) Spotlight on CYP4B1. *Int J Mol Sci* **24**: 2038 [PMID:36768362]


# DNA topoisomerases

Enzymes → DNA topoisomerases

**Overview**: DNA topoisomerases regulate the supercoiling of nuclear DNA to influence the capacity for replication or transcription. The enzymatic function of this series of enzymes involves cutting the DNA to allow unwinding, followed by re-attachment to reseal the backbone. Members of the family are targetted 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 [173, 724] – Bovine | etoposide ($pIC_{50}$ 7.3), teniposide [177] – Mouse |



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**Further reading on DNA topoisomerases**

Baglini E *et al.* (2021) Multiple Topoisomerase I (TopoI), Topoisomerase II (TopoII) and Tyrosyl-DNA Phosphodiesterase (TDP) inhibitors in the development of anticancer drugs. *Eur J Pharm Sci* **156**: 105594 [PMID:33059042]

Bizard AH *et al.* (2020) The many lives of type IA topoisomerases. *J Biol Chem* **295**: 7138-7153 [PMID:32277049]

Buzun K *et al.* (2020) DNA topoisomerases as molecular targets for anticancer drugs. *J Enzyme Inhib Med Chem* **35**: 1781-1799 [PMID:32975138]

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

Dehshahri A *et al.* (2020) Topoisomerase inhibitors: Pharmacology and emerging nanoscale delivery systems. *Pharmacol Res* **151**: 104551 [PMID:31743776]

Riccio AA *et al.* (2020) Molecular mechanisms of topoisomerase 2 DNA-protein crosslink resolution. *Cell Mol Life Sci* **77**: 81-91 [PMID:31728578]

# E3 ubiquitin ligase components

Enzymes → E3 ubiquitin ligase components

**Overview**: Ubiquitination (a.k.a. ubiquitylation) is a protein post-translational modification that typically requires the sequential action of three enzymes: E1 (ubiquitin-activating enzymes), E2 (ubiquitin-conjugating enzymes), and E3 (ubiquitin ligases) [524]. Ubiquitination of proteins can target them for proteasomal degradation, or modulate cellular processes including cell cycle progression, transcriptional regulation, DNA repair and signal transduction.

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

E3 ligases are being exploited as pharmacological targets to facilitate targeted protein degradation (TPD), as an alternative to small molecule inhibitors [47], through the development of proteolysis targeting chimeras (PROTACs) and molecular glues.

| | |
|---|---|
| Nomenclature | cereblon |
| HGNC, UniProt | *CRBN*, Q96SW2 |
| Ligands | thalidomide (Binding) (p$K_d$ 8.1) [346] |
| Comments | Cereblon is the substrate-recognition module of the cullin-RING type E3 ubiquitin ligase CRL4 |

**Further reading on E3 ubiquitin ligase components**

Asatsuma-Okumura T *et al.* (2019) Molecular mechanisms of cereblon-based drugs. *Pharmacol Ther* **202**: 132-139 [PMID:31202702]

Chamberlain PP *et al.* (2019) Development of targeted protein degradation therapeutics *Nat Chem Biol***15**: 937-944 [PMID:31527835]

# Endocannabinoid turnover

Enzymes → Endocannabinoid turnover

**Overview**: The principle endocannabinoids are 2-acylglycerol esters, such as 2-arachidonoylglycerol (2-AG), and *N*-acylethanolamines, such as anandamide (*N*-arachidonoylethanolamine, AEA). The glycerol esters and ethanolamides are synthesised and hydrolysed by parallel, independent pathways. Mechanisms for release and re-uptake of endocannabinoids are unclear, although potent and selective inhibitors of facilitated diffusion of endocannabinoids across cell membranes have been developed [286]. FABP5 (Q01469) has been suggested to act as a canonical intracellular endocannabinoid transporter *in vivo* [113]. 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, [677]). A transacylation enzyme which forms *N*-acylphosphatidylethanolamines has been identified as a cytosolic enzyme, *PLA2G4E* (Q3MJ16) [555]. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism *via* cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [17, 216, 687].

# *N*-Acylethanolamine turnover

Enzymes → Endocannabinoid turnover → *N*-Acylethanolamine turnover

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

| | | | | |
|---|---|---|---|---|
| Nomenclature | *N*-Acylphosphatidyl-ethanolamine-phospholipase D | Fatty acid amide hydrolase | Fatty acid amide hydrolase-2 | *N*-Acylethanolamine acid amidase |
| Common abbreviation | NAPE-PLD | FAAH | FAAH2 | NAAA |
| HGNC, UniProt | *NAPEPLD*, Q6IQ20 | *FAAH*, O00519 | *FAAH2*, Q6GMR7 | *NAAA*, Q02083 |
| EC number | 3.1.4.54 | 3.5.1.99: The enzyme is responsible for the catabolism of neuromodulatory fatty acid amides, including anandamide and oleamide: anandamide + $H_2O$ <=> arachidonic acid + ethanolamine oleamide + $H_2O$ <=> oleic acid + $NH_3$ | 3.5.1.99: The enzyme is responsible for the catabolism of neuromodulatory fatty acid amides, including anandamide and oleamide: anandamide + $H_2O$ <=> arachidonic acid + ethanolamine oleamide + $H_2O$ <=> oleic acid + $NH_3$ | 3.5.1.- |
| Rank order of affinity | – | anandamide > oleamide > N-oleoylethanolamide > N-palmitoylethanolamine [783] | oleamide > N-oleoylethanolamide > anandamide > N-palmitoylethanolamine [783] | N-palmitoylethanolamine > MEA > SEA≥N-oleoylethanolamide > anandamide [747] |
| Inhibitors | hexachlorophene ($pIC_{50}$ 5) [9], bithionol ($pIC_{50}$ 5) [9], ARN19874 ($pIC_{50}$ 4.5) [94] | – | – | – |
| Selective inhibitors | LEI-401 ($pK_i$ 7.6) [517] | ASP8477 ($pIC_{50}$ 8.4) [775], PF-04457845 ($pIC_{50}$ 8.1) [12], JNJ1661010 ($pIC_{50}$ 7.8) [380], PF750 ($pIC_{50}$ 6.3–7.8) [10], OL135 ($pIC_{50}$ 7.4) [783], MM-433593 ($pIC_{50}$ 7), URB597 ($pIC_{50}$ 6.3–7) [783] | OL135 ($pIC_{50}$ 7.9–8.4) [377, 783], URB597 ($pIC_{50}$ 7.5–8.3) [377, 783], ASP8477 ($pIC_{50}$ 7.2) [775] | F215 ($pIC_{50}$ 8.1) [433, 434], ARN726 (Irreversible inhibition) ($pIC_{50}$ 7.6) [620], *S*-OOPP ($pIC_{50}$ 6.4) [689] – Rat, CCP ($pIC_{50}$ 5.3) [742] |
| Comments | NAPE-PLD activity appears to be enhanced by polyamines in the physiological range [450], but fails to transphosphatidylate with alcohols [584] unlike phosphatidylcholine-specific phospholipase D. Identified as a direct target of thiazide and thiazide-like diuretic drugs [112]. | Microdeletion in a pseudogene that is expressed in dorsal root ganglia and brain (*FAAH-OUT*), and a functional single-nucleotide polymorphism in FAAH conferring reduced expression and activity, have been identified in a patient with high anandamide concentrations and pain insensitivity, a discovery that points to a new mechanistic target for developing FAAH-based analgesic therapeutics [282]. | 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 [783]. | – |

**Comments**: Routes for *N*-acylethanolamine biosynthesis other than through NAPE-PLD activity have been identified [743].



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**Further reading on *N*-Acylethanolamine turnover**

Mock ED *et al.* (2023) Anandamide and other N-acylethanolamines: A class of signaling lipids with therapeutic opportunities. *Prog Lipid Res* **89**: 101194 [PMID:36150527]

# 2-Acylglycerol ester turnover

Enzymes → Endocannabinoid turnover → 2-Acylglycerol ester turnover

| Nomenclature | diacylglycerol lipase α | diacylglycerol lipase β | monoacylglycerol lipase | αβ-Hydrolase 6 | αβ-Hydrolase 12 |
|---|---|---|---|---|---|
| Common abbreviation | DAGLα | DAGLβ | MAGL | ABHD6 | ABHD12 |
| HGNC, UniProt | *DAGLA*, Q9Y4D2 | *DAGLB*, Q8NCG7 | *MGLL*, Q99685 | *ABHD6*, Q9BV23 | *ABHD12*, Q8N2K0 |
| EC number | 3.1.1.- | 3.1.1.- | 3.1.1.23 | 3.1.1.23 | 3.1.1.23 |
| Endogenous substrates | diacylglycerol | diacylglycerol | 2-oleoyl glycerol = 2-arachidonoylglycerol≫ anandamide [246] | 1-arachidonoylglycerol > 2-arachidonoylglycerol > 1-oleoylglycerol > 2-oleoyl glycerol [538] | – |
| Inhibitors | LEI105 ($pIC_{50}$ 8.5) [36], DH376 ($pIC_{50}$ 8.2) [553], DO34 ($pIC_{50}$ 8.2) [553], KT-109 ($pIC_{50}$ 5.6) [330] | DH376 ($pIC_{50}$ 8.6) [553], DO34 ($pIC_{50}$ 8.1) [553], LEI105 ($pIC_{50}$ 8.1) [36], KT-109 ($pIC_{50}$ 7.1) [330] | LEI-515 ($pIC_{50}$ 9.3) [356], MJN110 ($pIC_{50}$ 8) [544], CAY10499 ($pIC_{50}$ 6.8) [264] | – | – |
| Selective inhibitors | – | – | JJKK 048 ($pIC_{50}$ 9.3) [1], JNJ-42226314 ($pIC_{50}$ 8.9) [807], KML29 ($pIC_{50}$ 8.5) [100], JZL184 ($pIC_{50}$ 8.1) [457] | WWL70 ($pIC_{50}$ 7.2) [431], WWL123 ($pIC_{50}$ 6.4) [30] | DO264 ($pIC_{50}$ 8) [554] |
| Comments | – | – | – | ABHD6 has also been shown to accept diacylglycerol as a substrate, thereby producing 2-acylglycerols [750]. WWL70 has been suggested to have activity at oxidative metabolic pathways independent of ABHD6 [720]. | – |

**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 [783] and only a few of the inhibitors described have been assessed at this enzyme activity. 2-arachidonoylglycerol has been reported to be hydrolysed by multiple enzyme activities from neural preparations [37], including *ABHD2* (P08910) [509], *ABHD12* (Q8N2K0) [64] and carboxylesterase 1 (*CES1*, P23141 [808]). *ABHD2* (P08910) has also been described as a triacylglycerol lipase and ester hydrolase [473], while *ABHD12* (Q8N2K0) is also able to hydrolyse lysophosphatidylserine [739]. *ABHD12* (Q8N2K0) has been described to be inhibited selectively by pentacyclic triterpenoids, such as oleanolic acid [575].



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**Further reading on Endocannabinoid turnover**

Blankman JL *et al*. (2013) Chemical probes of endocannabinoid metabolism. *Pharmacol Rev* **65**: 849-71 [PMID:23512546]

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

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

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

Janssen FJ *et al*. (2016) Inhibitors of diacylglycerol lipases in neurodegenerative and metabolic disorders. *Bioorg Med Chem Lett* **26**: 3831-7 [PMID:27394666]

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

van Egmond N *et al*. (2021) Targeting Endocannabinoid Signaling: FAAH and MAG Lipase Inhibitors. *Annu Rev Pharmacol Toxicol* **61**: 441-463 [PMID:32867595]

# Eicosanoid turnover

Enzymes → Eicosanoid turnover

**Overview**: Eicosanoids are 20-carbon fatty acids, where the usual focus is the polyunsaturated analogue arachidonic acid and its metabolites. Arachidonic acid is thought primarily to derive from phospholipase A2 action on membrane phosphatidylcholine, and may be re-cycled to form phospholipid through conjugation with coenzyme A and subsequently glycerol derivatives. Oxidative metabolism of arachidonic acid is conducted through three major enzymatic routes: cyclooxygenases; lipoxygenases and cytochrome P450-like epoxygenases, particularly CYP2J2. Isoprostanes are structural analogues of the prostanoids (hence the nomenclature D-, E-, F-isoprostanes and isothromboxanes), which are produced in the presence of elevated free radicals in a non-enzymatic manner, leading to suggestions for their use as biomarkers of oxidative stress. Molecular targets for their action have yet to be defined.

