THE CONCISE GUIDE TO PHARMACOLOGY 2015/16: Enzymes

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Abstract

The Concise Guide to PHARMACOLOGY 2015/16 provides concise overviews of the key properties of over 1750 human drug targets with their pharmacology, 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. The full contents can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full. G protein-coupled receptors 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 Concise Guide is published in landscape format in order to facilitate comparison of related targets. It is a condensed version of material contemporary to late 2015, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in the previous Guides to Receptors & Channels and the Concise Guide to PHARMACOLOGY 2013/14. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and GRAC and provides a permanent, citable, point-in-time record that will survive database updates.

Conflict of interest

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

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

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

Although there are many more enzymes than receptors in biology, and many drugs that target prokaryotic enzymes are effective medicines, overall the number of enzyme drug targets is relatively small [367, 401], 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 promote a particular conformational change. Co-factors are tightly bound to the enzyme and include metal ions and heme groups. Co-enzymes are typically small molecules which accept or donate functional groups to assist in the enzymatic reaction. Examples include ATP, NAD, NADP and S-adenosylmethionine, as well as a number of vitamins, such as riboflavin (vitamin B1) and thiamine (vitamin B2). Where co-factors/co-enzymes have been identified, the Guide indicates their involvement.

### Family structure

This is a complete listing of enzyme families included in the online IUPHAR/BPS Guide to PHARMACOLOGY database. Summary information is provided for a subset of enzyme families (those with page numbers) in the tables below. Family members judged to be of significant pharmacological interest have been included, with further enzymes listed in the database.

| 6028 | Protein Kinases (EC 2.7.x.x) |
|------|-----------------------------|
| –    | AGC: Containing PKA, PKC, PKG families |
| –    | DMPK family |
| –    | GEK subfamily |
| –    | Other DMPK family kinases |
| 6028 | Rho kinase |
| –    | G protein-coupled receptor kinases |
| –    | BARK/GRK2 subfamily |
| –    | GRK1/3 subfamily |
| –    | MAST family |
| –    | NDR family |
| –    | PKD1 family |
| –    | Protein kinase A |
| –    | Protein kinase B |
| 6029 | Protein kinase C (PKC) |
| –    | Alpha subfamily |
| 6029 | Delta subfamily |
| 6030 | Eta subfamily |
| –    | lota subfamily |
| –    | Protein kinase G (PKG) |
| –    | Protein kinase N (PKN) family |
| –    | RSK family |
| –    | MSK subfamily |
| –    | p70 subfamily |
| –    | RSK subfamily |
| –    | RSKR subfamily |
| –    | RSKL family |
| –    | SGK family |
| –    | YANK family |
| –    | Atypical |
| –    | ABC1 family |
| –    | ABC1-A subfamily |
| –    | ABC1-B subfamily |
| –    | Alpha kinase family |
| –    | ChaK subfamily |
| –    | eEF2K subfamily |
| –    | Other alpha kinase family kinases |
| –    | BCR family |
| –    | Bromodomain kinase (BRD) family |
| –    | G11 family |
| –    | Phosphatidyl inositol 3’ kinase-related kinases |
| –    | (PIKK) family |
| –    | ATR subfamily |
| –    | FRAP subfamily |
| –    | SMG1 subfamily |
| –    | TRRAP subfamily |
| –    | Other PIKK family kinases |
| –    | CamK: Calcium/calmodulin-dependent protein kinases |
| –    | CAMK-like (CAMKL) family |
| –    | AMPK subfamily |
| –    | CDK1 subfamily |
| –    | CDK4 subfamily |
| –    | CDK5 subfamily |
| –    | CDK7 subfamily |
| –    | CDK9 subfamily |
| –    | CDK10 subfamily |
| –    | CRK7 subfamily |
| –    | PITSLRE subfamily |
| –    | TAIRE subfamily |
| –    | Cyclin-dependent kinase-like (CDKL) family |
| –    | Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase (DYRK) family |
| –    | Dyrk1 subfamily |
| –    | Dyrk2 subfamily |
| –    | HIPK subfamily |
| –    | PRP4 subfamily |
| –    | Glycogen synthase kinase (GSK) family |
GSK subfamily
- Mitogen-activated protein kinases (MAP kinases)
- ERK subfamily
- JNK subfamily
- p38 subfamily
- nmo subfamily
- RCK family
- SRPK family
- Other protein kinases
  - CAMKK family
  - Meta subfamily
  - Aurora kinase (Aur) family
  - Bub family
  - Bud32 family
  - Casein kinase 2 (CK2) family
  - CDC7 family
  - Haspin family
  - IKK family
  - Ire family
  - MOS family
  - NAK family
  - NIMA (never in mitosis gene a)-related kinase (NEK) family
  - NKFI family
  - NKF2 family
  - NKF4 family
  - NKF5 family
  - NKBHL family
  - Other-unique family

Polo-like kinase (PLK) family
- PEK family
- GCN2 subfamily
- PEK subfamily
- Other PEK family kinases
- SgK493 family
- SRob family
- TBCK family
- TOPK family
- Trosed-like kinase (TLK) family
- TTK family
- Unc-51-like kinase (ULK) family
- VPS15 family
- WEE family
- Wnk family
- Miscellaneous protein kinases
  - actin-binding proteins ADF family
  - TWINfilin subfamily
  - SCY1 family
  - Hexokinases
  - STE: Homologs of yeast Sterile 7, Sterile 11, Sterile 12

TK: Tyrosine kinase
- Interleukin-1 receptor-associated kinase (IRAK) family
- Leucine-rich repeat kinase (LRRK) family
- Mixed Lineage Kinase (MLK) family
- HH498 subfamily
- ILK subfamily
- LIM domain kinase (LISK) family

TKL: Tyrosine kinase-like
- Interleukin-1 receptor-associated kinase (IRAK) family
- Leucine-rich repeat kinase (LRRK) family
- LIM domain kinase (LISK) family

TKL-unique family

AA: Aspartic (A) Peptidases
- A1: Pepsin
- AD: Aspartic (A) Peptidases
- A22: Preprolin
- CA: Cysteine (C) Peptidases
  - C1: Papain
  - C2: Calpain
- C12: Ubiquitin C-terminal hydrolase
- C19: Ubiquitin-specific protease

Acetylcholine turnover

Arginase

Amino acid hydroxylases

Arginase

Achtylcholine turnover

Enzymes

S.P.H. Alexander et al. The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. British Journal of Pharmacology (2015) 172, 6024–6109

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of Concise Guide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full
| Enzymes | 6027 |
|--------|------|
| S.P.H. Alexander et al. | The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. British Journal of Pharmacology (2015) 172, 6024–6109 |
| Arginine:glycine amidinotransferase | Cytochrome P450 |
| Dimethylarginine dimethylaminohydrolases | CYP1 family |
| Nitric oxide synthases | CYP2 family |
| Carboxylases and decarboxylases | CYP3 family |
| Carboxylases | CYP4 family |
| Decarboxylases | CYP5, CYP7 and CYP8 families |
| Catecholamine turnover | CYP11, CYP17, CYP19, CYP20 and CYP21 families |
| Serine palmitoyltransferase | CYP24, CYP26 and CYP27 families |
| - 3-ketodihydrosphingosine reductase | CYP39, CYP46 and CYP51 families |
| Ceramide turnover | Eicosanoid turnover |
| - Ceramide synthase | Endocannabinoid turnover |
| - Sphingolipid \( \Delta^2 \)-desaturase | Cyclooxygenase |
| - Sphingomyelin synthase | Prostaglandin synthases |
| - Sphingomyelin phosphodiesterase | Lipoygenases |
| - Neutral sphingomyelinase coupling factors | Leukotriene and lipoxin metabolism |
| - Ceramide glucosyltransferase | GABA turnover |
| Acid ceramidase | Glycrophospholipid turnover |
| Neutral ceramidases | Lipid modifying kinases |
| Alkaline ceramidases | 1-phosphatidylinositol 4-kinase family |
| Ceramide kinase | Phosphatidylinositol 4-phosphate 5-kinase family |
| Chromatin modifying enzymes | 1-phosphatidylinositol-3-phosphate 5-kinase family |
| - Enzymatic bromodomain-containing proteins | Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family) |
| - Bromodomain kinase (BRDK) family | Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family) |
| - TAF1 family | Serine palmitoyltransferase |
| - TIF1 family | Phospholipid transferase |
| - 1.14.11.- Histone deacetylases | CYP1 family |
| - 2.1.1.43 Histone methyltransferases (HMTs) | CYP2 family |
| - 2.3.1.48 Histone acetyltransferases (HATs) | CYP3 family |
| - 3.6.1.3 ATPases | CYP4 family |
| 2.1.1.- Protein arginine N-methyltransferases | CYP5, CYP7 and CYP8 families |
| 3.5.1.- Histone deacetylases (HDACs) | CYP11, CYP17, CYP19, CYP20 and CYP21 families |
| Cyclic nucleotide turnover | CYP24, CYP26 and CYP27 families |
| Soluble guanylyl cyclase | CYP39, CYP46 and CYP51 families |
| Exchange protein activated by cyclic AMP (Epac) | CYP39, CYP46 and CYP51 families |
| Phosphodiesterases, 3’,5’-cyclic nucleotide | CYP39, CYP46 and CYP51 families |
| Searchable database: http://www.guidetopharmacology.org/index.jsp |
| Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full | Enzymes | 6027 |
Protein Kinases (EC 2.7.x.x)

Overview: Protein kinases (E.C. 2.7.11.-) use the co-substrate ATP to phosphorylate serine and/or threonine residues on target proteins. Analysis of the human genome suggests the presence of 518 protein kinases in man, with over 100 protein kinase-like pseudogenes [313]. It is beyond the scope of the Concise Guide to list all these protein kinase activities; the full listing may be seen at www.GuideToPHARMACOLOGY.org. 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 [103].

Further Reading

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

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 [269].

| Nomenclature | Rho-associated, coiled-coil containing protein kinase 1 | Rho-associated, coiled-coil containing protein kinase 2 |
|--------------|--------------------------------------------------------|--------------------------------------------------------|
| Systematic nomenclature | ROCK1 | ROCK2 |
| Common abbreviation | Rho kinase 1 | Rho kinase 2 |
| HGNC, UniProt | ROCK1, Q13464 | ROCK2, Q75116 |
| EC number | 2.7.11.1 | 2.7.11.1 |
| Inhibitors | RKI-1447 (pIC50 > 9) [387], Y27632 (pIC50 7.3) [529], fasudil (pKi 7) [403], Y27632 (pKi 6.8) [496], fasudil (pIC50 5.5) [403] | RKI-1447 (pIC50 > 9) [387], compound 11d [DOI: 10.1029/c0md00194e] (pIC50 > 9) [77], GSK269962A (pIC50 8.4) [118], compound 32 [PMID: 20471253] (pIC50 8.4) [45], compound 22 [PMID: 20462760] (pIC50 7.7) [529], Y27632 (pIC50 7.2) [529], Y27632 (pKi 6.8) [496], fasudil (pIC50 5.9) [403] |
| Selective inhibitors | GSK269962A (pIC50 8.8) [118] | – |
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). Members of the classical protein kinase C family are activated by Ca\(^{2+}\) and diacylglycerol, and may be inhibited by GF109203X, calphostin C, GÖ 6983, chelerythrine and Ro31-8220.

Novel protein kinase C isoforms: PKC\(\varepsilon\), PKC\(\eta\), PKC\(\iota\) and PKC\(\lambda\). Members of the classical protein kinase C family are activated by diacylglycerol and may be inhibited by calphostin C, GÖ 6983 and chelerythrine.

Atypical protein kinase C isoforms: PKC\(\alpha\), PKC\(\zeta\).

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 |
|--------------|------------------------|-------------------------|
| Common abreviation | PKC\(\beta\) | PKC\(\gamma\) |
| HGNC, UniProt | PRKCB, P05771 | PRKCG, P05129 |
| EC number | 2.7.11.13 | 2.7.11.13 |
| Inhibitors | sotraustaurin (pIC\(_{50}\) 8.7) [506], GÖ 6983 (pIC\(_{50}\) 8.1) [183], GF109203X (pIC\(_{50}\) 7.8) [490] – Bovine, 7-hydroxytaurosporine (pIC\(_{50}\) 7.5) [431] | GÖ 6983 (pIC\(_{50}\) 8.2) [183], 7-hydroxytaurosporine (pIC\(_{50}\) 7.5) [431] |
| Selective inhibitors | ruboxistaurin (pIC\(_{50}\) 8.2) [238], enzastaurin (pIC\(_{50}\) 7.5) [132], CGP53353 (pIC\(_{50}\) 6.4) [70] | – |

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 |
|--------------|------------------------|------------------------|
| Common abreviation | PKC\(\alpha\) | PKC\(\delta\) |
| HGNC, UniProt | PRKCA, P17252 | PRKCD, Q05655 |
| EC number | 2.7.11.13 | 2.7.11.13 |
| Activators | – | ingenol mebutate (pK\(_i\) 9.4) [252] |
### 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 |
|--------------------|---------------------------|
| Common abreviation | PKCe                      |
| HGNC, UniProt      | PRKCE, Q02156             |
| EC number          | 2.7.11.13                 |
| Inhibitors         | sotrastaurin (pIC50 8.2) [506] |

### FRAP subfamily

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

| Nomenclature                                           | mechanistic target of rapamycin (serine/threonine kinase) |
|--------------------------------------------------------|-----------------------------------------------------------|
| Common abreviation                                     | mTOR                                                      |
| HGNC, UniProt                                          | MTOR, P42345                                             |
| EC number                                              | 2.7.11.1                                                  |
| Inhibitors                                             | ridaforolimus (pIC50 9.7) [408], torin 1 (pIC50 9.5) [291], INK-128 (pIC50 9) [219], INK-128 (pKi 8.9) [219], gedatolisib (pIC50 8.8) [500], dactolisib (pIC50 8.2) [310], PP-242 (pIC50 8.1) [14], PP121 (pIC50 8) [14], XL388 (pIC50 8) [472], PF-04691502 (pKi 7.8) [290], apitolisib (pKi 7.8) [467] |
| Selective inhibitors                                   | everolimus (pIC50 8.7) [427], temsirolimus (pIC50 5.8) [266] |

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### CDK4 subfamily

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

| Nomenclature                  | cyclin-dependent kinase 4 | cyclin-dependent kinase 6 |
|-------------------------------|---------------------------|---------------------------|
| Common abbreviation           | CDK4                      | CDK6                      |
| HGNC, UniProt                 | CDK4, P11802              | CDK6, Q00534              |
| EC number                     | 2.7.11.22                 | 2.7.11.22                 |
| Inhibitors                    | R547 (pKᵢ 9) [107], palbociclib (pIC₅₀ 8) [151], Ro-0505124 (pIC₅₀ 7.7) [115], riviciclib (pIC₅₀ 7.2) [246], alvocidib (pKᵢ 7.2) [64] | palbociclib (pIC₅₀ 7.8) [151] |

### GSK subfamily

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

| Nomenclature                  | glycogen synthase kinase 3 beta |
|-------------------------------|---------------------------------|
| Common abbreviation           | GSK3β                           |
| HGNC, UniProt                 | GSK3β, P49841                   |
| EC number                     | 2.7.11.26                       |
| Inhibitors                    | CHIR-98014 (pIC₅₀ 9.2) [407], LY2090314 (pIC₅₀ 9) [125], CHIR-99021 (pIC₅₀ 8.2) [407], SB 216763 (pIC₅₀ ~8.1) [88], 1-azakenpaullone (pIC₅₀ 7.7) [272], SB-415286 (pIC₅₀ ~7.4) [88], IM-12 (pIC₅₀ 7.3) [424] |
| Selective inhibitors          | AZD2858 (pKᵢ 8.3) [29]          |
| Comments                      | Due to its Tau phosphorylating activity, small molecule inhibitors of GSK-3β are being investigated as potential treatments for Alzheimer’s disease (AD) [29]. 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 [317]. |

**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.13354/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full)
**Polo-like kinase (PLK) family**

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

| Nomenclature               | polo-like kinase 4               |
|---------------------------|----------------------------------|
| Common abbreviation       | PLK4                              |
| HGNC, UniProt             | PLK4, Q00444                      |
| EC number                 | 2.7.11.21                         |
| Inhibitors                | CFI-400945 (pIC\_50 8.6) [320]    |

**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 1 | mitogen-activated protein kinase 2 |
|---------------------------|------------------------------------|-----------------------------------|
| Common abbreviation       | MEK1                                | MEK2                              |
| HGNC, UniProt             | MAP2K1, Q02750                      | MAP2K2, P36507                    |
| EC number                 | 2.7.12.2                            | 2.7.12.2                          |
| Inhibitors                | trametinib (pIC\_50 9–9.1) [173, 336], PD 0325901 (pIC\_50 8.1) [195], binimetinib (pIC\_50 7.9) [382], refametinib (pIC\_50 7.3) [229], CI-1040 (pK\_d 6.9) [105] | trametinib (pIC\_50 8.7) [336], binimetinib (pIC\_50 7.9) [382], refametinib (pIC\_50 7.3) [229] |
Abl family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Abl family

| Nomenclature                      | ABL proto-oncogene 1, non-receptor tyrosine kinase |
|-----------------------------------|---------------------------------------------------|
| Common abbreviation               | Abl                                               |
| HGNC, UniProt                     | ABL1, P00519                                      |
| EC number                         | 2.7.10.2                                          |
| Inhibitors                        | compound 8h (pIC$_{50}$ 9.7) [487], dasatinib (pIC$_{50}$ 9.6) [258], compound 24 (pIC$_{50}$ 9.3) [110], PD-173955 (pIC$_{50}$ 9.2) [103], bosutinib (pIC$_{50}$ 9) [176], PD-173955 (pIC$_{50}$$\sim$8.3) [346], bafe tinib (pIC$_{50}$ 7.6–8.2) [216, 257], ponatinib (pIC$_{50}$ 8.1) [220], nilotinib (pIC$_{50}$ 7.8) [356], PP121 (pIC$_{50}$ 7.7) [14], imatinib (pIC$_{50}$ 6.7) [216], GNF-5 (pIC$_{50}$ 6.7) [549] |

