The Enzyme List
Class 6 — Ligases

Nomenclature Committee
of the
International Union of Biochemistry and Molecular Biology
(NC-IUBMB)

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Generated from the ExplorEnz database, May 2023

Contents

EC 6.1 Forming carbon-oxygen bonds

This subclass contains a single sub-subclass for enzymes that acylate a tRNA with the corresponding amino acid, forming a carbon-oxygen bond (amino-acid—tRNA ligases; EC 6.1.1).

EC 6.1.1 Ligases forming aminoacyl-tRNA and related compounds

EC 6.1.1.1

Accepted name: tyrosine—tRNA ligase
Reaction: ATP + L-tyrosine + $tRNA^{Tyr}$ = AMP + diphosphate + L-tyrosyl-$tRNA^{Tyr}$
Systematic name: L-tyrosine:$tRNA^{Tyr}$ ligase (AMP-forming)
References: [10, 89, 190, 454, 52]

[EC 6.1.1.1 created 1961, modified 2002]

EC 6.1.1.2

Accepted name: tryptophan—tRNA ligase
Reaction: ATP + L-tryptophan + $tRNA^{Trp}$ = AMP + diphosphate + L-tryptophyl-$tRNA^{Trp}$
Other name(s): tryptophanyl-tRNA synthetase; L-tryptophan-$tRNA^{Trp}$ ligase (AMP-forming); tryptophanyl-transfer ribonucleate synthetase; tryptophanyl-transfer ribonucleic acid synthetase; tryptophanyl-transfer RNA synthetase; tryptophanyl ribonucleic synthetase; tryptophanyl-transfer ribonucleic synthetase; tryptophanyl-tRNA synthase; tryptophan translase; TrpRS
Systematic name: L-tryptophan:$tRNA^{Trp}$ ligase (AMP-forming)
References: [99, 399, 551]

[EC 6.1.1.2 created 1961, modified 2002]

EC 6.1.1.3

Accepted name: threonine—tRNA ligase
Reaction: ATP + L-threonine + $tRNA^{Thr}$ = AMP + diphosphate + L-threonyl-$tRNA^{Thr}$
Other name(s): threonyl-tRNA synthetase; threonyl-transfer ribonucleate synthetase; threonyl-transfer RNA synthetase; threonyl-transfer ribonucleic acid synthetase; threonyl ribonucleic synthetase; threonine-transfer ribonucleate synthetase; threonine translase; threonyl-tRNA synthetase; TRS
Systematic name: L-threonine:$tRNA^{Thr}$ ligase (AMP-forming)
References: [10, 190]

[EC 6.1.1.3 created 1961]

EC 6.1.1.4

Accepted name: leucine—tRNA ligase
Reaction: ATP + L-leucine + $tRNA^{Leu}$ = AMP + diphosphate + L-leucyl-$tRNA^{Leu}$
Other name(s): leucyl-tRNA synthetase; leucyl-transfer ribonucleate synthetase; leucyl-transfer RNA synthetase; leucyl-transfer ribonucleic acid synthetase; leucine-tRNA synthetase; leucine translase
Systematic name: L-leucine:$tRNA^{Leu}$ ligase (AMP-forming)
References: [10, 38, 39]

[EC 6.1.1.4 created 1961]

EC 6.1.1.5

Accepted name: isoleucine—tRNA ligase

Reaction: ATP + L-isoleucine + $tRNA^{Ile}$ = AMP + diphosphate + L-isoleucyl-$tRNA^{Ile}$
Other name(s): isoleucyl-tRNA synthetase; isoleucyl-transfer ribonucleate synthetase; isoleucyl-transfer RNA synthetase; isoleucine-transfer RNA ligase; isoleucine-tRNA synthetase; isoleucine translase
Systematic name: L-isoleucine:$tRNA^{Ile}$ ligase (AMP-forming)
References: [10, 38, 39]

[EC 6.1.1.5 created 1961]

EC 6.1.1.6
Accepted name: lysine—tRNA ligase
Reaction: ATP + L-lysine + $tRNA^{Lys}$ = AMP + diphosphate + L-lysyl-$tRNA^{Lys}$
Other name(s): lysyl-tRNA synthetase; lysyl-transfer ribonucleate synthetase; lysyl-transfer RNA synthetase; L-lysine-transfer RNA ligase; lysine-tRNA synthetase; lysine translase
Systematic name: L-lysine:$tRNA^{Lys}$ ligase (AMP-forming)
References: [10, 76, 254, 478]