# Cyclooxygenase

Enzymes → Eicosanoid turnover → Cyclooxygenase

**Overview**: Prostaglandin (PG) G/H synthase, most commonly referred to as cyclooxygenase (COX, (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate,hydrogen-donor: oxygen oxidoreductase) activity, catalyses the formation of $PGG_2$ from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of $PGH_2$ from $PGG_2$. COX-1 and -2 can be nonselectively inhibited by ibuprofen, ketoprofen, naproxen, indomethacin and paracetamol (acetaminophen). $PGH_2$ may then be metabolised to prostaglandins and thromboxanes by various prostaglandin synthases in an apparently tissue-dependent manner.

| | | |
|---|---|---|
| Nomenclature | COX-1 | COX-2 |
| HGNC, UniProt | *PTGS1*, P23219 | *PTGS2*, P35354 |
| EC number | 1.14.99.1: Hydrogen donor + arachidonic acid + $2O_2$ = hydrogen acceptor + $H_2O$ + $PGH_2$ arachidonic acid => $PGG_2$ => $PGH_2$ This enzyme is also associated with the following reaction: docosahexaenoic acid => $PGH_3$ | 1.14.99.1: Hydrogen donor + arachidonic acid + $2O_2$ = hydrogen acceptor + $H_2O$ + $PGH_2$ arachidonic acid => $PGG_2$ => $PGH_2$ This enzyme is also associated with the following reaction: docosahexaenoic acid => $PGH_3$ |
| Inhibitors | bromfenac ($pIC_{50}$ 8.1) [27], diclofenac ($pIC_{50}$ 7.9) [850], meclofenamic acid ($pIC_{50}$ 7.3) [370], flurbiprofen ($pIC_{50}$ 7.1) [774], fenoprofen ($pIC_{50}$ 6.8) [27], ketoprofen ($pIC_{50}$ 6.5) [57], suprofen ($pIC_{50}$ 6.2) [57] | benzquinamide ($pIC_{50}$ 8.3) [27], flurbiprofen ($pIC_{50}$ 8) [43], meclofenamic acid ($pIC_{50}$ 7.4) [370], carprofen ($pIC_{50}$ 7) [317], ketorolac ($pIC_{50}$ 6.9) [759], nimesulide ($pIC_{50}$ 6.2) [566], ketoprofen ($pIC_{50}$ 6.2) [57] |
| Selective inhibitors | ketorolac ($pIC_{50}$ 9.7) [774], FK-881 ($pIC_{50}$ 8.3) [339], SC-560 ($pIC_{50}$ 8.1) [683], FR122047 ($pIC_{50}$ 7.5) [552] | celecoxib ($pIC_{50}$ 8.7) [62], SC-236 ($pIC_{50}$ 8–8.3) [248, 581], valdecoxib ($pIC_{50}$ 8.3) [719], SC-58125 ($pIC_{50}$ 7.4) [248], rofecoxib ($pIC_{50}$ 6.1–6.5) [774], lumiracoxib ($pK_i$ 6.5) [65], NS-398 ($pIC_{50}$ 5.4) [541] |



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**Further reading on Cyclooxygenase**

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

# Prostaglandin synthases

Enzymes → Eicosanoid turnover → Prostaglandin synthases

**Overview**: Subsequent to the formation of $PGH_2$, 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 enzyme activities are able to generate prostaglandin $E_2$ ($PGE_2$), prostaglandin $D_2$ ($PGD_2$) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). $PGD_2$ can be metabolised to 9α,11β-prostacyclin $F_{2\alpha}$ through the multifunctional enzyme activity of AKR1C3. $PGE_2$ can be metabolised to 9α,11β-prostaglandin $F_{2\alpha}$ 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 |
|---|---|---|---|---|
| Common abbreviation | Thromboxane-A synthase | Prostacyclin synthase | – | – |
| HGNC, UniProt | *TBXAS1*, P24557 | *PTGIS*, Q16647 | *PTGES*, O14684 | *PTGES2*, Q9H7Z7 |
| EC number | 5.3.99.5: $PGH_2$ = thromboxane $A_2$ | 5.3.99.4 | 5.3.99.3: $PGH_2$ = $PGE_2$ | 5.3.99.3: $PGH_2$ = $PGE_2$ |
| Cofactors | – | – | glutathione | dihydrolipoic acid |
| Inhibitors | dazoxiben ($pIC_{50}$ 8.5) [609], furegrelate sodium ($pIC_{50}$ 7.8) [260], picotamide ($pIC_{50}$ 3.8) [268], camonagrel [273] | compound 7p ($pIC_{50}$>6) [201], tranylcypromine [272] | compound 44 ($pIC_{50}$ 9) [250] | compound 30 ($pIC_{50}$<6) [623] |
| Selective inhibitors | ozagrel ($pIC_{50}$ 8.4) [319, 344, 780] | – | MF63 ($pIC_{50}$ 8.9) [809], compound 39 ($pIC_{50}$ 8.4) [672], compound III ($pIC_{50}$ 7.1) [421] | – |
| Comments | Ozagrel has been used in a number of clinical trials across diverse therapeutic areas, including ischemic stroke (NCT00200356) and dry eye syndrome (NCT01211951). | Converts prostaglandin $H_2$ ($PGH_2$) to thromboxane $A_2$ (thromboxane $A_2$) [301]. | – | Heme-free mPGES2 catalyses the isomerisation of prostaglandin $H_2$ ($PGE_2$) to prostaglandin $E_2$ ($PGE_2$) in the presence of glutathione (GSH); in contrast heme-bound mPGES2 catalyses the degradation of $PGH_2$ to 12-hydroxyheptadecatrienoic acid (HHT) and malondialdehyde (MDA) [718, 813, 814]. In colon cancer cells artemisinin has been reported to bind reversibly to mPGES2 (occupying the $PGH_2$ site), with the effect of blocking $PGE_2$ biosynthesis and inhibiting cell proliferation [245]. |



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| Nomenclature | cPGES | L-PGDS | H-PGDS | AKR1C3 | CBR1 | HPGD |
|---|---|---|---|---|---|---|
| HGNC, UniProt | *PTGES3*, Q15185 | *PTGDS*, P41222 | *HPGDS*, O60760 | *AKR1C3*, P42330 | *CBR1*, P16152 | *HPGD*, P15428 |
| EC number | 5.3.99.3: $PGH_2$ = $PGE_2$ | 5.3.99.2: $PGH_2$ = $PGD_2$ | 5.3.99.2: $PGH_2$ = $PGD_2$ | 1.1.1.188: $PGD_2$ + $NADP^+$ = $PGF_{2\alpha}$ + NADPH + $H^+$ 1.3.1.20 1.1.1.213 1.1.1.239 1.1.1.64 | 1.1.1.197 1.1.1.184 1.1.1.189: $PGE_2$ + $NADP^+$ = $PGF_{2\alpha}$ + NADPH + $H^+$ | 1.1.1.141 15-hydroxyprostaglandins => 15-ketoprostaglandins $LXA_4$ => 15-keto-lipoxin $A_4$ |
| Cofactors | – | – | – | $NADP^+$ | $NADP^+$ | – |
| Inhibitors | – | – | TFC007 ($pIC_{50}$ 7.1) [530], HQL-79 ($pIC_{50}$ 5.3–5.5) [24] | tolfenamic acid ($pK_i$ 8.1) [602] flufenamic acid, indomethacin, flavonoids such as 2′-hydroxyflavanone ($pIC_{50}$ 6.5) [490, 682] | wedelolactone ($pIC_{50}$ 5.4) [849] | compound 3 ($pIC_{50}$ 8.1) [803], ML148 ($pIC_{50}$ 7.2) [350] |
| Selective inhibitors | – | AT-56 ($pK_i$ 4.1) [341] | – | – | – | – |
| Comments | Phosphorylated and activated by casein kinase 2 (CK2) [392]. Appears to regulate steroid hormone function by interaction with dimeric hsp90 [97, 363]. | – | – | AKR1C3 also exhibits an hydroxysteroid dehydrogenase activity. | – | – |

**Comments**: YS121 has been reported to inhibit mPGES1 and 5-LOX with a $pIC_{50}$value of 5.5 [396].

### Further reading on Prostaglandin synthases

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

# Lipoxygenases

Enzymes → Eicosanoid turnover → Lipoxygenases

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



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| 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 + $O_2$ = $LTA_4$ + $H_2O$ | 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 [470] | – | – | – | – | – |
| Inhibitors | BW B70C ($pIC_{50}$ 6.7) [578] | – | – | ML351 ($pIC_{50}$ 6.7) [606], PD-146176 ($pK_i$ 6.7) [661] | compound 21n ($pIC_{50}$ 7.3) [785], MLS000536924 ($pK_i$ 5.6) [353] | – |
| Selective inhibitors | CJ13610 ($pIC_{50}$ 7.2) [207], PF-04191834 ($pIC_{50}$ 6.6) [488], zileuton ($pIC_{50}$ 6.4) [92] | – | ML355 ($pIC_{50}$ 6.5) [465] | compound 34 ($pK_i$>8) [607] | – | – |
| Comments | FLAP activity can be inhibited by MK-886 [172] and BAY-X1005 [302] leading to a selective inhibition of 5-LOX activity | – | – | – | A novel class of inhibitors for the human enzyme has been recently identified by virtual screening [760]. | E-LOX metabolises the product from the 12R-lipoxygenase (12R-HPETE) to a specific epoxyalcohol compound [831]. |

**Comments**: An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 [228]. Some general LOX inhibitors are nordihydroguiaretic 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 [636]. 2-TEDC is used as 5-, 12- and 15-LOX inhibitor [116].



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# Leukotriene and lipoxin metabolism

Enzymes → Eicosanoid turnover → Leukotriene and lipoxin metabolism

**Overview**: Leukotriene $A_4$ ($LTA_4$), 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 $LTA_4$ at the 6 position with reduced glutathione to generate $LTC_4$ occurs under the influence of leukotriene $C_4$ synthase, with the subsequent formation of $LTD_4$ and $LTE_4$, all three of which are agonists at CysLT receptors. $LTD_4$ formation is catalysed by γ-glutamyltransferase, and subsequently dipeptidase 2 removes the terminal glycine from $LTD_4$ to generate $LTE_4$. Leukotriene $A_4$ hydrolase converts the 5,6-epoxide $LTA_4$ to the 5-hydroxylated $LTB_4$, an agonist for BLT receptors. $LTA_4$ is also acted upon by 12S-LOX to produce the trihydroxyeicosatetraenoic acids lipoxins $LXA_4$ and $LXB_4$. Treatment with a $LTA_4$ hydrolase inhibitor in a murine model of allergic airway inflammation increased $LXA_4$ levels, in addition to reducing $LTB_4$, in lung lavage fluid [611]. $LTA_4$ 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 $LTA_4$ hydrolase converted chiral 5S(6)-epoxide-containing intermediates to resolvin E1 and 18S-resolvin E1 [556].

| Nomenclature | Leukotriene C4 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 $LTC_4$ + $H_2O$ => $LTD_4$ + L-glutamate | 3.4.13.19: $LTD_4$ + $H_2O$ = $LTE_4$ + glycine | | 3.3.2.6 |
| Inhibitors | AZD9898 ($pIC_{50}$ 9.5) [528, 629], example 36 ($pIC_{50}$ 8.1) [629] | acivicin ($pIC_{50}$ 6.2) [18], GGsTop ($pK_i$ 3.8) [290] | cilastatin ($pK_i$ 6) [263] | – | bestatin ($pK_i$ 5.4) [563] |
| Selective inhibitors | GJG057 ($pIC_{50}$ 7.4) [736] | – | – | – | LYS006 ($pIC_{50}$ 8.4) [483], DG-051 ($pIC_{50}$ 7.3) [642] |

**Comments**: LTA4H is a member of a family of arginyl aminopeptidases (ENSFM00250000001675), which also includes aminopeptidase B (*RNPEP*, 9H4A4) and aminopeptidase B-like 1 (*RNPEPL1*, Q9HAU8). Dipeptidase 1 and 2 are members of a family of membrane dipeptidases, which also includes (*DPEP3*, Q9H4B8) for which $LTD_4$ appears not to be a substrate.

### Further reading on Eicosanoid turnover


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Häfner AK *et al.* (2019) Beyond leukotriene formation-The noncanonical functions of 5-lipoxygenase. *Prostaglandins Other Lipid Mediat* **142**: 24-32 [PMID:30930090]

Imig JD. (2020) Eicosanoid blood vessel regulation in physiological and pathological states. *Clin Sci (Lond)***134**: 2707-2727 [PMID:33095237]

Mitchell JA *et al.* (2019) Eicosanoids, prostacyclin and cyclooxygenase in the cardiovascular system. *Br J Pharmacol* **176**: 1038-1050 [PMID:29468666]

Orafaie A *et al.* (2020) An overview of lipoxygenase inhibitors with approach of in vivo studies. *Prostaglandins Other Lipid Mediat* **148**: 106411 [PMID:31953016]

Seo MJ *et al.* (2017) Prostaglandin synthases: Molecular characterization and involvement in prostaglandin biosynthesis. *Prog Lipid Res* **66**: 50-68 [PMID:28392405]

Thulasingam M *et al.* (2020) Integral Membrane Enzymes in Eicosanoid Metabolism: Structures, Mechanisms and Inhibitor Design. *J Mol Biol* **432**: 4999-5022 [PMID:32745470]

Xu D *et al.* (2021) Pathophysiological role of prostaglandin E synthases in liver diseases. *Prostaglandins Other Lipid Mediat* **154**: 106552 [PMID:33930567]




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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 [193] where GABA is principally accumulated in vesicles through the action of the vesicular inhibitory amino acid transporter SLC32A1. The role of γ-aminobutyraldehyde dehydrogenase (ALDH9A1) in neurotransmitter GABA synthesis is less clear. Following release from neurons, GABA may interact with either $GABA_A$ or $GABA_B$ receptors and may be accumulated in neurones and glia through the action of members of the SLC6 family of transporters. Successive metabolism through GABA transaminase and succinate semialdehyde dehydrogenase generates succinic acid, which may be further metabolized in the mitochondria in the tricarboxylic acid cycle.

| | | |
|---|---|---|
| Nomenclature | Glutamic acid decarboxylase 1 | Glutamic acid decarboxylase 2 |
| Common abbreviation | GAD1 | GAD2 |
| HGNC, UniProt | *GAD1*, Q99259 | *GAD2*, Q05329 |
| EC number | 4.1.1.15: L-glutamic acid + $H^+$ -> GABA + $CO_2$ | 4.1.1.15: L-glutamic acid + $H^+$ -> GABA + $CO_2$ |
| Endogenous substrates | L-glutamic acid, L-aspartic acid | L-glutamic acid, L-aspartic acid |
| Products | GABA | GABA |
| Cofactors | pyridoxal 5-phosphate | pyridoxal 5-phosphate |
| Selective inhibitors | s-allylglycine | s-allylglycine |
| Comments | L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [800]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading) | |

| | | | |
|---|---|---|---|
| Nomenclature | aldehyde dehydrogenase 9 family member A1 | 4-aminobutyrate aminotransferase | aldehyde dehydrogenase 5 family member A1 |
| Common abbreviation | – | GABA-T | SSADH |
| HGNC, UniProt | *ALDH9A1*, P49189 | *ABAT*, P80404 | *ALDH5A1*, P51649 |
| EC number | 1.2.1.47: 4-trimethylammoniobutanal + NAD + $H_2O$ = 4-trimethylammoniobutanoate + NADPH + $2H^+$ 1.2.1.3: an aldehyde + $H_2O$ + NAD = a carboxylate + $2H^+$ + NADH 1.2.1.19: 4-aminobutanal + NAD + $H_2O$ = GABA + NADH + $H^+$ | 2.6.1.19: GABA + α-ketoglutaric acid = L-glutamic acid + 4-oxobutanoate 2.6.1.22: (S)-3-amino-2-methylpropanoate + α-ketoglutaric acid = 2-methyl-3-oxopropanoate + L-glutamic acid | 1.2.1.24: 4-oxobutanoate + NAD + $H_2O$ = succinic acid + NADH + $2H^+$ 4-hydroxy-trans-2-nonenal + NAD + $H_2O$ = 4-hydroxy-trans-2-nonenoate + NADH + $2H^+$ |
| Cofactors | NAD | pyridoxal 5-phosphate | NAD [666] |
| Inhibitors | – | vigabatrin (Irreversible inhibition) (p$K_i$ 3.1) [442, 674] | 4-acryloylphenol (p$IC_{50}$ 6.5) [725] |