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Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full

Ack family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Ack family

| Nomenclature                      | tyrosine kinase, non-receptor, 2 |
|-----------------------------------|----------------------------------|
| Common abbreviation               | Ack                              |
| HGNC, UniProt                     | TNK2, Q07912                     |
| EC number                         | 2.7.10.2                         |
| Inhibitors                        | compound 30 (pIC$_{50}$ 9) [114] |

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

Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full
### Janus kinase (JakA) family

| Nomenclature | Janus kinase 1 | Janus kinase 2 | Janus kinase 3 | tyrosine kinase 2 |
|--------------|---------------|---------------|---------------|------------------|
| Common abreviation | JAK1 | JAK2 | JAK3 | Tyk2 |
| HGNC, UniProt | JAK1, P23458 | JAK2, O60674 | JAK3, P52333 | TYK2, P29597 |
| EC number | 2.7.10.2 | 2.7.10.2 | 2.7.10.2 | 2.7.10.2 |
| Inhibitors | ruxolitinib (pIC_{50} 8.5–10.1) [191, 395], filgotinib (pIC_{50} 8) [497] | NS-018 (pIC_{50} 9.1) [350], BMS-911543 (pIC_{50} 9) [393], AT-9283 (pIC_{50} 8.9) [218], XL019 (pIC_{50} 8.7) [143], fedratinib (pIC_{50} 8.5) [311, 521], gandotinib (pIC_{50} 8.4) [308] | AT-9283 (pIC_{50} 9) [218] | – |
| Selective inhibitors | – | compound 1d (pIC_{50} >9) [509] | – | – |
| Comments | The JAK2 V617F mutation, which causes constitutive activation, plays an oncogenic role in the pathogenesis of the myeloproliferative disorders, polycythemia vera, essential thrombocytopenia, and idiopathic myelofibrosis [58, 109]. Small molecule compounds which inhibit aberrant JAK2 activity are being developed as novel anti-cancer pharmaceuticals. | – | – |

### 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 |
|--------------|-----------------------------------------------|---------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Common abreviation | Blk | FRK | Fyn | Lyn | Src |
| HGNC, UniProt | BLK, P51451 | FRK, P42685 | FYN, P06241 | LYN, P07948 | SRC, P12931 |
| EC number | 2.7.10.2 | 2.7.10.2 | 2.7.10.2 | 2.7.10.2 | 2.7.10.2 |
### Tec family

**Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Tec family**

| Nomenclature | BMX non-receptor tyrosine kinase | Bruton agammaglobulinemia tyrosine kinase | TXK tyrosine kinase |
|--------------|----------------------------------|------------------------------------------|---------------------|
| Common abreviation | Etk | Btk | TXK |
| HGNC, UniProt | BMX, PS1813 | BTK, Q06187 | TXK, P42681 |
| EC number | 2.7.10.2 | 2.7.10.2 | 2.7.10.2 |
| Inhibitors | - | ibrutinib (pIC$_{50}$ 9.3) [370], compound 31 [PMID: 24915291] (pIC$_{50}$ 8.4) [285], compound 38 [PMID: 24915291] (pIC$_{50}$ >8.4) [285] | - |
| Selective inhibitors | - | CGI1746 (pIC$_{50}$ 8.7) [112] | - |

### RAF family

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

| Nomenclature | B-Raf proto-oncogene, serine/threonine kinase | Raf-1 proto-oncogene, serine/threonine kinase |
|--------------|-----------------------------------------------|-----------------------------------------------|
| Common abreviation | B-Raf | c-Raf |
| HGNC, UniProt | BRAF, P15056 | RAF1, P04049 |
| EC number | 2.7.11.1 | 2.7.11.1 |
Nomenclature: B-Raf proto-oncogene, serine/threonine kinase
Inhibitors: GDC-0879 (pIC_{50} 9.7–9.9) [105, 193], dabrafenib (pIC_{50} 8.5) [277], regorafenib (pIC_{50} 7.6) [545], vemurafenib (pIC_{50} 7) [510], PLX-4720 (pK_{d} 6.5) [105], compound 2 [PMID: 26061392] (pK_{d} 6.3) [215], CHIR-265 (pK_{d} 5.9) [105]
Selective inhibitors: –

Selective inhibitors – GW5074 (pIC_{50} 8.1) [80]

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) 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.-). 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.

A1: Pepsin

Nomenclature: renin
HGNC, UniProt: REN, P00797
EC number: 3.4.23.15
Inhibitors: aliskiren (pIC_{50} 9.2) [532]
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) [249] in the generation of amyloid beta (Aβ) [6, 471]. 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 [177]. 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 [111]. The most active small peptides in this report were P4 [PMID: 25923432] and P8 [PMID: 25923432], from the amino-terminal domain of PS-1.

C14: Caspase

Overview: Caspases, (E.C. 3.4.22.-) which derive their name from Cysteine ASPartate-specific proteASES, include at least two families; initiator caspases (caspases 2, 8, 9 and 10), which are able to hydrolyse and activate a second family of effector caspases (caspases 3, 6 and 7), which themselves are able to hydrolyse further cellular proteins to bring about programmed cell death. Caspases are heterotetrameric, being made up of two pairs of subunits, generated by a single gene product, which is proteolysed to form the mature protein. Members of the mammalian inhibitors of apoptosis proteins (IAP) are able to bind the procaspases, thereby preventing maturation to active proteinases.

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

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 [480].
M2: Angiotensin-converting (ACE and ACE2)

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

| Nomenclature | Angiotensin-converting enzyme |
|--------------|------------------------------|
| Common abreviation | ACE |
| HGNC, UniProt | ACE, P12821 |
| EC number | 3.4.15.1 |
| Endogenous substrates | angiotensin I (AGT, P01019) → angiotensin II (AGT, P01019) |
| Inhibitors | zofenoprilat (pKi 9.4) [270] – Rabbit, captopril (pKi 8.4) [331], zofenopril |
| Selective inhibitors | perindoprilat (pIC50 9) [67], cilazaprilat (pIC50 8.7) [514] – Rabbit, imidaprilat (pIC50 8.7) [409], lisinopril-tryptophan (C-domain assay) (pIC50 8.2) [515], RXP-407 (N-domain selective inhibition) (pIC50 8.1) [434], fosinoprilat (pIC50 8) [106] – Rabbit, enalaprilat (pIC50 7.5) [79], benazeprilat (pIC50 6.6) [282] |
| Comments | Reports of ACE GPI hydrolase activity [265] have been refuted [283] |

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. [501]) on functional and structural bases into gelatinases, collagenases, stromyelinas and matrilysins, as well as membrane type-MMP (MT-MMP).

| Nomenclature | MMP2 |
|--------------|------|
| HGNC, UniProt | MMP2, P08253 |
| EC number | 3.4.24.24 |
| Selective inhibitors | ARP100 [493] |

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)

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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.

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 (ENSG00000235812) and ADAMDEC1 (decysin 1, ENSG00000134028). Other ADAMTS family members include AC14758.12-5 (FLJ00317 protein Fragment ENSG00000231463), AC139425.3-1 (ENSG00000225577), and AC126339.6-1 (ENSG00000225734).

M28: Aminopeptidase Y

Enzymes → Peptidases and proteinases → MH: Metallo (M) Peptidases → M28: Aminopeptidase Y

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

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

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Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full
## M19: Membrane dipeptidase

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

| Nomenclature | Dipeptidase 1 |
|--------------|--------------|
| HGNC, UniProt | DPEP1, P16444 |
| EC number    | 3.4.13.19: LTD₄ + H₂O = LTE₄ + glycine |
| Inhibitors   | cilastatin (pKᵢ 6) [179] – Unknown |

## S1: Chymotrypsin

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

| Nomenclature | complement component 1, r subcomponent |
|--------------|----------------------------------------|
| HGNC, UniProt | C1R, P00736 |
| EC number    | 3.4.21.41 |
| Inhibitors   | nafamostat (pIC₅₀ 4.9) [203] |

| Selective inhibitors | AR-H067637 (pIC₅₀ 8.4) [108] | – |

| Nomenclature | coagulation factor II (thrombin) |
|--------------|----------------------------------|
| HGNC, UniProt | F2, P00734 |
| EC number    | 3.4.21.5 |
| Inhibitors   | lepirudin (pKᵢ 13) [511], desirudin (pKᵢ 12.7) [242], AZ12971554 (pKᵢ 9.5) [16], melagatran (pKᵢ 8.7) [186], bivalirudin (pKᵢ 8.6) [527], dabigatran (pKᵢ 8.3) [198], argatroban (pKᵢ 7.7) [225] |

| Nomenclature | coagulation factor X |
|--------------|----------------------|
| HGNC, UniProt | F10, P00742 |
| EC number    | 3.4.21.6 |
| Inhibitors   | rivaroxaban (pKᵢ 9.4) [380], edoxaban (pKᵢ 9.2) [385], apixaban (pKᵢ 9.1) [528] |

| Nomenclature | elastase, neutrophil expressed |
|--------------|--------------------------------|
| HGNC, UniProt | ELANE, P08246 |
| EC number    | 3.4.21.37 |
| Inhibitors   | alvelestat (pKᵢ 8) [463], sivelestat (pIC₅₀ 7.4) [96] |

Selective inhibitors

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Nomenclature  
HGNC, UniProt  
EC number  
Inhibitors  
Selective inhibitors

| Nomenclature | plasminogen | plasminogen activator, tissue | protease, serine, 1 (trypsin 1) | tryptase alpha/beta 1 |
|--------------|-------------|-------------------------------|----------------------------------|-----------------------|
| HGNC, UniProt| PLG, P00747 | PLAT, P00750                  | PRSS1, P00747                    | TPSAB1, Q15661        |
| EC number    | 3.4.21.7    | 3.4.21.68                     | 3.4.21.4                         | 3.4.21.59             |
| Inhibitors   | aprotinin  | 6-aminocaproic acid           | nafamostat (pIC₅₀ 7.8) [203]     | nafamostat (pIC₅₀ 10) [342] |
|              | (Bovine) (Binding) (pIC₅₀ 6.8) [454], tranexamic acid (Binding) (pIC₅₀ 3.6) [454], 6-aminocaproic acid (Binding) | | |
| Selective inhibitors | – | – | – | gabexate (pIC₅₀ 8.5) [127] |

**T1: Proteasome**

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

**Overview:** The T1 macropain beta subunits form the catalytic proteinase core of the 20S proteasome complex [86]. This catalytic core enables the degradation of peptides with Arg, Phe, Tyr, Leu, and Glu adjacent to the cleavage site. The β5 subunit is the principal target of the approved drug proteasome inhibitor bortezomib.

| Nomenclature | proteasome (prosome, macropain) subunit, beta type, 5 |
|--------------|------------------------------------------------------|
| HGNC, UniProt| PSM85, P28074                                        |
| EC number    | 3.4.25.1                                             |
| Inhibitors   | bortezomib (pIC₅₀ 7.7) [347]                         |
| Selective inhibitors | ixazomib (pKᵯ 9) [273] |

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S8: Subtilisin

Enzymes → Peptidases and proteinases → S8: 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 [297, 416, 462]. 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 [99, 139, 146].

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) [184], linagliptin (pKᵢ 9) [122], sitagliptin (pIC₅₀ 8.1) [104], vildagliptin (pKᵢ 7.8) [184]

Acetylcholine turnover

Enzymes → Acetylcholine turnover

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

| choline O-acetyltransferase | acetylcholinesterase (Yt blood group) | butyrylcholinesterase |
|---------------------------|--------------------------------------|-----------------------|
| ChAT                      | ACHE                                 | BCHE                  |
| HGNC, UniProt             | ACHE, P22303                         | BCHE, P06276          |

### EC number

- **2.3.1.6:** acetyl CoA + choline = acetylcholine + coenzyme A
- **3.1.1.7:** acetylcholine + H₂O = acetic acid + choline + H⁺
- **3.1.1.7:** acetylcholine + H₂O = acetic acid + choline + H⁺

### Inhibitors

- **(Sub)family-selective inhibitors**
  - *phystostigmine* (pIC₅₀ 7.6–7.8) [305]
- **Selective inhibitors**
  - *donepezil* (pIC₅₀ 7.7–8.3) [62, 160, 305], BW284C51 (pIC₅₀ 7.7) [172]
- *bambuterol* (pIC₅₀ 8.5) [172]

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### Comments

- Splice variants of choline O-acetyltransferase are suggested to be differentially distributed in the periphery and CNS (see [28]).
- 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 [505].
Adenosine turnover

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

| Nomenclature | Adenosine deaminase | Adenosine kinase | Ecto-5'-Nucleotidase | S-Adenosylhomocysteine hydrolase |
|--------------|---------------------|------------------|----------------------|---------------------------------|
| Common abbreviation | ADA | ADK | NT5E | SAHH |
| HGNC, UniProt | ADA, P00813 | ADK, P55263 | NT5E, P21589 | AHCY, P23526 |
| EC number | 3.5.4.4: adenosine + H2O = inosine + NH3 | 2.7.1.20 | 3.1.3.5 | 3.3.1.1 |
| Endogenous substrates | – | – | – | S-adenosylhomocysteine |
| Rank order of affinity | 2'-deoxyadenosine -> adenosine | adenosine | adenosine 5'-monophosphate, 5'-GMP, 5'-inosine monophosphate, 5'-UMP > 5'-dAMP, 5'-dGMP | – |
| Products | 2'-deoxyinosine, inosine | adenosine 5'-monophosphate | uridine, inosine, guanine, adenosine | adenosine |
| Inhibitors | – | pentostatin (pIC50 10.8) [3], EHNA (pK1 8.8) [3] | A134974 (pIC50 10.2) [325], ABT702 (pIC50 8.8) [236] | 3-deazaadenosine (pIC50 8.5) [185] |
| Selective inhibitors | – | – | αβ-methyleneADP (pIC50 8.7) [50] | DZNep (pK1 12.3) [174] – Hamster |

Comments: An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, CECRI, Q9NZK5) has been identified [94, 309], which is insensitive to EHNA [546]. 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, K88DSRB, Interferon-inducible protein 4); ADARB1 (EC 3.5.4.-. , also known as dsRNA adenosine deaminase) and ADARB2 (EC 3.5.4.-. , 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 [248].

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Amino acid hydroxylases

**Enzymes → Amino acid hydroxylases**

**Overview:** The amino acid hydroxylases (monooxygenases), EC.1.14.16.-, are iron-containing enzymes which utilise molecular oxygen and sapropterin as co-substrate and co-factor, respectively. In humans, as well as in other mammals, there are two distinct L-Tryptophan hydroxylase 2 genes. In humans, these genes are located on chromosomes 11 and 12 and encode two different homologous enzymes, TPH1 and TPH2.

| Nomenclature | L-Phenylalanine hydroxylase | L-Tyrosine hydroxylase | L-Tryptophan hydroxylase 1 | L-Tryptophan hydroxylase 2 |
|--------------|-----------------------------|------------------------|-----------------------------|-----------------------------|
| HGNC, UniProt| PAH, P00439                 | TH, P07101              | TPH1, P17752                 | TPH2, Q8IWU9                 |
| EC number   | 1.14.16.1: L-phenylalanine + O2 -> L-tyrosine | 1.14.16.2: L-tyrosine + O2 -> levodopa | 1.14.16.4 | 1.14.16.4 |
| Endogenous activators | Protein kinase A-mediated phosphorylation (Rat) [1] | Protein kinase A-mediated phosphorylation [239] | Protein kinase A-mediated phosphorylation [240] | Protein kinase A-mediated phosphorylation [240] |
| Endogenous substrates | L-phenylalanine | L-tyrosine | L-tryptophan | L-tryptophan |
| Products | L-tyrosine | levodopa | 5-hydroxy-L-tryptophan | 5-hydroxy-L-tryptophan |
| Cofactors | sapropterin | sapropterin, Fe^{2+} | – | – |
| Selective activators | sapropterin (pK_{i} 5.4) [481] | – | – | – |
| Inhibitors | – | methyltyrosine | – | – |
| Selective inhibitors | α-methylphenylalanine [180] – Rat, fenclonine | α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine | α-propyldopacetamide, 6-fluorotryptophan [352], fenclonine, fenfluramine | α-propyldopacetamide, 6-fluorotryptophan [352], fenclonine, fenfluramine |
| Comments | PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monoxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria | TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [102]. | – | – |

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L-Arginine turnover

Overview: L-Arginine is a basic amino acid with a guanido 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},N\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.

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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.

Comments: N⁶-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 N⁶-hydroxy-nor-L-arginine [483], S-(2-boronoethyl)-L-cysteine [90, 256] and 2(S)-amino-6-boronohexanoic acid [22, 90].

