THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Enzymes

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Abstract
The Concise Guide to PHARMACOLOGY 2017/18 provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full. Enzymes are one of the eight major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, other ion channels, nuclear hormone receptors, catalytic receptors and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading.

The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2017, and supersedes data presented in the 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature Committee of the Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

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

Overview: Enzymes are protein catalysts facilitating the conversion of substrates into products. The Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB) classifies enzymes into families, using a four-number code, on the basis of the reactions they catalyse. There are six main families:
EC 1... Oxidoreductases;
EC 2... Transferases;
EC 3... Hydrolases;
EC 4... Lyases;
EC 5... Isomerases;
EC 6... Ligases.

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

The majority of drugs which act on enzymes act as inhibitors; one exception is metformin, which appears to stimulate activity of AMP-activated protein kinase, albeit through an imprecisely-defined mechanism. Kinetic assays allow discrimination of competitive, non-competitive, and un-competitive inhibitors. The majority of inhibitors are competitive (acting at the enzyme’s ligand recognition site), non-competitive (acting at a distinct site; potentially interfering with co-factor or co-enzyme binding) or of mixed type. One rare example of an uncompetitive inhibitor is lithium ions, which are effective inhibitors at inositol monophosphatase only in the presence of high substrate concentrations. Some inhibitors are irreversible, including a group known as suicide substrates, which bind to the ligand recognition site and then couple covalently to the enzyme. It is beyond the scope of the Guide to give mechanistic information about the inhibitors described, although generally this information is available from the indicated literature.

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

| Kinases (EC 2.7.x.x) | S275 |
|----------------------|------|
| AGC: Containing PKA, PKG, PKC families | S276 |
| DAMP family | S277 |
| GEK subfamily | S277 |
| Other DAMP family kinases | S277 |
| Rho kinase | S278 |
| GRK4 subfamily | S278 |
| MAST family | S278 |
| NDR family | S278 |
| Protein kinase A | S278 |
| Akt (Protein kinase B) | S278 |
| Protein kinase C (PKC) | S278 |
| Alpha subfamily | S278 |
| Delta subfamily | S278 |
| Eta subfamily | S278 |
| Iota subfamily | S278 |
| Protein kinase G (PKG) | S278 |
| Protein kinase N (PNK) family | S278 |
| RSK family | S278 |
| MSK subfamily | S278 |
| p70 subfamily | S278 |
| RSK subfamily | S278 |
| RSKR subfamily | S278 |
| RSKI, family | S278 |
| SGK family | S278 |
| YANK family | S278 |
| Atypical | S278 |
| ABC1 family | S278 |
| ABC1-A subfamily | S278 |
| ABC1-B subfamily | S278 |
| Alpha kinase family | S278 |
| ChaK subfamily | S278 |
| eEF2K subfamily | S278 |
| Other alpha kinase family kinases | S278 |
| BCR family | S278 |
| Bromodomain kinase (BRD) family | S278 |
| G11 family | S278 |
| Phosphatidyl inositol 3' kinase-related | S278 |
| kinases (PI3K) family | S278 |
| | S279 |
| ATR subfamily | S279 |
| FRAP subfamily | S279 |
| SMG1 subfamily | S279 |
| TRRAP subfamily | S279 |
| Other PIKK family kinases | S279 |
| RIO family | S279 |
| RIO1 family | S279 |
| RIO2 family | S279 |
| RIO3 family | S279 |
| PDHK family | S279 |
| Pyruvate dehydrogenase kinase (PDHK) family | S279 |
| TAF1 family | S279 |
| CAMK: Calcium/calmodulin-dependent protein kinases | S279 |
| CAMK1 family | S279 |
| CAMK2 family | S279 |
| CAMK-like (CAMKL) family | S279 |
| AMPK subfamily | S279 |
| BRK family | S279 |
| CHK1 family | S279 |
| HUNK subfamily | S279 |
| LKB subfamily | S279 |
| MARK subfamily | S279 |
| MELK subfamily | S279 |
| NIM1 subfamily | S279 |
| NuA family | S279 |
| PASK subfamily | S279 |
| QIK family | S279 |
| SNRK family | S279 |
| CAMK-unique family | S279 |
| CASK family | S279 |
| DCAMKL family | S279 |
| Death-associated kinase (DAPK) family | S279 |
| MAPK-Activated Protein Kinase (MAPKAPK) family | S279 |
| MAPKAPK subfamily | S279 |
| MKN subfamily | S279 |
| Myosin Light Chain Kinase (MLCK) family | S279 |
| Phosphorylase kinase (PHK) family | S279 |
| PIM family | S279 |
| Protein kinase D (PKD) family | S279 |
| PSK family | S279 |
| | S279 |
| RAD53 family | S279 |
| Testis specific kinase (TSSK) family | S279 |
| Trb family | S279 |
| Trio family | S279 |
| CK1: Casein kinase 1 | S279 |
| Casein kinase 1 (CK1) family | S279 |
| Tau tubulin kinase (TTBK) family | S279 |
| Vaccina related kinase (VRK) family | S279 |
| CMGC: Containing CDK, MAPK, GSK3, CLK families | S279 |
| | S279 |
| Cyclin-dependent kinase (CDK) family | S279 |
| CCKR subfamily | S279 |
| CDK1 subfamily | S279 |
| CDK4 subfamily | S279 |
| CDK5 subfamily | S279 |
| CDK7 subfamily | S279 |
| CDK8 subfamily | S279 |
| CDK9 subfamily | S279 |
| CDK10 subfamily | S279 |
| CRK7 subfamily | S279 |
| PITSRE subfamily | S279 |
| TAIRE subfamily | S279 |
| Cyclin-dependent kinase-like (CDKL) family | S279 |
| Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase (DYRK) family | S279 |
| Dyrk1 subfamily | S279 |
| Dyrk2 subfamily | S279 |
| HIPK subfamily | S279 |
| PRP4 subfamily | S279 |
| Glycogen synthase kinase (GSK) family | S279 |
| GSK subfamily | S279 |
| Mitogen-activated protein kinases | S279 |
| (MAP kinases) | S279 |
| ERK subfamily | S279 |
| Erk7 subfamily | S279 |
| JNK subfamily | S279 |
| JNK subfamily | S279 |
| p38 subfamily | S279 |
| nmo subfamily | S279 |
| RCK family | S279 |
| SRPK family | S279 |
| Other protein kinases | S279 |
| CAMKK family | S279 |
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
- NKF family
- NKF2 family
- NK4 family
- NKF5 family
- NRBP family
- Numb-associated kinase (NAK) family
- Other-unique family
- Pole-like kinase (PLK) family
- PEK family
- GCN2 subfamily
- PEK subfamily
- Other PEK family kinases
- SgK493 family
- Slat 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

- actinbinding proteins ADF family
- Twinfilin subfamily
- SCY1 family
- Hexokinases
- STE: Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases

- STE7 family
- STE1 family
- STE20 family
- FRAY subfamily
- KHS subfamily
- MSN subfamily
- MST subfamily
- NinA subfamily
- NAK subfamily
- PAKA subfamily
- PAKB subfamily
- SLK subfamily
- STLK subfamily
- TAO subfamily
- YSK subfamily
- STE20 family
- STE-unique family
- TK: Tyrosine kinase
- Non-receptor tyrosine kinases (nRTKs)

- 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
- LZH subfamily
- MLK subfamily
- TAK1 subfamily

- Peptidases and proteinases
- AA: Aspartic (A) Peptidases
- AD: Aspartic (A) Peptidases
- CA: Cysteine (C) Peptidases
- C1: Papain
- C2: Calpain
- C12: Ubiquitin C-terminal hydrolase
- C19: Ubiquitin-specific protease
- C54: Aut2 peptidase
- C101: OTULIN peptidase
- CD: Cysteine (C) Peptidases
- C13: Legumain

- AC: Amino acid hydroxylases
- L-Arginine turnover
- Amino acid hydroxylases
- Adenosine turnover
- Acetylcholine turnover

- Enzymes

- Meta subfamily
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- Bub family
- Bud32 family
- Casein kinase 2 (CK2) family
- CDC7 family
- Haspin family
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- IRE family
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- Wnk family
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- actinbinding proteins ADF family
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- SCY1 family
- Hexokinases
- STE: Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases
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- STE1 family
- STE20 family
- FRAY subfamily
- KHS subfamily
- MSN subfamily
- MST subfamily
- NinA subfamily
- PAKA subfamily
- PAKB subfamily
- SLK subfamily
- STLK subfamily
- TAO subfamily
- YSK subfamily
- STE20 family
- STE-unique family
- TK: Tyrosine kinase
- Non-receptor tyrosine kinases (nRTKs)

- 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
- LZH subfamily
- MLK subfamily
- TAK1 subfamily

- Peptidases and proteinases
- AA: Aspartic (A) Peptidases
- AD: Aspartic (A) Peptidases
- CA: Cysteine (C) Peptidases
- C1: Papain
- C2: Calpain
- C12: Ubiquitin C-terminal hydrolase
- C19: Ubiquitin-specific protease
- C54: Aut2 peptidase
- C101: OTULIN peptidase
- CD: Cysteine (C) Peptidases
- C13: Legumain

- AC: Amino acid hydroxylases
- L-Arginine turnover
- Amino acid hydroxylases
- Acetylcholine turnover

- Enzymes
Enzymes → Kinases (EC 2.7.x.x)

**Overview:** Protein kinases (EC 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 18 protein kinases in man (divided into 15 subfamilies), with over 100 protein kinase-like pseudogenes [335]. It is beyond the scope of the Concise Guide to list all these protein kinase activities, but full listings are available on the 'Detailed page' provided for each enzyme. Most inhibitors of these enzymes have been assessed in cell-free investigations and so may appear to 'lose' potency and 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 [110].

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Kinases (EC 2.7.x.x) S275
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 Go12/13 subunits [282].

| Nomenclature          | ROCK1                                            | ROCK2                                            |
|-----------------------|--------------------------------------------------|--------------------------------------------------|
| Systematic nomenclature | ROCK1, Q13464                                   | ROCK2, Q75116                                    |
| EC number             | 2.7.11.1                                         | 2.7.11.1                                         |
| Common abbreviation   | Rho kinase 1                                    | Rho kinase 2                                     |
| Inhibitors            | RKI-1447 (pIC50 > 9) [414], Y27632 (pIC50 5.9–7.3) [328, 575], fasudil (pK7) [434], Y27632 (pK7 6.8) [540], fasudil (pIC50 5.5–5.6) [328, 434] | RKI-1447 (pIC50 > 9) [414], compound 11d [DOI: 10.1039/c0md00194e] (pIC50 > 9) [90], GSK269962A (pIC50 8.4) [126], compound 32 (pIC50 8.4) [49], compound 22 (pIC50 7.7) [575], Y27632 (pIC50 6.3–7.2) [328, 575], Y27632 (pK7 6.8–6.9) [328, 540], fasudil (pIC50 5.9–5.9) [328, 434] |
| Selective inhibitors  | GSK269962A (pIC50 8.8) [126]                     | –                                                |

Further reading on Rho kinases

Feng, Y, PV LoGrasso, O Defert and R Li 2016 Rho Kinase (ROCK) Inhibitors and Their Therapeutic Potential J Med Chem 59: 2269-300 [PMID:26486225]
Nishioka, T, MH Shohag, M Amano and K Kaibuchi 2015 Developing novel methods to search for substrates of protein kinases such as Rho-kinase Biochim Biophys Acta 1854: 1663-6 [PMID:25770685]

Protein kinase C (PKC)

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

Classical protein kinase C isoforms: PKCα, PKCβ, and PKCγ are activated by Ca2+ and diacylglycerol, and may be inhibited by GF109203X, calphostin C, Gö 6983, chelerythrine and Ro31-8220.

Novel protein kinase C isoforms: PKCδ, PKCε, PKCη, PKCζ and PKCμ are activated by diacylglycerol and may be inhibited by calphostin C, Gö 6983 and chelerythrine.
Atypical protein kinase C isoforms: PKCι, PKCζ.
## Alpha subfamily

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

| Nomenclature | protein kinase C beta | protein kinase C gamma |
|--------------|-----------------------|------------------------|
| HGNC, UniProt| PRKCB, P05771         | PRKCG, P05129          |
| EC number    | 2.7.11.13             | 2.7.11.13              |
| Common abreviation | PKCβ                     | PKCγ                       |
| Inhibitors   | sotrastaurin (pIC$_{50}$ 8.7) [548], Gö 6983 (pIC$_{50}$ 8.1) [195], GF109203X (pIC$_{50}$ 7.8) [533] – Bovine, 7-hydroxystaurosporine (pIC$_{50}$ 7.5) [468] | Gö 6983 (pIC$_{50}$ 8.2) [195], 7-hydroxystaurosporine (pIC$_{50}$ 7.5) [469] – |
| Selective inhibitors | ruboxistaurin (pIC$_{50}$ 8.2) [250], enzastaurin (pIC$_{50}$ 7.5) [140], CGP53353 (pIC$_{50}$ 6.4) [75] | sotrastaurin (pIC$_{50}$ 8.9) [548], Gö 6983 (pIC$_{50}$ 8) [195] – |

## Delta subfamily

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

| Nomenclature | protein kinase C alpha | protein kinase C delta |
|--------------|-----------------------|------------------------|
| HGNC, UniProt| PRKCA, P17252         | PRKCD, Q05655          |
| EC number    | 2.7.11.13             | 2.7.11.13              |
| Common abreviation | PKCα                     | PKCδ                       |
| Activators   | –                     | ingenol mebutate (pK$_{i}$ 9.4) [263] |
| Inhibitors   | sotrastaurin (pIC$_{50}$ 8.7) [548], Gö 6983 (pIC$_{50}$ 8.1) [195], 7-hydroxystaurosporine (pIC$_{50}$ 7.5) [468] | sotrastaurin (pIC$_{50}$ 8.9) [548], Gö 6983 (pIC$_{50}$ 8) [195] – |

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## Eta subfamily

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

| Nomenclature | protein kinase C epsilon |
|--------------|--------------------------|
| HGNC, UniProt| PRKCE, Q02156            |
| EC number    | 2.7.11.13                |
| Common abreviation | PKCe                |
| Inhibitors   | sotrastaurin (pIC$_{50}$ 8.2) [548]|

### Further reading on Protein kinase C

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

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

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

## FRAP subfamily

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

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

### Further reading on FRAP subfamily

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

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

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

### CDK4 subfamily

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

| Nomenclature          | cyclin dependent kinase 4 | cyclin dependent kinase 6 |
|-----------------------|---------------------------|---------------------------|
| HGNC, UniProt         | CDK4, P11802              | CDK6, Q00534              |
| EC number             | 2.7.11.22                 | 2.7.11.22                 |
| Common abreviation    | CDK4                      | CDK6                      |
| Inhibitors            | R547 (pKᵢ 9) [117], palbociclib (pIC₅₀ 8) [160], Ro-0505124 (pIC₅₀ 7.7) [129], riviciclib (pIC₅₀ 7.2) [258], alvocidib (pKᵢ 7.2) [70] | palbociclib (pIC₅₀ 7.8) [160] |

### GSK subfamily

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

| Nomenclature          | glycogen synthase kinase 3 beta |
|-----------------------|----------------------------------|
| HGNC, UniProt         | GSK3B, P49841                    |
| EC number             | 2.7.11.26                        |
| Common abreviation    | GSK3B                            |
| Inhibitors            | CHIR-98014 (pIC₅₀ 9.2) [440], LY2090314 (pIC₅₀ 9) [133], CHIR-99021 (pIC₅₀ 8.2) [440], SB 216763 (pIC₅₀ 8.1) [95], 1-azakenpaullone (pIC₅₀ 7.7) [285], SB-415286 (pIC₅₀ 7.4) [95], IM-12 (pIC₅₀ 7.3) [460] |
| Selective inhibitors  | AZD2858 (pKᵢ 8.3) [31]           |
| Comments              | Due to its Tau phosphorylating activity, small molecule inhibitors of GSK-3β are being investigated as potential treatments for Alzheimer's disease (AD) [31]. GSK-3β also plays a role in canonical Wnt pathway signalling, the normal activity of which is crucial for the maintenance of normal bone mass. It is hypothesised that small molecule inhibitors of GSK-3β may provide effective therapeutics for the treatment of diseases characterised by low bone mass [320]. |

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Polo-like kinase (PLK) family

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

| Nomenclature          | polo like kinase 4 |
|-----------------------|--------------------|
| HGNC, UniProt         | PLK4, O00444       |
| EC number             | 2.7.11.21          |
| Common abbreviation   | PLK4               |
| Inhibitors            | CFI-400945 (pIC\textsubscript{50} 8.6) [343] |

STE7 family

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

| Nomenclature          | mitogen-activated protein kinase kinase 1 | mitogen-activated protein kinase kinase 2 |
|-----------------------|------------------------------------------|------------------------------------------|
| HGNC, UniProt         | MAP2K1, Q02750                           | MAP2K2, P36507                           |
| EC number             | 2.7.12.2                                 | 2.7.12.2                                 |
| Common abbreviation   | MEK1                                      | MEK2                                      |
| Inhibitors            | trametinib (pIC\textsubscript{50} 9-9.1) [183, 589], PD 0325901 (pIC\textsubscript{50} 8.1) [208] | trametinib (pIC\textsubscript{50} 8.7) [589] |
| Allosteric modulators | binimetinib (Negative) (pIC\textsubscript{50} 7.9) [428], refametinib (Negative) (pIC\textsubscript{50} 7.7) [242], CI-1040 (Negative) (pK\textsubscript{d} 6.9) [112] | binimetinib (Negative) (pIC\textsubscript{50} 7.9) [428], refametinib (Negative) (pIC\textsubscript{50} 7.3) [242] |
| Selective allosteric modulators | cobimetinib (Negative) (pIC\textsubscript{50} 9.1) [457] | – |

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### Abl family

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

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

### Ack family

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

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

### Janus kinase (JakA) family

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

| Nomenclature                  | Janus kinase 1 | Janus kinase 2 | Janus kinase 3 | Janus kinase 4 | Janus kinase 5 |
|-------------------------------|----------------|---------------|---------------|---------------|---------------|
| HGNC, UniProt                 | JAK1, P23458   | JAK2, O60674   | JAK3, P52333   | JAK4, P28007   | JAK5, T30002   |
| EC number                     | 2.7.10.2       | 2.7.10.2       | 2.7.10.2       | 2.7.10.2       | 2.7.10.2       |
| Common abbreviation           | JAK1           | JAK2           | JAK3           | JAK4           | JAK5           |

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(continued)

| Nomenclature | Janus kinase 1 | Janus kinase 2 | Janus kinase 3 | tyrosine kinase 2 |
|--------------|--------------|---------------|-------------|---------------|
| Inhibitors   | ruxolitinib (pIC₅₀ 8.5–10.1) [203, 423], filgotinib (pIC₅₀ 8) [341] | NS-018 (pIC₅₀ 9.1) [374], BMS-911543 (pIC₅₀ 9) [420], AT-9283 (pIC₅₀ 8.9) [230], XL019 (pIC₅₀ 8.7) [152], fedratinib (pIC₅₀ 8.5) [333, 566], gandotinib (pIC₅₀ 8.4) [330] | AT-9283 (pIC₅₀ 9) [230] | – |
| Selective inhibitors | – | compound 1d (pIC₅₀ > 9) [554] | – | – |
| Comments | – | The JAK2V617F mutation, which causes constitutive activation, plays an oncogenic role in the pathogenesis of the myeloproliferative disorders, polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis [64, 115]. Small molecule compounds which inhibit aberrant JAK2 activity are being developed as novel anti-cancer pharmaceuticals. | – | – |

**Src family**

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

| Nomenclature | BLK proto-oncogene, Src family tyrosine kinase | fyn related Src family tyrosine kinase | FYN proto-oncogene, Src family tyrosine kinase | LYN proto-oncogene, Src family tyrosine kinase | SRC proto-oncogene, non-receptor tyrosine kinase |
|--------------|-----------------------------------------------|-------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| HGNC, UniProt | BLK, PS1451 | FRK, P42685 | FYN, P06241 | LYN, P07948 | SRC, P12931 |
| EC number    | 2.7.10.2 | 2.7.10.2 | 2.7.10.2 | 2.7.10.2 | 2.7.10.2 |
| Common abbreviation | Blk | FRK | Fyn | Lyn | Src |
| Inhibitors   | – | – | PP1 (pIC₅₀ 8.2) [205] | bafetinib (pIC₅₀ 8) [228] | WH-4-023 (pIC₅₀ 8.2) [340], PD166285 (pKi 8.1) [396], PP121 (pIC₅₀ 7.8) [15], ENMD-2076 (pIC₅₀ 7.7) [416] |

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
### Tec family

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

| Nomenclature | BMX non-receptor tyrosine kinase | Bruton tyrosine kinase | TXK tyrosine kinase |
|--------------|----------------------------------|------------------------|---------------------|
| HGNC, UniProt| BMX, P51813                      | 8T2, Q06187            | TXK, P42681         |
| EC number    | 2.7.10.2                         | 2.7.10.2               | 2.7.10.2            |
| Common abreviation | Etk                           | Btk                    | TXK               |
| Inhibitors   | compound 38 (pIC₅₀ 9.1) [300], ibrutinib (pIC₅₀ 9.1) [318], compound 31 (pIC₅₀ 8.7) [300] | ibrutinib (pIC₅₀ 9.3) [395], compound 31 (pIC₅₀ 8.4) [300], compound 38 (pIC₅₀ > 8.4) [300] | – |
| Selective inhibitors | BMX-IN-1 (pIC₅₀ 8.1) [307] | CGI1746 (pIC₅₀ 8.7) [120], CHMFL-BTK-11 (Irreversible inhibition) (pIC₅₀ 7.6) [576] | – |

### RAF family

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

| Nomenclature | B-Raf proto-oncogene, serine/threonine kinase | Raf-1 proto-oncogene, serine/threonine kinase |
|--------------|-----------------------------------------------|-----------------------------------------------|
| HGNC, UniProt| BRAF, P15056                                 | RAF1, P04049                                 |
| EC number    | 2.7.11.1                                      | 2.7.11.1                                      |
| Common abreviation | B-Raf                        | c-Raf                                         |
| Inhibitors   | GDC-0879 (pIC₅₀ 9.7–9.9) [112, 206], dabrafenib (pIC₅₀ 8.5) [305], regorafenib (pIC₅₀ 7.6) [594], vemurafenib (pIC₅₀ 7) [555], PLX-4720 (pK_d 6.5) [112], compound 2 (pK_d 6.3) [227], CHIR-265 (pK_d 5.9) [112] | – |
| Selective inhibitors | –                                    | GW5074 (pIC₅₀ 8.1) [88]                      |

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

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

Graves LM *et al.* (2015) The dynamic nature of the kinome. *Biochem. J.* **455**: 1-8 [PMID:23343193]

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

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

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

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

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 [450] (with whom we collaborate) as an information resource [432].