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**Further reading on GABA turnover**

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Koenig MK *et al.* (2017) Phenotype of GABA-transaminase deficiency. *Neurology* **88**: 1919-1924 [PMID:28411234]

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

# Glycerophospholipid turnover

Enzymes → Glycerophospholipid turnover

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

# Phosphoinositide-specific phospholipase C

Enzymes → Glycerophospholipid turnover → Phosphoinositide-specific phospholipase C

**Overview**: Phosphoinositide-specific phospholipase C (PLC, EC 3.1.4.11), catalyses the hydrolysis of $PIP_2$ to $IP_3$ 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. $Ca^{2+}$ ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC-δ activity. PLC has been suggested to be activated non-selectively by the small molecule *m*3M3FBS [35], although this mechanism of action has been questioned [407]. The aminosteroid U73122 has been described as an inhibitor of phosphoinositide-specific PLC [684], although its selectivity among the isoforms is untested and it has been reported to occupy the $H_1$ histamine receptor [334].

| 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 + $H_2O$ = 1D-*myo*-inositol 1,4,5-trisphosphate + diacylglycerol | | | |
| Endogenous activators | Gαq, Gα11, Gβγ [314, 574, 686] | Gα16, Gβγ, Rac2 (*RAC2*, P15153) [86, 337, 338, 422, 574] | Gαq, Gβγ [91, 422, 574] | Gαq [355] |



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| Nomenclature | PLCγ1 | PLCγ2 | PLCδ1 | PLCδ3 | PLCδ4 |
|---|---|---|---|---|---|
| HGNC, UniProt | *PLCG1*, P19174 | *PLCG2*, P16885 | *PLCD1*, P51178 | *PLCD3*, Q8N3E9 | *PLCD4*, Q9BRC7 |
| EC number | 3.1.4.11: 1-phosphatidyl-1D-*myo*-inositol 4,5-bisphosphate + $H_2O$ = 1D-*myo*-inositol 1,4,5-trisphosphate + diacylglycerol | | | | |
| Endogenous activators | $PIP_3$ [34] | $PIP_3$, Rac1 (*RAC1*, P63000), Rac2 (*RAC2*, P15153), Rac3 (*RAC3*, P60763) [34, 587, 764] | Transglutaminase II, p122-RhoGAP {Rat}, spermine, Gβγ [281, 324, 529, 574] | – | – |
| Endogenous inhibitors | – | – | Sphingomyelin [577] | – | – |
| Inhibitors | – | CCT129957 ($pIC_{50}$ 5.5) [619] | – | – | – |

| Nomenclature | PLCε1 | PLCζ1 | PLCη1 | PLCη2 |
|---|---|---|---|---|
| HGNC, UniProt | *PLCE1*, Q9P212 | *PLCZ1*, Q86YW0 | *PLCH1*, Q4KWH8 | *PLCH2*, O75038 |
| EC number | 3.1.4.11: 1-phosphatidyl-1D-*myo*-inositol 4,5-bisphosphate + $H_2O$ = 1D-*myo*-inositol 1,4,5-trisphosphate + diacylglycerol | | | |
| Endogenous activators | Ras, rho [690, 795] | – | – | Gβγ [845] |

**Comments**: A series of PLC-like proteins (*PLCL1*, Q15111; *PLCL2*, Q9UPR0 and *PLCH1*, Q4KWH8) form a family with PLCδ and PLCζ1 isoforms, but appear to lack catalytic activity. PLC-δ2 has been cloned from bovine sources [503].

### Further reading on Phosphoinositide-specific phospholipase C

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

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



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# Phospholipase $A_2$

Enzymes → Glycerophospholipid turnover → Phospholipase $A_2$

**Overview**: Phospholipase $A_2$ ($PLA_2$, EC 3.1.1.4) cleaves the *sn*-2 fatty acid of phospholipids, primarily phosphatidylcholine, to generate lysophosphatidylcholine and arachidonic acid. Most commonly-used inhibitors (*e.g.* bromoenol lactone, arachidonyl trifluoromethyl ketone or methyl arachidonyl fluorophosphonate) are either non-selective within the family of phospholipase $A_2$ enzymes or have activity against other eicosanoid-metabolising enzymes.
**Secreted or extracellular forms:** $sPLA_2$-1B, $sPLA_2$-2A, $sPLA_2$-2D, $sPLA_2$-2E, $sPLA_2$-2F, $sPLA_2$-3, $sPLA_2$-10 and $sPLA_2$-12A
**Cytosolic, calcium-dependent forms:** $cPLA_2$-4A, $cPLA_2$-4B, $cPLA_2$-4C, $cPLA_2$-4D, $cPLA_2$-4E and $cPLA_2$-4F
**Other forms:** $PLA_2$-G5, $iPLA_2$-G6, $PLA_2$-G7 and PAFAH2 (platelet-activating factor acetylhydrolase 2)

| Nomenclature | $sPLA_2$-1B | $sPLA_2$-2D | $sPLA_2$-2E | $sPLA_2$-2F | $sPLA_2$-3 | $cPLA_2$-4A |
|---|---|---|---|---|---|---|
| HGNC, UniProt | *PLA2G1B*, P04054 | *PLA2G2D*, Q9UNK4 | *PLA2G2E*, Q9NZK7 | *PLA2G2F*, Q9BZM2 | *PLA2G3*, Q9NZ20 | *PLA2G4A*, P47712 |
| EC number | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 |
| Inhibitors | compound 28xvii ($pIC_{50}$ 8.9) [284] | compound 12e ($pIC_{50}$ 8.1) [565] | compound 12e ($pIC_{50}$ 8.1) [565] | compound 12e ($pIC_{50}$ 7.3) [565] | – | compound 57 ($pIC_{50}$ 8.4) [466] |
| Comments | – | – | – | – | – | $cPLA_2$-4A also expresses lysophospholipase (EC 3.1.1.5) activity [670]. |

| Nomenclature | $cPLA_2$-4B | $cPLA_2$-4C | $cPLA_2$-4D | $cPLA_2$-4E | $cPLA_2$-4F | $PLA_2$-G5 |
|---|---|---|---|---|---|---|
| HGNC, UniProt | *PLA2G4B*, P0C869 | *PLA2G4C*, Q9UP65 | *PLA2G4D*, Q86XP0 | *PLA2G4E*, Q3MJ16 | *PLA2G4F*, Q68DD2 | *PLA2G5*, P39877 |
| EC number | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 |
| Inhibitors | – | – | – | – | – | BAY-439 ($pIC_{50}$ 8.1) [665], compound 12e ($pIC_{50}$ 7.5) [565], BAY-439 (Binding) ($pK_d$ 6.7) [665] |

| Nomenclature | $iPLA_2$-G6 | $sPLA_2$-10 | $sPLA_2$-12A | platelet activating factor acetylhydrolase 2 |
|---|---|---|---|---|
| HGNC, UniProt | *PLA2G6*, O60733 | *PLA2G10*, O15496 | *PLA2G12A*, Q9BZM1 | *PAFAH2*, Q99487 |
| EC number | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.47 |
| Inhibitors | – | compound 12e ($pIC_{50}$ 7.7) [565] | – | – |
| Comments | – | – | – | PAFAH2 also expresses PAF hydrolase activity (EC 3.1.1.47) |

**Comments**: The sequence of $PLA_2$-2C suggests a lack of catalytic activity, while $PLA_2$-12B (GXIIB, GXIII $sPLA_2$-like) appears to be catalytically inactive [634]. A further fragment has been identified with sequence similarities to Group II $PLA_2$ members. Otoconin 90 (OC90) shows sequence homology to $PLA_2$-G10.

A binding protein for secretory phospholipase $A_2$ has been identified which shows modest selectivity for $sPLA_2$-1B over $sPLA_2$-2A, and also binds snake toxin phospholipase $A_2$ [20]. The binding protein appears to have clearance function for circulating secretory phospholipase $A_2$, as well as signalling functions, and is a candidate antigen for idiopathic membraneous nephropathy [45]. $PLA_2$-G7 and PAFAH2 also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47).



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**Further reading on Phospholipase $A_2$**

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

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

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

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

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

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

# Phosphatidylcholine-specific phospholipase D

Enzymes → Glycerophospholipid turnover → Phosphatidylcholine-specific phospholipase D

**Overview**: Phosphatidylcholine-specific phospholipase D (PLD, EC 3.1.4.4) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidylation reaction [610].

| Nomenclature | PLD1 | PLD2 |
|---|---|---|
| HGNC, UniProt | *PLD1*, Q13393 | *PLD2*, O14939 |
| EC number | 3.1.4.4 | 3.1.4.4 A phosphatidylcholine + $H_2O$ <=> choline + a phosphatidate |
| Endogenous activators | ADP-ribosylation factor 1 (*ARF1*, P84077), $PIP_2$, RhoA, PKC evoked phosphorylation, RalA [288, 469] | ADP-ribosylation factor 1 (*ARF1*, P84077), $PIP_2$ [459], oleic acid [644] |
| Endogenous inhibitors | Gβγ [598] | Gβγ [598] |
| Inhibitors | FIPI ($pIC_{50}$ 8) [657] | – |
| Selective inhibitors | compound 69 ($pIC_{50}$ 7.3) [657] | VU0364739 ($pIC_{50}$ 7.7) [419] |

**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 [253]). Additionally, an N-acylethanolamine-specific phospholipase D (*NAPEPLD*, Q6IQ20) has been characterized, which appears to have a role in the generation of endocannabinoids/endovanilloids, including anandamide [561]. This enzyme activity appears to be enhanced by polyamines in the physiological range [450] and fails to transphosphatidylate with alcohols [584].

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 [564]. PLD4 is described not to have phospholipase D catalytic activity [826], but has been associated with inflammatory disorders [560, 709, 731]. Sequence analysis suggests that PLD5 is catalytically inactive.

**Further reading on Phosphatidylcholine-specific phospholipase D**

Brown HA *et al*. (2017) Targeting phospholipase D in cancer, infection and neurodegenerative disorders. *Nat Rev Drug Discov* **16**: 351-367 [PMID:28209987]

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

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

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# 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 | 3.1.3.16 3.1.3.48 3.1.3.67 |
| Substrates | – | phosphatidic acid | – | – | phosphatidic acid | – | phosphatidylinositol (3,4,5)-trisphosphate |

**Further reading on Lipid phosphate phosphatases**


Csolle MP *et al.* (2020) PTEN and Other PtdIns(3,4,5)$P_3$ Lipid Phosphatases in Breast Cancer. *Int J Mol Sci* **21**: [PMID:33276499]

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

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

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

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

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


# Phosphatidylinositol kinases

Enzymes → Glycerophospholipid turnover → Phosphatidylinositol kinases

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

**Phosphatidylinositol 3-kinases**
Phosphatidylinositol 3-kinases (PI3K, provisional nomenclature) catalyse the introduction of a phosphate into the 3-position of phosphatidylinositol (PI), phosphatidylinositol 4-phosphate (PIP) or phosphatidylinositol 4,5-bisphosphate ($PIP_2$). 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 p110α, p110β and p110δ catalytic subunits, with predominantly p85 and p55 regulatory subunits. The single catalytic subunit that forms Class IB PI3K is p110γ. 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-C2α, β and β, and include Ras-binding, Phox homology and two C2 domains.