[EC 6.1.1.6 created 1961]

EC 6.1.1.7
Accepted name: alanine—tRNA ligase
Reaction: ATP + L-alanine + $tRNA^{Ala}$ = AMP + diphosphate + L-alanyl-$tRNA^{Ala}$
Other name(s): alanyl-tRNA synthetase; alanyl-transfer ribonucleate synthetase; alanyl-transfer RNA synthetase; alanyl-transfer ribonucleic acid synthetase; alanine-transfer RNA ligase; alanine transfer RNA synthetase; alanine tRNA synthetase; alanine translase; alanyl-transfer ribonucleate synthase; AlaRS; Ala-tRNA synthetase
Systematic name: L-alanine:$tRNA^{Ala}$ ligase (AMP-forming)
References: [191, 535]

[EC 6.1.1.7 created 1961]

[6.1.1.8 Deleted entry. D-alanine-sRNA synthetase]

[EC 6.1.1.8 created 1961, deleted 1965]

EC 6.1.1.9
Accepted name: valine—tRNA ligase
Reaction: ATP + L-valine + $tRNA^{Val}$ = AMP + diphosphate + L-valyl-$tRNA^{Val}$
Other name(s): valyl-tRNA synthetase; valyl-transfer ribonucleate synthetase; valyl-transfer RNA synthetase; valyl-transfer ribonucleic acid synthetase; valine transfer ribonucleate ligase; valine translase
Systematic name: L-valine:$tRNA^{Val}$ ligase (AMP-forming)
References: [38, 39]

[EC 6.1.1.9 created 1961]

EC 6.1.1.10
Accepted name: methionine—tRNA ligase
Reaction: ATP + L-methionine + $tRNA^{Met}$ = AMP + diphosphate + L-methionyl-$tRNA^{Met}$
Other name(s): methionyl-tRNA synthetase; methionyl-transfer ribonucleic acid synthetase; methionyl-transfer ribonucleate synthetase; methionyl-transfer RNA synthetase; methionine translase; MetRS
Systematic name: L-methionine:$tRNA^{Met}$ ligase (AMP-forming)
Comments: In those organisms producing *N*-formylmethionyl-$tRNA^{fMet}$ for translation initiation, this enzyme also recognizes the initiator $tRNA^{fMet}$ and catalyses the formation of L-methionyl-$tRNA^{fMet}$, the substrate for EC 2.1.2.9, methionyl-tRNA formyltransferase.

References: [39, 261]

[EC 6.1.1.10 created 1961, modified 2002]

EC 6.1.1.11

Accepted name: serine—tRNA ligase
Reaction: ATP + L-serine + $tRNA^{Ser}$ = AMP + diphosphate + L-seryl-$tRNA^{Ser}$
Other name(s): seryl-tRNA synthetase; SerRS; seryl-transfer ribonucleate synthetase; seryl-transfer RNA synthetase; seryl-transfer ribonucleic acid synthetase; serine translase
Systematic name: L-serine:$tRNA^{Ser}$ ligase (AMP-forming)
Comments: This enzyme also recognizes $tRNA^{Sec}$, the special tRNA for selenocysteine, and catalyses the formation of L-seryl-$tRNA^{Sec}$, the substrate for EC 2.9.1.1, L-seryl-$tRNA^{Sec}$ selenium transferase.
References: [226, 291, 537, 371]

[EC 6.1.1.11 created 1961, modified 2002]

EC 6.1.1.12

Accepted name: aspartate—tRNA ligase
Reaction: ATP + L-aspartate + $tRNA^{Asp}$ = AMP + diphosphate + L-aspartyl-$tRNA^{Asp}$
Other name(s): aspartyl-tRNA synthetase; aspartyl ribonucleic synthetase; aspartyl-transfer RNA synthetase; aspartic acid translase; aspartyl-transfer ribonucleic acid synthetase; aspartyl ribonucleate synthetase
Systematic name: L-aspartate:$tRNA^{Asp}$ ligase (AMP-forming)
References: [147, 367]

[EC 6.1.1.12 created 1965]