A1: Pepsin

Nomenclature: renin
HGNC, UniProt: REN, P00797
EC number: 3.4.23.15
Inhibitors: aliskiren (pIC_{50} 9.2) [580]

A22: Presenilin

Overview: Presenilin (PS)-1 or -2 act as the catalytic component/essential co-factor of the γ-secretase complex responsible for the final carboxy-terminal cleavage of amyloid precursor protein (APP) [260] in the generation of amyloid beta (Aβ) [7, 510]. 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 [187]. Several small molecule inhibitors of PS-1 have been investigated, with some reaching early clinical trials, but none have been formally approved. Dewji et al. (2015) have reported that small peptide fragments of human PS-1 can significantly inhibit Aβ production (total Aβ, Aβ40 and Aβ42) both in vitro and when infused in to the brains of APP transgenic mice [119]. The most active small peptides in this report were P4 and P8, from the amino-terminal domain of PS-1.

Information on members of this family may be found in the online database.
C14: Caspase

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

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

M1: Aminopeptidase N

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

**Overview:** Aminopeptidases catalyze the cleavage of amino acids from the amino (N) terminus of protein or peptide substrates, and are involved in many essential cellular functions. Members of this enzyme family may be monomeric or multi-subunit complexes, and many are zinc metalloenzymes [522].

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

M2: Angiotensin-converting (ACE and ACE2)

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

| Nomenclature | Angiotensin-converting enzyme |
|--------------|------------------------------|
| HGNC, UniProt| **ACE, P12821**              |
| EC number   | 3.4.15.1                     |
| Common abreviation | **ACE**                      |
| Endogenous substrates | angiotensin I (AGT, P01019) > angiotensin II (AGT, P01019) |
| Inhibitors  | zofenoprilat (pKᵢ 9.4) [283] – Rabbit, captopril (pKᵢ 8.4) [354], zofenopril                      |
| Selective inhibitors | perindoprilat (pIC₅₀ 9) [73], cilazapril (pIC₅₀ 8.7) [559] – Rabbit, imidaprilat (pIC₅₀ 8.7) [443], lisinopril-tryptophan (C-domain assay) (pIC₅₀ 8.2) [560], RXP-407 (N-domain selective inhibition) (pIC₅₀ 8.1) [472], fosinoprilat (pIC₅₀ 8) [113] – Rabbit, enalaprilat (pIC₅₀ 7.5) [87], benazeprilat (pIC₅₀ 6.6) [296] |
| Comments    | Reports of ACE GPI hydrolase activity [277] have been refuted [298] |

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M10: Matrix metallopeptidase

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

Overview: Matrix metalloproteinases (MMP) are calcium- and zinc-dependent proteinases regulating the extracellular matrix and are often divided (e.g. \[545\]) on functional and structural bases into gelatinases, collagenases, stromelysinases and matrilysins, as well as membrane type-MMP (MT-MMP).

| Nomenclature | MMP2 | MMP8 |
|--------------|------|------|
| HGNC, UniProt | MMP2, P08253 | MMP8, P22894 |
| EC number    | 3.4.24.24 | 3.4.24.34 |
| Selective inhibitors | ARP100 [S37] | – |
| 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 (ENSG0000018520) and ADAMDEC1 (decysin 1, ENSG00000134028). Other ADAMTS family members include AC104743.2-1 (ENSG00000113446), AC139432.3-1 (ENSG00000225577), and AC126339.6-1 (ENSG00000225734).

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**M28: Aminopeptidase Y**

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

**Comments:** Folate hydrolase is also known as NAALADase as it is responsible for the hydrolysis of N-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.

**M19: Membrane dipeptidase**

Dipeptidase 1
HGNC, UniProt: DPEP1, P16444
Inhibitors: cilastatin (pKᵢ 6) [189]
S1: Chymotrypsin
Enzymes → Peptidases and proteinases → PA: Serine (S) Peptidases → S1: Chymotrypsin

| Nomenclature | complement C1r | coagulation factor II, thrombin | coagulation factor X |
|--------------|----------------|--------------------------------|----------------------|
| HGNC, UniProt| C1R, P00736    | F2, P00734                      | F10, P00742          |
| EC number    | 3.4.21.41      | 3.4.21.5                        | 3.4.21.6             |
| Inhibitors   | nafamostat (pIC₅₀ 4.9) [216] | lepirudin (pKᵢ 13) [506], desirudin (pKᵢ 12.7) [254], AZ12971554 (pKᵢ 9.5) [19], melagatran (pKᵢ 8.7) [198], bivalirudin (pKᵢ 8.6) [573], dabigatran (pKᵢ 8.3) [211], argatroban (pKᵢ 7.7) [238] | rivaroxaban (pKᵢ 9.4) [407], edoxaban (pKᵢ 9.2) [412], apixaban (pKᵢ 9.1) [574] |
| Selective inhibitors | – | Dup-714 (pKᵢ 10.4) [175], AR-H067637 (pIC₅₀ 8.4) [114] | – |

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

Overview: The T1 macropain beta subunits form the catalytic proteasome core of the 20S proteasome complex [93]. This catalytic core enables the degradation of peptides with Arg, Phe, Tyr, Leu, and Glu adjacent to the cleavage site. The β5 subunit is the principal target of the approved drug proteasome inhibitor bortezomib.

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**S8: Subtilisin**

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

**Overview**: One member of this family has garnered intense interest as a clinical drug target. As liver PCSK9 acts to maintain cholesterol homeostasis, it has become a target of intense interest for clinical drug development. Inhibition of PCSK9 can lower low-density cholesterol (LDL-C) by clearing LDLR-bound LDL particles, thereby lowering circulating cholesterol levels. It is hypothesised that this action may improve outcomes in patients with atherosclerotic cardiovascular disease [315, 452, 501]. Therapeutics which inhibit PCSK9 are viewed as potentially lucrative replacements for statins, upon statin patent expiry. 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 [106, 147, 155].

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

**S9: Prolyl oligopeptidase**

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

| Nomenclature            | dipeptidyl peptidase 4 |
|-------------------------|------------------------|
| HGNC, UniProt           | DPP4, P27487           |
| EC number               | 3.4.14.5               |
| Endogenous substrates   | glucagon-like peptide 1 (GCG, P01275) |
| Inhibitors              | saxagliptin (pKᵢ 9.2) [196], linagliptin (pKᵢ 9) [130], sitagliptin (pIC₅₀ 8.1) [111], vildagliptin (pKᵢ 7.8) [196] |
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
  - CHAT, P28329
- acetylcholinesterase (Cartwright blood group)
  - AChE, P22303
- butyrylcholinesterase
  - BChE, P06276
- EC number
  - 2.3.1.6: acetyl CoA + choline = acetylcholine + coenzyme A
  - 3.1.1.7: acetylcholine + H2O = acetic acid + choline + H+  
- Common abbreviation
  - ChAT
- Inhibitors
  - compound 2 (pIC50 6.5) [190] – Mouse
  - physostigmine (pIC50 7.6–7.8) [325]
- Sub/family-selective inhibitors
  - –
- Selective inhibitors
  - –
- Comments
  - Splice variants of choline O-acetyltransferase are suggested to be differentially distributed in the periphery and CNS (see [30]).

Comments: A number of organophosphorus compounds inhibit acetylcholinesterase and cholinesterase irreversibly, including pesticides such as chlorpyrifos-oxon, and nerve agents such as tabun, soman and sarin. AChE is unusual in its exceptionally high turnover rate which has been calculated at 740 000/min/molecule [570].

Further reading on Acetylcholine turnover
- Li Q et al. (2017) Recent progress in the identification of selective butyrylcholinesterase inhibitors for Alzheimer’s disease. *Eur J Med Chem* **132**: 294-309 [PMID:28371641]
- Lockridge O. (2015) Review of human butyrylcholinesterase structure, function, genetic variants, history of use in the clinic, and potential therapeutic uses. *Pharmacol Ther* **148**: 34-46 [PMID:25448037]
- Masson P et al. (2016) Slow-binding inhibition of cholinesterases, pharmacological and toxicological relevance. *Arch Biochem Biophys* **593**: 60-8 [PMID:26874196]
- Rotundo RL. (2017) Biogenesis, assembly and trafficking of acetylcholinesterase. *J Neurochem* [PMID:28326552]
- Silman I et al. (2017) Recent developments in structural studies on acetylcholinesterase. *J Neurochem* [PMID:28503857]

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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-Adenosyl/homocysteine hydrolase |
|--------------|---------------------|-----------------|---------------------|----------------------------------|
| Systematic nomenclature | – | – | CD73 | – |
| HGNC, UniProt | ADA, P00813 | ADK, P55263 | – | NTSE, P21589 |
| EC number | 3.5.4.4: adenosine + H2O = inosine + NH3 | 2.7.1.20 | – | 3.1.3.5 |
| Common abbreviation | ADA | ADK | NTSE | AHCY, P23526 |
| Rank order of affinity | 2'-deoxyadenosine > adenosine | 2'-deoxyinosine, inosine | adenosine 5'-monophosphate, S'-monophosphate, S'-GMP, S'-inosine monophosphate, S'-UMP > 5'-dAMP, 5'-dGMP | adenosine 5'-monophosphate, S'-GMP, S'-inosine monophosphate, S'-UMP > 5'-dAMP, 5'-dGMP |
| Endogenous substrates | – | – | – | – |
| Products | 2'-deoxyinosine, inosine | adenosine 5'-monophosphate, uridine, inosine, guanine, adenosine | adenosine | adenosine |
| Inhibitors | pentostatin (pIC50 10.8) [4], EHNA (pKi 8.8) [4] | A134974 (pIC50 10.2) [348], ABT702 (pIC50 8.8) [248] | αβ-methyleneADP (pIC50 8.7) [56] | 3-deazaadenosine (pIC50 8.5) [197] |
| Selective inhibitors | – | – | – | – |
| Comments | The enzyme exists in two isoforms derived from alternative splicing of a single gene product: a short isoform, ADK-S, located in the cytoplasm is responsible for the regulation of intra- and extracellular levels of adenosine and hence adenosine receptor activation; a long isoform, ADK-L, located in the nucleus contributes to the regulation of DNA methylation [48, 569]. | Pharmacological inhibition of CD73 is being investigated as a novel cancer immunotherapy strategy [552]. | – | – |

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**Comments:** An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, CECRI, Q9NZK5) has been identified [101, 331], which is insensitive to EHNA [595]. Other forms of adenosine deaminase act on ribonucleic acids and may be divided into two families: *ADAT1* (Q9BUB4) deaminates transfer RNA; *ADAR* (EC 3.5.4.37, also known as 136 kDa double-stranded RNA-binding protein, P136, K88DSRP, Interferon-inducible protein 4); *ADAR1* (EC 3.5.-.-, also known as dsRNA adenosine deaminase) and *ADAR2* (EC 3.5.-.-, also known as dsRNA adenosine deaminase B2, RNA-dependent adenosine deaminase 3) act on double-stranded RNA. Particular polymorphisms of the ADA gene result in loss-of-function and severe combined immunodeficiency syndrome. Adenosine deaminase is able to complex with dipeptidyl peptidase IV (EC 3.4.14.5, DPP4, also known as T-cell activation antigen CD26, TP103, adenosine deaminase complexing protein 2) to form a cell-surface activity [259].

**Further reading on Adenosine turnover**

Boison D. (2013) Adenosine kinase: exploitation for therapeutic gain. *Pharmacol. Rev.* 65: 906-43 [PMID:23592612]

Cortés A et al. (2015) Moonlighting adenosine deaminase: a target protein for drug development. *Med Res Rev* 35: 85-125 [PMID:24933472]

Nishikura K (2016) A-to-I editing of coding and non-coding RNAs by ADARs. *Nat Rev Mol Cell Biol* 17: 83-96 [PMID:26648264]

Amino acid hydroxylases

**Enzymes → Amino acid hydroxylases**

**Overview:** The amino acid hydroxylases (monoxygenases), 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, P81WU9                 |
| EC number                     | 1.14.16.1: L-phenylalanine + O₂ → L-tyrosine | 1.14.16.2: L-tyrosine + O₂ → 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*, Fe²⁺      | –                            | –                            |
| Endogenous activators         | Protein kinase A-mediated phosphorylation (Rat) [2] | Protein kinase A-mediated phosphorylation [251] | Protein kinase A-mediated phosphorylation [252] | Protein kinase A-mediated phosphorylation [252] |
| Inhibitors                    | –                           | methylyrosine            | telotristat ethyl [267]      | –                            |
| Selective inhibitors          | α-methylphenylalanine [191] – Rat, fenclonine | α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine | α-propyldopacetamide, 6-fluorotryptophan [377], fenclonine, fenfluramine | α-propyldopacetamide, 6-fluorotryptophan [377], fenclonine, fenfluramine |

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Full Contents of Concise Guide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
Further reading on Amino acid hydroxylases

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Flydal MI et al. (2013) Phenylalanine hydroxylase: function, structure, and regulation. IUBMB Life 65: 341-9 [PMID:23457044]
Roberts KM et al. (2013) Mechanisms of tryptophan and tyrosine hydroxylase. IUBMB Life 65: 350-7 [PMID:23441081]
Tekin I et al. (2014) Complex molecular regulation of tyrosine hydroxylase. J Neural Transm 121: 1451-81 [PMID:24866693]
Waloen K et al. (2017) Tyrosine and tryptophan hydroxylases as therapeutic targets in human disease. Expert Opin Ther Targets 21: 167-180 [PMID:27973928]

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\textsuperscript{G}\textsuperscript{G}-dimethyl-L-arginine (ADMA), which is an endogenous inhibitor of nitric oxide synthase activities. ADMA is hydrolysed by dimethylarginine dimethylhydrolase activities to generate L-citrulline and dimethylamine.

Further reading on L-Arginine turnover

Lai L et al. (2016) Modulating DDAH/NOS Pathway to Discover Vasoprotective Insulin Sensitizers. J Diabetes Res 2016: 1982096 [PMID:26770984]
Pekarova M et al. (2015) The crucial role of L-arginine in macrophage activation: What you need to know about it. Life Sci 137: 44-8 [PMID:26188591]

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full
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 2.1.1.1-) encompass histone arginine N-methyltransferases (PRMT4, PRMT7, EC 2.1.1.125) and myelin basic protein N-methyltransferases (PRMT7, EC 2.1.1.126). They are dimeric or tetrameric enzymes which use S-adenosyl methionine as a methyl donor, generating S-adenosylhomocysteine as a by-product. They generate both mono-methylated and di-methylated products; these may be symmetric (SDMA) or asymmetric (N\(^\omega\),N\(^\omega\)-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 [525], S-(2-boronoethyl)-L-cysteine [97, 268] and 2(S)-amino-6-boronohexanoic acid [24, 97].

Arginine:glycine amidinotransferase

Enzymes → L-Arginine turnover → Arginine:glycine amidinotransferase

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

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full
Dimethylarginine dimethylaminohydrolases

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

| Nomenclature | $N^G,N^G$-Dimethylarginine dimethylaminohydrolase 1 | $N^G,N^G$-Dimethylarginine dimethylaminohydrolase 2 |
|--------------|---------------------------------------------|---------------------------------------------|
| HGNC, UniProt| DDAH1, O94760                               | DDAH2, O95865                               |
| EC number    | 3.5.3.18                                    | 3.5.3.18                                    |
| Cofactors    | $Zn^{2+}$                                   | -                                           |
| Inhibitors   | compound 2e ($pK_i$ 5.7) [279]               | -                                           |

Nitric oxide synthases

**Overview:** Nitric oxide synthases (NOS, E.C. 1.14.13.39) are a family of oxidoreductases that synthesize nitric oxide (NO) via the NADPH and oxygen-dependent consumption of L-arginine with the resultant by-product, L-citrulline. There are 3 NOS isoforms and they are related by their capacity to produce NO, highly conserved organization of functional domains and significant homology at the amino acid level. NOS isoforms are functionally distinguished by the cell type where they are expressed, intracellular targeting and transcriptional and post-translation mechanisms regulating enzyme activity. The nomenclature suggested by NC-IUPHAR of NOS I, II and III [363] has not gained wide acceptance, and the 3 isoforms are more commonly referred to as neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) which reflect the location of expression (nNOS and eNOS) and inducible expression (iNOS). All are dimeric enzymes that shuttle electrons from NADPH, which binds to a C-terminal reductase domain, through the flavins FAD and FMN to the oxygenase domain of the other monomer to enable the BH4-dependent reduction of heme bound oxygen for insertion into the substrate, L-arginine. Electron flow from reductase to oxygenase domain is controlled by calmodulin binding to canonical calmodulin binding motif located between these domains. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affinity for $Ca^{2+}$/calmodulin (CALM1 CALM2 CALM3, P62158) with great avidity and is essentially calcium-independent and constitutively active. Efficient stimulus-dependent coupling of nNOS and eNOS is achieved via subcellular targeting through respective N-terminal PDZ and fatty acid acylation domains whereas iNOS is largely cytosolic and function is independent of intracellular location. nNOS is primarily expressed in the brain and neuronal tissue, iNOS in immune cells such as macrophages and eNOS in the endothelial layer of the vasculature although exceptions in other cells have been documented. L-NAME and related modified arginine analogues are inhibitors of all three isoforms, with IC$_{50}$ values in the micromolar range.
### Nomenclature

| Type               | HGNC, UniProt | EC number | Common abreviation | Endogenous Substrate | Products                                                                 |
|--------------------|--------------|-----------|-------------------|----------------------|--------------------------------------------------------------------------|
| Endothelial NOS    | NOS3, P29474 | 1.14.13.39| eNOS              | L-arginine           | NO, L-citrulline, oxygen, BH4, Zn2+, flavin mononucleotide, NADPH, heme, flavin adenine dinucleotide |
| Inducible NOS      | NOS2, P35228 | 1.14.13.39| iNOS              | L-arginine           | NO, L-citrulline, heme, flavin mononucleotide, flavin adenine dinucleotide, oxygen, NADPH, Zn2+, BH4 |
| Neuronal NOS       | NOS1, P29475 | 1.14.13.39| nNOS              | L-arginine           | NO, L-citrulline, flavin adenine dinucleotide, heme, oxygen, BH4, flavin mononucleotide, NADPH, Zn2+ |