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

**Phosphatidylinositol 4-kinases**

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

| Nomenclature | phosphatidylinositol 4-kinase alpha | phosphatidylinositol 4-kinase beta | phosphatidylinositol 4-kinase type 2 alpha | phosphatidylinositol 4-kinase type 2 beta |
|---|---|---|---|---|
| Common abbreviation | PI4KIIIα/PIK4CA | PI4KIIIβ/PIK4CB | PI4KIIα/PI4K2A | PI4KIIβ/PI4K2B |
| HGNC, UniProt | *PI4KA*, P42356 | *PI4KB*, Q9UBF8 | *PI4K2A*, Q9BTU6 | *PI4K2B*, Q8TCG2 |
| EC number | 2.7.1.67 | 2.7.1.67 | 2.7.1.67 | 2.7.1.67 |
| Endogenous activation | – | PKD-mediated phosphorylation [304] | – | – |
| Sub/family-selective inhibitors | wortmannin ($pIC_{50}$ 6.7–6.8) [244, 504] | wortmannin ($pIC_{50}$ 6.7–6.8) [244, 504] | adenosine ($pIC_{50}$ 4.5–5) [712] | adenosine ($pIC_{50}$ 4.5–5) [712] |
| Selective inhibitors | – | PIK-93 ($pIC_{50}$ 7.7) [40, 391] | – | – |

| 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 | C2α/PIK3C2A | C2β/PIK3C2B | C2γ/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) [451] | PI-103 ($pIC_{50}$ 8) [305] | – |

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



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| Nomenclature | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta |
|---|---|---|---|---|
| Common abbreviation | PI3Kα | PI3Kβ | PI3Kγ | PI3Kδ |
| HGNC, UniProt | *PIK3CA*, P42336 | *PIK3CB*, P42338 | *PIK3CG*, P48736 | *PIK3CD*, O00329 |
| EC number | 2.7.1.153 2.7.11.1 | 2.7.1.153 | 2.7.1.153 | 2.7.1.153 |
| Inhibitors | PIK-75 ($pIC_{50}$ 9.5) [305], gedatolisib ($pIC_{50}$ 9.4) [756], PF-04691502 ($pK_i$ 9.2) [447], PI-103 ($pIC_{50}$ 8.7) [617], BGT-226 ($pIC_{50}$ 8.4) [484], KU-0060648 ($pIC_{50}$ 8.4) [87], dactolisib ($pIC_{50}$ 8.4) [477], apitolisib ($pIC_{50}$ 8.3) [708], PIK-75 ($pIC_{50}$ 8.2) [391] | KU-0060648 ($pIC_{50}$ 9.3) [87], PI-103 ($pIC_{50}$ 8.5) [617], AZD6482 ($pIC_{50}$ 8) [550], ZSTK474 ($pIC_{50}$ 7.4–7.8) [801, 812], apitolisib ($pIC_{50}$ 7.6) [708], BGT-226 ($pIC_{50}$ 7.2) [484] | dactolisib ($pIC_{50}$ 8.3) [477], apitolisib ($pIC_{50}$ 7.8) [708], PI-103 ($pIC_{50}$ 7.8) [617], BGT-226 ($pIC_{50}$ 7.4) [484], ZSTK474 ($pIC_{50}$ 7.3–7.3) [801, 812], TG-100-115 ($pIC_{50}$ 7.1) [569], alpelisib ($pIC_{50}$ 6.6) [226], KU-0060648 ($pIC_{50}$ 6.2) [87] | KU-0060648 ($pIC_{50}$>10) [87], idelalisib (*in vitro* activity against recombinant enzyme) ($pIC_{50}$ 8.6) [416], PI-103 ($pIC_{50}$ 8.5) [617], ZSTK474 ($pIC_{50}$ 8.2–8.3) [801, 812], apitolisib ($pIC_{50}$ 8.2) [708], dactolisib ($pIC_{50}$ 8.1) [477], alpelisib ($pIC_{50}$ 6.5) [226] |
| Sub/family-selective inhibitors | pictilisib ($pIC_{50}$ 8.5) [211] | pictilisib ($pIC_{50}$ 7.5) [211] | pictilisib ($pIC_{50}$ 7.1) [211] | pictilisib ($pIC_{50}$ 8.5) [211] |
| Selective inhibitors | GSK1059615 ($pIC_{50}$ 8.7) [390] | – | CZC 24832 ($pIC_{50}$ 7.6) [53] | – |

**Comments**: Wortmannin also inhibits type III phosphatidylinositol 4-kinases and polo-like kinase [453]. PIK93 also inhibits PI 3-kinases [391]. Adenosine activates adenosine receptors.

### Further reading on Phosphatidylinositol kinases

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

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

Wang D *et al.* (2019) Upstream regulators of phosphoinositide 3-kinase and their role in diseases. *J Cell Physiol***234**: 14460-14472 [PMID:30710358]

# Phosphatidylinositol phosphate kinases

Enzymes → Glycerophospholipid turnover → Phosphatidylinositol phosphate kinases

**Overview**: $PIP_2$ is generated by phosphorylation of PI 4-phosphate or PI 5-phosphate by type I PI 4-phosphate 5-kinases or type II PI 5-phosphate 4-kinases.

| Nomenclature | phosphatidylinositol-4-phosphate 5-kinase type 1 alpha | phosphatidylinositol-4-phosphate 5-kinase type 1 beta | phosphatidylinositol-4-phosphate 5-kinase type 1 gamma |
|---|---|---|---|
| Common abbreviation | PIP5K1A | PIP5K1B | PIP5K1C |
| HGNC, UniProt | *PIP5K1A*, Q99755 | *PIP5K1B*, O14986 | *PIP5K1C*, O60331 |
| EC number | 2.7.1.68 | 2.7.1.68 | 2.7.1.68 |
| Inhibitors | ISA-2011B [660] | – | – |



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

### Further reading on Glycerophospholipid turnover

Cauvin C *et al.* (2015) Phosphoinositides: Lipids with informative heads and mastermind functions in cell division. *Biochim Biophys Acta* **1851**: 832-43 [PMID:25449648]
Irvine RF. (2016) A short history of inositol lipids. *J Lipid Res* **57**: 1987-1994 [PMID:27623846]
Poli A *et al.* (2016) Nuclear Phosphatidylinositol Signaling: Focus on Phosphatidylinositol Phosphate Kinases and Phospholipases C. *J Cell Physiol* **231**: 1645-55 [PMID:26626942]

# Haem oxygenase

Enzymes → Haem oxygenase

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

| Nomenclature | Haem oxygenase 1 | Haem oxygenase 2 |
|---|---|---|
| Common abbreviation | HO1 | HO2 |
| HGNC, UniProt | *HMOX1*, P09601 | *HMOX2*, P30519 |
| EC number | 1.14.14.18 Protoheme + 3 [reduced NADPH-hemoprotein reductase] + 3 O(2) <=> 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) [761] – 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 [308]. The chemical tin protoporphyrin IX acts as a haem oxygenase inhibitor in rat liver with an $IC_{50}$ value of 11 nM [178].

### Further reading on Haem oxygenase

Campbell NK *et al.* (2021) Regulation of inflammation by the antioxidant haem oxygenase 1. *Nat Rev Immunol* **21**: 411-425 [PMID:33514947]
Drummond GS *et al.* (2019) HO-1 overexpression and underexpression: Clinical implications. *Arch Biochem Biophys* **673**: 108073 [PMID:31425676]
Ryter SW. (2019) Heme oxygenase-1/carbon monoxide as modulators of autophagy and inflammation. *Arch Biochem Biophys* **678**: 108186 [PMID:31704095]
Sasson A *et al.* (2021) The pivotal role of heme Oxygenase-1 in reversing the pathophysiology and systemic complications of NAFLD. *Arch Biochem Biophys* **697**: 108679 [PMID:33248947]
Szade A *et al.* (2021) The role of heme oxygenase-1 in hematopoietic system and its microenvironment. *Cell Mol Life Sci* **78**: 4639-4651 [PMID:33787980]



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# 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 ($H_2S$) and the enzymatic characteristics are described accordingly. Cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) are pyridoxal phosphate (PLP)-dependent enzymes. 3-mercaptopyruvate sulfurtransferase (3-MPST) functions to generate $H_2S$; only CAT is PLP-dependent, while 3-MPST is not. Thus, this third pathway is sometimes referred to as PLP-independent. CBS and CSE are predominantly cytosolic enzymes, while 3-MPST is found both in the cytosol and the mitochondria. For an authoritative review on the pharmacological modulation of $H_2S$ levels, see Szabo and Papapetropoulos, 2017 [711].

| Nomenclature | Cystathionine β-synthase | Cystathionine γ-lyase | L-Cysteine:2-oxoglutarate aminotransferase | 3-Mercaptopyruvate sulfurtransferase |
|---|---|---|---|---|
| Common abbreviation | CBS | CSE | CAT | MPST |
| HGNC, UniProt | *CBS*, P35520 | *CTH*, P32929 | *KYAT1*, Q16773 | *MPST*, P25325 |
| EC number | 4.2.1.22 | 4.4.1.1 | 4.4.1.13 | 2.8.1.2 |
| Endogenous substrates | L-homocysteine [104], L-cysteine ($K_m$6 × $10^{-3}$M) [104] | L-cysteine | L-cysteine | 3-mercaptopyruvic acid ($K_m$1.2 × $10^{-3}$M) [531] |
| Products | cystathionine | pyruvic acid, $NH_3$ | pyruvic acid, $NH_3$ | pyruvic acid |
| Cofactors | pyridoxal 5-phosphate | pyridoxal 5-phosphate | pyridoxal 5-phosphate | $Zn^{2+}$ |
| Inhibitors | aminooxyacetic acid ($pIC_{50}$ 5.1) [26], benserazide ($pIC_{50}$~4.5) [179] | aminoethoxyvinylglycine ($pIC_{50}$ 6) [26], aminooxyacetic acid ($pIC_{50}$ 6) [26], β-Cyano-L-alanine ($pIC_{50}$ 5.8) [26], propargylglycine ($pIC_{50}$ 4.4) [26] | – | I3MT-3 ($pIC_{50}$ 5.6) [292] |
| Comments | A copper-containing metabolite of disulfiram acts as a direct inhibitor of CBS and $H_2S$ scavenger [851]. | – | – | Pioglitazone and rosiglitazone inhibit bacterial 3-MST [137], but have not been shown to inhibit the mammalian orthologue. |

### Further reading on Hydrogen sulphide synthesis

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

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



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# Hydrolases & Lipases

Enzymes → Hydrolases & Lipases

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

| | | |
|---|---|---|
| Nomenclature | carboxylesterase 1 | ectonucleoside triphosphate diphosphohydrolase 1 |
| Systematic nomenclature | – | CD39 |
| Common abbreviation | CES1 | NTPDase-1 |
| HGNC, UniProt | *CES1*, P23141 | *ENTPD1*, P49961 |
| EC number | 3.1.1.1 | 3.6.1.5 Hydrolyzes NTPs to nucleotide monophosphates (NMPs): A nucleoside 5′-triphosphate + 2 $H_2O$ <=> a nucleoside 5′-phosphate + 2 phosphate |
| Endogenous substrates | – | – |
| Inhibitors | – | – |
| Sub/family-selective inhibitors | – | – |
| Selective inhibitors | – | – |
| Comments | – | ENTPD1 sequentially converts extracellular purine nucleotides (ATP and ADP) to the monophosphate form. Adenosine is then generated by the action of Ecto-5′-Nucleotidase (CD73). ENTPD1 is the rate-limiting step. Extracellular ATP acts as a damage-associated molecular pattern (DAMP) that activates innate immune cells through P2X and P2Y receptors. |

| | | | |
|---|---|---|---|
| Nomenclature | ectonucleoside triphosphate diphosphohydrolase 2 | lipase E, hormone sensitive type | lipase G, endothelial type |
| Systematic nomenclature | CD39L1 | – | – |
| Common abbreviation | NTPDase-2 | LIPE | LIPG |
| HGNC, UniProt | *ENTPD2*, Q9Y5L3 | *LIPE*, Q05469 | *LIPG*, Q9Y5X9 |
| EC number | 3.6.1.- Hydrolyzes extracellular nucleotide 5′-triphosphates: NTP>NMP + 2 phosphate | 3.1.1.79 | 3.1.1.3 |
| Rank order of affinity | – | – | – |
| Inhibitors | – | compound 41 ($pIC_{50}$ 9) [152] | – |
| Selective inhibitors | PSB-6426 ($pK_i$ 5.1) [75] | – | – |
| Comments | – | – | Endothelial lipase (EL) activity is implicated in HDL metabolism and in atherosclerotic plaque development. Small molecule EL inhibitors are being investigated as a potential therapeutuc intervention for the treatment of dyslipidemia related cardiovascular disease [258, 358, 706]. |



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| | | |
|---|---|---|
| Nomenclature | pancreatic lipase | PLD2 |
| Common abbreviation | PNLIP | – |
| HGNC, UniProt | *PNLIP*, P16233 | *PLD2*, O14939 |
| EC number | 3.1.1.3 | 3.1.4.4 A phosphatidylcholine + $H_2O$ <=> choline + a phosphatidate |
| Endogenous substrates | – | – |
| Endogenous activators | – | ADP-ribosylation factor 1 (*ARF1*, P84077), $PIP_2$ [459], oleic acid [644] |
| Endogenous inhibitors | – | Gβγ [598] |
| Inhibitors | orlistat ($pIC_{50}$ 8.9) [78], cetilistat ($pIC_{50}$ 8.2) [815] | – |
| Selective inhibitors | – | VU0364739 ($pIC_{50}$ 7.7) [419] |

**Further reading on Hydrolases & Lipases**


Coleman RA. (2020) The "discovery" of lipid droplets: A brief history of organelles hidden in plain sight *Biochim Biophys Acta Mol Cell Biol Lipids* **1865**: 158762 [PMID:32622088]

Haas CB *et al*. (2021) Ectonucleotidases in Inflammation, Immunity, and Cancer. *J Immunol* **206**: 1983-1990 [PMID:33879578]

Kishore BK *et al*. (2018) CD39-adenosinergic axis in renal pathophysiology and therapeutics. *Purinergic Signal* **14**: 109-120 [PMID:29332180]

Lan L *et al*. (2020) Detection techniques of carboxylesterase activity: An update review. *Bioorg Chem* **94**: 103388 [PMID:31676115]

Zimmermann H. (2021) Ectonucleoside triphosphate diphosphohydrolases and ecto-5′-nucleotidase in purinergic signaling: how the field developed and where we are now. *Purinergic Signal* **17**: 117-125 [PMID:33336318]

Zou LW *et al*. (2018) Carboxylesterase Inhibitors: An Update. *Curr Med Chem* **25**: 1627-1649 [PMID:29210644]


# Inositol phosphate turnover

Enzymes → Inositol phosphate turnover

**Overview**: The sugar alcohol D-*myo*-inositol is a component of the phosphatidylinositol signalling cycle, where the principal second messenger is inositol 1,4,5-trisphosphate, $IP_3$, 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 phosphatidyinositol 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*CALM2CALM3, P62158) [129].

Information on members of this family may be found in the online database.



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# 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 [649].

# Inositol monophosphatase

Enzymes → Inositol phosphate turnover → Inositol monophosphatase

**Overview**: Inositol monophosphatase (E.C. 3.1.3.25, IMPase, *myo*-inositol-1(or 4)-phosphate phosphohydrolase) is a magnesium-dependent homodimer which hydrolyses *myo*-inositol monophosphate to generate *myo*-inositol and phosphate. Glycerol may be a physiological phosphate acceptor. $Li^+$ is a nonselective un-competitive inhibitor more potent at IMPase 1 ($pK_i$ *ca.* 3.5, [494]; $pIC_{50}$ 3.2, [557]) than IMPase 2 ($pIC_{50}$ 1.8-2.1, [557]). IMPase activity may be inhibited competitively by L690330 ($pK_i$ 5.5, [494]), 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 [494] | – |
| Inhibitors | $Li^+$ (p$K_i$ 3.5) [494] | – |

**Comments**: Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder [680, 681, 827]. Disruption of the gene encoding IMPase 1, but not IMPase 2, appears to mimic the effects of $Li^+$ in mice [139, 140].