EC 6.1.1.13

Accepted name: D-alanine—poly(phosphoribitol) ligase
Reaction: ATP + D-alanine + poly(ribitol phosphate) = AMP + diphosphate + *O*-D-alanyl-poly(ribitol phosphate)
Other name(s): D-alanyl-poly(phosphoribitol) synthetase; D-alanine: membrane acceptor ligase; D-alanine-D-alanyl carrier protein ligase; D-alanine-membrane acceptor ligase; D-alanine-activating enzyme
Systematic name: D-alanine:poly(phosphoribitol) ligase (AMP-forming)
Comments: A thioester bond is formed transiently between D-alanine and the sulfhydryl group of the 4′-phosphopantetheine prosthetic group of D-alanyl carrier protein during the activation of the alanine. Involved in the synthesis of teichoic acids.
References: [26, 422, 388, 180, 103]

[EC 6.1.1.13 created 1965, modified 2001]

EC 6.1.1.14

Accepted name: glycine—tRNA ligase
Reaction: ATP + glycine + $tRNA^{Gly}$ = AMP + diphosphate + glycyl-$tRNA^{Gly}$
Other name(s): glycyl-tRNA synthetase; glycyl-transfer ribonucleate synthetase; glycyl-transfer RNA synthetase; glycyl-transfer ribonucleic acid synthetase; glycyl translase
Systematic name: glycine:$tRNA^{Gly}$ ligase (AMP-forming)
References: [137, 362]

[EC 6.1.1.14 created 1972]

EC 6.1.1.15

Accepted name: proline—tRNA ligase
Reaction: ATP + L-proline + $tRNA^{Pro}$ = AMP + diphosphate + L-prolyl-$tRNA^{Pro}$
Other name(s): prolyl-tRNA synthetase; prolyl-transferRNA synthetase; prolyl-transfer ribonucleate synthetase; proline translase; prolyl-transfer ribonucleic acid synthetase; prolyl-s-RNA synthetase; prolinyl-tRNA ligase
Systematic name: L-proline:$tRNA^{Pro}$ ligase (AMP-forming)
References: [366, 391]

[EC 6.1.1.15 created 1972]

EC 6.1.1.16

Accepted name: cysteine—tRNA ligase
Reaction: ATP + L-cysteine + $tRNA^{Cys}$ = AMP + diphosphate + L-cysteinyl-$tRNA^{Cys}$
Other name(s): cysteinyl-tRNA synthetase; cysteinyl-transferRNA synthetase; cysteinyl-transfer ribonucleate synthetase; cysteine translase
Systematic name: L-cysteine:$tRNA^{Cys}$ ligase (AMP-forming)
References: [312]

[EC 6.1.1.16 created 1972]

EC 6.1.1.17

Accepted name: glutamate—tRNA ligase
Reaction: ATP + L-glutamate + $tRNA^{Glu}$ = AMP + diphosphate + L-glutamyl-$tRNA^{Glu}$
Other name(s): glutamyl-tRNA synthetase; glutamyl-transfer ribonucleate synthetase; glutamyl-transfer RNA synthetase; glutamyl-transfer ribonucleic acid synthetase; glutamate-tRNA synthetase; glutamic acid translase
Systematic name: L-glutamate:$tRNA^{Glu}$ ligase (AMP-forming)
References: [414]

[EC 6.1.1.17 created 1972]

EC 6.1.1.18

Accepted name: glutamine—tRNA ligase
Reaction: ATP + L-glutamine + $tRNA^{Gln}$ = AMP + diphosphate + L-glutaminyl-$tRNA^{Gln}$
Other name(s): glutaminyl-tRNA synthetase; glutaminyl-transfer RNA synthetase; glutaminyl-transfer ribonucleate synthetase; glutamine-tRNA synthetase; glutamine translase; glutamate-tRNA ligase; glutaminyl ribonucleic acid; GlnRS
Systematic name: L-glutamine:$tRNA^{Gln}$ ligase (AMP-forming)
References: [414]

[EC 6.1.1.18 created 1972]

EC 6.1.1.19

Accepted name: arginine—tRNA ligase
Reaction: ATP + L-arginine + $tRNA^{Arg}$ = AMP + diphosphate + L-arginyl-$tRNA^{Arg}$
Other name(s): arginyl-tRNA synthetase; arginyl-transfer ribonucleate synthetase; arginyl-transfer RNA synthetase; arginyl transfer ribonucleic acid synthetase; arginine-tRNA synthetase; arginine translase
Systematic name: L-arginine:$tRNA^{Arg}$ ligase (AMP-forming)
References: [12, 317, 333]