### Products

- NO, L-citrulline
- Flavin mononucleotide, NADPH, heme
- Flavin adenine dinucleotide, oxygen, NADPH, heme, flavin mononucleotide

### Cofactors

- Oxygen, BH4, Zn2+, flavin mononucleotide, NADPH
- Heme, flavin mononucleotide, flavin adenine dinucleotide, oxygen, NADPH, Zn2+, BH4

### Selective inhibitors

- 1400W (pIC50 8.2) [178]
- 2-amino-4-methylpyridine (pIC50 7.4) [139], PIBTU (pIC50 7.3) [179], NIL (pIC50 5.5) [364], aminoguanidine [99]
- 3-bromo-7Ni (pIC50 6.1–6.5) [43], 7Ni (pIC50 5.3) [20]

### Comments

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

### Further reading on Nitric oxide synthases

- Bogdan, C. (2015) Nitric oxide synthase in innate and adaptive immunity: An update. *Trends Immunol* 36: 161-78 [PMID:25687683]
- Lundberg JO et al. (2015) Strategies to increase nitric oxide signalling in cardiovascular disease. *Nat Rev Drug Discov* 14: 623-41 [PMID:26265312]
- Oliveira-Paula GH et al. (2016) Endothelial nitric oxide synthase: From biochemistry and gene structure to clinical implications of NOS3 polymorphisms. *Gene* 575: 584-99 [PMID:26428312]
- Shu X et al. (2015) Endothelial nitric oxide synthase in the microcirculation. *Cell Mol Life Sci* 72: 4561-75 [PMID:26390975]
- Zhao Y et al. (2015) Vascular nitric oxide: Beyond eNOS. *J Pharmacol Sci* 129: 83-94 [PMID:26499181]

### Carboxylases and decarboxylases

- **Enzymes** → Carboxylases and decarboxylases

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Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
Carboxylases

**Overview:** The carboxylases allow the production of new carbon-carbon bonds by introducing $\text{HCO}_3^- \text{ or CO}_3$ into target molecules. Two groups of carboxylase activities, some of which are bidirectional, can be defined on the basis of the cofactor requirement, making use of biotin (EC 6.4.1.-) or vitamin K hydroquinone (EC 4.1.1.-).

| Nomenclature | Pyruvate carboxylase | Acetyl-CoA carboxylase 1 | Acetyl-CoA carboxylase 2 | Propionyl-CoA carboxylase | \(\gamma\)-Glutamyl carboxylase |
|--------------|----------------------|--------------------------|--------------------------|---------------------------|-------------------------------|
| HGNC, UniProt | PC, P11498            | ACACA, Q13085            | ACACB, O00763            | --                        | GGCX, P38435                  |
| Subunits     | --                   | --                       | --                       | Propionyl-CoA carboxylase\(\beta\) subunit, Propionyl-CoA carboxylase \(\alpha\) subunit | --                            |
| EC number    | 6.4.1.1              | 6.4.1.2                  | 6.4.1.2                  | 6.4.1.3                   | 4.1.1.90                      |
| Common abbreviation | PC | ACC1 | ACC2 | PCCA, PCCB | GGCX |
| Endogenous substrates | ATP, pyruvic acid | ATP, acetyl CoA | acetyl CoA, ATP | Propionyl-CoA, ATP | glutamyl peptides |
| Products | P\(_i\), ADP, oxalacetic acid | P\(_i\), ADP, malonyl-CoA | P\(_i\), ADP, malonyl-CoA | ADP, methylmalonyl-CoA, P\(_i\) | carboxyglutamyl peptides |
| Cofactors | biotin | biotin | biotin | biotin | vitamin K hydroquinone, NADPH |
| Inhibitors | -- | -- | -- | -- | anisindione |
| Selective inhibitors | -- | TOFA (pIC\(_{50}\) 4.9) [599] | TOFA (pIC\(_{50}\) 4.9) [599] | -- | -- |
| Comments | -- | Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase. | Propionyl-CoA carboxylase is able to function in both forward and reverse activity modes, as a ligase (carboxylase) or lyase (decarboxylase), respectively. | Loss-of-function mutations in \(\gamma\)-glutamyl carboxylase are associated with clotting disorders. | -- |

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

Enzymes → Carboxylases and decarboxylases → Decarboxylases

**Overview:** The decarboxylases generate CO$_2$ and the indicated products from acidic substrates, requiring pyridoxal phosphate or pyruvic acid as a co-factor.

| Nomenclature                  | Glutamic acid decarboxylase 1 | Glutamic acid decarboxylase 2 | Histidine decarboxylase |
|-------------------------------|-------------------------------|-------------------------------|-------------------------|
| HGNC, UniProt                 | 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                 |
| Common abbreviation           | GAD1                          | GAD2                          | HDC                     |
| Endogenous substrates         | L-glutamic acid, L-aspartic acid | L-glutamic acid, L-aspartic acid | L-histidine             |
| Products                      | GABA                          | GABA                          | histamine               |
| Cofactors                     | pyridoxal phosphate           | pyridoxal phosphate           | pyridoxal phosphate      |
| Selective inhibitors          | s-allylglycine                 | s-allylglycine                 | AMA, FMH [174]           |
| Comments                      | L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [577]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading). | | – |

| Nomenclature                  | L-Arginine decarboxylase | L-Aromatic amino-acid decarboxylase | Malonyl-CoA decarboxylase | Ornithine decarboxylase | Phosphatidylserine decarboxylase | S-Adenosylmethionine decarboxylase |
|-------------------------------|--------------------------|-------------------------------------|---------------------------|-------------------------|---------------------------------|-----------------------------------|
| HGNC, UniProt                 | AZIN2, Q96A70            | DDC, P20711                         | MLYCD, Q95822             | ODC1, P11926             | PISD, Q9UG56                    | AMD1, P17707                      |
| EC number                     | 4.1.1.19                 | 4.1.1.28: levodopa -> dopamine + CO$_2$ | 4.1.1.9                  | 4.1.1.17                | 4.1.1.65                        | 4.1.1.50                         |
| Common abbreviation           | ADC                      | AADC                                | MLYCD                     | ODC                     | PSDC                            | SAMDC                            |
| EC number                     | 4.1.1.19                 | 4.1.1.28: levodopa -> dopamine + CO$_2$ | 4.1.1.9                  | 4.1.1.17                | 4.1.1.65                        | 4.1.1.50                         |

Comments: This enzyme also catalyses the following reaction: L-tryptophan -> tryptamine + CO$_2$
Nomenclature

| Nomenclature                  | Endogenous substrates                  | Products                  | Cofactors                  | Selective inhibitors                                      | Comments |
|-------------------------------|----------------------------------------|---------------------------|---------------------------|-----------------------------------------------------------|----------|
| L-Arginine decarboxylase      | L-arginine                             | agmatine [601]            | pyridoxal phosphate       | The presence of a functional ADC activity in human tissues has been questioned [96]. | AADC is a homodimer. |
| L-Aromatic amino-acid decarboxylase | levodopa, 5-hydroxy-L-tryptophan, L-tryptophan | 5-hydroxytryptamine, dopamine | pyridoxal phosphate       | –                                                         | Inhibited by AMP-activated protein kinase-evoked phosphorylation [451] |
| Malonyl-CoA decarboxylase     | malonyl-CoA                            | acetyl CoA                 | pyridoxal phosphate       | APA (pIC_{50} 7.5) [494], efornithine (pK_{d} 4.9) [422] | The activity of ODC is regulated by the presence of an antizyme (ENSG00000104904) and an ODC antizyme inhibitor (ENSG00000155096). |
| Ornithine decarboxylase       | L-ornithine                            | putrescine                | pyridoxal phosphate       | –                                                         | S-allylglycine is also an inhibitor of SAMDC [393]. |
| Phosphatidylserine decarboxylase | phoshatidyserine                      | phosphatidylethanolamine  | pyruvic acid              | –                                                         | s-allylglycine is also an inhibitor of SAMDC [393]. |
| S-Adenosylmethionine decarboxylase | S-adenosyl methionine                | S-adenosyl-L-methioninamine | pyruvic acid              | sardomozide (pIC_{50} 8) [493] | |

**Further reading on Carboxylases and decarboxylases**

Bale S et al. (2010) Structural biology of S-adenosylmethionine decarboxylase. *Amino Acids* **38**: 451-60 [PMID:19997761]

Jitrapakdee S et al. (2008) Structure, mechanism and regulation of pyruvate carboxylase. *Biochem. J.* **413**: 369-87 [PMID:18613815]

Lietzan AD et al. (2014) Functionally diverse biotin-dependent enzymes with oxaloacetate decarboxylase activity. *Arch. Biochem. Biophys.* **544**: 75-86 [PMID:24184447]

Moya-García AA et al. (2009) Structural features of mammalian histidine decarboxylase reveal the basis for specific inhibition. *Br. J. Pharmacol.* **157**: 4-13 [PMID:19413567]

Tong L. (2013) Structure and function of biotin-dependent carboxylases. *Cell. Mol. Life Sci.* **70**: 863-91 [PMID:22869039]

Vance JE et al. (2013) Formation and function of phosphatidyserine and phosphatidylethanolamine in mammalian cells. *Biochim. Biophys. Acta* **1831**: 543-54 [PMID:22960354]
Catecholamine turnover

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

| Nomenclature                  | L-Phenylalanine hydroxylase | Tyrosine aminotransferase | L-Tyrosine hydroxylase | Dopamine beta-hydroxylase (dopamine beta-monoxygenase) | L-Aromatic amino-acid decarboxylase |
|------------------------------|-----------------------------|---------------------------|------------------------|---------------------------------------------------|-----------------------------------|
| HGNC, UniProt                | PAH, P00439                 | TAT, P17735               | TH, P07101             | DBH, P09172                                       | DDC, P20711                       |
| EC number                    | 1.14.16.1: L-phenylalanine + O₂ -> L-tyrosine | 2.6.1.5: L-tyrosine + α-ketoglutaric acid -> 4-hydroxyphenylpyruvic acid + L-glutamic acid | 1.14.16.2: L-tyrosine + O₂ -> levodopa | 1.14.17.1: dopamine + O₂ = (-)-noradrenaline + H₂O | 4.1.1.28: levodopa -> dopamine + CO₂ |
| Common abreviation           | –                           | TAT                       | –                      | DBH                                              | AADC                              |
| Endogenous substrates        | L-phenylalanine              | –                         | L-tyrosine             | –                                                | levodopa, S-hydroxy-L-tryptophan, L-tryptophan | S-hydroxytryptamine, dopamine |
| Products                     | L-tyrosine                  | –                         | levodopa               | –                                                | –                                 |
| Cofactors                    | sapropterin                 | pyridoxal phosphate       | sapropterin, Fe²⁺    | Cu²⁺, L-ascorbic acid                            | pyridoxal phosphate               |
| Endogenous activators        | Protein kinase              | A-mediated phosphorylation (Rat) [2] | Protein kinase | A-mediated phosphorylation [251]                    | –                                 |
| Nomenclature | PAH | Tyrosine transaminase | L-Tyrosine hydroxylase | Dopamine beta-hydroxylase (dopamine beta-monooxygenase) | L-Aromatic amino-acid decarboxylase |
|-------------|-----|-----------------------|------------------------|---------------------------------------------------------|-----------------------------------|
| Selective inhibitors | α-methylphenylalanine [191] – Rat, fenclonine | – | α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine | nepicatstat (pIC_{50} 8) [496] | 3-hydroxybenzylhydrizine, L-α-methyldopa, benserazide [108], carbidopa |
| Comments | PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monooxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria | Tyrosine may also be metabolized in the liver by tyrosine transaminase to generate 4-hydroxyphenylpyruvic acid, which can be further metabolized to homogentisic acid. TAT is a homodimer, where loss-of-function mutations are associated with type II tyrosinemia. | TH is a homotramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [109]. | DBH is a homotetramer. A protein structurally-related to DBH (MOKDJ, Q6UVY6) has been described and for which a function has yet to be identified [76]. | AADC is a homodimer. |

| Nomenclature | Phenylethanolamine N-methyltransferase | Monoamine oxidase A | Monoamine oxidase B | Catechol-O-methyltransferase |
|-------------|--------------------------------------|---------------------|---------------------|-----------------------------|
| HGNC, UniProt | PNMT, P11086 | MAOA, P21397 | MAOB, P27338 | COMT, P21964 |
| EC number | 2.1.1.28; (-)-noradrenaline -> (-)-adrenaline | 1.4.3.4 (-)-adrenaline -> 3,4-dihydroxymandelic acid + NH\textsubscript{3} (-)-noradrenaline -> 3,4-dihydroxymandelic acid + NH\textsubscript{3} tyramine -> 4-hydroxyphenyl acetaldehyde + NH\textsubscript{3} dopamine -> 3,4-dihydroxyphenylacetaldehyde + NH\textsubscript{3} 5-hydroxytryptamine -> 5-hydroxyindole acetaldehyde + NH\textsubscript{3} | 1.4.3.4 | 2.1.1.6: S-adenosyl-L-methionine + a catechol = S-adenosyl-L-homocysteine + a quaiacol (-)-noradrenaline -> normetanephrine dopamine -> 3-methoxytyramine 3,4-dihydroxymandelic acid -> vanillylmandelic acid (-)-adrenaline -> metanephrine |
| Common abbreviation | PNMT | MAO-A | MAO-B | COMT |
| Cofactors | S-adenosyl methionine | flavin adenine dinucleotide | flavin adenine dinucleotide | S-adenosyl methionine |

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Nomenclature

Phenylethanolamine N-methyltransferase

Monoamine oxidase A

Monoamine oxidase B

Catechol-O-methyltransferase

Inhibitors

LY134046 (pKᵢ 7.6) [163]
moclobemide (pKᵢ 8.3) [247], phenelzine (Irreversible inhibition) (pKᵢ 7.3) [39], tranylcypromine (pIC₅₀ 4.7) [587], selegiline (pKᵢ 4.2) [357], befloxatone [107], clorgiline, pirlindole [350]

rasagiline (pIC₅₀ 7.8) [591], phenelzine (Irreversible inhibition) (pKᵢ 7.8) [39], lazabemide (pKᵢ 7.1) [200, 532], selegiline (pKᵢ 5.7–6) [121, 357], tranylcypromine (pIC₅₀ 4.7) [587]
safinamide (pKᵢ 6.3) [38]

tolcapone (soluble enzyme) (pKᵢ 9.6) [317], tolcapone (membrane-bound enzyme) (pKᵢ 9.5) [317], entacapone (soluble enzyme) (pKᵢ 9.5) [317], entacapone (membrane-bound enzyme) (pKᵢ 8.7) [317]

Selective inhibitors –

Comments –

COMT appears to exist in both membrane-bound and soluble forms. COMT has also been described to methylate steroids, particularly hydroxyestriadiols.

Further reading on Catecholamine turnover

Dauvilliers Y et al. (2015) Catechol-O-methyltransferase, dopamine, and sleep-wake regulation. Sleep Med Rev 22: 47-53 [PMID:25466290]
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]
Fisar Z. (2016) Drugs related to monoamine oxidase activity. Prog Neuropsychopharmacol Biol Psychiatry 69: 112-24 [PMID:26944656]

Ceramide turnover

Enzymes → Ceramide turnover

Overview: Ceramides are a family of sphingophospholipids synthesized in the endoplasmic reticulum, which mediate cell stress responses, including apoptosis, autophagy and senescence. Serine palmitoyltransferase generates 3-ketosphinganine, which is reduced to sphinganine (dihydro sphingosine). 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 [202]. Complexes involving SPT3 appeared more broad in substrate selectivity, with incorporation of myristoylCoA prominent for SPT1/SPT3/ssSPTa complexes, while SPT1/SPT3/ssSPTb complexes had similar activity with C16, C18 and C20 acylCoAs [202].

**Nomenclature**
- serine palmitoyltransferase
- long chain base subunit 1: SPTLC1, O15269
- long chain base subunit 2: SPTLC2, O15270
- long chain base subunit 3: SPTLC3, Q9NUV7
- small subunit A: SPTSSA, Q969W0
- small subunit B: SPTSSB, Q8NFR3

**Cofactors**
- pyridoxal phosphate

**Selective inhibitors**
- myriocin (pKi 9.6) [358]
- Mouse

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: CERS1, P27544
- ceramide synthase 2: CERS2, Q96G23
- ceramide synthase 3: CERS3, Q8IU89
- ceramide synthase 4: CERS4, Q9HA82
- ceramide synthase 5: CERS5, Q8N5B7
- ceramide synthase 6: CERS6, Q6ZMG9

**EC number**
- 2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A
- sphingosine + acylCoA -> ceramide + coenzyme A

**Common abbreviation**
- CERS1
- CERS2
- CERS3
- CERS4
- CERS5
- CERS6

**Substrates**
- C18-CoA [543]
- C24- and C26-CoA [292]
- C26-CoA and longer [361, 424]
- C16-CoA [288, 438]
- C14- and C16-CoA [360]
Sphingolipid $\Delta^4$-desaturase

Enzymes $\rightarrow$ Ceramide turnover $\rightarrow$ 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   | RBM2-1B (pIC$_{50}$ 4.7) [63]        |                                     |
| Comments     | Myristoylation of DEGS1 enhances its activity and targets it to the mitochondria [28]. | |

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

Sphingomyelin synthase

Enzymes $\rightarrow$ Ceramide turnover $\rightarrow$ 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, Q86VZS            | SGMS2, Q8NHU3            | SAMO8, Q96LT4                           |
| EC number    | 2.7.8.27: ceramide + phosphatidylcholine -> sphingomyelin + diacylglycerol | 2.7.8.27: ceramide + phosphatidylcholine -> sphingomyelin + diacylglycerol | 2.7.8.-: ceramide + phosphatidylethanolamine -> ceramide phosphoethanolamine |
| Inhibitors   | compound 1J (pIC$_{50}$ 5.7) [301] | compound D24 (pIC$_{50}$ 4.9) [116] | –                                       |
| Comments     | –                        | Palmitoylation of sphingomyelin synthase 2 may allow targeting to the plasma membrane [517]. | –                                      |
Sphingomyelin phosphodiesterase

Overview: Also known as sphingomyelinase.

| Nomenclature | spergomyelin phosphodiesterase 1 | spergomyelin phosphodiesterase 2 | spergomyelin phosphodiesterase 3 | spergomyelin phosphodiesterase 4 | spergomyelin phosphodiesterase acid-like 3A | spergomyelin phosphodiesterase acid-like 3B |
|--------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| HGNC, UniProt| SMPD1, P17405                   | SMPD2, Q60906                   | SMPD3, Q9NY59                   | SMPD4, Q9NXE4                   | SMPDL3A, Q92484                 | SMPDL3B, Q92485                 |
| EC number    | 3.1.4.12: sphingomyelin \rightarrow ceramide + phosphocholine | inhibitor A (pK_i 5.8) [586] – Bovine | –                               | –                               | 3.1.A. : sphingomyelin \rightarrow ceramide + phosphocholine | –                               |

Neutral sphingomyelinase coupling factors

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

| Nomenclature | embryonic ectoderm development | neutral sphingomyelinase activation associated factor |
|--------------|---------------------------------|------------------------------------------------------|
| HGNC, UniProt| EED, Q75330                     | NSMAF, Q92636                                       |
| Selective inhibitors | A-395 (Binding) (pK_i 9.4) [217] | –                                                   |
### Ceramide glucosyltransferase

**Enzymes → Ceramide turnover → Ceramide glucosyltransferase**

| Nomenclature | UDP-glucose ceramide glucosyltransferase |
|--------------|------------------------------------------|
| HGNC, UniProt| UGCC, Q16739                             |
| EC number    | 2.4.1.80: UDP-glucose + ceramide = uridine diphosphate + glucosylceramide |
| Inhibitors   | miglustat (pKᵢ 5.1) [63]                 |
| 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 [274]. |
Neutral ceramidases
Enzymes → Ceramide turnover → Neutral ceramidases

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

| Nomenclature | N-acylsphingosine amidohydrolase 2 | N-acylsphingosine amidohydrolase 2B |
|--------------|------------------------------------|-------------------------------------|
| HGNC, UniProt | ASAH2, Q9NR71                       | ASAH2B, P0C7U1                       |
| EC number    | 3.5.1.23: ceramide - > sphingosine + a fatty acid | – |
| Comments     | The enzyme is associated with the plasma membrane [S16]. | – |