### 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 $IP_3$. *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]



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# 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 [479]. 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 [149] .

# 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 [404].

| | | |
|---|---|---|
| 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) [590], Y27632 ($pIC_{50}$ 5.9–7.3) [456, 798], fasudil ($pK_i$ 7) [616], Y27632 ($pK_i$ 6.8) [748], fasudil ($pIC_{50}$ 5.5–5.6) [456, 616] | RKI-1447 ($pIC_{50}$>9) [590], compound 11d [DOI: 10.1039/c0md00194e] ($pIC_{50}$>9) [108], GSK269962A ($pIC_{50}$ 8.4) [174], compound 32 ($pIC_{50}$ 8.4) [69], compound 22 ($pIC_{50}$ 7.7) [798], Y27632 ($pIC_{50}$ 6.3–7.2) [456, 798], Y27632 ($pK_i$ 6.8–6.9) [456, 748], fasudil ($pIC_{50}$ 5.9–5.9) [456, 616] |
| Selective inhibitors | GSK269962A ($pIC_{50}$ 8.8) [174] | – |

### Further reading on Rho kinase

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

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



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# Protein kinase C (PKC) family

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

**Overview**: Protein kinase C is the target for the tumour-promoting phorbol esters, such as tetradecanoyl-β-phorbol acetate (TPA, also known as phorbol 12-myristate 13-acetate). Subfamilies of protein kinase C are identified on the basis of sequence similarities, although functional division into the groups of **classical protein kinase C isoforms** (PKCα, PKCβ, and PKCγ) activated by $Ca^{2+}$ and diacylglycerol, **novel protein kinase C isoforms** (PKCδ, PKCε, PKCη, and PKCθ) activated by diacylglycerol and **atypical protein kinase C isoforms** (PKCι and PKCζ) are useful.

# Alpha subfamily

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

**Overview**: These two classical PKC isoforms are Ser/Thr kinases. They are activated by $Ca^{2+}$ and diacylglycerol, and may be inhibited by GF109203X, calphostin C, Gö 6983, chelerythrine and Ro31-8220.

| | | |
|---|---|---|
| Nomenclature | protein kinase C beta | protein kinase C gamma |
| Common abbreviation | PKCβ | PKCγ |
| HGNC, UniProt | *PRKCB*, P05771 | *PRKCG*, P05129 |
| EC number | 2.7.11.13 | 2.7.11.13 |
| Inhibitors | sotrastaurin ($pIC_{50}$ 8.7) [762], Gö 6983 ($pIC_{50}$ 8.1) [274], GF109203X ($pIC_{50}$ 7.8) [741] – Bovine, 7-hydroxystaurosporine ($pIC_{50}$ 7.5) [664] | Gö 6983 ($pIC_{50}$ 8.2) [274], 7-hydroxystaurosporine ($pIC_{50}$ 7.5) [664] |
| Selective inhibitors | ruboxistaurin ($pIC_{50}$ 8.2) [359], enzastaurin ($pIC_{50}$ 7.5) [200], CGP53353 ($pIC_{50}$ 6.4) [98] | – |

# Delta subfamily

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

**Overview**: PKCδ and PKCθ are PKC isoforms that are activated by diacylglycerol and may be inhibited by calphostin C, Gö 6983 and chelerythrine.

| | | | |
|---|---|---|---|
| Nomenclature | protein kinase C alpha | protein kinase C delta | protein kinase C theta |
| Common abbreviation | PKCα | PKCδ | PKCθ |
| HGNC, UniProt | *PRKCA*, P17252 | *PRKCD*, Q05655 | *PRKCQ*, Q04759 |
| EC number | 2.7.11.13 | 2.7.11.13 | 2.7.11.13 |
| Activators | – | ingenol mebutate ($pK_i$ 9.4) [379] | – |
| Inhibitors | sotrastaurin ($pIC_{50}$ 8.7) [762], Gö 6983 ($pIC_{50}$ 8.1) [274], 7-hydroxystaurosporine ($pIC_{50}$ 7.5) [664] | sotrastaurin ($pIC_{50}$ 8.9) [762], Gö 6983 ($pIC_{50}$ 8) [274] | sotrastaurin ($pIC_{50}$ 9) [762] |



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# Eta subfamily

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

**Overview**: PKCε and PKCη are PKC isoforms that are activated by diacylglycerol and may be inhibited by calphostin C, Gö 6983 and chelerythrine.

| | | |
|---|---|---|
| Nomenclature | protein kinase C epsilon | protein kinase C eta |
| Common abbreviation | PKCε | PKCη |
| HGNC, UniProt | *PRKCE*, Q02156 | *PRKCH*, P24723 |
| EC number | 2.7.11.13 | 2.7.11.13 |
| Inhibitors | sotrastaurin ($pIC_{50}$ 8.2) [762] | balanol ($pIC_{50}$ 8.5) [153], sotrastaurin ($pIC_{50}$ 8.2) [762] |

# Iota subfamily

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

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

| | | |
|---|---|---|
| Nomenclature | protein kinase C iota | protein kinase C zeta |
| Common abbreviation | PKCι | PKCζ |
| HGNC, UniProt | *PRKCI*, P41743 | *PRKCZ*, Q05513 |
| EC number | 2.7.11.13 | 2.7.11.13 |
| Endogenous activators | – | arachidonic acid [527] |
| Inhibitors | – | Gö 6983 ($pIC_{50}$ 7.2) [274] |
| Comments | Known as PKCλ in rodents | – |

**Further reading on Protein kinase C (PKC) family**

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

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

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

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



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# FRAP subfamily

Enzymes → Kinases (EC 2.7.x.x) → Atypical → Phosphatidyl inositol 3′ kinase-related kinases (PIKK) family → FRAP subfamily

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

| | |
|---|---|
| Nomenclature | mechanistic target of rapamycin kinase |
| Common abbreviation | mTOR |
| HGNC, UniProt | *MTOR*, P42345 |
| EC number | 2.7.11.1 |
| Inhibitors | ridaforolimus ($pIC_{50}$ 9.7) [626], torin 1 ($pIC_{50}$ 9.5) [448], sapanisertib ($pIC_{50}$ 9) [329], sapanisertib ($pK_i$ 8.9) [329], gedatolisib ($pIC_{50}$ 8.8) [756], dactolisib ($pIC_{50}$ 8.2) [477], PP121 ($pIC_{50}$ 8) [23], XL388 ($pIC_{50}$ 8) [716], PF-04691502 ($pK_i$ 7.8) [447], apitolisib ($pK_i$ 7.8) [708] |
| Selective inhibitors | everolimus ($pIC_{50}$ 8.7) [658], PP-242 ($pIC_{50}$ 8.1) [23], temsirolimus ($pIC_{50}$ 5.8) [399] |

### Further reading on FRAP subfamily


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

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

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

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


# CAMK: Calcium/calmodulin-dependent protein kinases

Enzymes → Kinases (EC 2.7.x.x) → CAMK: Calcium/calmodulin-dependent protein kinases

### Further reading on CAMK: Calcium/calmodulin-dependent protein kinases


Wellendorph P *et al.* (2025) International Union of Basic and Clinical Pharmacology. CXX. γ-Hydroxybutyrate protein targets in the mammalian brain-beyond classic receptors. *Pharmacol Rev* **77**: 100064 [PMID:40449125]




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# 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 [70, 397, 437].

# CDK4 subfamily

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

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

| | | |
|---|---|---|
| Nomenclature | cyclin dependent kinase 4 | cyclin dependent kinase 6 |
| Common abbreviation | CDK4 | CDK6 |
| HGNC, UniProt | *CDK4*, P11802 | *CDK6*, Q00534 |
| EC number | 2.7.11.22 | 2.7.11.22 |
| Inhibitors | R547 ($pK_i$ 9) [157], palbociclib ($pIC_{50}$ 8) [222], Ro-0505124 ($pIC_{50}$ 7.7) [169], riviciclib ($pIC_{50}$ 7.2) [368], alvocidib ($pK_i$ 7.2) [90] | palbociclib ($pIC_{50}$ 7.8) [222] |

**Comments on Cyclin-dependent kinase (CDK) family**: The development of CDK inhibitors as anticancer drugs is reviewed in [641], 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 [367], as most of them are more promiscuous in their selectivity than indicated. To make their findings easily accessible the Jorda data is hosted on the cyclin-dependent kinase inhibitor database (CDKiDB).

# GSK subfamily

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

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



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| | |
|---|---|
| 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) [624], LY2090314 ($pIC_{50}$ 9) [188], laduviglusib ($pIC_{50}$ 8.2) [624], SB 216763 ($pIC_{50}$~8.1) [125], 1-azakenpaullone ($pIC_{50}$ 7.7) [409], SB-415286 ($pIC_{50}$~7.4) [125], IM-12 ($pIC_{50}$ 7.3) [651] |
| Selective inhibitors | AZD2858 ($pK_i$ 8.3) [52] |
| Comments | Due to its Tau phosphorylating activity, small molecule inhibitors of GSK-3β are being investigated as potential treatments for Alzheimer's disease (AD) [52]. 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 [485]. |

**Further reading on GSK subfamily**

Beurel E *et al*. (2015) Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacol Ther* **148**: 114-31 [PMID:25435019]

Domoto T *et al*. (2016) Glycogen synthase kinase-3β is a pivotal mediator of cancer invasion and resistance to therapy. *Cancer Sci* **107**: 1363-1372 [PMID:27486911]

Khan I *et al*. (2017) Natural and synthetic bioactive inhibitors of glycogen synthase kinase. *Eur J Med Chem***125**: 464-477 [PMID:27689729]

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

# Polo-like kinase (PLK) family

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

**Overview**: The Polo-like kinases (PLK) are Ser/Thr kinases of the cell cycle that are involved in regulating mitotic entry, mitotic exit, spindle formation, cytokinesis, and meiosis [41, 640]. PLK inhibitors are predicted to offer anti-proliferative potential for application in oncology [654, 842].

| | |
|---|---|
| Nomenclature | polo like kinase 4 |
| Common abbreviation | PLK4 |
| HGNC, UniProt | *PLK4*, O00444 |
| EC number | 2.7.11.21 |
| Inhibitors | ocifisertib ($pIC_{50}$ 8.6) [489] |



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# STE7 family

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

**Overview**: STE7 (also known as MAPKK, MAP2K or MEK) kinases are part of the MAPK signalling cascades. They are activated by phosphorylation by upstream STE11 (MAP3K, MAPKKK) kinases and phosphorylate downstream MAPK kinases. Small molecule pharmacological inhibitors, including negative allosteric modulators, of MEKs are used to disrupt signalling *via* the RAS-RAF-MEK-ERK pathway that drives proliferation in certain cancers.

| | | |
|---|---|---|
| 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) [249, 816], mirdametinib ($pIC_{50}$ 8.1) [300] | trametinib ($pIC_{50}$ 8.7) [816] |
| Allosteric modulators (Negative) | binimetinib ($pIC_{50}$ 7.9) [585], refametinib ($pIC_{50}$ 7.7) [347], CI-1040 ($pK_d$ 6.9) [151] | binimetinib ($pIC_{50}$ 7.9) [585], refametinib ($pIC_{50}$ 7.3) [347] |
| Selective allosteric modulators | cobimetinib (Negative) ($pIC_{50}$ 9.1) [621] | – |

**Further reading on STE7 family**

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

# Abl family

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

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

| | |
|---|---|
| Nomenclature | ABL proto-oncogene 1, non-receptor tyrosine kinase |
| Common abbreviation | Abl |
| HGNC, UniProt | *ABL1*, P00519 |
| EC number | 2.7.10.2 |
| Inhibitors | compound 8h ($pIC_{50}$ 9.7) [737], dasatinib ($pIC_{50}$ 9.6) [389], compound 24 ($pIC_{50}$ 9.3) [158], PD-173955 ($pK_d$ 9.2) [151], bosutinib ($pIC_{50}$ 9) [254], PD-173955 ($pIC_{50}$~8.3) [532], bafetinib ($pIC_{50}$ 7.6–8.2) [326, 388], ponatinib ($pIC_{50}$ 8.1) [331], nilotinib ($pIC_{50}$ 7.8) [551], PP121 ($pIC_{50}$ 7.7) [23], imatinib ($pIC_{50}$ 6.7) [326], GNF-5 ($pIC_{50}$ 6.7) [838] |



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# Ack family

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

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

| | |
|---|---|
| Nomenclature | tyrosine kinase non receptor 2 |
| Common abbreviation | Ack |
| HGNC, UniProt | *TNK2*, Q07912 |
| EC number | 2.7.10.2 |
| Inhibitors | compound 30 ($pIC_{50}$ 9) [168] |

# 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) [291, 604], filgotinib ($pIC_{50}$ 8) [751] | ilginatinib ($pIC_{50}$ 9.1) [537], BMS-911543 ($pIC_{50}$ 9) [600], AT-9283 ($pIC_{50}$ 8.9) [328], XL019 ($pIC_{50}$ 8.7) [213], fedratinib ($pIC_{50}$ 8.5) [478, 788], gandotinib ($pIC_{50}$ 8.4) [474] | AT-9283 ($pIC_{50}$ 9) [328] | – |
| Selective inhibitors | – | compound 1d ($pIC_{50}$>9) [770] | – | – |
| 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 [85, 155]. Small molecule compounds which inhibit aberrant JAK2 activity are being developed as novel anti-cancer pharmaceuticals. | – | – |



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**Further reading on Janus kinase (JakA) family**