[EC 6.1.1.19 created 1972]

EC 6.1.1.20

Accepted name: phenylalanine—tRNA ligase
Reaction: ATP + L-phenylalanine + $tRNA^{Phe}$ = AMP + diphosphate + L-phenylalanyl-$tRNA^{Phe}$
Other name(s): phenylalanyl-tRNA synthetase; phenylalanyl-transfer ribonucleate synthetase; phenylalanine-tRNA synthetase; phenylalanyl-transfer RNA synthetase; phenylalanyl-tRNA ligase; phenylalanyl-transfer RNA ligase; L-phenylalanyl-tRNA synthetase; phenylalanine translase
Systematic name: L-phenylalanine:$tRNA^{Phe}$ ligase (AMP-forming)
References: [481]

[EC 6.1.1.20 created 1972]

EC 6.1.1.21

Accepted name: histidine—tRNA ligase
Reaction: ATP + L-histidine + $tRNA^{His}$ = AMP + diphosphate + L-histidyl-$tRNA^{His}$
Other name(s): histidyl-tRNA synthetase; histidyl-transfer ribonucleate synthetase; histidine translase
Systematic name: L-histidine:$tRNA^{His}$ ligase (AMP-forming)
References: [504]

[EC 6.1.1.21 created 1972]

EC 6.1.1.22

Accepted name: asparagine—tRNA ligase
Reaction: ATP + L-asparagine + $tRNA^{Asn}$ = AMP + diphosphate + L-asparaginyl-$tRNA^{Asn}$
Other name(s): asparaginyl-tRNA synthetase; asparaginyl-transfer ribonucleate synthetase; asparaginyl transfer RNA synthetase; asparaginyl transfer ribonucleic acid synthetase; asparagyl-transfer RNA synthetase; asparagine translase
Systematic name: L-asparagine:$tRNA^{Asn}$ ligase (AMP-forming)
References: [100]

[EC 6.1.1.22 created 1976]

EC 6.1.1.23

Accepted name: aspartate—$tRNA^{Asn}$ ligase
Reaction: ATP + L-aspartate + $tRNA^{Asx}$ = AMP + diphosphate + L-aspartyl-$tRNA^{Asx}$
Other name(s): nondiscriminating aspartyl-tRNA synthetase
Systematic name: L-aspartate:$tRNA^{Asx}$ ligase (AMP-forming)
Comments: When this enzyme acts on $tRNA^{Asp}$, it catalyses the same reaction as EC 6.1.1.12, aspartate—tRNA ligase. It has, however, diminished discrimination, so that it can also form aspartyl-$tRNA^{Asn}$. This relaxation of specificity has been found to result from the absence of a loop in the tRNA that specifically recognizes the third position of the anticodon [202]. This accounts for the ability of this enzyme in, for example, *Thermus thermophilus*, to recognize both $tRNA^{Asp}$ (GUC anticodon) and $tRNA^{Asn}$ (GUU anticodon). The aspartyl-$tRNA^{Asn}$ is not used in protein synthesis until it is converted by EC 6.3.5.6, asparaginyl-tRNA synthase (glutamine-hydrolysing), into asparaginyl-$tRNA^{Asn}$.
References: [202, 449, 31]

[EC 6.1.1.23 created 2002]

EC 6.1.1.24

Accepted name: glutamate—$tRNA^{Gln}$ ligase
Reaction: ATP + L-glutamate + $tRNA^{Glx}$ = AMP + diphosphate + L-glutamyl-$tRNA^{Glx}$
Other name(s): nondiscriminating glutamyl-tRNA synthetase
Systematic name: L-glutamate:$tRNA^{Glx}$ ligase (AMP-forming)

Comments: When this enzyme acts on $tRNA^{Glu}$, it catalyses the same reaction as EC 6.1.1.17, glutamate—tRNA ligase. It has, however, diminished discrimination, so that it can also form glutamyl-$tRNA^{Gln}$. This relaxation of specificity has been found to result from the absence of a loop in the tRNA that specifically recognizes the third position of the anticodon [202]. This accounts for the ability of this enzyme in, for example, *Bacillus subtilis*, to recognize both $tRNA_1^{Gln}$ (UUG anticodon) and $tRNA^{Glu}$ (UUC anticodon) but not $tRNA_2^{Gln}$ (CUG anticodon). The ability of this enzyme to recognize both $tRNA^{Glu}$ and one of the $tRNA^{Gln}$ isoacceptors derives from their sharing a major identity element, a hypermodified derivative of U^{34} (5-methylaminomethyl-2-thiouridine). The glutamyl-$tRNA^{Gln}$ is not used in protein synthesis until it is converted by EC 6.3.5.7, glutaminyl-tRNA synthase (glutamine-hydrolysing), into glutaminyl-$tRNA^{Gln}$.
References: [202, 449, 235]