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

Alkaline ceramidases
Enzymes → Ceramide turnover → Alkaline ceramidases

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

| Nomenclature | alkaline ceramidase 1 | alkaline ceramidase 2 | alkaline ceramidase 3 |
|--------------|-----------------------|-----------------------|-----------------------|
| HGNC, UniProt | ACER1, Q8TDN7         | ACER2, Q5QJU3         | ACER3, Q9NUN7         |
| EC number    | 3.5.1.23: ceramide - > sphingosine + a fatty acid | 3.5.1.23: ceramide - > sphingosine + a fatty acid | 3.5.1- |
| Comments     | ACER1 is associated with the ER [S05]. | ACER2 is associated with the Golgi apparatus [S82]. | ACER3 is associated with the ER and Golgi apparatus [S336]. |

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
# 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 (pIC50 7.9) [188] |

**Comments:** A ceramide kinase-like protein has been identified in the human genome (CERKL, Q49M13).

**Further reading on Ceramide turnover**

- Aburasayn H et al. (2016) Targeting ceramide metabolism in obesity. *Am J Physiol Endocrinol Metab* **311**: E423-35 [PMID:27382035]
- Adada M et al. (2016) Inhibitors of the sphingomyelin cycle: Sphingomyelin synthases and sphingomyelinases. *Chem Phys Lipids* **197**: 45-59 [PMID:26200918]
- Casals N et al. (2016) Carnitine palmitoyltransferase IC: From cognition to cancer. *Prog Lipid Res* **61**: 134-48 [PMID:26708865]
- Casasampere M et al. (2016) Inhibitors of dihydroceramide desaturase 1: Therapeutic agents and pharmacological tools to decipher the role of dihydroceramides in cell biology. *Chem Phys Lipids* **197**: 33-44 [PMID:26248324]
- Fuchu R et al. (2017) Ceramides and mitochondrial fatty acid oxidation in obesity. *FASEB J* **31**: 1263-1272 [PMID:28003342]
- Hernandez-Corbacho MJ et al. (2017) Sphingolipids in mitochondria. *Biochim Biophys Acta* **1862**: 56-68 [PMID:27697478]
- Ilan Y. (2016) Compounds of the sphingomyelin-ceramide-glycosphingolipid pathways as secondary messenger molecules: new targets for novel therapies for fatty liver disease and insulin resistance. *Am J Physiol Gastrointest Liver Physiol* **310**: G1102-17 [PMID:2713510]
- Iqbal J et al. (2017) Sphingolipids and Lipoproteins in Health and Metabolic Disorders. *Trends Endocrinol Metab* **28**: 506-518 [PMID:28462811]
- Kihara A. (2016) Synthesis and degradation pathways, functions, and pathology of ceramides and epidermal acylceramides. *Prog Lipid Res* **63**: 50-69 [PMID:27107674]
- Petracek I et al. (2016) Ceramide Signaling and Metabolism in Pathophysiological States of the Lung. *Annu Rev Physiol* **78**: 463-80 [PMID:26667073]
- Rodriguez-Cuenca S et al. (2017) Sphingolipids and glycerophospholipids - The “ying and yang” of lipotoxicity in metabolic diseases. *Prog Lipid Res* **66**: 14-29 [PMID:28104532]
- Sasset L et al. (2016) Sphingolipid De Novo Biosynthesis: A Rheostat of Cardiovascular Homeostasis. *Trends Endocrinol Metab* **27**: 807-819 [PMID:27562337]
- Vogt D et al. (2017) Therapeutic Strategies and Pharmacological Tools Influencing S1P Signaling and Metabolism. *Med Res Rev* **37**: 3-51 [PMID:27480072]
- Wegner MS et al. (2016) The enigma of ceramide synthase regulation in mammalian cells. *Prog Lipid Res* **63**: 93-119 [PMID:27180613]
Chromatin modifying enzymes

Overview: Chromatin modifying enzymes, and other chromatin-modifying proteins, fall into three broad categories: writers, readers and erasers. The function of these proteins is to dynamically maintain cell identity and regulate processes such as differentiation, development, proliferation and genome integrity via recognition of specific 'marks' (covalent post-translational modifications) on histone proteins and DNA [280]. In normal cells, tissues and organs, precise co-ordination of these proteins ensures expression of only those genes required to specify phenotype or which are required at specific times, for specific functions. Chromatin modifications allow DNA modifications not coded by the DNA sequence to be passed on through the genome and underlies heritable phenomena such as X chromosome inactivation, aging, heterochromatin formation, reprogramming, and gene silencing (epigenetic control). To date at least eight distinct types of modifications are found on histones. These include small covalent modifications such as acetylation, methylation, and phosphorylation, the attachment of larger modifiers such as ubiquitination or sumoylation, and ADP ribosylation, proline isomerization and deimination. Chromatin modifications and the functions they regulate in cells are reviewed by Kouzarides (2007) [280].

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

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

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

Dysregulated epigenetic control can be associated with human diseases such as cancer [137], where a wide variety of cellular and protein aberrations are known to perturb chromatin structure, gene transcription and ultimately cellular pathways [27, 477]. Due to the reversible nature of epigenetic modifications, chromatin regulators are very tractable targets for drug discovery and the development of novel therapeutics. Indeed, small molecule inhibitors of writers (e.g. azacitidine and decitabine target the DNA methyltransferases DNMT1 and DNMT3 for the treatment of myelodysplastic syndromes [175, 565]) and erasers (e.g. the HDAC inhibitors vorinostat, romidepsin and belinostat for the treatment of T-cell lymphomas [153, 265]) are already being used in the clinic. The search for the next generation of compounds with improved specificity against chromatin-associated proteins is an area of intense basic and clinical research [61]. Current progress in this field is reviewed by Simó-Ruudalbas and Esteller (2015) [478].

2.1.1.- Protein arginine N-methyltransferases

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

Information on members of this family may be found in the online database.
3.5.1.- Histone deacetylases (HDACs)

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

**Overview:** Histone deacetylases act as erasers of epigenetic acetylation marks on lysine residues in histones. Removal of the acetyl groups facilitates tighter packing of chromatin (heterochromatin formation) leading to transcriptional repression. The histone deacetylase family has been classified into five subfamilies based on phylogenetic comparison with yeast homologues:

- **Class I** contains HDACs 1, 2, 3 and 8
- **Class IIa** contains HDACs 4, 5, 7 and 9
- **Class IIb** contains HDACs 6 and 10
- **Class III** contains the sirtuins (SIRT1-7)
- **Class IV** contains only HDAC11.

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

Dysregulated HDAC activity has been identified in cancer cells and tumour tissues, making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer. Several small molecule HDAC inhibitors are already approved for clinical use: romidepsin, belinostat, vorinostat, panobinostat, valproic acid and tucidinostat. HDACs and HDAC inhibitors currently in development as potential anticancer therapeutics are reviewed by Simó-Riudalbas and Esteller (2015). Information on members of this family may be found in the online database.

Cyclic nucleotide turnover/signalling

Enzymes → Cyclic nucleotide turnover/signalling

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

Adenylyl cyclases (ACs)

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

**Overview:** Adenylyl cyclase, EC.4.6.1.1, converts ATP to cyclic AMP and pyrophosphate. Mammalian membrane-bound adenylyl cyclases are typically made up of two clusters of six TM domains separating two intracellular, overlapping catalytic domains that are the target for the nonselective activators forskolin and KH477 (except AC9 and AC11) and Go, (the stimulatory G protein subunit). Adenosine and its derivatives (e.g. 2',5'-dideoxyadenosine), acting through the P-site, appear to be physiological inhibitors of adenylyl cyclase activity. Three families of adenylyl cyclase are distinguishable: calmodulin (CALM1, CALM2, CALM3, P62158)-stimulated (AC1, AC3 and AC8), Ca2+-inhibitable (AC5, AC6 and AC9) and Ca2+-insensitive (AC2, AC4 and AC7) forms.

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full
### Nomenclature

| Adenyl cyclase 1 | Adenyl cyclase 2 (brain) | Adenyl cyclase 3 | Adenyl cyclase 4 |
|------------------|--------------------------|------------------|------------------|
| ADCY1, Q08828    | ADCY2, Q08462            | ADCY3, O60266    | ADCY4, Q8NF4     |

**Common abbreviation:** AC1, AC2, AC3, AC4

**Endogenous activators:**
- calmodulin (CALM1, CALM2, CALM3, P62158), PKC-evoked phosphorylation
- Gβγ, PKC-evoked phosphorylation

**Endogenous inhibitors:**
- Gαi, Gαo, Gβγ
- Ca2+/calcinurin

### Comments

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

### Further reading on Adenyl cyclases

- Dessauer CW et al. (2017) International Union of Basic and Clinical Pharmacology. Cl. Structures and Small Molecule Modulators of Mammalian Adenylyl Cyclases. *Pharmacol Rev* 69: 93-139 [PMID:28255005]
- Halls ML et al. (2017) Adenyl cyclase signalling complexes - Pharmacological challenges and opportunities. *Pharmacol Ther* 172: 171-180 [PMID:28132906]
- Wu L et al. (2016) Adenylate cyclase 3: a new target for anti-obesity drug development. *Obes Rev* 17: 907-14 [PMID:27256589]

### Searchable database

- [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
- [Adenyl cyclases (ACs) S311](http://www.guidetopharmacology.org/index.jsp)
Exchange protein 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 \[134\]. Once activated, Epacs induce an enhanced activity of the monomeric G proteins, Rap1 and Rap2 by facilitating binding of guanosine-5'-triphosphate in place of guanosine 5'-diphosphate, leading to activation of phospholipase C \[459\].

| Nomenclature       | Rap guanine nucleotide exchange factor 3 | Rap guanine nucleotide exchange factor 4 |
|--------------------|----------------------------------------|----------------------------------------|
| HGNC, UniProt      | RAPGEF3, Q95398                        | RAPGEF4, QBWZ42                        |
| Common abbreviation| Epac1                                   | Epac2                                   |
| Inhibitors         | ESI-09 (pIC\(_{50}\) 5.5) [12]          | HJC 0350 (pIC\(_{50}\) 6.5) [78], ESI-09 (pIC\(_{50}\) 4.4–5.2) [12, 79] |

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

Fujita T et al. (2017) The role of Epac in the heart. *Cell Mol Life Sci* **74**: 591-606 [PMID:27549789]
Parnell E et al. (2015) The future of EPAC-targeted therapies: agonism versus antagonism. *Trends Pharmacol Sci* **36**: 203-14 [PMID:25744542]

Wang P et al. (2017) Exchange proteins directly activated by cAMP (EPACs): Emerging therapeutic targets. *Bioorg Med Chem Lett* **27**: 1633-1639 [PMID:28283242]

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

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

| Subunits | Guanylyl cyclase, α1β1 subunit | Guanylyl cyclase, α2β1 subunit | Guanylyl cyclase, β1 subunit | Guanylyl cyclase, α2 subunit |
|----------|--------------------------------|--------------------------------|----------------------------|------------------------------|
| Common abbreviation | GC-1 | GC-2 | NO, CO | GC-2 |
| Endogenous ligands | NO, CO | NO, CO | NO, CO | NO, CO |
| Selective activators | YC-1 [159, 272, 449], cinaciguat [apo-GC-1] [500], riociguat [498, 499] | YC-1 [272, 449], cinaciguat [apo-GC-2] [500], riociguat [500, 499] | ODQ (pIC50 7.5) [177] | ODQ |
| Selective inhibitors | NS 2028 (pIC50 8.1) [389] – Bovine, ODQ (pIC50 7.5) [177] | NS 2028 (pIC50 8.1) [389] – Bovine, ODQ (pIC50 7.5) [177] | NS 2028 (pIC50 8.1) [389] – Bovine, ODQ (pIC50 7.5) [177] | NS 2028 (pIC50 8.1) [389] – Bovine, ODQ (pIC50 7.5) [177] |

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

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

Papapetropoulos A et al. (2015) Extending the translational potential of targeting NO/cGMP-regulated pathways in the CVS. Br J Pharmacol 172: 1397-414 [PMID:25302549]
Pechanova O et al. (2015) Cardiac NO signalling in the metabolic syndrome. Br J Pharmacol 172: 1415-33 [PMID:25297560]

Vanhoutte PM et al. (2016) Thirty Years of Saying NO: Sources, Fate, Actions, and Misfortunes of the Endothelium-Derived Vasodilator Mediator. Circ Res 119: 375-96 [PMID:27390338]
Yetik-Anacak G et al. (2015) Gas what: NO is not the only answer to sexual function. Br J Pharmacol 172: 1434-54 [PMID:24661203]

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

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

Overview: 3′,5′-Cyclic nucleotide phosphodiesterases (PDEs, 3′,5′-cyclic-nucleotide 5′-nucleotidohydrolase), E.C. 3.1.4.17, catalyse the hydrolysis of a 3′,5′-cyclic nucleotide (usually cyclic AMP or cyclic GMP). Isobutylmethylxanthine is a nonselective inhibitor with an IC50 value in the millimolar range for all isoforms except PDE 8A, 8B and 9A. A 2′,3′-cyclic nucleotide 3′-phosphodiesterase (E.C. 3.1.4.37 CNPase) activity is associated with myelin formation in the development of the CNS.
| Nomenclature                  | phosphodiesterase 1A | phosphodiesterase 1B | phosphodiesterase 1C |
|------------------------------|----------------------|----------------------|----------------------|
| HGNC, UniProt                | PDE1A, P54750        | PDE1B, Q01064        | PDE1C, Q14123        |
| Common abbreviation          | PDE1A                | PDE1B                | PDE1C                |
| Rank order of affinity       | cyclic GMP > cyclic AMP | cyclic GMP > cyclic AMP | cyclic GMP = cyclic AMP |
| Endogenous activators        | calmodulin (CALM1 CALM2 CALM3, P62158) | calmodulin (CALM1 CALM2 CALM3, P62158) | calmodulin (CALM1 CALM2 CALM3, P62158) |
| Inhibitors                   | crisaborole (pIC$_{50}$ 5.2) [8] | –                    | –                    |
| Selective inhibitors         | SCH51866 (pIC$_{50}$ 7.2) [542], vinpocetine (pIC$_{50}$ 5.1) [319] | SCH51866 (pIC$_{50}$ 7.2) [542] | SCH51866 (pIC$_{50}$ 7.2) [542], vinpocetine (pIC$_{50}$ 4.3) [319] |
|                              |                      |                      |                      |
| Nomenclature                  | phosphodiesterase 2A | phosphodiesterase 3A | phosphodiesterase 3B |
| HGNC, UniProt                | PDE2A, O00408        | PDE3A, Q14432        | PDE3B, Q13370        |
| Common abbreviation          | PDE2A                | PDE3A                | PDE3B                |
| Rank order of affinity       | cyclic AMP ≫ cyclic GMP | –                    | –                    |
| Endogenous activators        | cyclic GMP           | cyclic GMP           | cyclic GMP           |
| Endogenous inhibitors        | –                    | –                    | –                    |
| Inhibitors                   | milrinone (pIC$_{50}$ < 6.5) [504] | cilostazol (pIC$_{50}$ 6.7) [504], inamrinone (pIC$_{50}$ 4.8) [480] | –                    |
| Selective inhibitors         | BAY607550 (pIC$_{50}$ 8.3–8.8) [47], EHNA (pIC$_{50}$ 5.3) [355] | cilostamide (pIC$_{50}$ 7.5) [504], anagrelide (pIC$_{50}$ 7.1–7.3) [257, 341, 349], milrinone (pIC$_{50}$ 6.3–6.4) [131, 504] | cilostamide (pIC$_{50}$ 7.3) [504], cilostazol (pIC$_{50}$ 6.4) [504], milrinone (pIC$_{50}$ 6) [504], inamrinone (pIC$_{50}$ 4.5) [504] |
| Comments                     | EHNA is also an inhibitor of adenosine deaminase (E.C. 3.5.4.4). | –                    | –                    |

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Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
| Nomenclature | phosphodiesterase 4A | phosphodiesterase 4B | phosphodiesterase 4C | phosphodiesterase 4D | phosphodiesterase 5A |
|--------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| HGNC, UniProt| PDE4A, P27815        | PDE4B, Q07343        | PDE4C, Q08493        | PDE4D, Q08499        | PDE5A, Q76074         |
| Common abreviation | PDE4A | PDE4B | PDE4C | PDE4D | PDE5A |
| Rank order of affinity | cyclic AMP $\gg$ cyclic GMP | cyclic AMP $\gg$ cyclic GMP | cyclic AMP $\gg$ cyclic GMP | cyclic AMP $\gg$ cyclic GMP | cyclic GMP $\gg$ cyclic AMP |
| Endogenous activators | – | – | – | – | Protein kinase A, protein kinase G [100] |
| Inhibitors | ibudilast (pIC$_{50}$ 7.3) [275], RS-25344 (pIC$_{50}$ 7.2) [453] | roflumilast (pIC$_{50}$ 9.4) [321], ibudilast (pIC$_{50}$ 7.2) [275], RS-25344 (pIC$_{50}$ 6.5) [453] | RS-25344 (pIC$_{50}$ 8.1) [453], ibudilast (pIC$_{50}$ 7.2) [275] | ibudilast (pIC$_{50}$ 6.6) [275], RS-25344 (pIC$_{50}$ 7.2) [453] | RS-25344 (pIC$_{50}$ 8.1) [453], gisadenafil (pIC$_{50}$ 8.9) [433], milrinone (pIC$_{50}$ 7.3) |
| Sub/family-selective inhibitors | rolipram (pIC$_{50}$ 9) [553], CDP840 (pK$_{i}$ 8) [406], Ro20-1724 (pIC$_{50}$ 6.5) [553] | rolipram (pIC$_{50}$ 9) [553], Ro20-1724 (pIC$_{50}$ 6.4) [553] | CDP840 (pK$_{i}$ 7.7) [406], rolipram (pIC$_{50}$ 6.5) [553], Ro20-1724 (pIC$_{50}$ 5.4) [553] | CDP840 (pK$_{i}$ 8.1) [406], rolipram (pIC$_{50}$ 7.2) [553], Ro20-1724 (pIC$_{50}$ 6.2) [553] | – |
| Selective inhibitors | YM976 (pIC$_{50}$ 8.3) [14], apremilast (pIC$_{50}$ 7.8) [457] | – | apremilast (pIC$_{50}$ 6.9) [457] | – | vardenafil (pIC$_{50}$ 9.7) [51], T0156 (pIC$_{50}$ 9.5) [362], sildenafil (pIC$_{50}$ 8.4–9) [538, 551], tadalafil (pIC$_{50}$ 8.5) [379], SCH51866 (pIC$_{50}$ 7.2) [542], zaprinast (pIC$_{50}$ 6.8) [538] |

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**Full Contents of Concise Guide:** [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
### Nomenclature

| HGNC, UniProt | phosphodiesterase 7A | phosphodiesterase 7B | phosphodiesterase 8A | phosphodiesterase 8B |
|--------------|----------------------|----------------------|----------------------|----------------------|
| PDE7A, Q13946 | PDE7B, Q9NP56 | PDE8A, O60658 | PDE8B, Q95263 |

### Common abbreviation

| PDE7A | PDE7B | PDE8A | PDE8B |
|-------|-------|-------|-------|

### Rank order of affinity

| Inhibitors | cyclic AMP | cyclic GMP |
|------------|------------|------------|
| crisaborole (pIC<sub>50</sub> 6.1) | [353] | [353] |
| BRL50481 (pIC<sub>50</sub> 4.9) | [176] | [146] |

### Selective inhibitors

| Inhibitors | cyclic AMP | cyclic GMP |
|------------|------------|------------|
| dipyridamole (pIC<sub>50</sub> 6.7–6.8) | [455] | [455] |
| dipyridamole (pIC<sub>50</sub> 6.1) | [176] | [146] |

### Comments

- PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively.