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

# Src family

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

**Overview**: Activation of Src-family kinases leads to both stimulatory and inhibitory signaling responses, with cell-specific and signaling pathway-specific outcomes and redundancy of kinase function.
**Immune system:**
In immune cells Src kinases are involved in many signalling pathways, including ITAM- and ITIM-domain-containing receptor signaling, integrin signaling, and responses to chemokines/chemoattractants, cytokines, innate immune stimuli and a large variety of non-immune cell specific stimuli (UV irradiation, heat, osmotic shock *etc.*). In many cases Src kinases signal to MAP kinase or NF-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) [294] | bafetinib ($pIC_{50}$ 8) [326] | WH-4-023 ($pIC_{50}$ 8.2) [486], PD166285 ($pK_i$ 8.1) [572], PP121 ($pIC_{50}$ 7.8) [23], ENMD-2076 ($pIC_{50}$ 7.7) [593] |

# 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) [432], ibrutinib ($pIC_{50}$ 9.1) [462], compound 31 ($pIC_{50}$ 8.7) [432] | ibrutinib ($pIC_{50}$ 9.3) [571], compound 31 ($pIC_{50}$ 8.4) [432], compound 38 ($pIC_{50}$>8.4) [432] | – |
| Selective inhibitors | BMX-IN-1 ($pIC_{50}$ 8.1) [444] | CGI1746 ($pIC_{50}$ 8.7) [163], CHMFL-BTK-11 (Irreversible inhibition) ($pIC_{50}$ 7.6) [799] | – |

# RAF family

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

**Overview**: The RAF (acronym for rapidly accelerated fibrosarcoma) kinases are a family of related Ser/Thr kinases that are important for normal cellular and physiological processes, but are also associated with oncogenesis [426]. They are components of the Ras-Raf-MAPK signalling pathway.

| | | |
|---|---|---|
| Nomenclature | B-Raf proto-oncogene, serine/threonine kinase | Raf-1 proto-oncogene, serine/threonine kinase |
| Common abbreviation | B-Raf | c-Raf |
| HGNC, UniProt | *BRAF*, P15056 | *RAF1*, P04049 |
| EC number | 2.7.11.1 | 2.7.11.1 |
| Inhibitors | GDC-0879 ($pIC_{50}$ 9.7–9.9) [151, 295], dabrafenib ($pIC_{50}$ 8.5) [417], regorafenib ($pIC_{50}$ 7.6) [834], vemurafenib ($pIC_{50}$ 7) [771], PLX-4720 ($pK_d$ 6.5) [151], compound 2 ($pK_d$ 6.3) [325], CHIR-265 ($pK_d$ 5.9) [151] | – |
| Selective inhibitors | – | GW5074 ($pIC_{50}$ 8.1) [115] |

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


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

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

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

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

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

Zhou Y *et al.* (2023) Rational Design of Covalent Kinase Inhibitors by an Integrated Computational Workflow (Kin-Cov). *J Med Chem* **66**: 7405-7420 [PMID:37220641]


# Lanosterol biosynthesis pathway

Enzymes → Lanosterol biosynthesis pathway

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

| | | |
|---|---|---|
| Nomenclature | acetyl-CoA acetyltransferase 1 | acetyl-CoA acetyltransferase 2 |
| HGNC, UniProt | *ACAT1*, P24752 | *ACAT2*, Q9BWD1 |
| EC number | 2.3.1.9: 2acetyl CoA = acetoacetyl CoA + coenzyme A | 2.3.1.9: 2acetyl CoA = acetoacetyl CoA + coenzyme A |
| Comments | – | Inhibition ACAT2-mediated glutamate-cysteine ligase modifier (*GCLM*) lactylation that promotes ferroptosis resistance has been proposed as a therapeutic strategy for KRAS-mutant cancers [107]. |



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| | | |
|---|---|---|
| Nomenclature | hydroxymethylglutaryl-CoA synthase 1 | hydroxymethylglutaryl-CoA synthase 2 |
| HGNC, UniProt | *HMGCS1*, Q01581 | *HMGCS2*, P54868 |
| EC number | 2.3.3.10: acetyl CoA + $H_2O$ + acetoacetyl CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A | 2.3.3.10: acetyl CoA + $H_2O$ + 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 + H2O -> (R)-mevalonate + $NADP^+$ |
| Inhibitors | lovastatin (Competitive) ($pK_i$ 9.2) [15], rosuvastatin (Competitive) ($pIC_{50}$ 8.3) [345], cerivastatin (Competitive) ($pK_i$ 8.2) [88], atorvastatin (Competitive) ($pIC_{50}$ 8.1) [345], cerivastatin (Competitive) ($pIC_{50}$ 8) [735], simvastatin (Competitive) ($pIC_{50}$ 8) [345], fluvastatin (Competitive) ($pIC_{50}$ 7.6) [345] |
| 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 | *IDI1*, Q13907 | *IDI2*, Q9BXS1 | *GGPS1*, O95749 |
| EC number | 5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate | | 2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate<br>2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate<br>2.5.1.29: trans,trans-farnesyl diphosphate + isopentenyl diphosphate -> geranylgeranyl diphosphate + diphosphate |



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| Nomenclature | farnesyl diphosphate synthase | squalene synthase | squalene monooxygenase | lanosterol synthase |
|---|---|---|---|---|
| HGNC, UniProt | *FDPS*, P14324 | *FDFT1*, P37268 | *SQLE*, Q14534 | *LSS*, P48449 |
| EC number | 2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate | 2.5.1.21: 2trans,trans-farnesyl diphosphate -> presqualene diphosphate + diphosphate presqualene diphosphate + NAD(P)H + $H^+$ -> squalene + diphosphate + $NAD(P)^+$ | 1.14.13.132: $H^+$ + NADPH + $O_2$ + squalene = $H_2O$ + $NADP^+$ + (*S*)-2,3-epoxysqualene | 5.4.99.7: (*S*)-2,3-epoxysqualene = lanosterol |
| Cofactors | – | NADPH | – | – |
| Inhibitors | risedronate ($pIC_{50}$ 8.4) [54], zoledronic acid ($pK_i$ 7.1) [181], alendronate ($pIC_{50}$ 6.3) [54] | zaragozic acid A ($pK_i$ 10.1) [55] – Rat, zaragozic acid A ($pIC_{50}$ 9.2) [738] | – | – |
| Selective inhibitors | ibandronic acid ($pK_i$ 6.7) [181], pamidronic acid ($pIC_{50}$ 6.7) [181] | – | – | – |

**Further reading on Lanosterol biosynthesis pathway**

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

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

Moutinho M *et al*. (2017) The mevalonate pathway in neurons: It's not just about cholesterol. *Exp Cell Res* **360**: 55-60 [PMID:28232115]

Mullen PJ *et al*. (2016) The interplay between cell signalling and the mevalonate pathway in cancer. *Nat Rev Cancer* **16**: 718-731 [PMID:27562463]

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

# Nucleoside synthesis and metabolism

Enzymes → Nucleoside synthesis and metabolism

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

| Nomenclature | dihydrofolate reductase | phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase | dihydroorotate dehydrogenase (quinone) | inosine monophosphate dehydrogenase 1 | inosine monophosphate dehydrogenase 2 | thymidylate synthetase |
|---|---|---|---|---|---|---|
| Common abbreviation | DHFR | GART | DHODH | IMPDH1 | IMPDH2 | TYMS |
| HGNC, UniProt | *DHFR*, P00374 | *GART*, P22102 | *DHODH*, Q02127 | *IMPDH1*, P20839 | *IMPDH2*, P12268 | *TYMS*, P04818 |
| EC number | 1.5.1.3 | 2.1.2.2 6.3.3.1 6.3.4.13 | 1.3.5.2 | 1.1.1.205 | 1.1.1.205 | 2.1.1.45 |



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| | | | | | | |
|---|---|---|---|---|---|---|
| Inhibitors | – | pemetrexed ($pK_i$ 5) [671] – Mouse | teriflunomide ($pK_i$ 7.5) [311] | mycophenolic acid ($pIC_{50}$ 7.7) [539] | mycophenolic acid ($pIC_{50}$ 7.7) [539] | – |
| Selective inhibitors | methotrexate ($pK_i$ 8.9) [632] | – | – | – | – | raltitrexed ($pIC_{50}$ 6.5) [233] |

| Nomenclature | purine nucleoside phosphorylase | xanthine dehydrogenase | ribonucleotide reductase catalytic subunit M1 | ribonucleotide reductase regulatory subunit M2 | ribonucleotide reductase regulatory TP53 inducible subunit M2B |
|---|---|---|---|---|---|
| Common abbreviation | PNP | XDH | ribonucleotide reductase M1 | ribonucleotide reductase M2 | ribonucleotide reductase M2B (TP53 inducible) |
| HGNC, UniProt | *PNP*, P00491 | *XDH*, P47989 | *RRM1*, P23921 | *RRM2*, P31350 | *RRM2B*, Q7LG56 |
| EC number | 1.4.2.1 Purine-nucleoside phosphorylase: Purine nucleoside + phosphate <=> purine + alpha-D-ribose 1-phosphate Purine deoxynucleoside + phosphate <=> purine + 2'-deoxy-alpha-D-ribose 1-phosphate | 1.17.1.4 | 1.17.14.1 | 1.17.4.1 | 1.17.1.4 |
| Inhibitors | – | febuxostat ($pIC_{50}$ 8.9) [197], topiroxostat | – | – | – |

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

### Further reading on Nucleoside synthesis and metabolism

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

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



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# Paraoxonase (PON) family

Enzymes → Paraoxonase (PON) family

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

| | | | |
|---|---|---|---|
| Nomenclature | paraoxonase 1 | paraoxonase 2 | paraoxonase 3 |
| Common abbreviation | PON1 | PON2 | PON3 |
| HGNC, UniProt | *PON1*, P27169 | *PON2*, Q15165 | *PON3*, Q15166 |
| EC number | 3.1.1.2 A phenyl acetate + H(2)O <=> a phenol + acetate<br>3.1.1.81<br>An N-acyl-L-homoserine lactone + H(2)O <=> an N-acyl-L-homoserine<br>3.1.8.1<br>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<br>3.1.1.81<br>A N-acyl-L-homoserine lactone + H(2)O <=> a N-acyl-L-homoserine | 3.1.1.2 A phenyl acetate + H(2)O <=> a phenol + acetate<br>3.1.1.81<br>A N-acyl-L-homoserine lactone + H(2)O <=> a N-acyl-L-homoserine<br>3.1.8.1<br>An aryl dialkyl phosphate + H(2)O <=> dialkyl phosphate + an aryl alcohol |
| Comments | PON1 forms homodimers. Loss-of-function mutations in PON1 are associated with microvascular complications of diabetes [374, 375]. | PON2 forms heterotrimers [176]. | PON3 likely forms heterodimers *in vivo* [176]. |

**Further reading on Paraoxonase (PON) family**

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]

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

# Peptidases and proteinases

Enzymes → Peptidases and proteinases

**Overview**: Peptidases and proteinases hydrolyse peptide bonds, and can be simply divided on the basis of whether terminal peptide bonds are cleaved (exopeptidases and exoproteinases) at the amino terminus (aminopeptidases) or carboxy terminus (carboxypeptidases). Non-terminal peptide bonds are cleaved by endopeptidases and endoproteinases, which are divided into serine endopeptidases (EC 3.4.21.-), cysteine endopeptidases (EC 3.4.22.-), aspartate endopeptidases (EC 3.4.23.-), 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 [613] (with whom we collaborate) as an information resource [614].



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# Blood coagulation components

Enzymes → Peptidases and proteinases → Blood coagulation components

**Overview**: Coagulation as a process is interpreted as a mechanism for reducing excessive blood loss through the generation of a gel-like clot local to the site of injury. The process involves the activation, adhesion (see Integrins), degranulation and aggregation of platelets, as well as proteins circulating in the plasma. The coagulation cascade involves multiple proteins being converted to more active forms from less active precursors (for example, prothrombin [Factor II] is converted to thrombin [Factor IIa]), typically through proteolysis (see Proteases). Listed here are the components of the coagulation cascade targeted by agents in current clinical usage or at an advanced level of development.

| | | | |
|---|---|---|---|
| Nomenclature | coagulation factor II, thrombin | coagulation factor III, tissue factor | coagulation factor V |
| Systematic nomenclature | prothrombin | – | – |
| HGNC, UniProt | *F2*, P00734 | *F3*, P13726 | *F5*, P12259 |
| EC number | 3.4.21.5 | – | – |
| Inhibitors | lepirudin (p$K_i$ 13) [659, 773], desirudin (p$K_i$ 12.7) [192, 364], bivalirudin (p$K_i$ 8.6) [702, 796], dabigatran (Antithrombotic effects occur via inhibition of the activated form, factor IIa) (p$K_i$ 8.3) [303, 790], argatroban (p$K_i$ 7.7) [340, 659] | – | – |
| Selective inhibitors | – | – | drotrecogin alfa (Antithrombotic effect thought to occur via inhibition of factors Va and VIIIa) [373, 376] |
| Antibodies | – | tisotumab vedotin (Binding) [74] | – |
| Comments | – | Factor 3 (tissue factor) is the main physiological trigger for blood coagulation in response to vascular damage. The F3/factor VIIa complex catalyses the proteolytic activation of coagulation factors IX and X. It is a member of the cytokine receptor family. F3 binds to interferon-α receptor 1 (IFNAR1) and inhibits receptor signalling [480]; loss of this repressive interaction promotes thrombo-inflammation. | – |



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| Nomenclature | coagulation factor VIII | coagulation factor X | coagulation factor XI | serpin family C member 1 |
|---|---|---|---|---|
| Common abbreviation | – | – | – | antithrombin, antithrombin III |
| HGNC, UniProt | *F8*, P00451 | *F10*, P00742 | *F11*, P03951 | *SERPINC1*, P01008 |
| EC number | – | 3.4.21.6 | 3.4.21.27 | – |
| Ligands | – | – | fesomersen (Synthesis reducer) [452] | – |
| Selective activators | – | – | – | heparin ($pK_d$ 7.8) [261], fondaparinux ($pK_d$ 7.5) [573], dalteparin [323], danaparoid [144, 535], enoxaparin [191], tinzaparin [219] |
| Inhibitors | – | – | milvexian ($pK_i$ 10) [167] | – |
| Selective inhibitors | drotrecogin alfa (Antithrombotic effect thought to occur via inhibition of factors Va and VIIIa) [373, 376] | apixaban ($pK_i$ 10.1) [797], rivaroxaban ($pK_i$ 9.4) [583], edoxaban ($pK_i$ 9.2) [230, 589], JTV-803 (Antithrombotic effect occurs via the inhibition of the activated form, Xa) ($pK_i$ 7.7) [306, 336], DX-9065a (Antithrombotic effect occurs via the inhibition of the activated form, Xa) ($pK_i$ 7.4) [296, 336] | – | – |
| Antibodies | – | – | abelacimab (Inhibition) ($pK_d$ 11.9) [786, 822], abelacimab (Inhibition) ($pK_d$ 11.3) [786], osocimab (Inhibition) ($pK_d$ 8.6) [647], gruticibart (Inhibition) [460] | – |

**Comments**: Antithrombin is an inhibitor of thrombin, Factor Xa and multiple other proteinases. Lepirudin has been withdrawn from market. Drotrecogin alfa (activated; Xigris®) was voluntarily withdrawn from market due to lack of efficacy [501].