Arginine:glycine amidinotransferase

Enzymes → L-Arginine turnover → Arginine:glycine amidinotransferase

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

Dimethylarginine dimethylaminohydrolases

Enzymes → L-Arginine turnover → Dimethylarginine dimethylaminohydrolases

Overview: Dimethylarginine dimethylaminohydrolases (DDAH, EC 3.5.3.18) are cytoplasmic enzymes which hydrolyse N⁵⁷,N⁷⁷-dimethyl-L-arginine to form dimethylamine and L-citrulline.

| Nomenclature | N⁵⁷,N⁷⁷-Dimethylarginine dimethylaminohydrolase 1 | N⁵⁷,N⁷⁷-Dimethylarginine dimethylaminohydrolase 2 |
|---------------|---------------------------------|---------------------------------|
| Common abreviation | DDAH1 | DDAH2 |
| HGNC, UniProt | DDAH1, O94760 | DDAH2, O95865 |
| EC number | 3.5.3.18 | 3.5.3.18 |
| Cofactors | Zn²⁺ | – |
Nitric oxide synthases

Overview: Nitric oxide synthases (NOS, E.C. 1.14.13.39) utilise L-arginine (not D-arginine) and molecular oxygen to generate nitric oxide and L-citrulline. The nomenclature suggested by NC-IUPHAR of NOS I, II and III [340] has not gained wide acceptance. 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) and thus appears to be constitutively active. All the three isoforms are homodimers and require sapropterin, flavin adenine dinucleotide, flavin mononucleotide and NADPH for catalytic activity. L-NAME is an inhibitor of all three isoforms, with an IC\(_{50}\) value in the micromolar range.

| Nomenclature       | Endothelial NOS | Inducible NOS | Neuronal NOS |
|--------------------|-----------------|---------------|--------------|
| Common abreviation | eNOS            | iNOS          | nNOS         |
| HGNC, UniProt      | NOS3, P29474    | NOS2, P35228  | NOS1, P29475 |
| EC number          | 1.14.13.39      | 1.14.13.39    | 1.14.13.39   |
| Inhibitors         | –               | –             | N\(^{6}\)-propyl-L-arginine (pK\(_i\) 7.2) [548] – Rat |
| Selective inhibitors | –             | 1400W (pIC\(_{50}\) 8.2) [168], 2-amino-4-methylpyridine (pIC\(_{50}\) 7.4) [31], PIBTU (pIC\(_{50}\) 7.3) [169], NIL (pIC\(_{50}\) 5.5) [341], aminoguanidine [92] | 3-bromo-7NI (pIC\(_{50}\) 6.1–6.5) [40], 7NI (pIC\(_{50}\) 5.3) [19] |

Comments: The reductase domain of NOS catalyses the reduction of cytochrome c and other redox-active dyes [322]. NADPH:O\(_2\) oxidoreductase catalyses the formation of superoxide anion/H\(_2\)O\(_2\) in the absence of L-arginine and sapropterin.

Carboxylases and decarboxylases

Enzymes → Carboxylases and decarboxylases

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## Carboxylases

### Enzymes → Carboxylases and decarboxylases → Carboxylases

**Overview:** The carboxylases allow the production of new carbon-carbon bonds by introducing $\text{HCO}_3^-$ or $\text{CO}_2$ into target molecules. Two groups of carboxylase activities, some of which are bidirectional, can be defined on the basis of the cofactor requirement, making use of biotin (EC 6.4.1.-) or vitamin K hydroquinone (EC 4.1.1.-).

| Nomenclature                  | Pyruvate carboxylase | Acetyl-CoA carboxylase 1 | Acetyl-CoA carboxylase 2 |
|-------------------------------|----------------------|--------------------------|--------------------------|
| Common abbreviation           | PC                   | ACC1                     | ACC2                     |
| HGNC, UniProt                 | PC, P11498           | ACACA, Q13085            | ACACB, O00763            |
| EC number                     | 6.4.1.1              | 6.4.1.2                  | 6.4.1.2                  |
| Endogenous substrates         | ATP, pyruvic acid    | ATP, acetyl CoA          | acetyl CoA, ATP          |
| Products                      | $P_i$, adenosine diphosphate, oxalacetic acid | $P_i$, adenosine diphosphate, malonyl-CoA | $P_i$, adenosine diphosphate, malonyl-CoA |
| Cofactors                     | biotin               | biotin                   | biotin                   |
| Selective inhibitors          | –                    | TOFA [294]               | TOFA [294]               |
| Comments                      | –                    | Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase. | Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase. |

### Propionyl-CoA carboxylase

| Nomenclature                  | Propionyl-CoA carboxylase | γ-Glutamyl carboxylase |
|-------------------------------|----------------------------|------------------------|
| Common abbreviation           | PCCA, PCCB                | GGCX                   |
| HGNC, UniProt                 | PCCA, P05165              | GGCX, P38435           |
| Subunits                      | Propionyl-CoA carboxylase $\alpha$ subunit | Propionyl-CoA carboxylase $\beta$ subunit |
| EC number                     | 6.4.1.3                   | 4.1.1.90               |
| Endogenous substrates         | propionyl-CoA, ATP        | glutamyl peptides      |
| Products                      | adenosine diphosphate, methylmalonyl-CoA, $P_i$ | carboxyglutamyl peptides |
| Cofactors                     | biotin                    | vitamin K hydroquinone, NADPH |

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Decarboxylases

**Decarboxylases**

Enzymes → Carboxylases and decarboxylases → Decarboxylases

**Overview:** The decarboxylases generate CO₂ and the indicated products from acidic substrates, requiring pyridoxal phosphate or pyruvic acid as a co-factor.

| Nomenclature       | S-Adenosylmethionine decarboxylase | L-Arginine decarboxylase | L-Aromatic amino-acid decarboxylase | Glutamic acid decarboxylase 1 | Glutamic acid decarboxylase 2 |
|--------------------|------------------------------------|--------------------------|-------------------------------------|-------------------------------|--------------------------------|
| Common abbreviation| SAMDC                              | ADC                      | AADC                                | GAD1                          | GAD2                           |
| HGNC, UniProt      | AMD1, P17707                       | AZIN2, Q96A70            | DDC, P20711                          | GAD1, Q99259                  | GAD2, Q05329                   |
| EC number          | 4.1.1.50                           | 4.1.1.19                 | 4.1.1.28: levodopa → dopamine + CO₂ | 4.1.1.15: L-glutamic acid + H⁺ → GABA + CO₂ | 4.1.1.15: L-glutamic acid + H⁺ → GABA + CO₂ |
| Substrates         | –                                  | –                        | Deuterium-substituted L-DOPA [312] | –                             | –                              |
| Endogenous substrates | S-adenosyl methionine               | L-arginine               | L-glutamic acid, L-aspartic acid     | L-glutamic acid, L-aspartic acid | L-glutamic acid, L-aspartic acid |

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.
**Nomenclature**

| Nomenclature                                      | Enzyme Name                  |
|---------------------------------------------------|------------------------------|
| S-Adenosylmethionine decarboxylase                | S-Adenosylmethionine decarboxylase |
| L-Arginine decarboxylase                          | L-Arginine decarboxylase      |
| L-Aromatic amino-acid decarboxylase 1             | Glutamic acid decarboxylase 1 |
| Glutamic acid decarboxylase 2                     | Glutamic acid decarboxylase 2 |

**Products**

| Product                                          | Enzyme Name                  |
|--------------------------------------------------|------------------------------|
| S-adenosyl-L-argininamine                        | S-adenosyl-L-argininamine    |
| agmatine [552]                                   | agmatine [552]               |
| 5-hydroxytryptamine, dopamine                    | 5-hydroxytryptamine, dopamine |
| GABA                                             | GABA                         |

**Cofactors**

| Cofactor                                         | Enzyme Name                  |
|--------------------------------------------------|------------------------------|
| pyruvic acid                                     | pyruvic acid                 |
| pyridoxal phosphate                              | pyridoxal phosphate          |
| pyridoxal phosphate                              | pyridoxal phosphate          |
| pyridoxal phosphate                              | pyridoxal phosphate          |
| pyridoxal phosphate                              | pyridoxal phosphate          |
| 3-hydroxybenzylhydrazine, L-α-methyldopa, benserazide [101], carbidopa | 3-hydroxybenzylhydrazine, L-α-methyldopa, benserazide [101], carbidopa |

**Selective inhibitors**

| Inhibitor                                         | Enzyme Name                  |
|---------------------------------------------------|------------------------------|
| sardomozide (pIC₅₀ 8) [455]                       | sardomozide (pIC₅₀ 8) [455]  |
| –                                                 | –                            |
| –                                                 | –                            |
| –                                                 | –                            |

**Comments**

- s-allylglycine is also an inhibitor of SAMDC [368].
- The presence of a functional ADC activity in human tissues has been questioned [89].
- AADC is a homodimer.
- L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [530]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading).
- L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [530]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading).

**Nomenclature**

| Nomenclature                                      | Enzyme Name                  |
|---------------------------------------------------|------------------------------|
| Histidine decarboxylase                           | Histidine decarboxylase      |
| Malonyl-CoA decarboxylase                         | Malonyl-CoA decarboxylase    |
| Ornithine decarboxylase                           | Ornithine decarboxylase      |
| Phosphatidylyserine decarboxylase                 | Phosphatidylyserine decarboxylase |

**Common abbreviation**

| Common abbreviation                              | Enzyme Name                  |
|---------------------------------------------------|------------------------------|
| HDC                                               | HDC                          |
| MLYCD                                             | MLYCD                        |
| ODC                                               | ODC                          |
| PISD                                              | PISD                         |

**HGNC, UniProt**

| HGNC, UniProt                                     | Enzyme Name                  |
|---------------------------------------------------|------------------------------|
| HDC, P19113                                       | HDC                          |
| MLYCD, O95822                                     | MLYCD                        |
| ODC1, P11926                                      | ODC1                        |
| PISD, Q9UG56                                      | PISD                         |

**EC number**

| EC number                                         | Enzyme Name                  |
|---------------------------------------------------|------------------------------|
| 4.1.1.22                                          | 4.1.1.22                     |
| 4.1.1.17                                          | 4.1.1.17                     |
| 4.1.1.9                                           | 4.1.1.9                      |
| 4.1.1.65                                          | 4.1.1.65                     |

**Endogenous substrates**

| Endogenous substrates                             | Enzyme Name                  |
|---------------------------------------------------|------------------------------|
| L-histidine                                       | L-histidine                  |
| malonyl-CoA                                       | malonyl-CoA                  |
| L-ornithine                                       | L-ornithine                  |

**Products**

| Product                                          | Enzyme Name                  |
|--------------------------------------------------|------------------------------|
| histamine                                        | histamine                    |
| acetyl CoA                                        | acetyl CoA                   |
| putrescine                                        | putrescine                   |
| pyridoxal phosphate                              | pyridoxal phosphate          |
| pyridoxal phosphate                              | pyridoxal phosphate          |
| phosphatidylethanolamine                         | phosphatidylethanolamine     |

**Cofactors**

| Cofactor                                         | Enzyme Name                  |
|--------------------------------------------------|------------------------------|
| pyridoxal phosphate                              | pyridoxal phosphate          |
| pyridoxal phosphate                              | pyridoxal phosphate          |
| pyridoxal phosphate                              | pyridoxal phosphate          |
| pyruvic acid                                     | pyruvic acid                 |

**Selective inhibitors**

| Inhibitor                                         | Enzyme Name                  |
|---------------------------------------------------|------------------------------|
| AMA, FMH [164]                                    | AMA, FMH [164]               |
| APA (pIC₅₀ 7.5) [456], eflorentine (pKᵢ 4.9) [394]| APA (pIC₅₀ 7.5) [456], eflorentine (pKᵢ 4.9) [394] |

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Further Reading

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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]

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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 or methylation via catechol O-methyltransferase.

Catecholamine turnover

Enzymes → Catecholamine turnover

Nomenclature

| Enzyme | Nomenclature | Comments |
|--------|-------------|---------|
| Histidine decarboxylase | Inhibited by AMP-activated protein kinase-evoked phosphorylation [415] |
| Malonyl-CoA decarboxylase | |
| Ornithine decarboxylase | The activity of ODC is regulated by the presence of an antizyme (ENSG00000104904) and an ODC antizyme inhibitor (ENSG00000155096). |
| Phosphatidyserine decarboxylase | S-allylglycine is also an inhibitor of SAMDC [368]. |

Nomenclature

| Enzyme | Nomenclature | Common abreviation | HGNC, UniProt |
|--------|-------------|-------------------|--------------|
| L-Phenylalanine hydroxylase | | | PAH, P00439 |
| Tyrosine aminotransferase | TAT | TAT, P17735 |
| L-Aromatic amino-acid decarboxylase | AADC | DDC, P20711 |

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### L-Phenylalanine hydroxylase

| Nomenclature | Tyrosine aminotransferase | L-Aromatic amino-acid decarboxylase |
|--------------|---------------------------|------------------------------------|
| 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 |
| Endogenous activators | Protein kinase A-mediated phosphorylation (Rat) [1] | – |
| Substrates   | – | – |
| Endogenous substrates | L-phenylalanine | – |
| Products     | L-tyrosine | – |
| Cofactors    | sapropterin | pyridoxal phosphate |
| Selective activators | sapropterin (pKᵢ 5.4) [481] | – |
| Selective inhibitors | α-methylphenylalanine [180] – Rat, fenclonine | – |
| Comments     | PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monoxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria | Tyrosine may also be metabolized in the liver by tyrosine transaminase to generate 4-hydroxyphenylpyruvic acid, which can be further metabolized to homogentisic acid. TAT is a homodimer, where loss-of-function mutations are associated with type II tyrosinemia. AADC is a homodimer. |

### L-Tyrosine hydroxylase

| Nomenclature | Dopamine beta-hydroxylase | Phenylethanolamine N-methyltransferase |
|--------------|---------------------------|--------------------------------------|
| Common abreviation | – | DBH (dopamine beta-monoxygenase) |
| HGNC, UniProt | TH, P07101 | DBH, P09712 |
| EC number | 1.14.16.2: L-tyrosine + O₂ → levodopa | 1.14.17.1: dopamine + O₂ = (-)-noradrenaline + H₂O |
| Endogenous activators | Protein kinase A-mediated phosphorylation [239] | – |
| Substrates   | L-tyrosine | – |
| Products     | levodopa | – |
| Cofactors    | sapropterin, Fe²⁺ | Cu²⁺, L-ascorbic acid |
| Comments     | – | S-adenosyl methionine |

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### Nomenclature

| Enzyme | L-Tyrosine hydroxylase | Dopamine beta-hydroxylase (dopamine beta-monoxygenase) | Phenylethanolamine N-methyltransferase |
|--------|------------------------|------------------------------------------------------|---------------------------------------|

### Inhibitors

- **methyltyrosine**
- **nepicastat** (pIC\(_{50}\) 8) [458]
- **LY134046** (pK\(_{i}\) 7.6) [154]

### Selective inhibitors

- **α-propyldopacetamide**, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine

### Comments

- TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [102].
- DBH is a homotetramer. A protein structurally-related to DBH (MOXD1, Q6UVY6) has been described and for which a function has yet to be identified [71].

### Nomenclature

| Enzyme | Monoamine oxidase A | Monoamine oxidase B | Catechol-O-methyltransferase |
|--------|---------------------|---------------------|-----------------------------|

#### Common abbreviation

- MAO-A
- MAO-B
- COMT

#### HGNC, UniProt

- MAOA, P21397
- MAOB, P27338
- COMT, P21964

#### EC number

- 1.4.3.4 (-)-adrenaline
- 3,4-dihydroxymandelic acid + NH\(_3\)
- (-)-noradrenaline
- 3,4-dihydroxymandelic acid + NH\(_3\)
- tyramine
- 4-hydroxyphenyl acetaldehyde + NH\(_3\)
- dopamine
- 3,4-dihydroxyphenylacetaldehyde + NH\(_3\)
- S-hydroxytryptamine ->
- S-hydroxyindole acetaldehyde + NH\(_3\)

#### Cofactors

- flavin adenine dinucleotide
- rasagiline (pIC\(_{50}\) 7.8) [542], phenelzine (Irreversible inhibition) (pK\(_{i}\) 7.3) [36], lazabemide (pK\(_{i}\) 7.1) [188, 489], selegiline (pK\(_{i}\) 5.7–6) [113, 333], tranylcypromine (pIC\(_{50}\) 4.7) [538]
- safinamide (pK\(_{i}\) 6.3) [35]
- S-adenosyl methionine
- tolcapone (soluble enzyme) (pK\(_{i}\) 9.6) [299], tolcapone (membrane-bound enzyme) (pK\(_{i}\) 9.5) [299], entacapone (soluble enzyme) (pK\(_{i}\) 9.5) [299], entacapone (membrane-bound enzyme) (pK\(_{i}\) 8.7) [299]

#### Inhibitors

- moclobemide (pK\(_{i}\) 8.3) [234], phenelzine (Irreversible inhibition) (pK\(_{i}\) 7.3) [36], tranylcypromine (pIC\(_{50}\) 4.7) [538], selegiline (pK\(_{i}\) 4.2) [333], benzofloxetine [100], clorgiline, pirlindole [327]
- safinamide (pK\(_{i}\) 6.3) [35]
- tolcapone (soluble enzyme) (pK\(_{i}\) 9.6) [299], tolcapone (membrane-bound enzyme) (pK\(_{i}\) 9.5) [299], entacapone (soluble enzyme) (pK\(_{i}\) 9.5) [299], entacapone (membrane-bound enzyme) (pK\(_{i}\) 8.7) [299]

#### Selective inhibitors

- –

#### Comments

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

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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 galactosyl ceramides. 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

**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 [190]. Complexes involving SPT3 appeared more broad in substrate selectivity, with incorporation of myristoylCoA prominent for SPT1/SPT3/ssSPTa complexes, while SP1/SPT3/ssSPTb complexes had similar activity with C16, C18 and C20 acylCoAs [190].

| Nomenclature                        | serine palmitoyltransferase, long chain base subunit 1 | serine palmitoyltransferase, long chain base subunit 2 | serine palmitoyltransferase, long chain base subunit 3 | serine palmitoyltransferase, small subunit A | serine palmitoyltransferase, small subunit B |
|-------------------------------------|-------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------|---------------------------------------------|---------------------------------------------|
| Common abbreviation                 | SPT1                                                  | SPT2                                                  | SPT3                                                  | SPTSSA                                       | SPTSSB                                       |
| HGNC, UniProt                       | SPTLC1, O15269                                        | SPTLC2, O15270                                        | SPTLC3, Q9NUV7                                        | SPTSSA, Q969W0                               | SPTSSB, Q8NFR3                               |

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Ceramide synthase

Enzymes → Ceramide turnover → Ceramide synthase

Overview: This family of enzymes, also known as sphingosine N-acyltransferase, is located in the ER facing the cytosol with an as-yet undefined topology and stoichiometry. Ceramide synthase in vitro is sensitive to inhibition by the fungal derived toxin, fumonisnin B1.
### Ceramide synthase 4 (CERS4)
- **Abbreviation:** CERS4
- **HGNC, UniProt:** CERS4, Q9HA82
- **EC Number:** 2.3.1.24: acylCoA + sphinganine → dihydroceramide + coenzyme A
- **Substrates:** C18-, C20- and C22-CoA

### Ceramide synthase 5 (CERS5)
- **Abbreviation:** CERS5
- **HGNC, UniProt:** CERS5, Q8N5B7
- **EC Number:** 2.3.1.24: acylCoA + sphinganine → dihydroceramide + coenzyme A
- **Substrates:** C16-CoA

### Ceramide synthase 6 (CERS6)
- **Abbreviation:** CERS6
- **HGNC, UniProt:** CERS6, Q6ZMG9
- **EC Number:** 2.3.1.24: acylCoA + sphinganine → dihydroceramide + coenzyme A
- **Substrates:** C14- and C16-CoA

### Sphingolipid Δ^4^-desaturase

**Enzymes** → **Ceramide turnover** → **Sphingolipid Δ^4^-desaturase**

**Overview:** DEGS1 and DEGS2 are 4TM proteins.

| Nomenclature       | Delta(4)-desaturase, sphingolipid 1 | Delta(4)-desaturase, sphingolipid 2 |
|--------------------|------------------------------------|-------------------------------------|
| HGNC, UniProt      | DEGS1, O15121                      | DEGS2, Q6QHCS                       |
| EC Number          | 1.14.14                           | 1.14.14                             |
| Cofactors          | NAD                               | NAD                                |
| Comments           | Myristoylation of DEGS1 enhances its activity and targets it to the mitochondria [26]. | –                                    |

**Comments:** DEGS1 activity is inhibited by a number of natural products, including curcumin and Δ^9^-tetrahydrocannabinol [130].