### Nomenclature

| HGNC, UniProt | phosphodiesterase 9A | phosphodiesterase 10A | phosphodiesterase 11A |
|--------------|----------------------|----------------------|----------------------|
| PDE9A, Q76083 | PDE10A, Q9Y233 | PDE11A, Q9HCR9 |

### Common abbreviation

| PDE9A | PDE10A | PDE11A |
|-------|-------|-------|

### Rank order of affinity

| Inhibitors | cyclic AMP | cyclic GMP |
|------------|------------|------------|
| SCH51866 (pIC<sub>50</sub> 5.8) | [455] | [455] |
| zaprinast (pIC<sub>50</sub> 4.5) | [145] | [145] |
| tadalafil (pIC<sub>50</sub> 6.5) | [379] | [379] |
| BC11-38 (pIC<sub>50</sub> 6.5) | [79] | [79] |

### Comments

- PDE9A, 1B and 1C appear to act as soluble homodimers, while PDE2A is a membrane-bound homodimer. PDE3A and PDE3B are membrane-bound. PDE4 isoforms are essentially cyclic AMP specific. The potency of YM976 at other members of the PDE4 family has not been reported. PDE4B–D long forms are inhibited by extracellular signal-regulated kinase (ERK)-mediated phosphorylation [224, 225]. PDE4A-D splice variants can be membrane-bound or cytosolic [229]. PDE4 isoforms may be labelled with [3H]rolipram. PDE6 is a membrane-bound tetramer composed of two catalytic chains (PDE6A or PDE6C and PDE6B), an inhibitory chain (PDE6G or PDE6H) and the PDE6D chain. The enzyme is essentially cyclic GMP specific and is activated by the α-subunit of transducin (Gαt) and inhibited by sildenafil, zaprinast and dipyridamole with potencies lower than those observed for PDE5A. Defects in PDE6B are a cause of retinitis pigmentosa and congenital stationary night blindness.

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

- Das A et al. (2015) PDE5 inhibitors as therapeutics for heart disease, diabetes and cancer. *Pharmacol Ther* 147:12-21 [PMID:25444755]
- Jorgensen C et al. (2015) Phosphodiesterase4D (PDE4D)–A risk factor for atrial fibrillation and stroke? *J Neurol Sci* 359:266-74 [PMID:26671126]
- Klussmann E. (2016) Protein-protein interactions of PDE4 family members - Functions, interactions and therapeutic value. *Cell Signal* 28:713-8 [PMID:26498857]
- Korkmaz-Icoz S et al. (2017) Targeting phosphodiesterase 5 as a therapeutic option against myocardial ischaemia/reperfusion injury and for treating heart failure. *Br J Pharmacol* [PMID:28213937]
- Leal LF et al. (2015) Phosphodiesterase 8B and cyclic AMP signaling in the adrenal cortex. *Endocrine* 50:27-31 [PMID:25971952]
- Movsesian M. (2016) Novel approaches to targeting PDE3 in cardiovascular disease. *Pharmacol Ther* 163:74-81 [PMID:27108947]

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**Full Contents of ConciseGuide:** [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
Cytochrome P450

Enzymes → Cytochrome P450

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

CYP1 family

Enzymes → Cytochrome P450 → CYP1 family

| Nomenclature | CYP1A1 | CYP1A2 | CYP1B1 |
|-------------|-------|-------|-------|
| HGNC, UniProt | CYP1A1, P04798 | CYP1A2, P05177 | CYP1B1, Q16678 |
| EC number | 1.14.1.1 | 1.14.1.1 | 1.14.1.1 |
| Comments | – | – | Mutations have been associated with primary congenital glaucoma [503] |

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Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
CYP2 family

Enzymes → Cytochrome P450 → CYP2 family

| Nomenclature | CYP2A6 | CYP2A7 | CYP2C8 | CYP2J2 | CYP2R1 |
|--------------|-------|-------|-------|--------|--------|
| HGNC, UniProt | CYP2A6, P11509 | CYP2A7, P20853 | CYP2C8, P10632 | CYP2J2, P51589 | CYP2R1, Q6VVX0 |
| EC number | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 | 1.14.13.15 |
| Inhibitors | – | – | phenelzine (pKi 5.1) [150] | terfenadine (pIC50 5.1) [287] | – |
| Comments | Metabolises nicotine. | CYP2A7 does not incorporate haem and is functionally inactive [162] | Converts arachidonic acid to 11(R)-12(S)-epoxyeicosatrienoic acid or 14(R)-15(S)-epoxyeicosatrienoic acid [596]. | Converts arachidonic acid to 14(R)-15(S)-epoxyeicosatrienoic acid [579]. | Converts vitamin D3 to calcifediol [85]. |

CYP3 family

Enzymes → Cytochrome P450 → CYP3 family

| Nomenclature | CYP3A4 |
|--------------|-------|
| HGNC, UniProt | CYP3A4, P08684 |
| EC number | 1.14.13.32: Albendazole + NADPH + O2 = albendazole S-oxide + NADP+ + H2 |
| | 1.14.13.157: 1,8-cineole + NADPH + O2 = 2-exo-hydroxy-1,8-cineole + NADP+ + H2O |
| | 1.14.13.97: Taurochenodeoxycholate + NADPH + O2 = taurochenodeoxycholate + NADP+ + H2O |
| | Lithocholate + NADPH + O2 = hyodeoxycholate + NADP+ + H2O 1.14.13.67: quinine + NADPH + O2 = 3-hydroxyquinine + NADP+ + H2O2 |
| Substrates | atorvastatin [155], codeine [155], diazepam [155], tamoxifen [155], erlotinib [155] |
| Products | 4-hydroxy-tamoxifen quinone methide [469], 4-hydroxy-tamoxifen [469] |
| Inhibitors | ritonavir (pKi > 7) [266] |
| Comments | Metabolises a vast range of xenobiotics, including antidepressants, benzodiazipines, calcium channel blockers, and chemotherapeutic agents. CYP3A4 catalyses the 25-hydroxylation of trihydroxycholestan in liver microsomes [166]. |

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### CYP4 family

**Enzymes** → **Cytochrome P450** → **CYP4 family**

| Nomenclature | CYP4A11 | CYP4F2 | CYP4F3 | CYP4F8 |
|--------------|--------|--------|--------|--------|
| HGNC, UniProt | CYP4A11, Q02928 | CYP4F2, P78329 | CYP4F3, Q08477 | CYP4F8, P98187 |
| EC number    | 1.14.15.3 | 1.14.13.30 | 1.14.13.30 | 1.14.14.1 |
| Inhibitors   | – | 17-octadecynoic acid (pKi 5.9) [470] | – | – |
| Comments     | Converts lauric acid to 12-hydroxyauric acid. | Responsible for ω-hydroxylation of LTB₄, LXB₄ [359], and tocopherols, including vitamin E [491] | Responsible for ω-hydroxylation of LTB₄, LXB₄ [359], and polyunsaturated fatty acids [143, 207] | Converts PGH₂ to 19-hydroxyPGH₂ [60] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [378]. |

| Nomenclature | CYP4F12 | CYP4F22 | CYP4X1 | CYP4Z1 |
|--------------|--------|--------|--------|--------|
| HGNC, UniProt | CYP4F12, Q9HCS2 | CYP4F22, Q6NT5S | CYP4X1, Q8N118 | CYP4Z1, Q86W10 |
| EC number    | 1.14.14.1 | 1.14.14.- | 1.14.14.1 | 1.14.14.1 |
| Comments     | AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12 | Converts arachidonic acid to 16-HETE and 18-HETE [378]. | Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [497]. | Converts lauric acid to 12-hydroxyauric acid. |

**Comments**: Converts lauric acid to 12-hydroxyauric acid.

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Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
# CYP5, CYP7 and CYP8 families

- **Enzymes → Cytochrome P450 → CYP5, CYP7 and CYP8 families**

| Nomenclature | CYP5A1 | CYP7A1 | CYP7B1 | CYP8A1 | CYP8B1 |
|--------------|--------|--------|--------|--------|--------|
| HGNC, UniProt | TBXAS1, P24557 | CYP7A1, P22680 | CYP7B1, Q7S881 | PGHS, Q16647 | CYP8B1, Q9UNU6 |
| EC number    | 5.3.99.5: PGH$_2$ = thromboxane A$_2$ | 1.14.13.17 | 1.14.13.100 | 5.3.99.4 | 1.14.13.95 |
| Common name  | Thromboxane synthase | – | – | Prostacyclin synthase | – |
| Comments     | Inhibited by dazoxiben [427] and camonagrel [194]. | Converts cholesterol to 7α-hydroxycholesterol [379]. | Converts dehydroepiandrosterone to 7α-DHEA [445]. | Converts PGH$_2$ to PGl$_2$ [209]. Inhibited by tranylcypromine [193] | Converts 7α-hydroxycholesterol-4-en-3-one to 7-alpha,12α-dihydroxycholesterol-4-en-3-one (in rabbit) [239] in the biosynthesis of bile acids. |

# CYP11, CYP17, CYP19, CYP20 and CYP21 families

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

| Nomenclature | CYP11A1 | CYP11B1 | CYP11B2 | CYP11B1 | CYP11B2 |
|--------------|--------|--------|--------|--------|--------|
| HGNC, UniProt | CYP11A1, P05108 | CYP11A1, P15538 | CYP11B1, P19099 | CYP11B2, P19099 |
| EC number    | 1.14.15.6 | 1.14.15.4 | 1.14.15.5 | 1.14.15.5 |
| Common name  | – | – | Aldosterone synthase | osilodrostat (pIC$_{50}$ 9.7) [585] |
| Inhibitors   | mitotane [297, 303] | metyrapone (pIC$_{50}$ 7.8) [602], mitotane | Converts deoxycortisone and 11-deoxycortisol to cortisone and cortisol, respectively. Loss-of-function mutations are associated with familial adrenal hyperplasia and hypertension. Inhibited by metyrapone [558] | Converts corticosterone to aldosterone |
| Comments     | Converts cholesterol to pregnenolone plus 4-methylpentanal. | Converts deoxycortisone and 11-deoxycortisol to cortisone and cortisol, respectively. Loss-of-function mutations are associated with familial adrenal hyperplasia and hypertension. Inhibited by metyrapone [558] | | |

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Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
### Nomenclature

| Enzyme   | HGNC, UniProt | EC number | Common name | Inhibitors | Selective inhibitors | Comments |
|----------|---------------|-----------|-------------|------------|----------------------|----------|
| CYP17A1  | CYP17A1, P05093 | 1.14.99.9 | –           | abiraterone (pIC<sub>50</sub> 7.1–8.4) [413, 417] | galeterone (pIC<sub>50</sub> 6.5) [204] | Converts pregnenolone and progesterone to 17α-hydroxyprogrenolone and 17α-hydroxyprogesterone, respectively. Converts 17α-hydroxyprogrenolone and 17α-hydroxyprogesterone to dehydroepiandrosterone and androstenedione, respectively. Converts corticosterone to cortisol. |
| CYP19A1  | CYP19A1, P11511 | 1.14.14.1 | –           | anastrozole (pIC<sub>50</sub> 7.8) [367], aminoglutethimide [405] | letrozole (pK<sub>i</sub> 10.7) [346], exemestane (pIC<sub>50</sub> 7.3) [92], testolactone (pK<sub>i</sub> 4.5) [102] | Converts androstenedione and testosterone to estrone and 17β-estradiol, respectively. Inhibited by anastrozole [415], and letrozole [35] |
| CYP20A1  | CYP20A1, Q6UW02 | 1.14.-.-   | –           | –          | –                    | Converts progesterone and 17α-hydroxyprogesterone to deoxycorticosterone and 11-deoxycorticisol, respectively. |
| CYP21A2  | CYP21A2, P08686 | 1.14.99.10 | –           | –          | –                    | –        |

### CYP24, CYP26 and CYP27 families

**Enzymes → Cytochrome P450 → CYP24, CYP26 and CYP27 families**

| Enzyme   | HGNC, UniProt | EC number | Common name | Comments |
|----------|---------------|-----------|-------------|----------|
| CYP24A1  | CYP24A1, Q07973 | 1.14.13.126 | –           | Converts 1,25-dihydroxyvitamin D3 (calcitriol) to 1α,24R,25-trihydroxyvitamin D3. |
| CYP26A1  | CYP26A1, Q03174 | 1.14.-.-   | –           | Converts retinoic acid to 4-hydroxyretinoic acid. Inhibited by liarozole |
| CYP26B1  | CYP26B1, Q9NR63 | 1.14.-.-   | –           | Converts retinoic acid to 4-hydroxyretinoic acid. |
| CYP27A1  | CYP27A1, Q02318 | 1.14.13.15 | Sterol 27-hydroxylase | Converts cholesterol to 27-hydroxycholesterol. |
| CYP27B1  | CYP27B1, Q15528 | 1.14.13.13 | –           | Converts 25-hydroxyvitamin D<sub>3</sub> to 1,25-dihydroxyvitamin D<sub>3</sub> (calcitriol) |

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CYP39, CYP46 and CYP51 families

Enzymes → Cytochrome P450 → CYP39, CYP46 and CYP51 families

| Nomenclature | CYP39A1 | CYP46A1 | CYP51A1 |
|--------------|---------|---------|---------|
| HGNC, UniProt| CYP39A1, Q9NYL5 | CYP46A1, Q9Y6A2 | CYP51A1, Q16850 |
| EC number   | 1.14.13.99 | 1.14.13.98 | – |
| Common name | – | Cholesterol 24-hydroxylase | Lanosterol 14-α-demethylase |
| Inhibitors  | – | – | azalanstat (pKᵢ 9.1) [549] |
| Comments    | Converts 24-hydroxycholesterol to 7α,24-dihydroxycholesterol [302]. | Converts cholesterol to 24(5)-hydroxycholesterol. | Converts lanosterol to 4,4-dimethylcholesta-8.14.24-trienol. |

Further reading on Cytochrome P450

Backman JT et al. (2016) Role of Cytochrome P450 2C8 in Drug Metabolism and Interactions. Pharmacol Rev 68: 168-241 [PMID:26721703]
Davis CM et al. (2017) Cytochrome P450 eicosanoids in cerebrovascular function and disease. Pharmacol Ther [PMID:28527918]
Ghosh D et al. (2016) Recent Progress in the Discovery of Next Generation Inhibitors of Aromatase from the Structure-Function Perspective. J Med Chem 59: 5131-48 [PMID:26689671]
Go RE et al. (2015) Cytochrome P450 1 family and cancers. J Steroid Biochem Mol Biol 147: 24-30 [PMID:25448748]
Guengerich FP et al. (2016) Recent Structural Insights into Cytochrome P450 Function. Trends Pharmacol Sci 37: 625-40 [PMID:27267697]
Isvoran A et al. (2017) Pharmacogenomics of the cytochrome P450 2C family: impacts of amino acid variations on drug metabolism. Drug Discov Today 22: 366-376 [PMID:27693711]
Jamieson KL et al. (2017) Cytochrome P450-derived eicosanoids and heart function. Pharmacol Ther [PMID:28551025]
Mak PJ et al. (2017) Spectroscopic studies of the cytochrome P450 reaction mechanisms. Biochim Biophys Acta [PMID:28668640]
Moutinho M et al. (2016) Cholesterol 24-hydroxylase: Brain cholesterol metabolism and beyond. Biochim Biophys Acta 1861: 1911-1920 [PMID:27663182]
Shalan H et al. (2017) Keeping the spotlight on cytochrome P450. Biochim Biophys Acta [PMID:28599858]
**Overview:** The principle endocannabinoids are 2-acylglycerol esters, such as 2-arachidonoylglycerol (2AG), 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 (and related entities) are unclear, although candidates for intracellular transport have been suggested. For the generation of 2-arachidonoylglycerol, the key enzyme involved is diacylglycerol lipase (DGL), whilst several routes for anandamide synthesis have been described, the best characterised of which involves N-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD, [476]). A transacylation enzyme which forms N-acylphosphatidylethanolamines has recently been identified as a cytosolic enzyme, PLA2G4E (Q3MJ16) [383]. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism via cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [11, 154, 488].

**N-Acylethanolamine turnover**

Enzymes → Endocannabinoid turnover → N-Acylethanolamine turnover

---

**Nomenclature**

| N-Acylphosphatidylethanolamine-phospholipase D | Fatty acid amide hydrolase | Fatty acid amide hydrolase-2 | N-Acylethanolamine acid amidase |
|-----------------------------------------------|---------------------------|-----------------------------|--------------------------------|
| HGNC, UniProt                                 | FAAH, O00519              | FAAH2, Q6GMR7               | NAAA, Q02083                   |
| EC number                                    | 3.5.1.99: anandamide + H2O => arachidonic acid + ethanolamine oleamide + H2O => oleic acid + NH3 The enzyme is responsible for the catabolism of neuromodulatory fatty acid amides, including anandamide and oleamide: anandamide + H2O => arachidonic acid + ethanolamine oleamide + H2O => oleic acid + NH3 | 3.5.1.99: anandamide + H2O => arachidonic acid + ethanolamine oleamide + H2O => oleic acid + NH3 The enzyme is responsible for the catabolism of neuromodulatory fatty acid amides, including anandamide and oleamide: anandamide + H2O => arachidonic acid + ethanolamine oleamide + H2O => oleic acid + NH3 | 3.5.1.99: anandamide + H2O => arachidonic acid + ethanolamine oleamide + H2O => oleic acid + NH3 |
| Common abbreviation                          | NAPE-PLD, Q6I2Q0          | FAAH2, Q6GMR7               | NAAA, Q02083                   |
| Rank order of affinity                       | FAAH                       | FAAH2, Q6GMR7               | NAAA, Q02083                   |
| Selective inhibitors                         | JNJ1661010 (pIC50 7.8) [264], PF750 (pIC50 6.3–7.8) [5], OL135 (pIC50 7.4) [563], URB597 (pIC50 6.3–7) [563], PF3845 (pIC50 6.6) [6] | OL135 (pIC50 7.9–8.4) [261], 563], URB597 (pIC50 7.5–8.3) [261, 563] | S-OOPP (pIC50 6.4) [489] – Rat, CCP (pIC50 5.3) [335] |

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Nomenclature

- **N-Acylphosphatidylethanolamine-phospholipase D**
- **Fatty acid amide hydrolase**
- **Fatty acid amide hydrolase-2**
- **N-Acylethanolamine acid amidase**

**Comments**

NAPE-PLD activity appears to be enhanced by polyamines in the physiological range [311], but fails to transphosphatidylylate with alcohols [408] unlike phosphatidylycholine-specific phospholipase D.

The FAAH2 gene is found in many primate genomes, marsupials, and other distantly related vertebrates, but not a variety of lower placental mammals, including mouse and rat [563].

**Comments**

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

### 2-Acylglycerol ester turnover

**Enzymes → Endocannabinoid turnover → 2-Acylglycerol ester turnover**

| Nomenclature | Diacylglycerol lipase α | Diacylglycerol lipase β | Monoacylglycerol lipase | αβ-Hydrolase 6 |
|--------------|------------------------|------------------------|------------------------|----------------|
| HGNC, UniProt | DAGLA, Q9Y4D2          | DAGLB, Q8NCG7          | MGLL, Q99685           | ABHD6, Q9BV23 |
| EC number    | 3.1.1.-                 | 3.1.1.-                 | 3.1.1.23               | 3.1.1.23       |
| Common abreviation | DAGLα                       | DAGLβ                       | MAGL                      | ABHD6                                 |
| Endogenous substrates | diacylglycerol            | diacylglycerol            | 2-oleoyl glycerol        | 1-arachidonoylglycerol > 2-arachidonoylglycerol >> anandamide [181] |
| Selective inhibitors | orlistat (pIC<sub>50</sub> 7.2) [40], RHC80267 (pIC<sub>50</sub> 4.2) [255] | orlistat (pIC<sub>50</sub> 7) [40], RHC80267 | JKK048 (pIC<sub>50</sub> 9.3) [1], KML29 (pIC<sub>50</sub> 8.5) [77], JZL184 (pIC<sub>50</sub> 8.1) [314] | WWL70 (pIC<sub>50</sub> 7.2) [299], WWL123 (pIC<sub>50</sub> 6.4) [21] |
| Comments | –                        | –                        | –                       | WWL70 has also been suggested to have activity at oxidative metabolic pathways independent of ABHD6 [513]. |

**Searchable database:** http://www.guidetopharmacology.org/index.jsp

**Full Contents of ConciseGuide:** http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full
Comments on Endocannabinoid turnover: Many of the compounds described as inhibitors are irreversible and so potency estimates will vary with incubation time. FAAH2 is not found in rodents [563] and few of the inhibitors described have been assessed at this enzyme activity. 2-arachidonoylglycerol has been reported to be hydrolysed by multiple enzyme activities from neural preparations, including ABHD2 (P08910) [356], ABHD12 (Q8N2K0) [44], neuropathy target esterase (PNPLA6, Q8IY17 [338]) and carboxylesterase 1 (CES1, P23141 [581]). ABHD2 (P08910) has also been described as a triacylglycerol lipase and ester hydrolase [329], while ABHD12 (Q8N2K0) is also able to hydrolyse lysophosphatidylserine [531]. ABHD12 (Q8N2K0) has been described to be inhibited selectively by triterpenoids, such as betulinic acid [401].