### Further reading on Blood coagulation components


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

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

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

Kalinin DV. (2021) Factor XII(a) inhibitors: a review of the patent literature. *Expert Opin Ther Pat* **31**: 1155-1176 [PMID:34142629]

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

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

Santagata D *et al.* (2023) Factor XI inhibitors for the prevention of cardiovascular disease: A new therapeutic approach on the horizon? *Blood Rev* **62**: 101119 [PMID:37580207]

Satpathy C *et al.* (2025) Factor XI and XII inhibitors-Dawn of a new era. *Indian Heart J* **77**: 122-129 [PMID:40015552]

Verstraete A *et al.* (2025) New horizons in the pharmacological management of venous thromboembolism. *Hemasphere* **9**: e70143 [PMID:40469483]

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




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# 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) [806] |

# 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) [372] in the generation of amyloid beta (Aβ) [11, 715]. Given that the accumulation and aggregation of Aβ in the brain is pivotal in the development of Alzheimer's disease (AD), inhibition of PS activity is one mechanism being investigated as a therapeutic option for AD [256]. 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 Aβ production (total Aβ, Aβ40 and Aβ42) both *in vitro* and when infused in to the brains of APP transgenic mice [161]. 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-1β converting enzyme, pseudo-ICE, ENSG00000204397) shares sequence similarity with some of the caspases.



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# 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 [728].

| | |
|---|---|
| Nomenclature | Leukotriene $A_4$ hydrolase |
| HGNC, UniProt | *LTA4H*, P09960 |
| EC number | 3.3.2.6 |
| Inhibitors | bestatin ($pK_i$ 5.4) [563] |
| Selective inhibitors | LYS006 ($pIC_{50}$ 8.4) [483], DG-051 ($pIC_{50}$ 7.3) [642] |

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

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

| | | |
|---|---|---|
| Nomenclature | Angiotensin-converting enzyme | Angiotensin-converting enzyme 2 |
| Common abbreviation | ACE | ACE2 |
| HGNC, UniProt | *ACE*, P12821 | *ACE2*, Q9BYF1 |
| EC number | 3.4.15.1 | 3.4.15.1 |
| Binding dissociation constants for SARS-CoVs (Kd) | – | SARS-CoV-2 (1.2 nM); SARS-CoV (5 nM); Binding of hACE2 ectodomain to immobilised $S^B$ domains of the viral strains in a biolayer interferometry assay. [765] |
| Substrates | Ac-SDKP | – |
| Endogenous substrates | angiotensin I (*AGT*, P01019) > angiotensin II (*AGT*, P01019) | angiotensin I (*AGT*, P01019) > angiotensin-(1-9) (*AGT*, P01019) [175] |
| Activators | – | XNT ($pEC_{50}$ 4.7) [315] |
| Inhibitors | zofenoprilat ($pK_i$ 9.4) [406] – Rabbit, captopril ($pK_i$ 8.4) [506], zofenopril | compound 28 ($pK_i$ 9.9) [522] |



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| | | |
|---|---|---|
| Selective inhibitors | perindoprilat ($pIC_{50}$ 9) [95], cilazaprilat ($pIC_{50}$ 8.7) [777] – Rabbit, imidaprilat ($pIC_{50}$ 8.7) [628], lisinopril-tryptophan (C-domain assay) ($pIC_{50}$ 8.2) [778], RXP-407 (N-domain selective inhibition) ($pIC_{50}$ 8.1) [669], fosinoprilat ($pIC_{50}$ 8) [154] – Rabbit, enalaprilat ($pIC_{50}$ 7.5) [111], benazeprilat ($pIC_{50}$ 6.6) [423] | MLN-4760 ($pIC_{50}$ 9.4) [522] |
| Comments | The cACE domain (C-terminal active site) is primarily responsible for the production of Ang II. The nACE domain (N-terminal active site) engages substrates including antifibrotic peptide N-acetyl-Ser-Asp-Lys-Pro (AcSDKP) [635] and gonadotropin-releasing hormone (GnRH). Reports of ACE GPI hydrolase activity [398] have been refuted [427]. | – |

# M10: Matrix metallopeptidase

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

**Overview**: Matrix metalloproteinases (MMP) are calcium- and zinc-dependent proteinases regulating the extracellular matrix and are often divided (*e.g.* [758]) on functional and structural bases into gelatinases, collagenases, stromyelinases and matrilysins, as well as membrane type-MMP (MT-MMP).

| | | |
|---|---|---|
| Nomenclature | MMP2 | MMP8 |
| HGNC, UniProt | *MMP2*, P08253 | *MMP8*, P22894 |
| EC number | 3.4.24.24 | 3.4.24.34 |
| Selective inhibitors | TP0556351 ($pIC_{50}$ 9.7) [717], ARP100 [744] | – |
| 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).



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# 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 |
| Inhibitors | vipivotide tetraxetan ($pK_i$ 9.4) [49] |
| Antibodies | capromab (Binding) |
| Comments | Folate hydrolase is also known as NAALADase as it is responsible for the hydrolysis of N-acetaspartylglutamate 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-acetaspartylglutamate 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.

### Further reading on M28: Aminopeptidase Y

Chen D *et al.* (2023) Development and evolution of human glutaminyl cyclase inhibitors (QCIs): an alternative promising approach for disease-modifying treatment of Alzheimer's disease. *Front Aging Neurosci* **15**: 1209863 [PMID:37600512]

Zhang Y *et al.* (2022) Glutaminyl cyclases, the potential targets of cancer and neurodegenerative diseases. *Eur J Pharmacol* **931**: 175178 [PMID:35948163]

# M19: Membrane dipeptidase

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

| | |
|---|---|
| Nomenclature | Dipeptidase 1 |
| HGNC, UniProt | *DPEP1*, P16444 |
| EC number | 3.4.13.19: $LTD_4 + H_2O = LTE_4 + glycine$ |
| Inhibitors | cilastatin ($pK_i$ 6) [263] |



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# S1: Chymotrypsin

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

| Nomenclature | complement C1r | coagulation factor II, thrombin | coagulation factor X | coagulation factor XI |
|---|---|---|---|---|
| Systematic nomenclature | – | prothrombin | – | – |
| HGNC, UniProt | *C1R*, P00736 | *F2*, P00734 | *F10*, P00742 | *F11*, P03951 |
| EC number | 3.4.21.41 | 3.4.21.5 | 3.4.21.6 | 3.4.21.27 |
| Ligands | – | – | – | fesomersen (Synthesis reducer) [452] |
| Inhibitors | nafamostat ($pIC_{50}$ 4.9) [309] | lepirudin ($pK_i$ 13) [659, 773], desirudin ($pK_i$ 12.7) [192, 364], bivalirudin ($pK_i$ 8.6) [702, 796], dabigatran (Antithrombotic effects occur via inhibition of the activated form, factor IIa) ($pK_i$ 8.3) [303, 790], argatroban ($pK_i$ 7.7) [340, 659] | – | milvexian ($pK_i$ 10) [167] |
| Selective inhibitors | – | – | apixaban ($pK_i$ 10.1) [797], rivaroxaban ($pK_i$ 9.4) [583], edoxaban ($pK_i$ 9.2) [230, 589], JTV-803 (Antithrombotic effect occurs via the inhibition of the activated form, Xa) ($pK_i$ 7.7) [306, 336], DX-9065a (Antithrombotic effect occurs via the inhibition of the activated form, Xa) ($pK_i$ 7.4) [296, 336] | – |
| Antibodies | – | – | – | abelacimab (Inhibition) ($pK_d$ 11.9) [786, 822], abelacimab (Inhibition) ($pK_d$ 11.3) [786], osocimab (Inhibition) ($pK_d$ 8.6) [647], gruticibart (Inhibition) [460] |

| Nomenclature | elastase, neutrophil expressed | plasminogen | plasminogen activator, tissue type |
|---|---|---|---|
| HGNC, UniProt | *ELANE*, P08246 | *PLG*, P00747 | *PLAT*, P00750 |
| EC number | 3.4.21.37 | 3.4.21.7 | 3.4.21.68 |
| Inhibitors | alvelestat ($pK_i$ 8) [701], sivelestat ($pIC_{50}$ 7.4) [136] | aprotinin {Bovine} (Binding) ($pIC_{50}$ 6.8) [693], tranexamic acid (Binding) ($pIC_{50}$ 3.6) [693] | – |
| Selective inhibitors | – | 6-aminocaproic acid (Binding) ($pIC_{50}$ 4.4) [110] | – |
| Comments | Neutrophil elastase (NE) is a destructive serine protease. It is stored in the primary granules of neutrophils and is endogenously inhibited by alpha1-proteinase inhibitor (a.k.a. alpha-1 antitrypsin). NE is a molecular target for neutrophil-mediated inflammatory lung diseases. | – | – |



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| | | | |
|---|---|---|---|
| Nomenclature | serine protease 1 | transmembrane serine protease 2 | tryptase alpha/beta 1 |
| HGNC, UniProt | *PRSS1*, P07477 | *TMPRSS2*, O15393 | *TPSAB1*, Q15661 |
| EC number | 3.4.21.4 | 3.4.21.- | 3.4.21.59 |
| Inhibitors | nafamostat ($pIC_{50}$ 7.8) [309] | – | nafamostat ($pIC_{50}$ 10) [523] |
| Selective inhibitors | – | – | gabexate ($pIC_{50}$ 8.5) [190] |

# 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 [122]. This catalytic core enables the degradation of peptides with Arg, Phe, Tyr, Leu, and Glu adjacent to the cleavage site. The β5 subunit is the principal target of the approved drug proteasome inhibitor bortezomib.

| | |
|---|---|
| Nomenclature | proteasome 20S subunit beta 5 |
| HGNC, UniProt | *PSMB5*, P28074 |
| EC number | 3.4.25.1 |
| Inhibitors | bortezomib ($pIC_{50}$ 7.7) [533] |
| Selective inhibitors | ixazomib ($pK_i$ 9) [411] |

# 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 [458, 638, 700]. Therapeutics which inhibit PCSK9 are viewed as potentially lucrative replacements for statins, upon statin patent expiry. Several monoclonal antibodies including alirocumab, evolocumab, bococizumab, RG-7652 and LY3015014 are under development. One RNAi therapeutic, code named ALN-PCS02, is also in development [142, 210, 217].
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

**Overview**: This is a family of serine proteases that share the capacity to cleave Xaa-Pro dipeptides from N-termini of their substrates.
DPP4 is a validated drug target with >10 approved DPP4 inhibitors in clinical use for the treatment of type 2 diabetes mellitus, including the orally active drug vildagliptin. DPP8 and DPP9 have been shown participate in multiple biological processes and diseases, including tumour development, immune regulation, the inflammatory response and immune cell pyroptosis, energy metabolism, cell proliferation and apoptosis, cell adhesion and migration, and COVID-19 [141, 520, 668]. The delevopment of selective DPP8 or DPP9 inhibitors is underway to help differentiate the specific roles of each enzyme in physiological and/or pathological processes [50, 51, 357, 384].