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**Sphingomyelin synthase**

*Enzymes → Ceramide turnover → Sphingomyelin synthase*

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

| Nomenclature | sphingomyelin synthase 1 | sphingomyelin synthase 2 | sterile alpha motif domain containing 8 |
|--------------|--------------------------|--------------------------|----------------------------------------|
| HGNC, UniProt| SGMS1, Q86VZ5            | SGMS2, Q8NHU3             | SAMD8, Q96LT4                           |
| EC number    | 2.7.8.27: ceramide + phosphatidylcholine - sphingomyelin + diacylglycerol | 2.7.8.27: ceramide + phosphatidylcholine - sphingomyelin + diacylglycerol | 2.7.8.-: ceramide + phosphatidylethanolamine - ceramide phosphoethanolamine |
| Comments     | –                        | Palmitoylation of sphingomyelin synthase 2 may allow targeting to the plasma membrane [476]. | –|

**Sphingomyelin phosphodiesterase**

*Enzymes → Ceramide turnover → Sphingomyelin phosphodiesterase*

**Overview:** Also known as sphingomyelinase.

| Nomenclature | sphingomyelin phosphodiesterase 1, acid lysosomal | sphingomyelin phosphodiesterase 2, neutral membrane (neutral sphingomyelinase) | sphingomyelin phosphodiesterase 3, neutral membrane (neutral sphingomyelinase II) |
|--------------|---------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| HGNC, UniProt| SMPD1, P17405                                      | SMPD2, O60906                                                               | SMPD3, Q9NY59                                                               |
| EC number    | 3.1.4.12: sphingomyelin -&gt; ceramide + phosphocholine | 3.1.4.12: sphingomyelin -&gt; ceramide + phosphocholine                     | 3.1.4.12: sphingomyelin -&gt; ceramide + phosphocholine                     |

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Neutral sphingomyelinase coupling factors

**Overview:** Protein FAN [2] and polycomb protein EED [383] allow coupling between TNF receptors and neutral sphingomyelinase phosphodiesterases.

Ceramide glucosyltransferase

**Overview:** 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

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 (acid ceramidase) 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 [261]. |

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 (non-lysosomal ceramidase) 2 | N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 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 [475].     |                                                            |

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 [466]. | ACER2 is associated with the Golgi apparatus [534]. | ACER3 is associated with the ER and Golgi apparatus [314]. |

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 + adenosine diphosphate |
| Inhibitors   | NVP 231 (pIC50 7.9) [178] |

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

Further Reading

Castro BM et al. (2014) Ceramide: a simple sphingolipid with unique biophysical properties. Prog. Lipid Res. 54: 53-67 [PMID:24513486]
Halmer R et al. (2014) Sphingolipids: important players in multiple sclerosis. Cell. Physiol. Biochem. 34: 111-8 [PMID:24977485]
Ito M et al. (2014) New insight into the structure, reaction mechanism, and biological functions of neutral ceramidase. Biochim. Biophys. Acta 1841: 682-91 [PMID:24064302]
Khavandgar Z et al. (2015) Sphingolipid metabolism and its role in the skeletal tissues. Cell. Mol. Life Sci. 72: 959-69 [PMID:25424644]
Lowther J et al. (2012) Structural, mechanistic and regulatory studies of serine palmitoyltransferase. Biochem. Soc. Trans. 40: 547-54 [PMID:22616865]
Saied EM et al. (2014) Small molecule inhibitors of ceramidases. Cell. Physiol. Biochem. 34: 197-212 [PMID:24977492]
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 [267]. 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 deamination. Chromatin modifications and the functions they regulate in cells are reviewed by Kouzarides (2007) [267].

Writers 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 [129], where a wide variety of cellular and protein abberations are known to perturb chromatin structure, gene transcription and ultimately cellular pathways [24, 439]. Due to the reversible nature of epigenetic modifications, chromatin regulatory targets 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 [165, 520]) and erasers (e.g. the HDAC inhibitors vorinostat, romidepsin and belinostat for the treatment of T-cell lymphomas [144, 254]) 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 [56]. Current progress in this field is reviewed by Simó-Rúdabalas and Esteller (2015) [440].

### 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 dimethylated products; these may be symmetric (SDMA) or asymmetric (N<sup>G</sup>,N<sup>G</sup>-dimethyl-L-arginine) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.

### 3.5.1.- Histone deacetylases (HDACs)

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

The histone deacetylase family has been classified in to five subfamilies based on phylogenetic comparison with yeast homologues:
- Class I contains HDACs 1, 2, 3 and 8
- Class IIa contains HDACs 4, 5, 7 and 9
- Class IIb contains HDACs 6 and 10
- Class III contains the sirtuins (SIRT1-7)
- Class IV contains only HDAC11.

Class I, II and IV use Zn<sup>2+</sup> as a co-factor, whereas catalysis by Class III enzymes requires NAD<sup>+</sup> as a co-factor, and members of this subfamily have ADP-ribose lyase activity in addition to protein deacetylase function [420]. HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [82] such as microtubules [221], the hsp90 chaperone [268] and the tumour suppressor p53 [302].

Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [288, 410], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [522]. Several small molecule HDAC inhibitors are already approved for clinical use: romidepsin, belinostat, vorinostat, panobinostat, belinostat, valproic acid and chidamide. HDACs and HDAC inhibitors currently in development as potential anti-cancer therapeutics are reviewed by Simó-Rúdabalas and Esteller (2015) [440].
Cyclic nucleotide turnover

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

Overview: Adenylyl cyclase, E.C. 4.6.1.1, converts ATP to cyclic AMP and pyrophosphate. Mammalian membrane-bound adenylyl cyclases are typically made up of two clusters of six TM domains separating two intracellular, overlapping catalytic domains that are the target for the nonselective activators forskolin, NKH477 (except AC9, [302]) and Gαs (the stimulatory G protein α subunit). Adenosine and its derivatives (e.g., 2',5'-dideoxyadenosine), acting through the P-site, appear to be physiological inhibitors of adenylyl cyclase activity [485]. Three families of adenylyl cyclase are distinguishable: calmodulin (CALM1, CALM2, CALM3, P62158)-stimulated (AC1, AC3 and AC8), Ca2+-inhibitable (AC5, AC6 and AC9) and Ca2+-insensitive (AC2, AC4 and AC7) forms.

| Nomenclature | AC1 | AC2 | AC3 | AC4 | AC5 |
|--------------|-----|-----|-----|-----|-----|
| HGNC, UniProt | ADCY1, Q08828 | ADCY2, Q08462 | ADCY3, Q60266 | ADCY4, Q8NFM4 | ADCY5, Q95622 |
| EC number | 4.6.1.1 | 4.6.1.1 | 4.6.1.1 | 4.6.1.1 | 4.6.1.1 |
| Endogenous activators | calmodulin (CALM1, CALM2, CALM3, P62158), PKC-evoked phosphorylation [233, 478] | Gβγ, PKC-evoked phosphorylation [73, 306, 478] | calmodulin (CALM1, CALM2, CALM3, P62158), PKC-evoked phosphorylation [81, 233] | Gβγ [163] | PKC-evoked phosphorylation [250] |
| Endogenous inhibitors | Gαi, Gαo, Gβγ [478, 479] | – | Gαi, RGS2, CaM kinase II-evoked phosphorylation [441, 479, 517] | PKC-evoked phosphorylation [554] | Gαi, Ca2+, PKA-evoked phosphorylation [227, 230, 479] |
| Selective inhibitors | – | – | – | – | NKY80 [364] |

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### Comments

Nitric oxide has been proposed to inhibit AC5 and AC6 selectively [210], although it is unclear whether this phenomenon is of physiological significance. A soluble adenylyl cyclase has been described (ADCY10, Q96PN6 [48]), unaffected by either G\alpha or G\beta\gamma subunits, which has been suggested to be a cytoplasmic bicarbonate (pH-insensitive) sensor [75]. It can be inhibited selectively by KH7 (pIC50 5.0-5.5) [208].

### Soluble guanylyl cyclase

**Overview:** Soluble guanylyl cyclase (GTP diphosphate-lyase (cyclising)), E.C. 4.6.1.2, is a heterodimer comprising \( \alpha \) and \( \beta \) chains, both of which have two subtypes in man (predominantly \( \alpha 1\beta 1 \); [544]). A haem group is associated with the \( \beta \) chain and is the target for the endogenous ligand nitric oxide (NO\( \alpha \)), and, potentially, carbon monoxide [150]. The enzyme converts guanosine-5'-triposphate to the intracellular second messenger 3',5'-guanosine monophosphate (cyclic GMP).
Subunits

| Nomenclature | α 1 subunit | α 2 subunit | β 1 subunit | β 2 subunit |
|--------------|-------------|-------------|-------------|-------------|
| HGNC, UniProt | GUCY1A3, Q02108 | GUCY1A2, P33402 | GUCY183, Q02153 | GUCY182, Q75343 |

Comments: ODQ also shows activity at other haem-containing proteins [134], while YC1 may also inhibit cGMP-hydrolysing phosphodiesterases [149, 159].

Exchange protein activated by cyclic AMP (Epac)

Enzymes → Cyclic nucleotide turnover → Exchange protein activated by cyclic AMP (Epac)

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, Q9UHV3). They are activated endogenously by cyclic AMP and with some pharmacological selectivity by 8-pCPT-2'-O-Me-cAMP [126]. 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 [423].

| Nomenclature | Epac1 | Epac2 |
|--------------|------|------|
| HGNC, UniProt | RAPGEF3, O95398 | RAPGEF4, Q8WZA2 |
| Inhibitors   | –    | HJC 0350 (pIC_{50} 6.5) [72], ESI-09 (pIC_{50} 4.4) [11] |
Phosphodiesterases, 3′,5′-cyclic nucleotide

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 | PDE1A | PDE1B | PDE1C |
|--------------|-------|-------|-------|
| HGNC, UniProt| PDE1A, P54750 | PDE1B, Q01064 | PDE1C, Q14123 |
| EC number    | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 |
| Rank order of affinity | cyclic GMP >> cyclic AMP | cyclic GMP >> cyclic AMP | cyclic GMP = cyclic AMP |
| Endogenous activators | calmodulin (CALM1 CALM2 CALM3, P62158) | calmodulin (CALM1 CALM2 CALM3, P62158) | calmodulin (CALM1 CALM2 CALM3, P62158) |
| Selective inhibitors | SCH51866 (pIC50 7.2) [498], vinpocetine (pIC50 5.1) [300] | SCH51866 (pIC50 7.2) [498] | SCH51866 (pIC50 7.2) [498], vinpocetine (pIC50 4.3) [300] |

| Nomenclature | PDE2A | PDE3A | PDE3B |
|--------------|-------|-------|-------|
| HGNC, UniProt| PDE2A, P500408 | PDE3A, Q14432 | PDE3B, Q13370 |
| EC number    | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 |
| Rank order of affinity | cyclic AMP >> cyclic GMP | cyclic GMP (Selective) | cyclic GMP (Selective) |
| Endogenous activators | cyclic GMP | cyclic GMP (Selective) | cyclic GMP (Selective) |
| Inhibitors | milrinone (pIC50 <6.5) [465] | cilostazol (pIC50 6.7) [465], inamrinone (pIC50 4.8) [442] | cilostazol (pIC50 7.3) [465], cilostamide (pIC50 7.0) [465], anagrelide (pIC50 7.1–7.3) [245, 319, 326], milrinone (pIC50 6.3–6.4) [123, 465], milrinone (pIC50 6.4) [465], inamrinone (pIC50 4.5) [465] |
| Selective inhibitors | BAY607550 (pIC50 8.3–8.8) [44], EHNA (pIC50 5.3) [332] | cilostamide (pIC50 7.5) [465], anagrelide (pIC50 7.1–7.3) [245, 319, 326], milrinone (pIC50 6.3–6.4) [123, 465], milrinone (pIC50 6.4) [465], inamrinone (pIC50 4.5) [465] | – |
| Comments | EHNA is also an inhibitor of adenosine deaminase (E.C. 3.5.4.4). | – | – |

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| Nomenclature | PDE4A | PDE4B | PDE4C | PDE4D | PDE5A |
|--------------|-------|-------|-------|-------|-------|
| HGNC, UniProt | PDE4A, P27815 | PDE4B, Q07343 | PDE4C, Q08493 | PDE4D, Q08499 | PDE5A, Q76074 |
| EC number    | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 |
| Activator    | – | – | – | PKA-mediated phosphorylation [217] | Protein kinase A, protein kinase C [93] |
| 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 |
| Inhibitors   | ibudilast (plC50 7.3) [262], RS-25344 (plC50 7.2) [417] | roflumilast (plC50 9.4) [301], ibudilast (plC50 7.2) [262], RS-25344 (plC50 6.5) [417] | RS-25344 (plC50 8.1) [417], ibudilast (plC50 6.6) [262] | RS-25344 (plC50 8.4) [417] | gisadenafil (plC50 8.9) [402], milrinone (plC50 7.3) |
| (Sub)family-selective inhibitors | rolipram (plC50 9) [508], Ro20-1724 (plC50 6.5) [508] | rolipram (plC50 9) [508], Ro20-1724 (plC50 6.5) [508] | rolipram (plC50 6.5) [508], Ro20-1724 (plC50 5.4) [508] | rolipram (plC50 7.2) [508], Ro20-1724 (plC50 6.2) [508] | – |
| Selective inhibitors | YM976 (plC50 8.3) [13] | – | – | – | vardenafil (plC50 9.7) [47], T0156 (plC50 9.5) [338], sildenafil (plC50 9) [494], tadalafil (plC50 8.5) [339], SCH51866 (plC50 7.2) [498], zaprinast (plC50 6.8) [494] |

| Nomenclature | PDE6A | PDE6B | PDE6C | PDE6D | PDE6G |
|--------------|-------|-------|-------|-------|-------|
| HGNC, UniProt | PDE6A, P16499 | PDE6B, P35913 | PDE6C, P51160 | PDE6D, O43924 | PDE6G, P18545 |
| EC number    | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 |

| Nomenclature | PDE7A | PDE7B | PDE8A | PDE8B |
|--------------|-------|-------|-------|-------|
| HGNC, UniProt | PDE7A, Q13946 | PDE7B, Q9NP56 | PDE8A, Q60658 | PDE8B, Q95263 |
| EC number    | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 | 3.1.4.17 |
| Rank order of affinity | cyclic AMP \(\gg\) cyclic GMP [330] | cyclic AMP \(\gg\) cyclic GMP [166] | cyclic AMP \(\gg\) cyclic GMP [138] | cyclic AMP \(\gg\) cyclic GMP [201] |

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### Table 1: Nomenclature and Inhibitors of PDE7A, PDE7B, PDE8A, and PDE8B

| Nomenclature | Inhibitors | Selective Inhibitors | Comments |
|--------------|------------|---------------------|----------|
| PDE7A        | –          | BRL50481 (pIC<sub>50</sub> 4.9) [7] | PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively |
| PDE7B        | BRL50481   | dipyridamole (pIC<sub>50</sub> 5.7–6.0) [166, 419], SCH51866 (pIC<sub>50</sub> 5.8) [419] | – |
| PDE8A        | –          | dipyridamole (pIC<sub>50</sub> 5.1) [138] | – |
| PDE8B        | –          | dipyridamole (pIC<sub>50</sub> 4.3) [201] | – |

### Table 2: Nomenclature and Inhibitors of PDE9A, PDE10A, and PDE11A

| Nomenclature | HGNC, UniProt | EC number | Rank order of affinity | Inhibitors | Selective Inhibitors |
|--------------|--------------|-----------|------------------------|------------|---------------------|
| PDE9A        | PDE9A, O76083| 3.1.4.17  | cyclic GMP ≫ cyclic AMP [137] | –          | SCH51866 (pIC<sub>50</sub> 5.8) [137], zaprinast (pIC<sub>50</sub> 4.5) [137] |
| PDE10A       | PDE10A, Q9Y233| 3.1.4.17  | cyclic AMP, cyclic GMP [152] | –          | – |
| PDE11A       | PDE11A, Q9HCR9| 3.1.4.17  | cyclic AMP, cyclic GMP [133] | –          | – |

**Comments:** PDE1A, 1B and 1C appear to act as soluble homodimers, while PDE2A is a membrane-bound homodimer. PDE3A and PDE3B are membrane-bound.