Further reading on Endocannabinoid turnover
Blankman JL et al. (2013) Chemical probes of endocannabinoid metabolism. Pharmacol. Rev. 65: 849-71 [PMID:23512546]
Janssen FJ et al. (2016) Inhibitors of diacylglycerol lipases in neurodegenerative and metabolic disorders. Bioorg. Med. Chem. Lett. 26: 3831-7 [PMID:27394666]
Ueda N et al. (2013) Metabolism of endocannabinoids and related N-acylethanolamines: canonical and alternative pathways. FEBS J. 280: 1874-94 [PMID:23425575]
Wellner N et al. (2013) N-acylation of phosphatidylethanolamine and its biological functions in mammals. Biochim. Biophys. Acta 1831: 652-62 [PMID:23000428]

Eicosanoid turnover
Enzymes → Eicosanoid turnover

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

Cyclooxygenase
Enzymes → Eicosanoid turnover → Cyclooxygenase

Overview: Prostaglandin (PG) G/H synthase, most commonly referred to as cyclooxygenase (COX, (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate,hydrogen-donor : oxygen oxidoreductase) activity, catalyses the formation of PGG2 from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of PGH2 from PGG2. COX-1 and -2 can be nonselectively inhibited by ibuprofen, ketoprofen, naproxen, indomethacin and paracetamol (acetaminophen). PGH2 may then be metabolised to prostaglandins and thromboxanes by various prostaglandin synthases in an apparently tissue-dependent manner.
**Nomenclature**

| Enzyme | EC Number | Cofactors | Comments |
|--------|-----------|-----------|----------|
| mPGES1 | 5.3.99.3: PGH₂ = PGE₂ | glutathione | – |
| mPGES2 | 5.3.99.3: PGH₂ = PGE₂ | dihydrolipoic acid | – |
| cPGES | 5.3.99.3: PGH₂ = PGE₂ | – | Phosphorylated and activated by casein kinase 2 (CK2) [370]. Appears to regulate steroid hormone function by interaction with dimeric hsp90 [74, 253]. |

**Selective Inhibitors**

- Celecoxib (pIC₅₀ 8.7) [41], Valdecoxib (pIC₅₀ 8.3) [512], Diclofenac (pIC₅₀ 7.7) [45], Rofecoxib (pIC₅₀ 6.1–6.5) [557], Lumiracoxib (pKᵢ 6.5) [46], Meloxicam (pIC₅₀ 6.3) [294], Etoricoxib (pIC₅₀ 6) [439].

**Prostaglandin synthases**

Enzymes → Eicosanoid turnover → Prostaglandin synthases

**Overview:** Subsequent to the formation of PGH₂, the cytochrome P450 activities thromboxane synthase (CYP5A1, TBXAS1, PTGIS, Q16647, EC 5.3.99.5) and prostacyclin synthase (CYP1A1, PTGES, O14684, EC 5.3.99.4) generate thromboxane A₂ and prostacyclin (PGI₂), respectively (see Cytochrome P450s). Additionally, multiple enzyme activities are able to generate prostaglandin E₂ (PGE₂), prostaglandin D₂ (PGD₂) and prostaglandin F₂α (PGF₂α). PGD₂ can be metabolised to 9α,11β-prostaglandin F₂α 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.
Lipoxygenases

Enzymes → Eicosanoid turnover → Lipoxygenases

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

| Nomenclature | H-PGDS | AKR1C3 | CBR1 | HPGD |
|--------------|--------|--------|------|------|
| HGNC, UniProt | HPGDS, O60760 | AKR1C3, P42300 | CBR1, P16152 | HPGD, P15428 |
| EC number | 5.3.99.2: PGH₂ = PGD₂ | 1.1.1.188: PGD₂ + NADP⁺ = PGF₂α + NADPH + H⁺ | 1.1.1.189: PGE₂ + NADP⁺ = PGF₂α + NADPH + H⁺ | 1.1.1.197 |

Cofactors –

Inhibitors

HQL-79 (pIC₅₀ 5.3–5.5) [16] tolfenamic acid (pKᵢ 8.1) [421] flufenamic acid, indomethacin, flavonoids [344, 484] wedelolactone (pIC₅₀ 5.4) [604]

Comments – Also acts as a hydroxysteroid dehydrogenase activity. YS121 has been reported to inhibit mPGES1 and 5-LOX with a pIC₅₀ value of 5.5 [276].

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Full Contents of Concise Guide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full
Nomenclature

| Nomenclature          | 5-LOX | 12R-LOX | 12S-LOX | 15-LOX-1 | 15-LOX-2 | E-LOX |
|-----------------------|-------|---------|---------|----------|----------|-------|
| Endogenous substrates | arachidonic acid | – | – | – | – | 12R-HPETE |
| Endogenous activators | 5-LOX activating protein (ALOX5AP, P20292) | – | – | – | – | – |
| Endogenous inhibitors | Protein kinase A-mediated phosphorylation [324] | – | – | – | – | – |
| Selective inhibitors | CJ13610 (pIC$_{50}$ 7.2) [144], PF-04191834 (pIC$_{50}$ 6.6) [342], zileuton | – | – | compound 34 (pK$_i$ > 8) [425] | – | – |
| Comments              | FLAP activity can be inhibited by MK-886 [124] and BAY-X1005 [210] leading to a selective inhibition of 5-LOX activity | – | – | – | – | E-LOX metabolises the product from the 12R-lipoxygenase (12R-HPETE) to a specific epoxyalcohol compound [592]. |

**Comments:** An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 [167]. Some general LOX inhibitors are nordihydroguaiaretic acid and esculetin. Zileuton and caffeic acid are used as 5-lipoxygenase inhibitors, while baicalein and CDC are 12-lipoxygenase inhibitors. The specificity of these inhibitors has not been rigorously assessed with all LOX forms: baicalein, along with other flavonoids, such as fisetin and luteolin, also inhibits 15-LOX-1 [450].

### Leukotriene and lipoxin metabolism

**Overview:** Leukotriene A$_4$ (LTA$_4$), produced by 5-LOX activity, and lipoxins may be subject to further oxidative metabolism; $\omega$-hydroxylation is mediated by CYP4F2 and CYP4F3, while $\beta$-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 $\gamma$-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 [429]. 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 [384].

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Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
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 [136] where GABA is principally accumulated in vesicles through the action of the vesicular inhibitory amino acid transporter SLC32A1. The role of γ-aminobutyraldehyde dehydrogenase (ALDH9A1) in neurotransmitter GABA synthesis is less clear. Following release from neurons, GABA may interact with either GABAA or GABAB 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.

Further reading on Eicosanoid turnover

Ackermann JA et al. (2017) The double-edged role of 12/15-lipoxygenase during inflammation and immunity. Biochim Biophys Acta 1862: 371-381 [PMID:27480217]

Grosser T et al. (2017) The Cardiovascular Pharmacology of Nonsteroidal Anti-Inflammatory Drugs. Trends Pharmacol Sci [PMID:28651847]

Horn T et al. (2015) Evolutionary aspects of lipoxigenases and genetic diversity of human leukotriene signaling. Prog Lipid Res 57: 13-39 [PMID:25435097]

Joshi YB et al. (2015) The 12/15-lipoxygenase as an emerging therapeutic target for Alzheimer’s disease. Trends Pharmacol Sci 36: 181-6 [PMID:25708151]

Koeberle A et al. (2015) Perspective of microsomal prostaglandin E2 synthase-1 as drug target in inflammation-related disorders. Biochim Pharmacol 98: 1-15 [PMID:26123522]

Kuhn H et al. (2015) Mammalian lipoxigenases and their biological relevance. Biochim Biophys Acta 1851: 308-30 [PMID:25316632]

Patrignani P et al. (2015) Cyclooxygenase inhibitors: From pharmacology to clinical read-outs. Biochim Biophys Acta 1851: 422-32 [PMID:25263946]

Radmark O et al. (2015) 5-Lipoxygenase, a key enzyme for leukotriene biosynthesis in health and disease. Biochim Biophys Acta 1851: 331-9 [PMID:25152163]

Sasaki Y et al. (2017) Role of prostacyclin synthase in carcinogenesis. Prostaglandins Other Lipid Mediat [PMID:28506876]

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

Vitale P et al. (2016) COX-1 Inhibitors: Beyond Structure Toward Therapy. Med Res Rev 36: 641-71 [PMID:27111555]
### Glutamic Acid Decarboxylase (GAD)

| Nomenclature                  | Glutamic acid decarboxylase 1 | Glutamic acid decarboxylase 2 |
|-------------------------------|-------------------------------|-------------------------------|
| HGNC, UniProt                 | GAD1, Q99259                  | GAD2, Q05329                  |
| EC number                     | 4.1.1.15: L-glutamic acid + H⁺ → GABA + CO₂ | 4.1.1.15: L-glutamic acid + H⁺ → GABA + CO₂ |
| Common abbreviation           | GAD1                          | GAD2                          |
| Endogenous substrates         | L-glutamic acid, L-aspartic acid | L-glutamic acid, L-aspartic acid |
| Products                      | GABA                          | GABA                          |
| Cofactors                     | pyridoxal phosphate           | pyridoxal phosphate           |
| Selective inhibitors          | s-allylglycine                 | s-allylglycine                 |
| Comments                      | L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [S77]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading). |

### Aldehyde Dehydrogenase (ALDH)

| Nomenclature                  | Aldehyde dehydrogenase 9 family member A1 | 4-aminobutyrate aminotransferase | Aldehyde dehydrogenase 5 family member A1 |
|-------------------------------|-------------------------------------------|---------------------------------|-------------------------------------------|
| HGNC, UniProt                 | ALDH9A1, P49189                           | ABAT, P80404                    | ALDH5A1, PS1649                          |
| EC number                     | 1.2.1.19: 4-aminobutanal + NAD + H₂O = 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 + H₂O = succinic acid + NADH + H⁺ |
| Common abbreviation           | –                                         | GABA-T                          | SSADH                                     |
| Cofactors                     | NAD                                        | pyridoxal phosphate             | NAD [469]                                |
| Inhibitors                    | –                                          | vigabatrin (Irreversible inhibition) (pKᵢ 3.1) [306, 475] | 4-acryloylphenol (pIC₅₀ 6.5) [519] |

**Further reading on GABA turnover**

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]

McQuail JA *et al.* (2015) Molecular aspects of age-related cognitive decline: the role of GABA signaling. *Trends Mol Med* 21: 450-60 [PMID:26070271]

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

Full Contents of Concise Guide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)

GABA turnover S330
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

Overview: Phosphoinositide-specific phospholipase C (PLC, EC 3.1.4.11), catalyses the hydrolysis of PIP2 to IP3 and 1,2-diacylglycerol, each of which have major second messenger functions. Two domains, X and Y, essential for catalytic activity, are conserved in the different forms of PLC. Isoforms of PLC-β are activated primarily by G protein-coupled receptors through members of the Gq/11 family of G proteins. Isoforms of PLC-γ are activated by Gq/11 family of G proteins. PLC-γ is involved in the activation of PLC-γ by receptor tyrosine kinases (RTK) in response to activation of a variety of growth factor receptors and immune system receptors. PLC-ε is activated by both G protein-coupled and catalytic receptors. Ca2+ ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC-δ activity. PLC has been suggested to be activated non-selectively by the small molecule m3M3FBS, although this mechanism of action has been questioned. The aminosteroid U73122 has been described as an inhibitor of phosphoinositide-specific PLC, although its selectivity among the isoforms is untested and it has been reported to occupy the H1 histamine receptor.

Nomenclature

| Nomenclature | PLCβ1 | PLCβ2 | PLCβ3 | PLCβ4 | PLCγ1 | PLCγ2 |
|--------------|-------|-------|-------|-------|-------|-------|
| HGNC, UniProt | PLCB1, Q9NQ66 | PLCB2, Q00722 | PLCB3, Q01970 | PLCB4, Q15147 | PLCG1, P19174 | PLCG2, P16885 |
| Endogenous activators | Goq, Gq11, Gβγ [220, 399, 487] | Go16, Gβγ, Rac2 (RAC2, P15153) [65, 236, 237, 297, 399] | Goq, Gβγ [71, 295, 399] | Goq [196] | PIP3 [22] |
| Inhibitors | – | – | – | – | – | CCT129957 (pIC50 5.5) [436] |

| Nomenclature | PLCδ1 | PLCδ3 | PLCδ4 | PLCε1 | PLCζ1 | PLCη1 | PLCη2 |
|--------------|-------|-------|-------|-------|-------|-------|-------|
| HGNC, UniProt | PLCD1, P51178 | PLCD3, Q8N3E9 | PLCD4, Q9BRC7 | PLEC1, Q9P212 | PLCZ1, Q86YW0 | PLCCH1, Q4KWH8 | PLCCH2, Q7OS38 |
| Endogenous activators | Transglutaminase II, p122-RhoGAP (Rat), spermine, Gβγ [199, 226, 368, 399] | – | – | Ras, rho [490, 571] | – | – | Gβγ [600] |
| Endogenous inhibitors | Sphingomyelin [404] | – | – | – | – | – | – |

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**Comments:** As a series of PLC-like proteins (PLCL1, Q15111; PLCL2, Q9UPR0 and PLCH1, Q4KWH8) form a family with PLCδ and PLCζ isozymes, they appear to lack catalytic activity. PLC-δ2 has been cloned from bovine sources [351].

**Further reading on Phosphoinositide-specific phospholipase C**

Cocco L et al. (2015) Phosphoinositide-specific phospholipase C in health and disease. *J Lipid Res* **56**:1853-60 [PMID:25821234]

Cockcroft S et al. (2016) Topological organisation of the phosphatidylinositol 4,5-bisphosphate-phospholipase C resynthesis cycle: PITPs bridge the ER-PM gap. *Biochem J* **473**:4289-4310 [PMID:27888240]

Litosch I. (2015) Regulating G protein activity by lipase-independent functions of phospholipase C. *Life Sci* **137**:116-24 [PMID:26239437]

Cocco L et al. (2015) Phosphoinositide-specific phospholipase C in health and disease. *J Lipid Res* **56**:1853-60 [PMID:25821234]

Swann K et al. (2016) The sperm phospholipase C-zeta and Ca2+ signalling at fertilization in mammals. *Biochem Soc Trans* **44**:267-72 [PMID:26862214]

**Phospholipase A2**

**Enzymes → Glycerophospholipid turnover → Phospholipase A2**

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

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

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

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

**Further reading on Phospholipase A2**

Leslie CC. (2015) Cytosolic phospholipase A(2): physiological function and role in disease. *J Lipid Res* **56**:1386-402 [PMID:25838312]

Ong WY et al. (2015) Synthetic and natural inhibitors of phospholipases A2: their importance for understanding and treatment of neurological disorders. *ACS Chem Neurosci* **6**:814-31 [PMID:25891385]

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

**Nomenclature**

| Nomenclature | sPLA2-1B | sPLA2-2A | sPLA2-2D | sPLA2-2E | sPLA2-2F | sPLA2-3 |
|--------------|----------|----------|----------|----------|----------|---------|
| HGNC, UniProt| PLA2G1B, P04054 | PLA2G2A, P14555 | PLA2G2D, Q9UNK4 | PLA2G2E, Q9NZK7 | PLA2G2F, Q9BZM2 | PLA2G3, Q9NZ20 |

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**Full Contents of ConciseGuide:** [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
Nomenclature | cPLA₂-4A | cPLA₂-4B | cPLA₂-4C | cPLA₂-4D | cPLA₂-4E | cPLA₂-4F  
---|---|---|---|---|---|---  
HGNC, UniProt | PLA2G4A, P47712 | PLA2G4B, P0C869 | PLA2G4C, Q9UP65 | PLA2G4D, Q86XP0 | PLA2G4E, Q3M1J6 | PLA2G4F, Q68DD2  
EC number | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4  
Inhibitors | compound 57 (pIC₅₀ 8.4) [320] | – | – | – | – | –  
Comments | cPLA₂-4A also expresses lysophospholipase (EC 3.1.1.5) activity [473]. | – | – | – | – | –  

### Nomenclature

| Nomenclature | PLA₂-G5 | iPLA₂-G6 | PLA₂-G7 | sPLA₂-10 | sPLA₂-12A | platelet activating factor acetylhydrolase 2  
---|---|---|---|---|---|---  
HGNC, UniProt | PLA2G5, P39877 | PLA2G6, Q60733 | PLA2G7, Q13093 | PLA2G10, O15496 | PLA2G12A, Q9B2M1 | PAFAH2, Q99487  
EC number | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.4 | 3.1.1.47  
Inhibitors | – | darapladib (pIC₅₀ 10) [42] | – | – | – | –  
Selective inhibitors | – | rilapladib (Competitive) (pIC₅₀ 9.6) [568] | – | – | – | –  

**Comments:** The sequence of PLA₂-2C suggests a lack of catalytic activity, while PLA₂-12B (GXIIb, GXIII sPLA₂-like) appears to be catalytically inactive [448]. A further fragment has been identified with sequence similarities to Group II PLA₂ members. Otoconin 90 (OC90) shows sequence homology to PLA₂-G10. 

A binding protein for secretory phospholipase A₂ has been identified which shows modest selectivity for sPLA₂-1B over sPLA₂-2A, and also binds snake toxin phospholipase A₂ [13]. The binding protein appears to have clearance function for circulating secretory phospholipase A₂, as well as signalling functions, and is a candidate antigen for idiopathic membranous nephropathy [29]. PLA₂-G7 and PAFAH2 also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47).
Phosphatidylcholine-specific phospholipase D

Overview: Phosphatidylcholine-specific phospholipase D (PLD, EC 3.1.4.4) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidylation reaction [428].

Nomenclature

| PLD1 | PLD2 |
|------|------|
| HGNC, UniProt | PLD1, Q13393 |
| EC number | 3.1.4.4 |

Endogenous activators

| ADP-ribosylation factor 1 (ARF1, P84077), PIP2, RhoA, PKC evoked phosphorylation, RaI [201, 323] | ADP-ribosylation factor 1 (ARF1, P84077), PIP2 [316], oleic acid [454] |

Endogenous inhibitors

| Gβγ [418] | Gβγ [418] |

Inhibitors

| FIP1 (pIC50 8) [463] | FIP1 (pIC50 7.8) [484] |

Selective inhibitors

| compound 69 (pIC50 7.3) [463] | VU0364739 (pIC50 7.7) [293] |

Comments: A lysophospholipase D activity (ENPP2, Q13822, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2, phosphodiesterase 1, nucleotide pyrophosphatase 2, autotaxin) has been described, which not only catalyses the production of lysophosphatidic acid (LPA) from lysophosphatidylcholine, but also cleaves ATP (see Goding et al., 2003 [185]). Additionally, an N-acylethanolamine-specific phospholipase D (NAPEPLD, Q6IQ20) has been characterized, which appears to have a role in the generation of endocannabinoids/endovanilloids, including anandamide [388]. This enzyme activity appears to be enhanced by polyamines in the physiological range [311] and fails to transphosphatidylate with alcohols [408].

Three further, less well-characterised isoforms are PLD3 (PLD3, Q8IV08, other names Choline phosphatase 3, HindIII K4L homolog, Hu-K4), PLD4 (PLD4, Q96BZ4, other names Choline phosphatase 4, Phosphatidylcholine-hydrolyzing phospholipase, D4C14orf175 UNQ2488/PRO5775) and PLD5 (PLD5, Q8N7P1). PLD3 has been reported to be involved in myogenesis [391]. PLD4 is described not to have phospholipase D catalytic activity [588], but has been associated with inflammatory disorders [386, 507, 526]. Sequence analysis suggests that PLD5 is catalytically inactive.