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| | |
|---|---|
| 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) [279], linagliptin ($pK_i$ 9) [184], sitagliptin ($pIC_{50}$ 8.1) [150], vildagliptin ($pK_i$ 7.8) [279] |
| Selective inhibitors | ZY15557 (Competitive) ($pK_i$ 8.3) [352] |
| Comments | DPP4 has an extracellular catalytic domain that cleaves and inactivates glucagon-like peptide 1 (GLP-1) to antagonise insulin secretion. Small-molecule DPP4 inhibitors are used clinically in the treatment of type II diabetes. |

# Peptidyl-prolyl cis/trans isomerases

Enzymes → Peptidyl-prolyl cis/trans isomerases

**Overview**: Peptidyl-prolyl cis/trans isomerases (PPIases) are an enzyme family which catalyse the cis/trans isomerisation of proline peptide bonds to promote the folding and re-folding of peptides and proteins. Three subfamilies have been identified: cyclophilins, FK506-binding proteins and parvulins. Individual PPIases are overexpressed in a number of cancers [625], and family members have been targetted for immunosuppressant effects.

| Nomenclature | FKBP prolyl isomerase 1A | FKBP prolyl isomerase 8 | FKBP prolyl isomerase 5 | FKBP prolyl isomerase 4 | FKBP prolyl isomerase like |
|---|---|---|---|---|---|
| Common abbreviation | FKBP12 | FKBP38 | FKBP51 | FKBP52 | – |
| HGNC, UniProt | *FKBP1A*, P62942 | *FKBP8*, Q14318 | *FKBP5*, Q13451 | *FKBP4*, Q02790 | *FKBPL*, Q9UIM3 |
| EC number | 5.2.1.8 | 5.2.1.8 | 5.2.1.8 | 5.2.1.8 | 5.2.1.8 |
| Inhibitors | zotarolimus (Binding) ($pIC_{50}$ 8.6) [240] | GPI-1046 ($pK_i$ 7.3) [185] | SLF ($pIC_{50}$ 5.2) [259] | SLF ($pIC_{50}$ 5) [259] | – |
| Selective inhibitors | tacrolimus ($pK_i$ 9.4) [287], pimecrolimus ($pIC_{50}$ 8.2) [335] – Rat | DM-CHX ($pK_i$ 7.1) [185] | SAFit1 ($pK_i$ 8.4) [231], SAFit2 ($pK_i$ 8.2) [231] | – | – |
| Comments | – | – | – | – | Peptides based on the non-functional PPIase domain of FKBPL (*e.g.* AD-01 and ALM201) have potent anti-tumour activity by inhibiting angiogenesis and promoting the differentiation of cancer stem cells [21, 495, 496, 749]. |



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| | | | |
|---|---|---|---|
| Nomenclature | peptidylprolyl cis/trans isomerase, NIMA-interacting 1 | peptidylprolyl isomerase A | peptidylprolyl isomerase D |
| Common abbreviation | – | Cyclophilin A | Cyclophilin D |
| HGNC, UniProt | *PIN1*, Q13526 | *PPIA*, P62937 | *PPID*, Q08752 |
| EC number | 5.2.1.8 | 5.2.1.8 | 5.2.1.8 |
| Inhibitors | BJP-06-005-3 ($pK_i$ 7.8) [588], AG-17724 ($pK_i$ 7.1) [278] | cyclosporin A (Inhibition of the phosphatase activity of calcineurin in Jurkat cells.) ($pIC_{50}$ 8.3) [221], voclosporin (Binding) ($pK_d$ 7.8) [408] | cyclosporin A ($pIC_{50}$ 8) [410, 594] |
| Comments | PIN1 isomerises phosphorylated serine/threonine-proline bonds. It plays roles in cell cycle control, neuropathologies and the immune system [194]. | – | Cyclosporin A (CsA) is the prototypical cyclophilin D (CyPD) inhibitor, but it also inhibits cyclophilin A and the calcineurin pathway, an effect that has long been used for immunosuppression in humans [594]. |

**Further reading on Peptidyl-prolyl cis/trans isomerases**

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Kang CB *et al.* (2008) FKBP family proteins: immunophilins with versatile biological functions. *Neurosignals***16**: 318-25 [PMID:18635947]

Schiene-Fischer C. (2015) Multidomain Peptidyl Prolyl cis/trans Isomerases. *Biochim Biophys Acta* **1850**: 2005-16 [PMID:25445709]

Schmidpeter PA *et al.* (2015) Control of protein function by prolyl isomerization. *Biochim Biophys Acta***1850**: 1973-82 [PMID:25542300]

Wang T *et al.* (2004) The immunophilin FKBP12: a molecular guardian of the TGF-beta family type I receptors. *Front Biosci* **9**: 619-31 [PMID:14766396]

# 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 HIF1α (*HIF1A*; Q16665) leading to an increased degradation through proteasomal hydrolysis. This action requires molecular oxygen and 2-oxoglutarate, and so reduced oxygen tensions prevents HIF1α hydroxylation, allowing its translocation to the nucleus and dimerisation with HIF1β (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*, Q96KS0 | *EGLN1*, Q9GZT9 | *EGLN3*, Q9H6Z9 |
| EC number | 1.14.11.29 | 1.14.11.29 | 1.14.11.29 |



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**Further reading on Prolyl hydroxylases**

Fan L *et al*. (2014) The hypoxia-inducible factor pathway, prolyl hydroxylase domain protein inhibitors, and their roles in bone repair and regeneration. *Biomed Res Int* **2014**: 239356 [PMID:24895555]

Jaakkola PM *et al*. (2013) The regulation, localization, and functions of oxygen-sensing prolyl hydroxylase PHD3. *Biol Chem* **394**: 449-57 [PMID:23380539]

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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 hexadecenal by sphingosine 1-phosphate lyase (EC 4.1.2.27). Recessive mutations in the S1P lyase (SPL) gene underlie a recently identified sphingolipidosis: SPL Insufficiency Syndrome (SPLIS). In general, S1P promotes cell survival, proliferation, migration, adhesion and inhibition of apoptosis. Intracellular S1P affects epigenetic regulation, endosomal processing, mitochondrial function and cell proliferation/senescence. S1P has myriad physiological functions, including vascular development, lymphocyte trafficking and neurogenesis. However, S1P is also involved in a number of diseases such as cancer, inflammation and fibrosis. Therefore, its GPCRs and enzymes of synthesis and degradation are a major focus for drug discovery.

# 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 phosphorylation. 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 (PPARγ). 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 $S1P_1$ receptors. Inhibitors of SPHK1 and SPHK2 have therapeutic potential in many diseases. Isoform-selective inhibitors are becoming available; some early inhibitors have recognised off-target effects.

| | | |
|---|---|---|
| Nomenclature | sphingosine kinase 1 | sphingosine kinase 2 |
| Common abbreviation | SPHK1 | SPHK2 |
| HGNC, UniProt | *SPHK1*, Q9NYA1 | *SPHK2*, Q9NRA0 |
| EC number | 2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADPdihydrosphingosine + ATP = dihydrosphingosine 1-phosphate + ADP | |
| Cofactors | $Mg^{2+}$ [666] | $Mg^{2+}$ |
| Inhibitors | compound 49 ($pIC_{50}$ 7.8) [6], SKI II ($pK_i$ 4.8) [218], MP-A08 ($pIC_{50}$ 4.6) [591] | compound 49 ($pIC_{50}$ 7.8) [6], MP-A08 ($pK_i$ 5.2) [591], SKI II ($pK_i$ 5.1) [236] |



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| | | |
|---|---|---|
| Selective inhibitors | PF-543 (p$K_i$ 8.4) [653] | compound 59 (p$IC_{50}$ 7.8) [6], compound 60 (p$IC_{50}$ 7.5) [6], compound 55 (p$IC_{50}$ 7.4) [6], SLC4101431 (p$K_i$ 7.1) [114], compound 27d (p$IC_{50}$ 6.8) [652], opaganib (p$K_i$ 5) [218], ROMe (p$K_i$ 4.8) [439] |
| Comments | SPHK1 inhibitors induce its proteasomal degradation [464, 499]. SPHK1 crystal structures confirm that it is dimeric [5]. | There is no crystal structure available for SPHK2. |

**Comments**: MP-A08 is competitive with ATP; other SPHK inhibitors are competitive with sphingosine. ABC294640 (opaganib) has known off-target effects on dihydroceramide desaturase (*DEGS1*) [499, 754]) and induces proteasomal degradation of SPHK1 [499]. 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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Powell JA *et al.* (2019) Kelch-like protein 5-mediated ubiquitination of lysine 183 promotes proteasomal degradation of sphingosine kinase 1. *Biochem J* **476**: 3211-3226 [PMID:31652307]

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.* (2020) Sphingosine Kinases as Druggable Targets. *Handb Exp Pharmacol* **259**: 49-76 [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 dihydrosphingosine 1-phosphate -> dihydrosphingosine + inorganic phosphate | 3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate dihydrosphingosine 1-phosphate -> dihydrosphingosine + inorganic phosphate |
| Comments | Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [428]. | – |

**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 [428].



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**Further reading on Sphingosine 1-phosphate phosphatase**

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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 USA* **97**: 7859-64 [PMID:10859351]

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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 | *SGPL1*, 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) [299, 455, 655, 784] |

**Comments**: THI (2-Acetyl-5-tetrahydroxybutyl imidazole) inhibits the enzyme activity in intact cell preparations [656]. Recessive mutations in the S1P lyase (*SGPL1*) gene underlie a recently identified sphingolipidosis: SPL Insufficiency Syndrome (SPLIS) [118]. A Phase 2 clinical trial of LX3305 (LX2931) for rheumatoid arthritis has been completed (see NCT00903383). A homozygous point mutation results in mislocalisation of S1P lyase from the endoplasmic reticulum in pediatric alveolar rhabdomyosarcoma [7].

**Further reading on Sphingosine 1-phosphate lyase**

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Choi YJ *et al.* (2019) Sphingosine phosphate lyase insufficiency syndrome (SPLIS): A novel inborn error of sphingolipid metabolism. *Adv Biol Regul* **71**: 128-140 [PMID:30274713]

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]

Schwiebs A *et al.* (2019) Cancer-induced inflammation and inflammation-induced cancer in colon: a role for S1P lyase. *Oncogene* **38**: 4788-4803 [PMID:30816345]



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# Thyroid hormone turnover

Enzymes → Thyroid hormone turnover

**Overview**:
The thyroid hormones triiodothyronine and thyroxine, usually abbreviated as triiodothyronine and $T_4$, respectively, are synthesized in the thyroid gland by sequential metabolism of tyrosine residues in the glycosylated homodimeric protein thyroglobulin (*TG*, P01266) under the influence of the haem-containing protein iodide peroxidase. Iodide peroxidase/TPO is a haem-containing enzyme, from the same structural family as eosinophil peroxidase (*EPX*, P11678), lactoperoxidase (LPO, P22079) and myeloperoxidase (MPO, P05164). Circulating thyroid hormone is bound to thyroxine-binding globulin (SERPINA7, P05543).

**Tissue deiodinases**
These are 1 TM selenoproteins that remove an iodine from $T_4$ (3,3′,5,5′-tetraiodothyronine) to generate triiodothyronine (3,3′,5-triiodothyronine, a more potent agonist at thyroid hormone receptors) or $rT_3$ (rT3, 3,3′,5′-triiodothyronine, a relatively inactive analogue). DIO1 is also able to deiodinate RT3 to form 3,3′-diidothyronine ($T_2$). 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 + $H_2O_2$ + $H^+$ + $I^-$ -> [Thyroglobulin]-3,5,3′-triiodo-L-thyronine + [thyroglobulin]-aminoacrylate + $H_2O$ | 1.97.1.10: $T_4$ -> triiodothyroninerT$_3$ -> $T_2$ | 1.97.1.10: $T_4$ -> triiodothyroninerT$_3$ -> $T_2$ | 1.97.1.11: $T_4$ -> triiodothyroninerT$_3$ -> $T_2$ | 1.22.1.1: 3-iodotyrosine -> L-tyrosine + $I^-$3,5-diiodo-L-tyrosine -> 3-iodotyrosine + $I^-$ |
| Cofactors | $Ca^{2+}$ | – | – | – | flavin adenine dinucleotide, NADPH |
| Inhibitors | methimazole [536], propylthiouracil [536] | – | – | – | – |
| Comments | Carbimazole is a pro-drug for methimazole | – | – | – | – |

**Further reading on Thyroid hormone turnover**


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Gereben B *et al.* (2015) Scope and limitations of iodothyronine deiodinases in hypothyroidism. *Nat Rev Endocrinol* **11**: 642-652 [PMID:26416219]

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Mondal S *et al.* (2017) Novel thyroid hormone analogues, enzyme inhibitors and mimetics, and their action. *Mol Cell Endocrinol* **458**: 91-104 [PMID:28408161]

van der Spek AH *et al.* (2017) Thyroid hormone metabolism in innate immune cells. *J Endocrinol* **232**: R67-R81 [PMID:27852725]




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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(+) + $H_2O$ |
| Comments | Kynurenine 3-monooxygenase participates in metabolism of the essential amino acid tryptophan. |

**Further reading on 1.14.13.9 Kynurenine 3-monooxygenase**


Collier ME *et al*. (2021) Inflammation control and improvement of cognitive function in COVID-19 infections: is there a role for kynurenine 3-monooxygenase inhibition? *Drug Discov Today* **26**: 1473-1481 [PMID:33609782]

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# 2.5.1.58 Protein farnesyltransferase

Enzymes → 2.5.1.58 Protein farnesyltransferase

**Overview**: Farnesyltransferase is a member of the prenyltransferases family which also includes geranylgeranyltransferase types I (EC 2.5.1.59) and II (EC 2.5.1.60) [93]. Protein farnesyltransferase catalyses the post-translational formation of a thioether linkage between the C-1 of an isoprenyl group and a cysteine residue fourth from the C-terminus of a protein (*ie* to the CaaX motif, where 'a' is an aliphatic amino acid and 'X' is usually serine, methionine, alanine or glutamine; leucine for EC 2.5.1.59) [227]. Farnesyltransferase is a dimer, composed of an alpha and beta subunit and requires $Mg^{2+}$ and $Zn^{2+}$ 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 in to five subfamilies based on phylogenetic comparison with yeast homologues:
Class I contains HDACs 1, 2, 3 and 8
Class IIa contains HDACs 4, 5, 7 and 9
Class IIb contains HDACs 6 and 10
Class III contains the sirtuins (SIRT1-7)
Class IV contains only HDAC11.
Classes I, II and IV use $Zn^+$ as a co-factor, whereas catalysis by Class III enzymes requires $NAD^+$ as a co-factor, and members of this subfamily have ADP-ribosylase activity in addition to protein deacetylase function [646].
HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [119] such as microtubules [332], the hsp90 chaperone [402] and the tumour suppressor p53 [468].
Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [440, 630], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [789]. 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 anticancer therapeutics are reviewed by Simó-Riudalbas and Esteller (2015) [676].

| | |
|---|---|
| Nomenclature | histone deacetylase 6 |
| HGNC, UniProt | *HDAC6*, Q9UBN7 |
| EC number | 3.5.1.98 |
| Inhibitors | trichostatin A ($pK_i$ 9) [72], vorinostat ($pK_i$ 8.8) [72], romidepsin ($pK_i$ 8) [72] |
| Selective inhibitors | ricolinostat ($pIC_{50}$ 8.3) [643] |

**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 [365]. 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 [59]. Pharmacological PADI inhibition reverses protein-hypercitrullination and disease in mouse models of multiple sclerosis [526].
Information on members of this family may be found in the online database.



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**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 [697], which leads to increased cell proliferation and decreased apoptosis [839]. Because of their importance in oncogenic transformation these proteins have become the targets of intense drug discovery effort [39].
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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