PDE4 isoforms are essentially cyclic AMP specific. The potency of YM976 at other members of the PDE4 family has not been reported. PDE4B-D long forms are inhibited by extracellular signal-regulated kinase (ERK)-mediated phosphorylation [212, 213]. PDE4A-D splice variants can be membrane-bound or cytosolic [217]. PDE4 isoforms may be labelled with [3H]rolipram.

PDE6 is a membrane-bound tetramer composed of two catalytic chains (PDE6A or PDE6C and PDE6B), an inhibitory chain (PDE6G or PDE6H) and the PDE6D chain. The enzyme is essentially cyclic GMP specific and is activated by the α-subunit of transducin (G<sub>α</sub><sub>T</sub>) and inhibited by sildenafil, zaprinast and dipyridamole with potencies lower than those observed for PDE5A. Defects in PDE6B are a cause of retinitis pigmentosa and congenital stationary night blindness.

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Cytochrome P450

Enzymes → Cytochrome P450

Overview: The cytochrome P450 enzyme family (CYP450), E.C. 1.14.-.-, were originally defined by their strong absorbance at 450 nm due to the reduced carbon monoxide-complexed haem component of the cytochromes. They are an extensive family of haem-containing monooxygenases with a huge range of both 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. Further family members are included on the online database at www.GuidetoPHARMACOLOGY.org

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 [464] |

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## CYP2 family

**Enzymes → Cytochrome P450 → CYP2 family**

| Nomenclature | CYP2A6 | CYP2A7 | CYP2C8 |
|--------------|--------|--------|--------|
| HGNC, UniProt| CYP2A6, P11509 | CYP2A7, P20853 | CYP2C8, P10632 |
| EC number    | 1.14.14.1 | 1.14.14.1 | 1.14.14.1 |
| Comments     | Metabolises nicotine | CYP2A7 does not incorporate haem and is functionally inactive [153]. | Converts arachidonic acid to 11(R)-12(S)-epoxyeicosatrienoic acid or 14(R)-15(S)-epoxyeicosatrienoic acid [547]. |

## CYP3 family

**Enzymes → Cytochrome P450 → CYP3 family**

| Nomenclature | CYP2J2 | CYP2R1 |
|--------------|--------|--------|
| HGNC, UniProt| CYP2J2, P51589 | CYP2R1, Q6VVX0 |
| EC number    | 1.14.14.1 | 1.14.13.15 |
| Comments     | Converts arachidonic acid to 14(R)-15(S)-epoxyeicosatrienoic acid [531]. | Converts vitamin D3 to 25-hydroxyvitamin D3 [78]. |

**CYP3 family**

| Nomenclature | CYP3A4 |
|--------------|--------|
| HGNC, UniProt| CYP3A4, P08684 |
| EC number    | 1.14.13.32: Albendazole + NADPH + O_2 = albendazole S-oxide + NADP^+ + H_2 O 1.14.13.157: 1,8-cineole + NADPH + O_2 = 2-exo-hydroxy-1,8-cineole + NADP^+ + H_2 O 1.14.13.97: Taurochenodeoxycholate + NADPH + O_2 = taurohyocholate + NADP^+ + H_2 O Lithocholate + NADPH + O_2 = hyodeoxycholate + NADP^+ + H_2 O 1.14.13.67: quinine + NADPH + O_2 = 3-hydroxyquinine + NADP^+ + H_2 O_2 |
| Substrates   | atorvastatin [140], codeine [140], diazepam [140], tamoxifen [140], erlotinib [140] |

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.13354/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full)
Nomenclature
Product
4-hydroxy-tamoxifen quinone methide [432], 4-hydroxy-tamoxifen [432]

Comments
Metabolises a vast range of xenobiotics, including antidepressants, benzodiazepines, calcium channel blockers, and chemotherapeutic agents. CYP3A4 catalyses the 25-hydroxylation of trihydrocholestanol in liver microsomes [157].

CYP4 family

Enzymes → Cytochrome P450 → CYP4 family

Nomenclature
HGNC, UniProt
EC number
Comments

CYP4A11
CYP4A11, Q02928
1.14.15.3
Converts lauric acid to 12-hydroxylauric acid.

CYP4F2
CYP4F2, P78329
1.14.13.30
Responsible for ω-hydroxylation of LTB4, LX84 [335], and tocopherols, including vitamin E [453].

CYP4F3
CYP4F3, Q08477
1.14.13.30
Responsible for ω-hydroxylation of LTB4, LX84 [335], and polyunsaturated fatty acids [135, 194].

CYP4F8
CYP4F8, P98187
1.14.14.1
Converts PGH2 to 19-hydroxyPGH2 [54] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [353].

CYP4F12
CYP4F12, Q9HCS2
1.14.14.1
AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12.

CYP4F22
CYP4F22, Q6NT55
1.14.14.-.
Converts arachidonic acid to 16-HETE and 18-HETE [353].

CYP4V2
CYP4V2, Q6ZWL3
1.14.-.
Converts myristic acid to 14-hydroxymyristic acid [348].

CYP4X1
CYP4X1, Q8N118
1.14.14.1
Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [459].

CYP4Z1
CYP4Z1, Q86W10
1.14.14.1
Converts lauric acid to 12-hydroxylauric acid.

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full
## CYP5, CYP7 and CYP8 families

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

| Nomenclature   | CYP5A1 | CYP8A1 | CYP7A1 | CYP7B1 | CYP8B1 |
|----------------|--------|--------|--------|--------|--------|
| Common name    | –      | Prostacyclin synthase | –      | –      | –      |
| HGNC, UniProt  | T8XAS1, P24557 | PTGIS, Q16647 | CYP7A1, P22680 | CYP7B1, O75881 | CYP8B1, Q9UNU6 |
| EC number      | 5.3.99.5: PGH2 = thromboxane A2 | 5.3.99.4 | 1.14.13.17 | 1.14.13.100 | 1.14.13.95 |
| Comments       | Inhibited by dazoxiben [398] and camonagrel [182]. | Converts PGH2 to PG12 [196]. Inhibited by tranylcypromine [181] | Converts cholesterol to 7α-hydroxycholesterol [354]. | Converts dehydroepiandrosterone to 7α-DHEA [411]. | Converts 7α-hydroxycholesterol-4-en-3-one to 7-alpha,12α-di-hydroxycholesterol-4-en-3-one (in rabbit) [226] in the biosynthesis of bile acids. |

## CYP11, CYP17, CYP19, CYP20 and CYP21 families

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

| Nomenclature   | CYP11A1 | CYP11B1 | CYP11B2 | CYP17A1 |
|----------------|---------|---------|---------|---------|
| Common name    | –       | –       | Aldosterone synthase | –       |
| HGNC, UniProt  | CYP11A1, P05108 | CYP11B1, P15538 | CYP11B2, P19099 | CYP17A1, P05093 |
| EC number      | 1.14.15.6 | 1.14.15.4 | 1.14.15.4 | 1.14.99.9 |
| Inhibitors     | mitotane | metyrapone (pIC50 7.8) [553], mitotane | osilodrostat (pIC50 9.7) [537] | abiraterone (pIC50 7.1–8.4) [386, 390] |
| Selective inhibitors | –       | –       | –       | galeterone (pIC50 6.5) [192] |
### Enzymes /

**CYP11A1**
- Converts cholesterol to pregnenolone plus 4-methylpentanal.

**CYP11B1**
- Converts deoxycorticosterone and 11-deoxycortisol to cortisone and cortisol, respectively. Loss-of-function mutations are associated with familial adrenal hyperplasia and hypertension. Inhibited by metyrapone [513]

**CYP11B2**
- Converts corticosterone to aldosterone

**CYP17A1**
- Converts pregnenolone and progesterone to 17α-hydroxyprogrenenolone and 17α-hydroxyprogesterone, respectively. Converts 17α-hydroxyprogrenenolone and 17α-hydroxyprogesterone to dehydroepiandrosterone and androstenedione, respectively. Converts corticosterone to cortisol.

**CYP19A1**
- Converts androstenedione and testosterone to estrone and 17β-estradiol, respectively. Inhibited by anastrozole [388] and letrozole [33]

**CYP20A1**
- Converts corticosterone to cortisol

**CYP21A2**
- Converts corticosterone to aldosterone

**CYP24, CYP26 and CYP27 families**

**CYP24A1**
- Sterol 27-hydroxylase

**CYP26A1**
- –

**CYP26B1**
- –

**CYP27A1**
- –

**CYP27B1**
- –

**CYP24, CYP26 and CYP27 families**

**CYP24A1**
- Sterol 27-hydroxylase

**CYP26A1**
- –

**CYP26B1**
- –

**CYP27A1**
- –

**CYP27B1**
- –

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CYP39, CYP46 and CYP51 families

Enzymes → Cytochrome P450 → CYP39, CYP46 and CYP51 families

| Nomenclature | CYP39A1 | CYP46A1 | CYP51A1 |
|--------------|---------|---------|---------|
| Common abreviation | – | Cholesterol 24-hydroxylase | Lanosterol 14-α-demethylase |
| HGNC, UniProt | CYP39A1, Q9NYL5 | CYP46A1, Q9Y6A2 | CYP51A1, Q16850 |
| EC number | 1.14.13.99 | 1.14.13.98 | – |
| Comments | Converts 24-hydroxycholesterol to 7α,24-dihydroxycholesterol [286]. | Converts cholesterol to 24(S)-hydroxycholesterol. | Converts lanosterol to 4,4-dimethylcholesta-8.14.24-trienol. |

Further Reading

Guengerich FP et al. (2011) Orphans in the human cytochrome P450 superfamily: approaches to discovering functions and relevance in pharmacology. *Pharmacol. Rev.* 63: 684-99 [PMID:21737533]

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

Orr ST et al. (2012) Mechanism-based inactivation (MBI) of cytochrome P450 enzymes: structure-activity relationships and discovery strategies to mitigate drug-drug interaction risks. *J. Med. Chem.* 55: 4896-933 [PMID:22409598]

Peñas-Lledó EM et al. (2014) CYP2D6 variation, behaviour and psychopathology: implications for pharmacogenomics-guided clinical trials. *Br J Clin Pharmacol* 77: 673-83 [PMID:24033670]

Ross AC et al. (2011) Cytochrome P450s in the regulation of cellular retinoic acid metabolism. *Annu. Rev. Nutr.* 31: 65-87 [PMID:21529158]

Shahabi P et al. (2014) Human cytochrome P450 epoxygenases: variability in expression and role in inflammation-related disorders. *Pharmacol. Ther.* 144: 134-61 [PMID:24882266]

Werk AN et al. (2014) Functional gene variants of CYP3A4. *Clin. Pharmacol. Ther.* 96: 340-8 [PMID:24926778]

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

Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full
## Endocannabinoid turnover

### Overview:

The principle endocannabinoids are 2-arachidonoylglycerol (2AG) and anandamide (N-arachidonoylethanolamine, AEA), thought to be generated on demand rather than stored, although this may not always be the case [10]. Mechanisms for release and re-uptake of endocannabinoids (and related entities) are unclear, although candidates for intracellular transport have been suggested. For the generation of 2-arachidonoylglycerol, the key enzyme involved is diacylglycerol lipase (DGL), whilst several routes for anandamide synthesis have been described, the best characterized of which involves N-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD, [438]). Inactivation of these endocannabinoids appears to occur predominantly through monoglycerol lipase (MGL) and fatty acid amide hydrolase (FAAH) for 2-arachidonoylglycerol and anandamide, respectively. Note that these enzymes also contribute to the turnover of many endogenous ligands inactive at CB1 and CB2 cannabinoid receptors, such as N-oleoylethanolamide, N-palmitoylethanolamine and 2-oleoylglycerol. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism via cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [9, 145, 450].

### Nomenclature

| Nomenclature | Common abbreviation | EC number | Selective inhibitors | Comments |
|--------------|---------------------|-----------|---------------------|----------|
| Diacylglycerol lipase α | DGLα | 3.1.1.- | orlistat (pIC₅₀ 7.2) [37], RHC80267 (pIC₅₀ 4.2) [243] | – |
| Diacylglycerol lipase β | DGLβ | 3.1.1.- | orlistat (pIC₅₀ 7) [37], RHC80267 | – |
| N-Acylphosphatidylethanolamine-phospholipase D | NAPE-PLD | – | – | NAPE-PLD activity appears to be enhanced by polyamines in the physiological range [292], but fails to transphosphatidylate with alcohols [381] unlike phosphatidylcholine-specific phospholipase D. |

| Nomenclature | Common abbreviation | EC number | Rank order of affinity |
|--------------|---------------------|-----------|-----------------------|
| Monoacylglycerol lipase | MGL | 3.1.1.23 | 2-oleoyl glycerol = 2-arachidonoylglycerol ⪰ anandamide [171] |
| Fatty acid amide hydrolase | FAAH | 3.5.1.- | anandamide > oleamide > N-oleoylethanolamide > N-palmitoylethanolamine [518] |
| Fatty acid amide hydrolase-2 | FAAH2 | 3.5.1.- | oleamide > N-oleoylethanolamide > anandamide > N-palmitoylethanolamine [518] |
| N-Acylethanolamine acid amidase | NAAA | 3.5.1.- | N-palmitoylethanolamine > MEA > SEA > N-oleoylethanolamide > anandamide [495] |

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Nomenclature

| Selective inhibitors | Monoacylglycerol lipase | Fatty acid amide hydrolase | Fatty acid amide hydrolase-2 | N-Acylethanolamine acid amidase |
|----------------------|-------------------------|---------------------------|-----------------------------|--------------------------------|
| JZL184 (pIC50 8.1)  | [295] [253]              | [253]                      | [518]                        | [451] – Rat,                    |
|                      |                         | [4]                       | [518]                        | CCP (pIC50 5.3)                 |

Comments: Many of the compounds described as inhibitors are irreversible and so potency estimates will vary with incubation time. FAAH2 is not found in rodents [518] and few of the inhibitors described have been assessed at this enzyme activity. 2-arachidonoylglycerol has been reported to be hydrolysied by multiple enzyme activities from neural preparations, including ABHD6 (Q9RY23) [41], ABHD12 (8N2K0) [41], neuropathy target esterase (PNPLA6, Q8IY17) [316] and carboxylesterase 1 (CES1, P23141 [533]). Although these have been incompletely defined, WWL70 has been described to inhibit ABHD6 selectively with a pIC50 value of 7.2 [284]. Other selective inhibitors of NAAA (with respect to FAAH) have been described, but these are not yet commercially available.

Further Reading

Blankman JL et al. (2013) Chemical probes of endocannabinoid metabolism. Pharmacol. Rev. 65: 849-71 [PMID:23512546]
Fowler CJ. (2013) Transport of endocannabinoids across the plasma membrane and within the cell. FEBS J. 280: 1895-904 [PMID:23441874]
Hermanson DJ et al. (2014) Substrate-selective COX-2 inhibition as a novel strategy for therapeutic endocannabinoid augmentation. Trends Pharmacol. Sci. 35: 358-67 [PMID:24845457]
Savinainen JR et al. (2012) The serine hydrolases MAGL, ABHD6 and ABHD12 as guardians of 2-arachidonoylglycerol signalling through cannabinoid receptors. Acta Physiol (Oxf) 204: 267-76 [PMID:21418147]

Ueda N et al. (2013) Metabolism of endocannabinoids and related N-acylethanolamines: canonical and alternative pathways. FEBS J. 280: 1874-94 [PMID:23423575]
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; lipooxygenases and cytochrome P450-like epoxygenases, particularly CYP2J2. Iso-prostanes 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.

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Cyclooxygenase

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

| Nomenclature | COX-1 | COX-2 |
|--------------|-------|-------|
| HGNC, UniProt | PTGS1, P23219 | PTGS2, P35354 |
| EC number | 1.14.99.1: Hydrogen donor + arachidonic acid + 2O2 = hydrogen acceptor + H2O + PGH2 | 1.14.99.1: Hydrogen donor + arachidonic acid + 2O2 = hydrogen acceptor + H2O + PGH2 |
| Inhibitors | bromfenac (pIC50 8.1) [17], diclofenac (pIC50 7.9) [556], meclofenamic acid (pIC50 7.3) [247], flurbiprofen (pIC50 7.1) [512], fenprofen (pIC50 6.8) [17], ketoprofen (pIC50 6.5) [55], suprofen (pIC50 6.2) [55], benzquinamide (pIC50 8.3) [17], flurbiprofen (pIC50 8) [25], meclofenamic acid (pIC50 7.4) [247], carprofen (pIC50 7) [209], ketorolac (pIC50 6.9) [503], nimesulide (pIC50 6.2) [366], ketoprofen (pIC50 6.2) [55] |
| Selective inhibitors | ketorolac (pIC50 9.7) [512], FR122047 (pIC50 7.5) [357], celecoxib (pIC50 8.7) [38], valdecoxib (pIC50 8.3) [473], diclofenac (pIC50 7.7) [42], rofecoxib (pIC50 6.1–6.5) [512], lumiracoxib (pK1 6.5) [43], meloxicam (pIC50 6.3) [280], etoricoxib (pIC50 6) [406] |

Prostaglandin synthases

Overview: Subsequent to the formation of PGH2, the cytochrome P450 activities thromboxane synthase (CYP5A1, TBXAS1, P24557, EC 5.3.99.5) and prostacyclin synthase (CYP1A1, PTGIS, Q16647, EC 5.3.99.4) generate thromboxane A2 and prostacyclin (PGI2), respectively. Additionally, multiple enzyme activities are able to generate prostaglandin E2 (PGE2), prostaglandin D2 (PGD2) and prostaglandin F2α (PGF2α). PGD2 can be metabolised to 9α,11β-prostaglandin F2α through the multifunctional enzyme activity of AKR1C3. PGE2 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.
### CYP5A1
- **Common name:** Prostacyclin synthase
- **HGNCS, UniProt:** TBXAS1, P24557
- **EC number:** 5.3.99.5: PGH$_2$ = thromboxane A$_2$
- **Cofactors:** Glutathione, dihydrolipoic acid
- **Comments:** Inhibited by dazoxiben [398] and camonagrel [182]. Converts PGH$_2$ to PGI$_2$ [196]. Inhibited by tranilcyrompine [181].