Further reading on Phospholipase D

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

Frohman MA. (2015) The phospholipase D superfamily as therapeutic targets. Trends Pharmacol Sci 36: 137-44 [PMID:25661257]

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

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

| Nomenclature | Lipin1 | Lipin2 | Lipin3 | PPA2A | PPA2B | PPA3A | phosphatase and tensin homolog |
|--------------|--------|--------|--------|-------|-------|-------|--------------------------------|
| HGNC, UniProt | LPIN1, Q14693 | LPIN2, Q92539 | LPIN3, Q9BQK8 | PLPP1, O14494 | PLPP3, O1449S | PLPP2, O43688 | PTEN, P60484 |
| EC number | 3.1.3.4 | 3.1.3.4 | 3.1.3.4 | 3.1.3.4 | 3.1.3.4 | 3.1.3.4 | 3.1.3.67 |
| Substrates | – | phosphatidic acid | – | phosphatidic acid | – | phosphatidic acid (3,4,5)-trisphosphate |

Phosphatidylinositol kinases

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

**Phosphatidylinositol 3-kinases**
Phosphatidylinositol 3-kinases (PI3K, provisional nomenclature) catalyse the introduction of a phosphate into the 3-position of phosphatidylinositol (PI), phosphatidylinositol 4-phosphate (PIP) or phosphatidylinositol 4,5-bisphosphate (PIP2). There is evidence that PI3K can also phosphorylate serine/threonine residues on proteins. In addition to the classes described below, further serine/threonine protein kinases, including ATM (Q13315) and mTOR (P42345), have been described to phosphorylate phosphatidylinositol and have been termed PI3K-related kinases. Structurally, PI3Ks have common motifs of at least one C2, calcium-binding domain and helical domains, alongside structurally-conserved catalytic domains. Wortmannin and LY 294002 are widely-used inhibitors of PI3K activities. Wortmannin is irreversible and shows modest selectivity between Class I and Class II PI3K, while LY294002 is reversible and selective for Class I compared to Class II PI3K.

**Class I PI3Ks** (EC 2.7.1.153) phosphorylate phosphatidylinositol 4,5-bisphosphate to generate phosphatidylinositol 3,4,5-trisphosphate and are heterodimeric, matching catalytic and regulatory subunits. Class IA PI3Ks include 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 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.

The only **class III PI3K** isom form (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.

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)  
Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
1-phosphatidylinositol 4-kinase family

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

| Nomenclature | phosphatidylinositol 4-kinase alpha | phosphatidylinositol 4-kinase beta |
|--------------|------------------------------------|-----------------------------------|
| HGNC, UniProt| PI4KA, P42356                       | PI4KB, Q9UBF8                     |
| EC number    | 2.7.1.67                           | 2.7.1.67                          |
| Common abreviation | PI4KIIIα/PIK4CA                   | PI4KIIIβ/PIK4CB                  |
| Endogenous activation | –                                  | PKD-mediated phosphorylation [212] |
| Sub/family-selective inhibitors | wortmannin (pIC<sub>50</sub> 6.7–6.8) [180, 352] | wortmannin (pIC<sub>50</sub> 6.7–6.8) [180, 352] |
| Selective inhibitors | –                                  | PIK-93 (pIC<sub>50</sub> 7.7) [26, 271] |

Phosphatidylinositol-4-phosphate 3-kinase family

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

| Nomenclature | phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 alpha | phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 beta | phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 gamma |
|--------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| HGNC, UniProt| PIK3C2A, O00443                                                          | PIK3C2B, O00750                                                        | PIK3C2G, O75747                                                          |
| EC number    | 2.7.1.154                                                                | 2.7.1.154                                                                | 2.7.1.154                                                                |
| Common abreviation | C2α/PIK3C2A                                                              | C2β/PIK3C2B                                                            | C2γ/PIK3C2G                                                             |
| Inhibitors   | torin 2 (pIC<sub>50</sub> 7.6) [312]                                       | PI-103 (pIC<sub>50</sub> 8) [213]                                        | –                                                                        |

Overview: PIP<sub>2</sub> is generated by phosphorylation of PI 4-phosphate or PI 5-phosphate by type I PI 4-phosphate 5-kinases or type II PI 5-phosphate 4-kinases.
## Phosphatidylinositol 3-kinase family

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

## Phosphatidylinositol-4,5-bisphosphate 3-kinase family

**Nomenclature**  
phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha  
**HGNC, UniProt**  
PIK3CA, P42336  
**EC number**  
2.7.1.153  
**Common abbreviation**  
PI3Ka  
**Inhibitors**  
PI-75 (pIC<sub>50</sub> 9.5) [213], gedatolisib (pIC<sub>50</sub> 9.4) [544], PF-04691502 (pKi 9.2) [309], PI-103 (pIC<sub>50</sub> 8.7) [435], BGT-226 (pIC<sub>50</sub> 8.4) [337], KU-0060648 (pIC<sub>50</sub> 8.4) [66], dactolisib (pIC<sub>50</sub> 8.4) [332], apitolisib (pIC<sub>50</sub> 8.3) [506]  
**Sub/family-selective inhibitors**  
pictilisib (pIC<sub>50</sub> 8.5) [149]

**Nomenclature**  
phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta  
**HGNC, UniProt**  
PIK3CB, P42338  
**EC number**  
2.7.1.153  
**Common abbreviation**  
PI3Kβ  
**Inhibitors**  
KU-0060648 (pIC<sub>50</sub> 9.3) [66], PI-103 (pIC<sub>50</sub> 8.5) [435], AZD6482 (pIC<sub>50</sub> 8) [380], ZSTK474 (pIC<sub>50</sub> 7.4–7.8) [578, 583], apitolisib (pIC<sub>50</sub> 7.6) [506], BGT-226 (pIC<sub>50</sub> 7.2) [337]  
**Sub/family-selective inhibitors**  
pictilisib (pIC<sub>50</sub> 7.5) [149]

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**Searchable database:** [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

**Full Contents of ConciseGuide:** [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
Nomenclature: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
HGNC, UniProt: PIK3CG, P48736
EC number: 2.7.1.153
Common abbreviation: PI3Kγ
Inhibitors: dactolisib (pIC₅₀ 8.3) [332], apitolisib (pIC₅₀ 7.8) [506], PI-103 (pIC₅₀ 7.8) [435], BGT-226 (pIC₅₀ 7.4) [337], ZSTK474 (pIC₅₀ 7.3–7.3) [578, 583], TG-100-115 (pIC₅₀ 7.1) [394], alpelisib (pIC₅₀ 6.6) [164], KU-0060648 (pIC₅₀ 6.2) [66]
Sub/family-selective inhibitors: pictilisib (pIC₅₀ 7.1) [149]
Selective inhibitors: CZC 24832 (pKᵣ 7.7) [32]

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

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

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

Overview: Type I PIP kinases are required for the production of the second messenger phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P₂) by phosphorylating PtdIns(4)P [426]. This enzyme family is also known as type I PIP(5)Ks.

Nomenclature: phosphatidylinositol-4-phosphate 5-kinase type 1 alpha
HGNC, UniProt: PIP5K1A, Q99755
EC number: 2.7.1.68
Common abbreviation: PIP5K1A
Inhibitors: ISA-2011B [465]
Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)

Overview: Type II PIP kinases are essential for the production of the second messenger phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2) by phosphorylating PtdIns(5)P [426]. This enzyme family is also known as type II PIP(5)Ks.

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

Further reading on Phosphatidylinositol kinases

Bauer TM et al. (2015) Targeting PI3 kinase in cancer. Pharmacol Ther 146: S3-60 [PMID:25240910]
Mayer IA et al. (2016) The PI3K/AKT Pathway as a Target for Cancer Treatment. Annu Rev Med 67: 11-28 [PMID:26473415]

Singh P et al. (2016) p110alpha and p110beta isoforms of PI3K signaling: are they two sides of the same coin? FEBS Lett 590: 3071-82 [PMID:27552098]
Zhu J et al. (2015) Discovery of selective phosphatidylinositol 3-kinase inhibitors to treat hematological malignancies. Drug Discov Today 20: 988-94 [PMID:25857437]

Further reading on Glycerophospholipid turnover

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

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
HGNC, UniProt: HMOX1, P09601
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
Common abreviation: HO1

Nomenclature: Haem oxygenase 2
HGNC, UniProt: 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
Common abreviation: HO2

Comments: The existence of a third non-catalytic version of haem oxygenase, HO3, has been proposed, although this has been suggested to be a pseudogene [215]. The chemical tin protoporphyrin IX acts as a haem oxygenase inhibitor in rat liver with an IC50 value of 11 nM [128].

Further reading on Haem oxygenase
Abraham NG et al. (2016) Translational Significance of Heme Oxygenase in Obesity and Metabolic Syndrome. Trends Pharmacol Sci 37: 17-36 [PMID:26515032]
Naito Y et al. (2014) Heme oxygenase-1 and anti-inflammatory M2 macrophages. Arch Biochem Biophys 564: 83-8 [PMID:25241054]
Otterbein LE et al. (2016) Heme Oxygenase-1 and Carbon Monoxide in the Heart: The Balancing Act Between Danger Signaling and Pro-Survival. Circ Res 118: 1940-59 [PMID:27283533]
Poulos TL. (2014) Heme enzyme structure and function. Chem. Rev. 114: 3919-62 [PMID:24400737]

Hydrogen sulphide synthesis
Enzymes → Hydrogen sulphide synthesis

Overview: Hydrogen sulfide is a gasotransmitter, with similarities to nitric oxide and carbon monoxide. Although the enzymes indicated below have multiple enzymatic activities, the focus here is the generation of hydrogen sulfide (H2S) and the enzymatic characteristics are described accordingly. Cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) are pyridoxal phosphate (PLP)-dependent enzymes. 3-mercaptopyruvate sulfurtransferase (3-MPST) functions to generate H2S; only CAT is PLP-dependent, while 3-MPST is not. Thus, this third pathway is sometimes referred to as PLP-independent. CBS and CSE are predominantly cytosolic enzymes, while 3-MPST is found both in the cytosol and the mitochondria.

Nomenclature: Cystathionine β-synthase
HGNC, UniProt: CBS, P35520
EC number: 4.2.1.22
Common abreviation: CBS
Endogenous substrates: L-cysteine (Km 6x10^{-3}M) [81], L-homocysteine
Products: cystathionine

Nomenclature: Cystathionine γ-lyase
HGNC, UniProt: CTH, P32929
EC number: 4.4.1.1
Common abreviation: CSE
Endogenous substrates: L-cysteine
Products: NH3, pyruvic acid

Nomenclature: L-Cysteine:2-oxoglutarate aminotransferase
HGNC, UniProt: KYAT1, Q16773
EC number: 2.8.1.2
Common abreviation: CAT
Endogenous substrates: L-cysteine
Products: L-cysteine

Nomenclature: 3-Mercaptopyruvate sulfurtransferase
HGNC, UniProt: MPST, P25325
EC number: 2.8.1.2
Common abreviation: MPST
Endogenous substrates: 3-mercaptopyruvic acid (Km 1.2x10^{-3}M) [369]
Products: NH3, pyruvic acid

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full
Nomenclature

Cystathionine β-synthase
Cystathionine γ-lyase
L-Cysteine:2-oxoglutarate aminotransferase
3-Mercaptopyruvate sulfurtransferase

Cofactors

pyridoxal phosphate
pyridoxal phosphate
pyridoxal phosphate
Zn²⁺

Inhibitors

aminoxyacetic acid (pIC₅₀ 5.1) [17]
aminoethoxyvinylglycine (pIC₅₀ 6) [17],
aminooxyacetic acid (pIC₅₀ 6) [17],
β-Cyano-L-alanine (pIC₅₀ 5.8) [17],
propargylglycine (pIC₅₀ 4.4) [17]

Further reading on Hydrogen sulphide synthesis

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

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

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

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

Hydrolases

Enzymes → Hydrolases

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

Nomenclature

pancreatic lipase
lipase G, endothelial type
carboxylesterase 1
lipase E, hormone sensitive type

HGNC, UniProt
PNLIP, P16233
LIPG, Q9Y5X9
CES1, P23141
LIPE, Q05469

EC number
3.1.1.3
3.1.1.3
3.1.1.1
3.1.1.79

Common abreviation
PNLIP
LIPG
CES1
LIPE

Inhibitors
orlistat (pIC₅₀ 8.9) [61]
–
–
–
Nomenclature
ectonucleoside triphosphate diphosphohydrolase 1
ectonucleoside triphosphate diphosphohydrolase 2
Systematic nomenclature
CD39
CD39L1
HGNC, UniProt
ENTPD1, P49961
ENTPD2, Q9Y5L3
EC number
3.6.1.5
Hydrolyzes NTPs to nucleotide monophosphates (NMPs): A nucleoside 5'-triphosphate + 2 H₂O ◄→ a nucleoside 5'-phosphate + 2 phosphate
3.6.1.-
Hydrolyzes extracellular nucleotide 5'-triphosphates: NTP > NMP + 2 phosphate
Common abbreviation
NTPDase-1
NTPDase-2
Selective inhibitors
PSB-6426 (pKᵢ 5.1) [53]
Comments
ENTPD1 sequentially converts extracellular purine nucleotides (ATP and ADP) to the monophosphate form. Adenosine is then generated by the action of Ecto-5'-Nucleotidase (CD73). ENTPD1 is the rate-limiting step. Extracellular ATP acts as a damage-associated molecular pattern (DAMP) that activates innate immune cells through adenosine-induced activation of P2X and P2Y purinergic receptors.

Further reading on Hydrolases
Markey GM. (2011) Carboxylesterase 1 (Ces1): from monocyte marker to major player. *J. Clin. Pathol.* 64:107-9 [PMID:21177752]
Takenaka MC et al. (2016) Regulation of the T Cell Response by CD39. *Trends Immunol* 37:427-39 [PMID:27236363]

Inositol phosphate turnover

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

Inositol 1,4,5-trisphosphate 3-kinases

**Overview:** Inositol 1,4,5-trisphosphate 3-kinases (E.C. 2.7.1.127, ENSEMBL002500000001260) catalyse the generation of inositol 1,3,4,5-tetrasphosphate (IP₄) from IP₃. IP₃ kinase activity is enhanced in the presence of calcium/calmodulin (CALM1 CALM2 CALM3, P62158) [98].

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

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
Inositol polyphosphate phosphatases

Overview: Members of this family exhibit phosphatase activity towards IP₃, as well as towards other inositol derivatives, including the phospholipids PIP₂ and PIP₃. With IP₃ as substrate, 1-phosphatase (EC 3.1.3.57) generates 4,5-IP₂, 4-phosphatases (EC 3.1.3.66, ENSFM0025000001432) generate 1,5-IP₂ and 5-phosphatases (E.C. 3.1.3.36 or 3.1.3.56) generate 1,4-IP₂.

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

Comments: In vitro analysis suggested IP₃ and IP₄ were poor substrates for SKIP, synaptojanin 1 and synaptojanin 2, but suggested that PIP₂ and PIP₃ were more efficiently hydrolysed [458].

Inositol monophosphatase

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 (pKᵢ ca. 3.5, [347]; pIC₅₀ 3.2, [385]) than IMPase 2 (pIC₅₀ 1.8-2.1, [385]). IMPase activity may be inhibited competitively by L690330 (pKᵢ 5.5, [347]), although the enzyme selectivity is not yet established.

Nomenclature
HGNC, UniProt
EC number
Rank order of affinity
Inhibitors

| IMPase 1 | IMPase 2 |
|----------|----------|
| IMPA1, P29218 | IMPA2, O14732 |
| 3.1.3.25 | 3.1.3.25 |
| myo-inositol-4-phosphate > myo-inositol-3-phosphate > myo-inositol-1-phosphate [347] | – |
| Li⁺ (pKᵢ 3.5) [347] | – |

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

Further reading on Inositol phosphate turnover

Irvine R. (2016) A tale of two inositol trisphosphates. Biochem Soc Trans 44: 202-11 [PMID:26862207]
Livermore TM et al. (2016) Phosphate, inositol and polyphosphates. Biochem Soc Trans 44: 253-9 [PMID:26862212]
Miyamoto A et al. (2017) Probes for manipulating and monitoring IP3. Cell Calcium 64: 57-64 [PMID:27887748]

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

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

| Nomenclature | acetyl-CoA acetyltransferase 1 | acetyl-CoA acetyltransferase 2 | hydroxymethylglutaryl-CoA synthase 1 | hydroxymethylglutaryl-CoA synthase 2 |
|--------------|--------------------------------|--------------------------------|-------------------------------------|-------------------------------------|
| HGNC, UniProt| ACAT1, P24752                  | ACAT2, Q9BWD1                   | HMGCS1, Q01581                      | HMGCS2, P54868                      |
| EC number    | 2.3.1.9: 2 acetyl CoA = acetoacetyl CoA + coenzyme A | 2.3.1.9: 2 acetyl CoA = acetoacetyl CoA + coenzyme A | 2.3.3.10: acetyl CoA + H₂O → (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A | 2.3.3.10: acetyl CoA + H₂O → (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A |
| Comments     | –                              | –                              | HMGCoA synthase is found in cytosolic (HMGCoA synthase 1) and mitochondrial (HMGCoA synthase 2) versions; the former associated with (R)-mevalonate synthesis and the latter with ketogenesis. | HMGCoA synthase is found in cytosolic (HMGCoA synthase 1) and mitochondrial (HMGCoA synthase 2) versions; the former associated with (R)-mevalonate synthesis and the latter with ketogenesis. |

| Nomenclature | hydroxymethylglutaryl-CoA reductase | mevalonate kinase | phosphomevalonate kinase | diphosphomevalonate decarboxylase |
|--------------|-------------------------------------|-------------------|--------------------------|---------------------------------|
| HGNC, UniProt| HMGR, P04035                        | MVK, Q03426       | PMVK, Q15126             | MVD, P53602                     |
| EC number    | 1.1.1.34: (S)-3-hydroxy-3-methylglutaryl-CoA + NADPH → (R)-mevalonate + coenzyme A + NADP⁺ | 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 + CO₂ + PO₄³⁻ |
| Inhibitors   | lovastatin (Competitive) (pKᵢ 9.2) [10], rosvastatin (Competitive) (pIC₅₀ 8.3) [241], cerivastatin (Competitive) (pKᵢ 8.2) [67], atorvastatin (Competitive) (pIC₅₀ 8.1) [241], cerivastatin (Competitive) (pIC₅₀ 8.1) [528], simvastatin (Competitive) (pIC₅₀ 8.1) [241], fluvastatin (Competitive) (pIC₅₀ 7.6) [241] | – | – | – |

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Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
Nomenclature | hydroxymethylglutaryl-CoA reductase | mevalonate kinase | phosphomevalonate kinase | diphosphomevalonate decarboxylase
---|---|---|---|---
Comments | HMGCoA reductase is associated with intracellular membranes; enzymatic activity is inhibited by phosphorylation by AMP-activated kinase. The enzymatic reaction is a three-step reaction involving the intermediate generation of mevaldehyde-CoA and mevaldehyde. | Mevalonate kinase activity is regulated by the downstream products farnesyl diphosphate and geranyl diphosphate as an example of feedback inhibition. | – | –

Nomenclature | isopentenyl-diphosphate Δ-isomerase 1 | isopentenyl-diphosphate Δ-isomerase 2 | geranyleranyl diphosphate synthase
---|---|---|---
HGNC, UniProt | IDI1, Q13907 | IDI2, Q9BXS1 | GDP51, Q95749
EC number | 5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate | 5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate | 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> geranyleranyl diphosphate + diphosphate
| 2.5.1.11: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate | 2.5.1.29: trans,trans-farnesyl diphosphate + isopentenyl diphosphate -> geranyleranyl diphosphate + diphosphate | 2.5.1.11: dimethylallyl diphosphate + isopentenyl diphosphate = geranyleranyl diphosphate + diphosphate

Nomenclature | farnesyl diphosphate synthase | squalene synthase | squalene monoxygenase | lanosterol synthase
---|---|---|---|---
HGNC, UniProt | FDP5, P14324 | FDFT1, P37268 | SQLE, Q14534 | LSS, P48449
EC number | 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate | 2.5.1.21: 2trans,trans-farnesyl diphosphate -> presqualene diphosphate + diposphosphate | 1.14.13.132: H⁺ + NADPH + O₂ + squalene = H₂O + NADP⁺ + (S)-2,3-epoxysqualene | 5.4.99.7: (S)-2,3-epoxysqualene = lanosterol
| 2.5.1.11: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate | presqualene diphosphate + NAD(P)H + H⁺ <-> squalene + diphosphate + NAD(P)⁺ | – | –

Cofactors | – | – | NADPH | –
Inhibitors | risedronate (pIC₅₀ 8.4) [33], zoledronic acid (pKᵢ 7.1) [129], alendronate (pIC₅₀ 6.3) [33] | zaragozic acid A (pKᵢ 10.1) [34] – Rat, zaragozic acid A (pIC₅₀ 9.2) [330] | – | –
Selective inhibitors | ibandronic acid (pKᵢ 6.7) [129], pamidronic acid (pIC₅₀ 6.7) [129] | – | – | –

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full)
Further reading on Lanosterol biosynthesis pathway

Moutinho M et al. (2017) The mevalonate pathway in neurons: It’s not just about cholesterol. Exp Cell Res [PMID:28232115]