[EC 6.1.1.24 created 2002]

[6.1.1.25 Deleted entry. lysine—$tRNA^{Pyl}$ ligase. The $tRNA^{Pyl}$ is now known only to be charged with pyrrolysine (cf. EC 6.1.1.26).]

[EC 6.1.1.25 created 2002, deleted 2012]

EC 6.1.1.26

Accepted name: pyrrolysine—$tRNA^{Pyl}$ ligase
Reaction: ATP + L-pyrrolysine + $tRNA^{Pyl}$ = AMP + diphosphate + L-pyrrolysyl-$tRNA^{Pyl}$
Other name(s): PylS; pyrrolysyl-tRNA synthetase
Systematic name: L-pyrrolysine:$tRNA^{Pyl}$ ligase (AMP-forming)
Comments: In organisms such as *Methanosarcina barkeri* that incorporate the modified amino acid pyrrolysine (Pyl) into certain methylamine methyltransferases, an unusual $tRNA^{Pyl}$, with a CUA anticodon, can be charged directly with pyrrolysine by this class II aminoacyl—tRNA ligase. The enzyme is specific for pyrrolysine as substrate as it cannot be replaced by lysine or any of the other natural amino acids [44].
References: [44, 397, 447]

[EC 6.1.1.26 created 2007]

EC 6.1.1.27

Accepted name: *O*-phospho-L-serine—tRNA ligase
Reaction: ATP + *O*-phospho-L-serine + $tRNA^{Cys}$ = AMP + diphosphate + *O*-phospho-L-seryl-$tRNA^{Cys}$
Other name(s): *O*-phosphoseryl-tRNA ligase; non-canonical *O*-phosphoseryl-tRNA synthetase; SepRS
Systematic name: *O*-phospho-L-serine:$tRNA^{Cys}$ ligase (AMP-forming)
Comments: In organisms like *Archaeoglobus fulgidus* lacking EC 6.1.1.16 (cysteine—tRNA ligase) for the direct Cys-$tRNA^{Cys}$ formation, Cys-$tRNA^{Cys}$ is produced by an indirect pathway, in which EC 6.1.1.27 (*O*-phosphoseryl-tRNA ligase) ligates *O*-phosphoserine to $tRNA^{Cys}$, and EC 2.5.1.73 (*O*-phospho-L-seryl-tRNA: Cys-tRNA synthase) converts the produced *O*-phospho-L-seryl-$tRNA^{Cys}$ to Cys-$tRNA^{Cys}$. The SepRS/SepCysS pathway is the sole route for cysteine biosynthesis in the organism [144]. *Methanosarcina mazei* can use both pathways, the direct route using EC 6.1.1.16 (cysteine—tRNA ligase) and the indirect pathway with EC 6.1.1.27 and EC 2.5.1.73 (*O*-phospho-L-seryl-tRNA: Cys-tRNA synthase) [178].
References: [144, 178]

[EC 6.1.1.27 created 2009]

[6.1.1.28 Deleted entry. proline/cysteine—tRNA ligase. Later published work having demonstrated that this was not a genuine enzyme, EC 6.1.1.28 was withdrawn at the public-review stage before being made official.]