### CYP8A1
- **Common name:** —
- **HGNCS, UniProt:** PTCIS, Q16647
- **EC number:** 5.3.99.4
- **Cofactors:** —
- **Comments:** —

### mPGES1
- **Common name:** —
- **HGNCS, UniProt:** PTGES, O14684
- **EC number:** 5.3.99.3: PGH$_2$ = PGE$_2$
- **Cofactors:** Glutathione
- **Comments:** Phosphorylated and activated by casein kinase 2 (CK2) [260]. Appears to regulate steroid hormone function by interaction with dimeric hsp90 [69, 241].

### mPGES2
- **Common name:** —
- **HGNCS, UniProt:** PTGES2, Q9H7Z7
- **EC number:** 5.3.99.3: PGH$_2$ = PGE$_2$
- **Cofactors:** Dihydrolipoic acid
- **Comments:** —

### cPGES
- **Common name:** —
- **HGNCS, UniProt:** PTGES3, Q15185
- **EC number:** 5.3.99.3: PGH$_2$ = PGE$_2$
- **Cofactors:** —
- **Comments:** —

### L-PGDS
- **Common name:** —
- **HGNCS, UniProt:** PTGDS, P41222
- **EC number:** 5.3.99.2: PGH$_2$ = PGD$_2$
- **Inhibitors:** Flufenamic acid, indomethacin, flavonoids [321, 446]
- **Cofactors:** NADP$^+$
- **Inhibitors:** HQL-79 (pIC$_{50}$ 5.3–5.5) [15]
- **Comments:** Also acts as a hydroxysteroid dehydrogenase activity.

### H-PGDS
- **Common name:** —
- **HGNCS, UniProt:** HPGDS, O60760
- **EC number:** 5.3.99.2: PGH$_2$ = PGD$_2$
- **Inhibitors:** —
- **Cofactors:** —
- **Inhibitors:** —
- **Comments:** —

### AKR1C3
- **Common name:** —
- **HGNCS, UniProt:** AKR1C3, P42330
- **EC number:** 1.3.1.20 1.1.1.188: PGD$_2$ + NADP$^+$ = PGF$_{2\alpha}$ + NADPH + H$^+$ 1.1.1.239 1.1.1.213
- **Inhibitors:** Flufenamic acid, indomethacin, flavonoids [321, 446]
- **Cofactors:** NADP$^+$
- **Inhibitors:** —
- **Comments:** —

### CBR1
- **Common name:** —
- **HGNCS, UniProt:** CBR1, P16152
- **EC number:** 1.1.1.184 1.1.1.189: PGE$_2$ + NADP$^+$ = PGF$_{2\alpha}$ + NADPH + H$^+$ 1.1.1.197
- **Inhibitors:** —
- **Cofactors:** NADP$^+$
- **Inhibitors:** Wedelolactone (pIC$_{50}$ 5.4) [555]
- **Comments:** —

### HPGD
- **Common name:** —
- **HGNCS, UniProt:** HPGD, P15428
- **EC number:** 1.1.1.141 15-hydroxyprostaglandins => 15-ketoprostaglandins LXA$_4$ => 15-keto-lipoxin A$_4$
- **Inhibitors:** —
- **Cofactors:** —
- **Inhibitors:** —
- **Comments:** —

**Comments:** YS121 has been reported to inhibit mPGES1 and 5-LOX with a pIC$_{50}$ value of 5.5 [263].
Lipoxygenases

Enzymes → Eicosanoid turnover → Lipoxygenases

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

| Nomenclature | 5-LOX | 12R-LOX | 12S-LOX | 15-LOX-1 | 15-LOX-2 | E-LOX |
|--------------|-------|---------|---------|----------|----------|-------|
| HGNC, UniProt | ALOX5, P09917 | ALOX12B, O75342 | ALOX12, P18054 | ALOX15, P16050 | ALOX15B, O15296 | ALOX3, Q9BY1 |
| EC number | 1.13.11.34: arachidonic acid + O2 = LTA4 + H2O | 1.13.11.31 arachidonic acid + O2 = 12R-HPETE | 1.13.11.31 arachidonic acid + O2 = 12S-HPETE | 1.13.11.33: arachidonic acid + O2 = 15S-HPETE linoleic acid + O2 = 15S-HPODE | 1.13.11.33: arachidonic acid + O2 = 15S-HPETE | 1.13.11.- |
| Endogenous inhibitor | Protein kinase A-mediated phosphorylation [304] | – | – | – | – | – |
| Substrates | methyl arachidionate | – | – | – | – | – |
| Endogenous substrates | arachidonic acid | – | – | – | – | 12R-HPETE |
| Endogenous activators | 5-LOX activating protein (ALOX5AP, P20292) | – | – | – | – | – |
| Selective inhibitors | CJ13610 (pIC50 7.2) [136], zileuton | – | – | – | – | – |
| Comments | FLAP activity can be inhibited by MK-886 [116] and BAY-X1005 [197] 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 [543]. |

**Comments:** An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 [158]. Some general LOX inhibitors are nordihydroguaiaretic acid and esculetin. Zileuton and caffeic acid are used as 5-lipoxygenase inhibitors, while baikaline and CDC are 12-lipoxygenase inhibitors. The specificity of these inhibitors has not been rigorously assessed with all LOX forms: baikaline, along with other flavonoids, such as fisetin and luteolin, also inhibits 15-LOX-1 [414].

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Leukotriene and lipoxin metabolism

Overview: Leukotriene A₄ (LTA₄), produced by 5-LOX activity, and lipoxins may be subject to further oxidative metabolism; ω-hydroxylation is mediated by CYP4F2 and CYP4F3, while β-oxidation in mitochondria and peroxisomes proceeds in a manner dependent on coenzyme A conjugation. Conjugation of LTA₄ at the 6 position with reduced glutathione to generate LTC₄ occurs under the influence of leukotriene C₄ synthase, with the subsequent formation of LTD₄ and LTE₄, all three of which are agonists at CysLT receptors. LTD₄ formation is catalysed by γ-glutamyltransferase, and subsequently dipeptidase 2 removes the terminal glycine from LTD₄ to generate LTE₄. Leukotriene A₄ hydrolase converts the 5,6-epoxide LTA₄ to the 5-hydroxylated LTB₄, an agonist for BLT receptors. LTA₄ is also acted upon by 12S-LOX to produce the trihydroxyeicosatetraenoic acids lipoxins LXA₄ and LXB₄. Treatment with a LTA₄ hydrolase inhibitor in a murine model of allergic airway inflammation increased LXA₄ levels, in addition to reducing LTB₄, in lung lavage fluid [400]. LTA₄ hydrolase is also involved in biosynthesis of resolvin Es. Aspirin has been reported to increase endogenous formation of 18S-hydroxyeicosapentaenoate (18S-HEPE) compared with 18R-HEPE, a resolvin precursor. Both enantiomers may be metabolised by human recombinant S-LOX; recombinant LTA₄ hydrolase converted chiral 5S(6)-epoxide-containing intermediates to resolvin E1 and 18S-resolvin E1 [358].

### Nomenclature

| Enzyme Name | HGNC, UniProt | EC Number | Inhibitors |
|-------------|--------------|-----------|------------|
| LTC₄S | Q16873 | 4.4.1.20: LTC₄ = glutathione + LTA₄ | – |
| γ-Glutamyltransferase | Q75223 | 2.3.2.2: (5-L-glutamyl)-peptide + an amino acid = a peptide + a 5-L-glutamyl amino acid LTC₄ + H₂O ± LTD₄ + L-glutamate | – |
| Dipeptidase 1 | P16444 | 3.4.13.19: LTD₄ + H₂O = LTE₄ + glycine | cilastatin (pKᵢ 6) [179] – Unknown |
| Dipeptidase 2 | Q9H4A9 | 3.4.13.19: LTD₄ + H₂O = LTE₄ + glycine | – |

### Comments

LTA4H is a member of a family of arginyl aminopeptidases (ENSFM0025000001675), which also includes aminopeptidase B (RNPEP, Q9H4A4) and aminopeptidase B-like 1 (RNPEP1, Q9HAU8). Dipeptidase 1 and 2 are members of a family of membrane dipeptidases, which also includes (DPEP3, Q9H4B8) for which LTD₄ appears not to be a substrate.

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GABA turnover

Enzymes → GABA turnover

**Overview:** The inhibitory neurotransmitter \( \gamma \)-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 [128] where GABA is principally accumulated in vesicles through the action of the vesicular inhibitory amino acid transporter SLC32A1. The role of \( \gamma \)-aminobutyraldehyde dehydrogenase (ALDH9A1) in neurotransmitter GABA synthesis is less clear. Following release from neurons, GABA may interact with either GABA\(_A\) or GABA\(_B\) receptors and may be accumulated in neurones and glia through the action of members of the SLC6 family of transporters. Successive metabolism through GABA transaminase and succinate semialdehyde dehydrogenase generates succinic acid, which may be further metabolized in the mitochondria in the tricarboxylic acid cycle.

| Nomenclature | Glutamic acid decarboxylase 1, decarboxylase 2 |
| ------------ | ----------------------------------------------- |
| Common abbreviation | GAD1, GAD2 |
| HGNC, UniProt | GAD1, Q99259, GAD2, Q05329 |
| EC number | 4.1.1.15: L-glutamic acid + H\(^+\) \rightarrow GABA + CO\(_2\) |
| Endogenous substrates | L-glutamic acid, L-aspartic acid |
| Products | GABA |
| Cofactors | pyridoxal phosphate |
| Inhibitors | — |
| Selective inhibitors | s-allylglycine, vigabatrin (Irreversible inhibition) (\(pK_i\) 3.1) [289, 437] |
| Comments | L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating \(\beta\)-alanine [530]. Autoantibodies against GAD1 and GAD2 are elevated in type I diabetes mellitus and neurological disorders (see Further reading). |

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Kim KJ et al. (2011) Succinic semialdehyde dehydrogenase: biochemical-molecular-clinical disease mechanisms, redox regulation, and functional significance. Antioxid. Redox Signal. 15: 691-718 [PMID:20973619]

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Glycerophospholipid turnover

Enzymes → Glycerophospholipid turnover

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

Phosphatidylinositol kinases

Enzymes → Glycerophospholipid turnover → Phosphatidylinositol kinases

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

Phosphatidylinositol 3-kinases

Phosphatidylinositol 3-kinases (PI3K, provisional nomenclature) catalyse the introduction of a phosphate into the 3-position of phosphatidylinositol (PI), phosphatidylinositol 4-phosphate (PIP) or phosphatidylinositol 4,5-bisphosphate (PIP2). There is evidence that PI3K can also phosphorylate serine/threonine residues on proteins. In addition to the classes described below, further serine/threonine protein kinases, including ATM (Q13315) and mTOR (P42345), have been described to phosphorylate phosphatidylinositol and have been termed PI3K-related kinases. Structurally, PI3K have common motifs of at least one C2, calcium-binding domain and helical domains, alongside structurally-conserved catalytic domains. Wortmannin and LY294002 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 p110γ catalytic subunits, with predominantly p85 and p55 regulatory subunits. The single catalytic subunit that forms Class IB PI3K is p110γ. Class IA PI3Ks are more associated with receptor tyrosine kinase pathways, while the Class IB PI3K is linked more with GPCR signalling.

Class II PI3Ks (EC 2.7.1.154) phosphorylate phosphatidylinositol to generate phosphatidylinositol 3-phosphate (and possibly phosphatidylinositol 4-phosphate to generate phosphatidylinositol 3,4-bisphosphate). Three monomeric members exist, PI3K-C2α, β and γ, and include Ras-binding, Phox homology and two C2domains. The only class III PI3K isoform (EC 2.7.1.137) is a heterodimer formed of a catalytic subunit (VPS34) and regulatory subunit (VPS15).

Phosphatidylinositol 4-kinases

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

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

| Nomenclature                          | phosphatidylinositol 4-kinase, catalytic, alpha | phosphatidylinositol 4-kinase, catalytic, beta |
|---------------------------------------|-------------------------------------------------|-----------------------------------------------|
| Common abbreviation                   | PI4KIIα/PIK4CA                                   | PI4KIIIβ/PIK4CB                                |
| HGNC, UniProt                         | PI4KA, P42356                                    | PI4KB, Q9UBF8                                  |
| EC number                             | 2.7.1.67                                        | 2.7.1.67                                      |
| Endogenous activation                 | --                                              | PKD-mediated phosphorylation [199]            |
| (Sub)family-selective inhibitors      | wortmannin (pIC₅₀ 6.7–6.8) [170, 329]            | wortmannin (pIC₅₀ 6.7–6.8) [170, 329]          |
| Selective inhibitors                  | --                                              | PIK-93 [259]                                   |

### Phosphatidylinositol-4-phosphate 3-kinase family

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

| Nomenclature                          | phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 alpha | phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 beta | phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 gamma |
|---------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Common abbreviation                   | C2α/PIK3C2A                                                                | C2β/PIK3C2B                                                               | C2γ/PIK3C2G                                                                |
| HGNC, UniProt                         | PIK3C2A, O00443                                                            | PIK3C2B, O00750                                                           | PIK3C2G, O75747                                                           |
| EC number                             | 2.7.1.154                                                                 | 2.7.1.154                                                                | 2.7.1.154                                                                 |

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## Phosphatidylinositol 3-kinase family

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

| Nomenclature | phospahatidylinositol 3-kinase, catalytic subunit type 3 |
|--------------|--------------------------------------------------------|
| Common abreviation | VPS34/PIK3C3 |
| HGNC, UniProt | PIK3C3, Q8NEB9 |
| EC number | 2.7.1.137 |

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

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

| Nomenclature | phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha |
|--------------|--------------------------------------------------------------------------|
| Common abreviation | p110α/PIK3CA |
| HGNC, UniProt | PIK3CA, P42336 |
| EC number | 2.7.1.153 |

| Inhibitors | PI-75 (pIC₅₀ 9.5) [200], gedatolisib (pIC₅₀ 9.4) [500], PF-04691502 (pKᵢ 9.2) [290], Pl-103 (pIC₅₀ 8.7) [404], BGT-226 (pIC₅₀ 8.4) [315], KU-0060648 (pIC₅₀ 8.4) [60], dactolisib (pIC₅₀ 8.3) [467], apitolisib (pIC₅₀ 8.3) [155], Plk-75 (pIC₅₀ 8.2) [259], buparlisib (pIC₅₀ 7.5) [49], PP121 (pIC₅₀ 7.3) [14] |
|------------|-----------------------------------------------------------------------------|
| KU-0060648 (pIC₅₀ 9.3) [60], Pl-103 (pIC₅₀ 8.5) [404], AZD6482 (pIC₅₀ 8) [355], ZSTK474 (pIC₅₀ 7.8) [355], apitolisib (pIC₅₀ 7.6) [467], BGT-226 (pIC₅₀ 7.2) [315] | dactolisib (pIC₅₀ 8.3) [310], apitolisib (pIC₅₀ 7.8) [467], Pl-103 (pIC₅₀ 7.8) [404], BGT-226 (pIC₅₀ 7.4) [315], ZSTK474 (pIC₅₀ 7.3) [355], TG-100-115 (pIC₅₀ 7.1) [369], alpelisib (pIC₅₀ 6.6) [155], KU-0060648 (pIC₅₀ 6.2) [60] |
| KU-0060648 (pIC₅₀ > 10) [60], idelalisib (in vitro activity against recombinant enzyme) (pIC₅₀ 8.6) [276], Pl-103 (pIC₅₀ 8.5) [404], ZSTK474 (pIC₅₀ 8.2) [355], apitolisib (pIC₅₀ 8.2) [467], dactolisib (pIC₅₀ 8.1) [310], alpelisib (pIC₅₀ 6.5) [155] |
(continued)

| Nomenclature                                                                 | (Sub)family-selective inhibitors |
|------------------------------------------------------------------------------|----------------------------------|
| phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha     | pictilisib (pIC\textsubscript{50} 8.5) [141] |
| pictilisib (pIC\textsubscript{50} 7.5) [141]                                |                                   |
| pictilisib (pIC\textsubscript{50} 7.1) [141]                                |                                   |
| pictilisib (pIC\textsubscript{50} 8.5) [141]                                |                                   |
| Selective inhibitors                                                        |                                   |
| CZC 24832 (pK\textsubscript{d} 7.7) [30]                                    |                                   |
| CZC 24832 (pIC\textsubscript{50} 7.6) [30]                                  |                                   |