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

Ness GC. (2015) Physiological feedback regulation of cholesterol biosynthesis: Role of translational control of hepatic HMG-CoA reductase and possible involvement of oxylanosterols. Biochim Biophys Acta 1851: 667-73 [PMID:25701719]

Nucleoside synthesis and metabolism

Enzymes → Nucleoside synthesis and metabolism

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

| Nomenclature                  | dihydrofolate reductase | dihydroorotate dehydrogenase (quinone) | inosine monophosphate dehydrogenase 1 | inosine monophosphate dehydrogenase 2 | xanthine dehydrogenase |
|-------------------------------|--------------------------|----------------------------------------|--------------------------------------|---------------------------------------|------------------------|
| HGNC, UniProt                 | DHFR, P00374             | DHODH, Q02127                          | IMPDH1, P20839                        | IMPDH2, P12268                        | XDH, P47989             |
| EC number                    | 1.5.1.3                  | 1.3.5.2                                | 1.1.1.205                            | 1.1.1.205                             | 1.17.1.4                |
| Inhibitors                    | pemetrexed (pKᵢ 8.1) [171, 474], pralatrexate (pKᵢ 7.3) [244] | teriflunomide (pKᵢ 7.5) [214], leflunomide (pKᵢ 4.9) [397] | mycophenolic acid (pIC₅₀ 7.7) [376], ribavirin (pIC₅₀ 5.6–6) [572], thioguanine [132, 546] | mycophenolic acid (pIC₅₀ 7.7) [376], ribavirin (pIC₅₀ 5.6–6) [572], thioguanine [132, 546] | febuxostat (pKᵢ 9.9) [387] – Bovine, allopurinol (pKᵢ 5.2) [36] |
| Selective inhibitors          | methotrexate (pKᵢ 8.9) [446] | –                                      | –                                    | –                                     | –                      |

Nucleoside synthesis and metabolism S346

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Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full
**Sphingosine 1-phosphate turnover**

**Enzymes** → Sphingosine 1-phosphate turnover

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

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

**Further reading on Nucleoside synthesis and metabolism**

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

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

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

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**Nomenclature**

| Nomenclature | ribonucleotide reductase catalytic subunit M1 | ribonucleotide reductase regulatory subunit M2 | ribonucleotide reductase regulatory TP53 inducible subunit M2B | thymidylate synthetase | phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminimidazole synthetase | purine nucleoside phosphorylase |
|--------------|--------------------------------------------|------------------------------------------|------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------------------|---------------------------------|
| HGNC, UniProt | RRM1, P23921                               | RRM2, P31350                             | RRM2B, Q7LG56                                    | TYSM, P04818             | GART, P22102                                                                                     | PNP, P00491                     |
| EC number    | 1.17.14.1                                  | 1.17.4.1                                 | 1.17.1.4                                         | 2.1.1.45                 | 2.1.2.2 6.3.3.1 6.3.4.13                                                                          | –                               |
| Common abbreviation | –                                       | –                                        | –                                               | –                        | GART                                                                               | –                               |
| Inhibitors   | clofarabine (pIC50 8.3) [400], fludarabine (pIC50 6) [534], hydroxyurea (pIC50 3.8) [471], gemcitabine [219] | –                                        | –                                               | pemetrexed (pK5 7) [474], capecitabine [69, 398]                                           | pemetrexed (pK5 5) [474] – Mouse | –                               |
| Selective inhibitors | –                                       | –                                        | –                                               | raltitrexed (pIC50 6.5) [172]                                                    | –                                                                                    | –                               |
Sphingosine kinase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine kinase

| Nomenclature                  | sphingosine kinase 1              | sphingosine kinase 2              |
|-------------------------------|-----------------------------------|-----------------------------------|
| HGNC, UniProt                 | SPHK1, Q9NYA1                     | SPHK2, Q9NRA0                     |
| EC number                     | 2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP | 2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP |
| Common abreviation            | SPHK1                             | SPHK2                             |
| Cofactors                     | Mg^{2+} [469]                     | Mg^{2+}                           |
| Sub/family-selective inhibitors| SKI-II (pIC_{50} 6.3) [156]       | ABC294640 (pK_{i} 5) [157], ROMe (pIC_{50} 4.6) [304] |
| Selective inhibitors          | PF-543 (pIC8.7) [556],            |

Further reading on Sphingosine kinases

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

Sphingosine 1-phosphate phosphatase

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

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

Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [231].

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Sphingosine 1-phosphate lyase

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

| Nomenclature | sphingosine-1-phosphate lyase 1 |
|--------------|---------------------------------|
| HGNC, UniProt| SGPL1, O95470                   |
| EC number   | 4.1.2.27: sphingosine 1-phosphate -> phosphoethanolamine + hexadecanal |
| Cofactors   | pyridoxal phosphate             |
| Inhibitors  | compound 31 (pIC_{50} 6.7) [564]|
| Comments    | THI (2-Acetyl-5-tetrahydroxybutyl imidazole) inhibits the enzyme activity in intact cell preparations [462].|

Further reading on Sphingosine 1-phosphate lyase

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

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

Thyroid hormone turnover

Enzymes → Thyroid hormone turnover

Overview:
The thyroid hormones triiodothyronine and thyroxine, usually abbreviated as triiodothyronine and T₄, respectively, are synthesized in the thyroid gland by sequential metabolism of tyrosine residues in the glycosylated homodimeric protein thyroglobulin (TG, P01266) under the influence of the haem-containing protein iodide peroxidase. Iodide peroxidase/TPO is a haem-containing enzyme, from the same structural family as eosinophil peroxidase (EPX, P11678), lactoperoxidase (LPO, P22079) and myeloperoxidase (MPO, P05164). Circulating thyroid hormone is bound to thyroxine-binding globulin (SERPINA7, P05543).

| Nomenclature | thyroid peroxidase |
|--------------|--------------------|
| HGNC, UniProt| TPO, P07202        |
| EC number   | 1.11.1.8: [Thyroglobulin]-L-tyrosine + H₂O₂ + H⁺ + I⁻ -> [Thyroglobulin]-3,5,3'-triiodo-L-thyronine + [thyroglobulin]-aminoacrylate + H₂O |
| Common abreviation | TPO |
| Cofactors   | Ca²⁺               |
| Inhibitors  | methimazole [373], propylthiouracil [373] |
| Comments    | Carbimazole is a pro-drug for methimazole |

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Tissue deiodinases
These are 1 TM selenoproteins that remove an iodine from T₄ (3,3',5,5'-tetraiodothyronine) to generate triiodothyronine (3,3',5-triiodothyronine, a more potent agonist at thyroid hormone receptors) or rT₃ (rT3, 3,3',5'-triiodothyronine, a relatively inactive analogue). DIO1 is also able to deiodinate RT3 to form 3,5'-diidothyronine (T₂). Iodotyrosine deiodinase is a 1TM homodimeric enzyme.

| Nomenclature                  | iodothyronine deiodinase 1 | iodothyronine deiodinase 2 | iodothyronine deiodinase 3 | iodothyrosine deiodinase |
|-------------------------------|---------------------------|----------------------------|---------------------------|--------------------------|
| HGNC, UniProt                 | DIO1, P49895              | DIO2, Q92813               | DIO3, P55073              | IYD, Q6PHW0              |
| EC number                     | 1.97.1.10: T₄ -> triiodothyronine rT₃ -> T₂ | 1.97.1.10: T₄ -> triiodothyronine rT₃ -> T₂ | 1.97.1.11: T₄ -> triiodothyronine rT₃ -> T₂ | 1.22.1.1: 3-iodotyrosine -> L-tyrosine + I⁻ |
| Common abbreviation           | DIO1                      | DIO2                       | DIO3                      | IYD                      |
| Cofactors                     | –                         | –                          | –                         | flavin adenine dinucleotide, NADPH |

Further reading on Thyroid hormone turnover
Darras VM et al. (2015) Intracellular thyroid hormone metabolism as a local regulator of nuclear thyroid hormone receptor-mediated impact on vertebrate development. Biochim. Biophys. Acta 1849: 130-41 [PMID:24844179]
Gereben B et al. (2015) Scope and limitations of iodothyronine deiodinases in hypothyroidism. Nat Rev Endocrinol 11: 642-52 [PMID:26416219]
Mondal S et al. (2017) Novel thyroid hormone analogues, enzyme inhibitors and mimetics, and their action. Mol Cell Endocrinol [PMID:28408161]
Schweizer U et al. (2015) New insights into the structure and mechanism of iodothyronine deiodinases. J Mol Endocrinol 55: R37-52 [PMID:26390881]
vander Spek AH et al. (2017) Thyroid hormone metabolism in innate immune cells. J Endocrinol 232: R67-R81 [PMID:27852725]

1.14.11.29 2-oxoglutarate oxygenases
Enzymes → 1.14.11.29 2-oxoglutarate oxygenases

Overview: Hypoxia inducible factor (HIF) is a transcriptional complex that is involved in oxygen homeostasis [466]. At normal oxygen levels, the alpha subunit of HIF (HIF-1α) is targeted for degradation by prolyl hydroxylation by the prolyl hydroxylases PHD proteins 1-3 (HIF-PHs) which are 2-oxoglutarate oxygenases responsible for the post-translational modification of a specific proline in each of the oxygen-dependent degradation domains of HIF-1α. Hydroxylated HIFs are then targeted for proteasomal degradation via the von Hippel-Lindau ubiquitination complex [245]. Under hypoxic conditions, the hydroxylation reaction is blunted which results in decreased HIF degradation. The surviving HIFs are then available to translocate to the nucleus where they heterodimerize with HIF-1β, effecting increased expression of hypoxia-inducible genes.

HIF-PH enzymes are being investigated as pharmacological targets as their inhibition mimics the hypoxic state and switches on transcription of genes associated with processes such as erythropoiesis and vasculogenesis [151]. Small molecule HIF-PH inhibitors are in clinical trial as novel therapies for the amelioration of anemia associated with chronic kidney disease [50].

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Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full
Further reading on 2-oxoglutarate oxygenases

Ivan M et al. (2017) The EGLN-HIF O2-Sensing System: Multiple Inputs and Feedbacks. Mol Cell 66: 772-779 [PMID:28622522]
Markolovic S et al. (2015) Protein Hydroxylation Catalyzed by 2-Oxoglutarate-dependent Oxygenases. J Biol Chem 290: 20712-22 [PMID:26152730]
Salminen A et al. (2015) 2-Oxoglutarate-dependent dioxygenases are sensors of energy metabolism, oxygen availability, and iron homeostasis: potential role in the regulation of aging process. Cell Mol Life Sci 72: 3897-914 [PMID:26118662]

Wu Y et al. (2017) Application of in-vitro screening methods on hypoxia inducible factor prolyl hydroxylase inhibitors. Bioorg Med Chem 25: 3891-3899 [PMID:28625716]
Zurlo G et al. (2016) New Insights into Protein Hydroxylation and Its Important Role in Human Diseases. Biochim Biophys Acta 1866: 208-220 [PMID:27663420]

1.14.13.9 kynurenine 3-monooxygenase

Enzymes → 1.14.13.9 kynurenine 3-monooxygenase

Further reading on Kynurenine 3-monooxygenases

Dounay AB et al. (2015) Challenges and Opportunities in the Discovery of New Therapeutics Targeting the Kynurenine Pathway. J Med Chem 58: 8762-82 [PMID:26207924]
Erhardt S et al. (2017) The kynurenine pathway in schizophrenia and bipolar disorder. Neuropsychopharmacology 112: 297-306 [PMID:27245499]
Fujigaki H et al. (2017) L-Tryptophan-kynurenine pathway enzymes are therapeutic target for neuropsychiatric diseases: Focus on cell type differences. Neuropsychopharmacology 112: 264-274 [PMID:26767951]

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

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Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full
2.4.2.30 poly(ADP-ribose)polymerases

Enzymes → 2.4.2.30 poly(ADP-ribose)polymerases

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

| Nomenclature                  | poly(ADP-ribose) polymerase 1                           | poly(ADP-ribose) polymerase 2                           | poly (ADP-ribose) polymerase 3                           |
|-------------------------------|---------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|
| HGNC, UniProt                 | PARP1, P09874                                           | PARP2, Q9UGNS                                           | PARP3, Q9Y6F1                                           |
| EC number                     | 2.4.2.30                                                | 2.4.2.30                                                | –                                                       |
| Common abreviation            | PARP1                                                   | PARP2                                                   | PARP3                                                   |
| Selective inhibitors          | AG14361 (pKi 8.2) [483]                                 | –                                                       | –                                                       |

Further reading on Poly(ADP-ribose)polymerases

Bai P. (2015) Biology of Poly(ADP-Ribose) Polymerases: The Factotums of Cell Maintenance. Mol Cell 58: 947-58 [PMID:26091343]
Bai P et al. (2015) Poly(ADP-ribose) polymerases as modulators of mitochondrial activity. Trends Endocrinol Metab 26: 75-83 [PMID:25497347]
Bock FJ et al. (2016) New directions in poly(ADP-ribose) polymerase biology. FEBS J 283: 4017-4031 [PMID:27087568]
Bock FJ et al. (2015) RNA Regulation by Poly(ADP-Ribose) Polymerases. Mol Cell 58: 959-69 [PMID:26091344]
Ryu KW et al. (2015) New facets in the regulation of gene expression by ADP-ribosylation and poly(ADP-ribose) polymerases. Chem Rev 115: 2453-81 [PMID:25575290]

2.5.1.58 Protein farnesyltransferase

Enzymes → 2.5.1.58 Protein farnesyltransferase

Overview: Farnesyltransferase is a member of the prenyltransferases family which also includes geranylgeranyltransferase types I (EC 2.5.1.59) and II (EC 2.5.1.60) [72]. Protein farnesyltransferase catalyses the post-translational formation of a thioether linkage between the C-1 of an isoprenyl group and a cysteine residue fourth from the C-terminus of a protein (i.e to the CaaX motif, where ‘a’ is an aliphatic amino acid and ‘X’ is usually serine, methionine, alanine or glutamine; leucine for EC 2.5.1.59) [165]. Farnesyltransferase is a dimer, composed of an alpha and beta subunit and requires 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.

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

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.

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### 3.5.1.- Histone deacetylases (HDACs)

**Enzymes → 3.5.1.- Histone deacetylases (HDACs)**

**Overview:** Histone deacetylases act as erasers of epigenetic acetylation marks on lysine residues in histones. Removal of the acetyl groups facilitates tighter packing of chromatin (heterochromatin formation) leading to transcriptional repression. The histone deacetylase family has been classified into five sub-families based on phylogenetic comparison with yeast homologues:

- **Class I** contains HDACs 1, 2, 3 and 8
- **Class IIa** contains HDACs 4, 5, 7 and 9
- **Class IIb** contains HDACs 6 and 10
- **Class III** contains the sirtuins (SIRT1-7)
- **Class IV** contains only HDAC11.

Class I, II and IV use Zn$^{2+}$ as a co-factor, whereas catalysis by Class III enzymes requires NAD$^+$ as a co-factor, and members of this subfamily have ADP-ribosylase activity in addition to protein deacetylase function [456].

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

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

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

### Further reading on Histone deacetylases

- **Maolanon AR et al. (2017)** Natural and Synthetic Macrocyclic Inhibitors of the Histone Deacetylase Enzymes. *ChemBioChem* **18**: S–49 [PMID:27748555]
- **Micelli C et al. (2015)** Histone deacetylases: structural determinants of inhibitor selectivity. *Drug Discov Today* **20**: 718–35 [PMID:25687212]
- **Millard CJ et al. (2017)** Targeting Class I Histone Deacetylases in a "Complex" Environment. *Trends Pharmacol Sci* **38**: 363-377 [PMID:28139258]
- **Roche J et al. (2016)** Inside HDACs with more selective HDAC inhibitors. *Eur J Med Chem* **121**: 451-83 [PMID:27318122]
- **Zagni C et al. (2017)** The Search for Potent, Small-Molecule HDACIs in Cancer Treatment: A Decade After Vorinostat. *Med Res Rev* [PMID:28181261]
3.5.3.15 Peptidyl arginine deiminases (PADI)

**Overview:** In humans, the peptidyl arginine deiminases (PADIs; HGNC family link) are a family of five enzymes, PADI1-4 and PADI6. PADIs catalyze the deimination of protein L-arginine residues to L-citrulline and ammonia, generating peptidyl-citrulline on histones, fibrinogen, and other biologically relevant proteins. The human isozymes exhibit tissue-specific expression patterns [256]. Overexpression and/or increased PADI activity is observed in several diseases, including rheumatoid arthritis, Alzheimer’s disease, multiple sclerosis, lupus, Parkinson’s disease, and cancer [37]. Pharmacological PADI inhibition reverses protein-hypercitrullination and disease in mouse models of multiple sclerosis [366].

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

**Further reading on Peptidyl arginine deiminases**
- Koushik S et al. (2017) PAD4: pathophysiology, current therapeutics and future perspective in rheumatoid arthritis. Expert Opin Ther Targets 21: 433-447 [PMID:28281906]
- Tu R et al. (2016) Peptidyl Arginine Deiminases and Neurodegenerative Diseases. Curr Med Chem 23: 104-114 [PMID:26577926]

RAS subfamily

**Overview:** The RAS proteins (HRAS, NRAS and KRAS) are small membrane-localised G protein-like molecules of 21 kd. They act as an on/off switch linking receptor and non-receptor tyrosine kinase activation to downstream cytoplasmic or nuclear events. Binding of GTP activates the switch, and hydrolysis of the GTP to GDP inactivates the switch. The RAS proto-oncogenes are the most frequently mutated class of proteins in human cancers. Common mutations compromise the GTP-hydrolysing ability of the proteins causing constitutive activation [495], which leads to increased cell proliferation and decreased apoptosis [598]. Because of their importance in oncogenic transformation these proteins have become the targets of intense drug discovery effort [25].

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

**Further reading on RAS subfamily**
- Dorard C et al. (2017) Deciphering the RAS/ERK pathway in vivo Biochem Soc Trans 45: 27-36 [PMID:28202657]
- Keeton AB et al. (2017) The RAS-Effecter Interaction as a Drug Target. Cancer Res 77: 221-226 [PMID:28062402]
- Lu S et al. (2016) Ras Conformational Ensembles, Allostery, and Signaling. Chem Rev 116: 6607-65 [PMID:26815308]
- Ostrem JM et al. (2016) Direct small-molecule inhibitors of KRAS: from structural insights to mechanism-based design. Nat Rev Drug Discov 15: 771-785 [PMID:27469033]
- Papke B et al. (2017) Drugging RAS: Know the enemy. Science 355: 1158-1163 [PMID:28302824]
- Quah SY et al. (2016) Pharmacological modulation of oncogenic Ras by natural products and their derivatives: Renewed hope in the discovery of novel anti-Ras drugs. Pharmacol Ther 162: 35-57 [PMID:27016467]
- Simanshu DK et al. (2017) RAS Proteins and Their Regulators in Human Disease. Cell 170: 17-33 [PMID:28666118]

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13877/full
4.2.1.1 Carbonate dehydratases

Enzymes → 4.2.1.1 Carbonate dehydratases

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

| Nomenclature | carbonic anhydrase 1 | carbonic anhydrase 7 | carbonic anhydrase 12 |
|--------------|----------------------|---------------------|----------------------|
| HGNC, UniProt| CA1, P00915          | CA7, P43166         | CA12, O43570         |
| EC number    | 4.2.1.1              | 4.2.1.1             | 4.2.1.1              |
| Inhibitors   | chlorthalidone (pK$_i$ 6.5) | methazolamide (pK$_i$ 8.7) [467], acetazolamide (pK$_i$ 8.6) [19], brinzolamide (pK$_i$ 8.6) [467], chlorthalidone (pK$_i$ 8.6) [524] | chlorthalidone (pK$_i$ 8.4) [524], diclofenamide (pK$_i$ 7.3) [547] |

**Further reading on 4.2.1.1 Carbonic anhydrases**

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

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

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5.99.1.2 DNA Topoisomerases

Enzymes → 5.99.1.2 DNA Topoisomerases

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

| Nomenclature | topoisomerase (DNA) I | topoisomerase (DNA) II alpha |
|--------------|-----------------------|-----------------------------|
| HGNC, UniProt| TOP1, P11387          | TOP2A, P11388               |
| EC number    | 5.99.1.2              | 5.99.1.2                    |
| Inhibitors   | irinotecan [125, 518] – Bovine | etoposide (pIC$_{50}$ 7.3), teniposide [127] – Mouse |

**Further reading on DNA topoisomerases**

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

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

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

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

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

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