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                                                                 | HGNC, UniProt                  | EC number |
|------------------------------------------------------------------------------|--------------------------------|-----------|
| phosphoinositate kinase, FYVE finger containing                              | PIKfyVE, Q9Y2I7-4              | 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)P\textsubscript{2}) by phosphorylating PtdIns(4)P [397]. This enzyme family is also known as type I PIP(5)Ks.

| Nomenclature                                                                 | HGNC, UniProt                  | Common abbreviation |
|------------------------------------------------------------------------------|--------------------------------|---------------------|
| phosphatidylinositol-4-phosphate 5-kinase, type I, alpha                     | PIPS1K1A                       | PIPS1K1A            |
| phosphatidylinositol-4-phosphate 5-kinase, type I, gamma                    | PIPS1K1C                       | PIPS1K1C, Q60331    |

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

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

**Overview:** Type II PIP kinases are essential for the production of the second messenger phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2) by phosphorylating PtdIns(5)P [397]. This enzyme family is also known as type II PIP(5)Ks.

| Nomenclature | phosphatidylinositol-5-phosphate 4-kinase, type II, alpha | phosphatidylinositol-5-phosphate 4-kinase, type II, beta | phosphatidylinositol-5-phosphate 4-kinase, type II, gamma |
|--------------|----------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------|
| Common abreviation | – | PIP4K2B | PIP4K2C |
| HGNC, UniProt | PIP4K2A, P48426 | PIP4K2B, P78356 | PIP4K2C, Q8TBX8 |
| EC number | 2.7.1.149 | 2.7.1.149 | 2.7.1.149 |
| Reaction | ATP + 1-phosphatidyl-1D-myo-inositol 5-phosphate \(\rightarrow\) ADP + 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate | ATP + 1-phosphatidyl-1D-myo-inositol 5-phosphate \(\rightarrow\) ADP + 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate | ATP + 1-phosphatidyl-1D-myo-inositol 5-phosphate \(\rightarrow\) ADP + 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate |

**Further Reading**

Neubauer HA et al. (2013) Roles, regulation and inhibitors of sphingosine kinase 2. *FEBS J.* 280: 5317-36 [PMID:23638983]

Truman JP et al. (2014) Evolving concepts in cancer therapy through targeting sphingolipid metabolism. *Biochim. Biophys. Acta* 1841: 1174-88 [PMID:24384461]
## Phosphoinositide-specific phospholipase C

**Overview:** Phosphoinositide-specific phospholipase C (PLC, EC 3.1.4.11), catalyses the hydrolysis of PIP$_2$ to IP$_3$ and 1,2-diacylglycerol, each of which have major second messenger functions. Two domains, X and Y, essential for catalytic activity, are conserved in the different forms of PLC. Isoforms of PLC-β are activated primarily by G protein-coupled receptors through members of the G$_q/11$ family of G proteins. Isoforms of PLC-γ are activated primarily by G protein-coupled receptors through members of the G$_q/11$ family of G proteins. The receptor-mediated activation of PLC-γ involves their phosphorylation by receptor tyrosine kinases (RTK) in response to activation of a variety of growth factor receptors and immune system receptors. PLC-ε1 may represent a point of convergence of signalling via both G protein-coupled and catalytic receptors. Ca$^{2+}$ ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC-ε activity. PLC has been suggested to be activated non-selectively by the small molecule m3M3FBS [21], although this mechanism of action has been questioned [271]. The aminosteroid U73122 has been described as an inhibitor of phosphoinositide-specific PLC [447], although its selectivity among the isoforms is untested and it has been reported to occupy the H1 histamine receptor [222].

### Nomenclature

| Nomenclature | PLCβ1 | PLCβ2 | PLCβ3 | PLCβ4 | PLCγ1 | PLCγ2 |
|---------------|-------|-------|-------|-------|-------|-------|
| HGNC, UniProt | PLCB1, Q9NQ66 | PLCB2, Q00722 | PLCB3, Q01970 | PLCB4, Q15147 | PLCG1, P19174 | PLCG2, P16885 |

### Endogenous activators

| Endogenous activators | Ga$_q$, Ga$_{11}$, G$_{ij}$ (207, 374, 449) | Ga$_{16}$, G$_{ij}$, Rac2 (RAC2, P15153) [59, 223, 224, 281, 374] | Ga$_q$, G$_{ij}$ [65, 281, 374] | Ga$_q$ [237] | PIP$_3$ [20] |

### Endogenous inhibitors

| Endogenous inhibitors | Sphingomyelin [378] | | | | |

### Comments: A series of PLC-like proteins (PLCL1, Q1S111; PLCL2, Q9UPR0 and PLC1H1, Q4KWH8) form a family with PLCβ and PLCγ isoforms, but appear to lack catalytic activity. PLC-ε2 has been cloned from bovine sources [328].
**Phospholipase A<sub>2</sub>**

Enzymes → Glycerophospholipid turnover → Phospholipase A<sub>2</sub>

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

**Secreted or extracellular forms:** sPLA<sub>2</sub>-1B, sPLA<sub>2</sub>-2A, sPLA<sub>2</sub>-2D, sPLA<sub>2</sub>-2E, sPLA<sub>2</sub>-2F, sPLA<sub>2</sub>-3, sPLA<sub>2</sub>-10 and sPLA<sub>2</sub>-12A

**Cytosolic, calcium-dependent forms:** cPLA<sub>2</sub>-4A, cPLA<sub>2</sub>-4B, cPLA<sub>2</sub>-4C, cPLA<sub>2</sub>-4D, cPLA<sub>2</sub>-4E and cPLA<sub>2</sub>-4F

**Other forms:** PLA<sub>2</sub>-G5, PLA<sub>2</sub>-G6, PLA<sub>2</sub>-G7 and PAFAH2 (platelet-activating factor acetylhydrolase 2)

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**Nomenclature**

| Nomenclature | sPLA<sub>2</sub>-1B | sPLA<sub>2</sub>-2A | sPLA<sub>2</sub>-2D | sPLA<sub>2</sub>-2E | sPLA<sub>2</sub>-2F |
|--------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| HGNC, UniProt| PLA2G1B, P04054    | PLA2G2A, P14555    | PLA2G2D, Q9UNK4    | PLA2G2E, Q9NZK7    | PLA2G2F, Q9BZM2    |

**Nomenclature**

| Nomenclature | sPLA<sub>2</sub>-3 | sPLA<sub>2</sub>-10 | sPLA<sub>2</sub>-12A | cPLA<sub>2</sub>-4A | cPLA<sub>2</sub>-4B |
|--------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| HGNC, UniProt| PLA2G3, Q9NZ20     | PLA2G10, Q15496    | PLA2G12A, Q9BZM1   | PLA2G4A, P47712    | PLA2G4B, P0C869    |
| Comments     | –                  | –                  | –                  | cPLA<sub>2</sub>-4A also expresses lysophospholipase (EC 3.1.1.5) activity [435]. | –                  |

**Nomenclature**

| Nomenclature | cPLA<sub>2</sub>-4C | cPLA<sub>2</sub>-4D | cPLA<sub>2</sub>-4E | cPLA<sub>2</sub>-4F |
|--------------|--------------------|--------------------|--------------------|--------------------|
| HGNC, UniProt| PLA2G4C, Q9UP6S    | PLA2G4D, Q86XP0    | PLA2G4E, Q3MJ16    | PLA2G4F, Q68DD2    |

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Comments: The sequence of PLA2-2C suggests a lack of catalytic activity, while PLA2-12B (GXIIIB, GXIII sPLA2-like) appears to be catalytically inactive [413]. 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 [12]. 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 [27]. PLA2-G7 and PAFAH2 also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47).

Phosphatidylcholine-specific phospholipase D

Enzymes → Glycerophospholipid turnover → Phosphatidylcholine-specific phospholipase D

Overview: Phosphatidylcholine-specific phospholipase D (PLD, EC 3.1.1.4) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidylation reaction [399].
**Lipid phosphate phosphatases**

**Enzymes → Glycerophospholipid turnover → Lipid phosphate phosphatases**

**Overview:** Lipid phosphate phosphatases, divided into phosphatidic acid phosphatases or lipins catalyse the dephosphorylation of phosphatidic acid (and other phosphorylated lipid derivatives) to generate inorganic phosphate and diacylglycerol. PTEN, a phosphatase and tensin homolog (BZS, MHAM, MMAC1, PTEN1, TEP1) is a phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase which acts as a tumour suppressor by reducing cellular levels of PI 3,4,5-P₃, 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, Q98QK | PPAP2A, O14494 | PPAP2B, O14495 | PPAP2C, 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 | 3.1.3.4 |
| Substrates  | –      | phosphatidic acid | –      | –     | phosphatidic acid | –     | phosphatidylinositol (3,4,5)-trisphosphate |

**Further Reading**

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Haem oxygenase

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

| Nomenclature  | Haem oxygenase 1 | Haem oxygenase 2 |
|---------------|-----------------|-----------------|
| Common abreviation | HO1             | HO2             |
| HGNC, UniProt  | HMOX1, P09601   | HMOX2, P30519   |
| EC number     | 1.14.99.3       | 1.14.99.3       |

**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 [202]. The chemical tin protoporphyrin IX acts as a haem oxygenase inhibitor in rat liver with an IC_{50} value of 11 nM [120].

**Further Reading**

Abraham NG et al. (2008) Pharmacological and clinical aspects of heme oxygenase. *Pharmacol. Rev.* **60**: 79-127 [PMID:18323402]

George EM et al. (2014) The heme oxygenases: important regulators of pregnancy and preeclampsia. *Ann. J. Physiol. Regul. Integr. Comp. Physiol.* **307**: R769-77 [PMID:24898840]

Gozzelino R et al. (2010) Mechanisms of cell protection by heme oxygenase-1. *Annu. Rev. Pharmacol. Toxictol.* **50**: 323-54 [PMID:20055707]

Poulos TL. (2014) Heme enzyme structure and function. *Chem. Rev.* **114**: 3919-62 [PMID:24400737]

Rochette L et al. (2015) Carbon monoxide: mechanisms of action and potential clinical implications. *Pharmacol. Ther.* **137**: 133-52 [PMID:23026155]

Wegiel B et al. (2013) The social network of carbon monoxide in medicine. *Trends Mol Med* **19**: 3-11 [PMID:23140858]
Hydrogen sulhide synthesis

Overview: Hydrogen sulhide is a putative gasotransmitter, with similarities to nitric oxide and carbon monoxide. Although the enzymes indicated have multiple enzymatic activities, the focus here is the generation of hydrogen sulhide and the enzymatic characteristics are described accordingly. Cystathionine β-synthase and cystathionine γ-lyase are pyridoxal phosphate-dependent enzymes, while 3-mercaptopyruvate sulfurtransferase functions as a pyridoxal phosphate-independent pathway.

| Nomenclature       | Cystathionine β-synthase | Cystathionine γ-lyase | L-Cysteine:2-oxoglutarate aminotransferase | 3-Mercaptopyruvate sulfurtransferase |
|--------------------|--------------------------|-----------------------|-----------------------------------------|-----------------------------------|
| Common abreviation | CBS                      | CSE                   | CAT                                     | MPST                              |
| HGNC, UniProt      | CBS, P35520              | CTH, P32929           | CCBL1, Q16773                           | MPST, P25325                      |
| EC number          | 4.2.1.22                 | 4.4.1.1               | 4.4.1.13                                | 2.8.1.2                           |
| Endogenous substrates | L-cysteine (K_m 6×10^{-3}M) [74], L-homocysteine | L-cysteine               | L-cysteine                             | 3-mercaptopyruvic acid (K_m 1.2×10^{-3}M) [345] |
| Products           | cystathionine            | NH_3, pyruvic acid    | NH_3, pyruvic acid                      | pyruvic acid                      |
| Cofactors          | pyridoxal phosphate      | pyridoxal phosphate   | pyridoxal phosphate                     | Zn^{2+}                           |
| Inhibitors         | aminooxyacetic acid      | propargylglycine       | –                                       | –                                 |

Further Reading

Beґtowski J. (2015) Hydrogen sulhide in pharmacology and medicine–An update. Pharmacol Rep 67: 647-58 [PMID:25933982]
Li L et al. (2011) Hydrogen sulhide and cell signaling. Annu. Rev. Pharmacol. Toxicol. 51: 169-87 [PMID:21210746]
Nagy P et al. (2014) Chemical aspects of hydrogen sulhide measurements in physiological samples. Biochim. Biophys. Acta 1840: 876-91 [PMID:23769856]
Wallace J.L et al. (2015) Hydrogen sulhide-based therapeutics: exploiting a unique but ubiquitous gasotransmitter. Nat Rev Drug Discov 14: 329-45 [PMID:25849904]
Wang R et al. (2015) The role of H2S bioavailability in endothelial dysfunction. Trends Pharmacol. Sci. [PMID:26071118]
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 aliphatc, 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, endothelial | carboxylesterase 1 | lipase, hormone-sensitive |
|---------------|-------------------|---------------------|--------------------|--------------------------|
| Common abbrev. | PNLIP              | LIPG                | CES1               | LIPE                     |
| 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                 |
| Inhibitors   | orlistat (pIC₅₀ 8.9) [51] | – | – | – |

Further Reading
Markey, G.M. (2011) Carboxylesterase 1 (Ces1): from monocyte marker to major player. J Clin Pathol 64: 107-109 [PMID:21177752]

Inositol phosphate turnover

Overview: The sugar alcohol D-myoinositol 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 phos-
**Inositol 1,4,5-trisphosphate 3-kinases**

Enzymes $\rightarrow$ Inositol phosphate turnover $\rightarrow$ Inositol 1,4,5-trisphosphate 3-kinases

**Overview:** Inositol 1,4,5-trisphosphate 3-kinases (E.C. 2.7.1.127, ENSFM00250000001260) catalyse the generation of inositol 1,3,4,5-tetrakisphosphate (IP$_4$) from IP$_3$. IP$_3$ kinase activity is enhanced in the presence of calcium/calmodulin (CALM1, CALM2, CALM3, P62158) [91].

**Inositol polyphosphate phosphatases**

Enzymes $\rightarrow$ Inositol phosphate turnover $\rightarrow$ Inositol polyphosphate phosphatases

**Overview:** Members of this family exhibit phosphatase activity towards IP$_3$, as well as towards other inositol derivatives, including the phospholipids PIP$_2$ and PIP$_3$. With IP$_3$ as substrate, 1-phosphatase (EC 3.1.3.57) generates 4,5-IP$_2$, 4-phosphatases (EC 3.1.3.66, ENSFM00250000001432) generate 1,5-IP$_2$ and 5-phosphatases (E.C. 3.1.3.36 or 3.1.3.56) generate 1,4-IP$_2$.

**Comments:** In vitro analysis suggested IP$_3$ and IP$_4$ were poor substrates for SKIP, synaptojanin 1 and synaptojanin 2, but suggested that PIP$_2$ and PIP$_3$ were more efficiently hydrolysed [422].

**Inositol monophosphatase**

Enzymes $\rightarrow$ Inositol phosphate turnover $\rightarrow$ Inositol monophosphatase

**Overview:** Inositol monophosphatase (E.C. 3.1.3.25, IMPase, myo-inositol-1(or 4)-phosphate phosphohydrolase) is a magnesium-dependent homodimer which hydrolyses myo-inositol monophosphate to generate myo-inositol and phosphate. Glycerol may be a physiological phosphate acceptor. Li$^+$ is a nonselective un-competitive inhibitor more potent at IMPase 1 ($pK_i$ ca. 3.5, [324]; $pIC_{50}$ 3.2, [359]) than IMPase 2 ($pIC_{50}$ 1.8-2.1, [359]). IMPase activity may be inhibited competitively by L690330 ($pK_i$ 5.5, [324]), although the enzyme selectivity is not yet established.

| Nomenclature | IMPase 1 | IMPase 2 |
|--------------|----------|----------|
| HGNC, UniProt| IMPA1, P29218 | IMPA2, O14732 |
| EC number   | 3.1.3.25 | 3.1.3.25 |
| Rank order of affinity | inositol 4-phosphate > inositol 3-phosphate > inositol 1-phosphate [324] | – |
| Inhibitors   | Li$^+$ ($pK_i$ 3.5) [324] | – |

**Comments:** Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder [443, 444, 540]. Disruption of the gene encoding IMPase 1, but not IMPase 2, appears to mimic the effects of Li$^+$ in mice [97, 98].

**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.13354/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full)
Further Reading

Barker CJ et al. (2013) New horizons in cellular regulation by inositol polyphosphates: insights from the pancreatic β-cell. *Pharmacol. Rev.* **65**, 641-69 [PMID:23429059]

Billcliff PG et al. (2014) Inositol lipid phosphatases in membrane trafficking and human disease. *Biochem. J.* **461**, 159-75 [PMID:24966051]

Chiu CT et al. (2010) Molecular actions and therapeutic potential of lithium in preclinical and clinical studies of CNS disorders. *Pharmacol. Ther.* **128**, 281-304 [PMID:20705090]

Pirruccello M et al. (2012) Inositol 5-phosphatases: insights from the Lowe syndrome protein OCRL. *Trends Biochem. Sci.* **37**, 134-43 [PMID:22381590]

Schell MJ. (2010) Inositol trisphosphate 3-kinases: focus on immune and neuronal signaling. *Cell. Mol. Life Sci.* **67**, 1755-78 [PMID:20066467]

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

| Nomenclature                           | HGNC, UniProt          | EC number                                      |
|----------------------------------------|------------------------|------------------------------------------------|
| acetyl-CoA acetyltransferase 1, acetyl-CoA acetyltransferase 2 | ACAT1, P24752, ACAT2, Q9BWD1 | 2.3.1.9: 2acetyl CoA = acetoacetyl CoA + coenzyme A |
| hydroxymethylglutaryl-CoA synthase 1, hydroxymethylglutaryl-CoA synthase 2 | HMGCS1, Q01581, HMGCS2, PS4868 | 2.3.3.10: acetyl CoA + H2O + acetoacetyl CoA --\(\rightarrow\) (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A |
| hydroxymethylglutaryl-CoA reductase | HMGCR, P04035         | 1.1.1.34: (S)-3-hydroxy-3-methylglutaryl-CoA + NADPH --\(\rightarrow\) (R)-mevalonate + coenzyme A + NADP* |
| mevalonate kinase                    | MVX, Q03426            | 2.7.1.36: ATP + (R)-mevalonate --\(\rightarrow\) (R)-5-phosphomevalonate |
| phosphomevalonate kinase             | PMVX, Q15126           | 2.7.4.2: ATP + (R)-5-phosphomevalonate --\(\rightarrow\) (R)-5-diphosphomevalonate |
| diphosphomevalonate decarboxylase    | MVD, PS3602            | 4.1.1.33: ATP + (R)-5-diphosphomevalonate --\(\rightarrow\) adenosine diphosphate + isopentenyl diphosphate + CO2 + PO34- |

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## Nomenclature

| Enzyme | Description | Inhibitors | Selective inhibitors |
|--------|-------------|------------|----------------------|
| HMGCoA reductase | | lovastatin (Competitive) ($pK_i$ 9.2) [8], rosuvastatin (Competitive) ($pIC_{50}$ 8.3) [228], cerivastatin (Competitive) ($pK_i$ 8.2) [61]. atorvastatin (Competitive) ($pIC_{50}$ 8.1) [228], simvastatin (Competitive) ($pIC_{50}$ 8) [228]. | |
| 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

- squalene synthase
- squalene monooxygenase
- lanosterol synthase

HGNC, UniProt

- FDFT1, P37268
- SQLE, Q14534
- LSS, P48449

EC number

- 2.5.1.21: trans,trans-farnesyl diphosphate -> presqualene diphosphate + diphosphate
- 1.14.13.132: H^+ + NADPH + O_2 + squalene + H_2O + NADP^+ + (S)-2,3-epoxysqualene
- 5.4.99.7: (S)-2,3-epoxysqualene = lanosterol

Cofactors

- NADPH
- –

Inhibitors

- zaragozic acid A (pK_i 10.1) [32] – Rat, zaragozic acid A (pIC_50 9.2) [188]
- –
- –

Further Reading

Miziorko HM. (2011) Enzymes of the mevalonate pathway of isoprenoid biosynthesis. Arch. Biochem. Biophys. 505: 131-43 [PMID:20932952]

Rozman D et al. (2010) Perspectives of the non-statin hypolipidemic agents. Pharmacol. Ther. 127: 19-40 [PMID:20420853]

Seiki S et al. (2009) Pharmacologic inhibition of squalene synthase and other downstream enzymes of the cholesterol synthesis pathway: a new therapeutic approach to treatment of hypercholesterolemia. Cardiol Rev 17: 70-6 [PMID:19367148]

Zhang H et al. (2014) Cholesterol and lipoprotein metabolism: Early Career Committee contribution. Arterioscler. Thromb. Vasc. Biol. 34: 1791-4 [PMID:25142876]

van der Burgh R et al. (2012) Mevalonate kinase deficiency, a metabolic autoinflammatory disease. Clin. Immunol. [PMID:23110805]

Nucleoside synthesis and metabolism

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

Nomenclature

- dihydrofolate reductase
- dihydroorotate dehydrogenase
- IMP (inosine 5'-monophosphate) dehydrogenase 1
- IMP (inosine 5'-monophosphate) dehydrogenase 2

HGNC, UniProt

- DHFR, P00374
- DHODH, Q02127
- IMPD1, P20839
- IMPDH2, P12268

EC number

- 1.5.1.3
- 1.3.5.2
- 1.1.1.205
- 1.1.1.205

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| Nomenclature                      | dihydrofolate reductase | dihydroorotate dehydrogenase (quinone) | IMP (inosine 5’-monophosphate) dehydrogenase 1 | IMP (inosine 5’-monophosphate) dehydrogenase 2 |
|----------------------------------|-------------------------|---------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Inhibitors**                   | pemetrexed \( p_{Ki} 8.1 \) [161, 436], pralatrexate \( p_{Ki} 7.3 \) [231] | teriflunomide \( p_{Ki} 7.5 \) [204], leflunomide \( p_{Ki} 4.9 \) [372] | mycophenolic acid \( p_{IC_{50}} 7.7 \) [351], ribavirin \( p_{IC_{50}} 5.6–6 \) [526], mycophenolate mofetil, thioguanine [124, 502] | mycophenolic acid \( p_{IC_{50}} 7.7 \) [351], ribavirin \( p_{IC_{50}} 5.6–6 \) [526], mycophenolate mofetil (See Inhibitor Comment below), thioguanine [124, 502] |
| **Selective inhibitors**         | methotrexate \( p_{Ki} 8.9 \) [412] | – | – | – |

**Nomenclature**

| Xanthine dehydrogenase          | Ribonucleotide reductase M1 | Ribonucleotide reductase M2 | Ribonucleotide reductase M2 B (TP53 inducible) |
|--------------------------------|-----------------------------|-----------------------------|-----------------------------------------------|
| HGNC, UniProt                   | XDH, P47989                 | RRM1, P23921                | RRM2, P31350                                  |
| EC number                       | 1.17.1.4                    | 1.17.14.1                   | 1.17.1.4                                     |
| **Inhibitors**                  | febuxostat \( p_{Ki} 9.9 \) [361] – Bovine, febuxostat \( p_{IC_{50}} 7.5 \) [255] – Bovine, allopurinol \( p_{IC_{50}} 5.4 \) [34], allopurinol \( p_{Ki} 5.2 \) [34] | clofarabine \( p_{IC_{50}} 8.3 \) [375], fludarabine \( p_{IC_{50}} 6 \) [491], hydroxyurea \( p_{IC_{50}} 3.8 \) [433], gemcitabine [205] | clofarabine \( p_{IC_{50}} 8.3 \) [375], fludarabine \( p_{IC_{50}} 6 \) [491], hydroxyurea \( p_{IC_{50}} 3.8 \) [433], gemcitabine [205] |

**Nomenclature**

| Thymidylate synthetase          | Phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminomimidazole synthetase | Purine nucleoside phosphorylase |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------|
| Common abbreviation             | –                                                                                                               | –                              |
| HGNC, UniProt                   | TYMS, P04818                                                                                                    | PNP, P00491                     |
| EC number                       | 2.1.1.45                                                                                                        | 2.1.2.2 6.3.3.1 6.3.4.13       |
Nomenclature

- thymidylate synthetase
- phosphoribosylglycinamide formyltransferase
- purine nucleoside phosphorylase

Inhibitors

- pemetrexed ($pK_i$ 7) [436], capcitabine [63, 373]
- pemetrexed ($pK_i$ 5) [436] – Mouse
- raltitrexed (pIC$_{50}$ 6.5) [162]

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 nucleotides.

Further Reading

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- Glander P et al. (2012) Inosine 5'-monophosphate dehydrogenase activity as a biomarker in the field of transplantation. Clin. Chim. Acta 413: 1391-7 [PMID:21889500]
- Munier-Lehmann H et al. (2013) On dihydroorotate dehydrogenases and their inhibitors and uses. J. Med. Chem. 56: 3148-67 [PMID:23452331]

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.

Further Reading

- Chan H et al. (2013) Post-translational regulation of sphingosine kinases. Biochim. Biophys. Acta 1831: 147-56 [PMID:22801036]
- Khavandgar Z et al. (2015) Sphingolipid metabolism and its role in the skeletal tissues. Cell. Mol. Life Sci. 72: 959-69 [PMID:25424644]
- Maceyka M et al. (2014) Sphingolipid metabolites in inflammatory disease. Nature 510: 58-67 [PMID:24893035]
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- Pyne S et al. (2011) Translational aspects of sphingosine 1-phosphate biology. Trends Mol Med 17: 463-72 [PMID:21514226]
- Rosen H et al. (2013) Sphingosine-1-phosphate and its receptors: structure, signaling, and influence. Annu. Rev. Biochem. 82: 637-62 [PMID:23527695]
- Schwalm S et al. (2014) Targeting the sphingosine kinase/sphingosine 1-phosphate pathway to treat chronic inflammatory kidney diseases. Basic Clin. Pharmacol. Toxicol. 114: 44-9 [PMID:23789924]
Sphingosine kinase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine kinase

| Nomenclature                      | sphingosine kinase 1, sphingosine kinase 2 |
|-----------------------------------|--------------------------------------------|
| Common abbreviation               | SPHK1, SPHK2                               |
| HGNC, UniProt                     | SPHK1, Q9NYA1 SPHK2, Q9NRA0                 |
| EC number                         | 2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + adenosine diphosphate |
|                                   | ATP + sphinganine = sphinganine 1-phosphate + adenosine diphosphate |
| Cofactors                         | Mg²⁺ [432]                                 |
| Inhibitors                        | PF-543 (pIC₅₀ 8.7) [425], SK1-I [377], ABC294640 [148], ROMe [287] |
| (Sub)family-selective inhibitors  | sphingosine kinase inhibitor (pIC₅₀ 6.3) [147] |

Further Reading

Neubauer HA et al. (2013) Roles, regulation and inhibitors of sphingosine kinase 2. *FEBS J.* **280:** 5317-36 [PMID:23638983]

Truman JP et al. (2014) Evolving concepts in cancer therapy through targeting sphingolipid metabolism. *Biochim. Biophys. Acta* **1841:** 1174-88 [PMID:24384461]

Sphingosine 1-phosphate phosphatase

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

| Nomenclature                      | sphingosine-1-phosphate phosphatase 1 | sphingosine-1-phosphate phosphatase 2 |
|-----------------------------------|--------------------------------------|--------------------------------------|
| Common abbreviation               | SCPP1                                 | SCPP2                                 |
| HGNC, UniProt                     | SCPP1, Q9BX95                         | SCPP2, Q8IWX5                         |
| EC number                         | 3.1.3.7: sphingosine 1-phosphate -> sphingosine + inorganic phosphate | 3.1.3.7: sphingosine 1-phosphate -> sphingosine + inorganic phosphate |
| Comments                          | Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [307]. |

Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [307].

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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 [PMID: 24809814] (pIC50 6.7) [519] |
| Comments                          | THI (2-Acetyl-5-tetrahydroxybutyl imidazole) inhibits the enzyme activity in intact cell preparations [426]. |

**Further Reading**

Bigaud M et al. (2014) Second generation S1P pathway modulators: research strategies and clinical developments. Biochim. Biophys. Acta 1841: 745-58 [PMID:24239768]

Van Veldhoven PP et al. (2000) Human sphingosine-1-phosphate lyase: cDNA cloning, functional expression studies and mapping to chromosome 10q22(1). Biochim. Biophys. Acta 1487: 128-34 [PMID:11018465]

**Thyroid hormone turnover**

Enzymes → Thyroid hormone turnover

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

**Tissue deiodinases**

These are 1 TM selenoproteins that remove an iodine from T4 (3,3',5,5'-tetraiodothyronine) to generate triiodothyronine (3,3',5-triiodothyronine, a more potent agonist at thyroid hormone receptors) or rT3 (3,3',5'-triiodothyronine, a relatively inactive analogue). DIO1 is also able to deiodinate RT3 to form 3,3'-diodothyronine (T2). Iodotyrosine deiodinase is a 1 TM homodimeric enzyme.
| Nomenclature                  | Enzyme Name                      | Type     | Enzyme Name                      | Type     | Enzyme Name                      | Type     | Enzyme Name                      | Type     |
|------------------------------|----------------------------------|----------|----------------------------------|----------|----------------------------------|----------|----------------------------------|----------|
| thyroid peroxidase           | deiodinase, iodothyronine        | type I   | deiodinase, iodothyronine        | type II  | deiodinase, iodothyronine        | type III | iodotyrosine deiodinase          |          |
| Common abbreviation          | TPO                              | DIO1     |                                  | DIO2     |                                  | DIO3     |                                  | IYD      |
| HGNC, UniProt                | TPO, P07202                      | DIO1, P49895 |                                | DIO2, Q92813 |                                | DIO3, P55073 |                                | IYD, Q6PHW0 |
| EC number                    | 1.11.1.8: [Thyroglobulin]-L-tyrosine + H₂O₂ + H⁺ + I⁻ → triiodothyronine | 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-iodothyronine → L-tyrosine + I⁻ | 3,5-diiodo-L-tyrosine → 3-iodothyronine + I⁻ |
| Cofactors                    | Ca²⁺                             |          |                                  |          |                                  |          |                                  | flavin adenine dinucleotide, NADPH |
| Inhibitors                   | methimazole [349]                |          |                                  |          |                                  |          |                                  |          |
|                               | propylthiouracil [349]           |          |                                  |          |                                  |          |                                  |          |
| Comments                     | Carbimazole is a pro-drug for    |          |                                  |          |                                  |          |                                  |          |
|                               | methimazole                      |          |                                  |          |                                  |          |                                  |          |

**Further Reading**

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Gereben B et al. (2008) Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. *Endocr. Rev.* 29: 898-938 [PMID:18815314]

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### 1.14.11.29 2-oxoglutarate oxygenases

**Overview:** The hypoxia inducible factor (HIF) is a transcriptional complex that is involved in oxygen homeostasis [429]. At normal oxygen levels, the alpha subunit of HIF (HIF-1α) is targeted for degradation by prolyl hydroxylation by the PHD proteins 1-3 (HIF-PHs) which are 2-oxoglutarate (2OG) oxygenases responsible for the post-translational modification of a specific proline in each of the oxygen-dependent degradation (ODD) domains of HIF-1α. Hydroxylated HIFs are then targeted for proteasomal degradation via the von Hippel-Lindau ubiquitination complex [232]. 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 [142]. Small molecule HIF-PH inhibitors are in clinical trial as novel therapies for the amelioration of anemia associated with chronic kidney disease [46].

| Nomenclature | egl-9 family hypoxia-inducible factor 2 | egl-9 family hypoxia-inducible factor 1 | egl-9 family hypoxia-inducible factor 3 |
|--------------|--------------------------------------|--------------------------------------|--------------------------------------|
| Common abreviation | PHD1 | PHD2 | PHD3 |
| HGNC, UniProt | EGLN2, Q96K30 | EGLN1, Q9GZT9 | EGLN3, Q9H6Z9 |
| EC number | – | 1.14.11.29 | 1.14.11.29 |
| Inhibitors | – | IOX2 (pIC₅₀ 7.7) [84] | – |

### 2.4.2.30 poly(ADP-ribose)polymerases

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

| Nomenclature | poly (ADP-ribose) polymerase 1 | poly (ADP-ribose) polymerase 2 | poly (ADP-ribose) polymerase 3 |
|--------------|---------------------------------|---------------------------------|---------------------------------|
| Common abreviation | PARP1 | PARP2 | PARP3 |
| HGNC, UniProt | PARP1, P09874 | PARP2, Q9UGN5 | PARP3, Q9Y6F1 |
| EC number | 2.4.2.30 | 2.4.2.30 | – |
| Selective inhibitors | AG14361 (pKᵢ 8.2) [445] | – | – |
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) [66]. 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) [156]. Farnesyltransferase is a dimer, composed of an alpha and beta subunit and requires Mg²⁺ and Zn²⁺ ions as cofactors. The active site is located between the subunits. Prenylation creates a hydrophobic domain on protein tails which acts as a membrane anchor. Substrates of the prenyltransferases include Ras, Rho, Rab, other Ras-related small GTP-binding proteins, G-protein γ-subunits, nuclear lamins, centromeric proteins and many proteins involved in visual signal transduction.

In relation to the causative association between oncogenic Ras proteins and cancer, farnesyltransferase has become an important mechanistic drug discovery target.

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. The human isozymes exhibit tissue-specific expression patterns [244].
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 I | carbonic anhydrase VII | carbonic anhydrase XII |
|---------------------|----------------------|------------------------|------------------------|
| HGNC, UniProt       | CA1, P00915          | CA7, P43166             | CA12, O43570           |
| EC number           | 4.2.1.1               | 4.2.1.1                 | 4.2.1.1                |
| Inhibitors          | chlorthalidone (pKᵢ 6.5) | methazolamide (pKᵢ 8.7) | chlorthalidone (pKᵢ 8.4) |

**Further Reading**

Alterio V *et al.* (2012) Multiple binding modes of inhibitors to carbonic anhydrases: how to design specific drugs targeting 15 different isoforms? *Chem. Rev.* **112**: 4421-68 [PMID:22607219]

Cummins EP *et al*. (2014) Carbon dioxide-sensing in organisms and its implications for human disease. *Cell. Mol. Life Sci.* **71**: 831-45 [PMID:24045706]

Imtaiyaz Hassan M *et al.* (2013) Structure, function and applications of carbonic anhydrase isozymes. *Bioorg. Med. Chem.* **21**: 1570-82 [PMID:22607884]

Sjöblom M. (2011) Duodenal epithelial sensing of luminal acid: role of carbonic anhydrases. *Acta Physiol (Oxf)* **201**: 85-95 [PMID:20632999]

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 170kDa |
|-------------------------------|-----------------------|-----------------------------------|
| HGNC, UniProt                 | TOP1, P11387           | TOP2A, P11388                      |
| EC number                     | 5.99.1.2               | 5.99.1.2                           |
| Inhibitors                    | irinotecan [117, 477] – Bovine | etoposide (pIC₅₀ 7.3), teniposide [119] – Mouse |

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.13354/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13354/full)
Castelli S et al. (2012) Interaction between natural compounds and human topoisomerase I. Biol. Chem. 393: 1127-40 [PMID:23109546]
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