[EC 6.1.1.28 created 2014, deleted 2014]

EC 6.1.2 acidâ€”alcohol ligases (ester synthases)

EC 6.1.2.1

Accepted name: D-alanine—(*R*)-lactate ligase
Reaction: D-alanine + (*R*)-lactate + ATP = D-alanyl-(*R*)-lactate + ADP + phosphate
Other name(s): VanA; VanB; VanD
Systematic name: D-alanine:(*R*)-lactate ligase (ADP-forming)
Comments: The product of this enzyme, the depsipeptide D-alanyl-(*R*)-lactate, can be incorporated into the peptidoglycan pentapeptide instead of the usual D-alanyl-D-alanine dipeptide, which is formed by EC 6.3.2.4, D-alanine—D-alanine ligase. The resulting peptidoglycan does not bind the glycopeptide antibiotics vancomycin and teicoplanin, conferring resistance on the bacteria.
References: [56, 327, 390]

[EC 6.1.2.1 created 2010]

EC 6.1.2.2

Accepted name: nebramycin 5′ synthase
Reaction: (1) tobramycin + carbamoyl phosphate + ATP + H_2O = nebramycin 5′ + AMP + diphosphate + phosphate (overall reaction)
(1a) carbamoyl phosphate + ATP + H_2O = diphosphate + *O*-carbamoyladenylate + phosphate
(1b) *O*-carbamoyladenylate + tobramycin = AMP + nebramycin 5′
(2) kanamycin A + carbamoyl phosphate + ATP + H_2O = 6″-*O*-carbamoylkanamycin A + AMP + diphosphate + phosphate (overall reaction)
(2a) carbamoyl phosphate + ATP + H_2O = diphosphate + *O*-carbamoyladenylate + phosphate
(2b) *O*-carbamoyladenylate + kanamycin A = AMP + 6″-*O*-carbamoylkanamycin A
Other name(s): tobramycin carbamoyltransferase; TobZ
Systematic name: tobramycin:carbamoyl phosphate ligase (AMP,phosphate-forming)
Comments: Requires Fe(III). The enzyme from the bacterium *Streptoalloteichus tenebrarius* catalyses the activation of carbamoyl phosphate to *O*-carbamoyladenylate and the subsequent carbamoylation of kanamycin and tobramycin.
References: [385]

[EC 6.1.2.2 created 2014]

EC 6.1.3 Cyclo-ligases

EC 6.1.3.1

Accepted name: olefin β-lactone synthetase
Reaction: ATP + a (2*R*,3*S*)-2-alkyl-3-hydroxyalkanoate = AMP + diphosphate + a *cis*-3-alkyl-4-alkyloxetan-2-one
Other name(s): *oleC* (gene name)
Systematic name: (2*R*,3*S*)-2-alkyl-3-hydroxyalkanoate ligase (β-lactone,AMP-forming)
Comments: The enzyme, found in certain bacterial species, participates in a pathway for the production of olefins. It forms a β-lactone. The alkyl group at C^2 of the substrate ends up as the 3-alkyl group of the product.
References: [484, 139, 224, 79]

[EC 6.1.3.1 created 2017]

EC 6.2 Forming carbon-sulfur bonds

This subclass contains enzymes that use the energy from NTP hydrolysis to catalyse the attachment of an acyl group to the sulfur atom of 4'-phosphopantetheine groups in coenzyme A and acyl-binding proteins, or of a cysteine residue, forming a carbon-sulfur bond.

EC 6.2.1 Acid-thiol ligases

EC 6.2.1.1

Accepted name: acetate—CoA ligase
Reaction: ATP + acetate + CoA = AMP + diphosphate + acetyl-CoA
Other name(s): acetyl-CoA synthetase; acetyl activating enzyme; acetate thiokinase; acyl-activating enzyme; acetyl coenzyme A synthetase; acetic thiokinase; acetyl CoA ligase; acetyl CoA synthase; acetyl-coenzyme A synthase; short chain fatty acyl-CoA synthetase; short-chain acyl-coenzyme A synthetase; ACS
Systematic name: acetate:CoA ligase (AMP-forming)
Comments: Also acts on propanoate and propenoate.
References: [78, 123, 182, 329]

[EC 6.2.1.1 created 1961]

EC 6.2.1.2

Accepted name: medium-chain acyl-CoA ligase
Reaction: ATP + a medium-chain fatty acid + CoA = AMP + diphosphate + a medium-chain acyl-CoA
Other name(s): *fadK* (gene name); *lvaE* (gene name); butyryl-CoA synthetase; fatty acid thiokinase (medium chain); acyl-activating enzyme; fatty acid elongase; fatty acid activating enzyme; fatty acyl coenzyme A synthetase; butyrate—CoA ligase; butyryl-coenzyme A synthetase; L-(+)-3-hydroxybutyryl CoA ligase; short-chain acyl-CoA synthetase; medium-chain acyl-CoA synthetase; butanoate:CoA ligase (AMP-forming)
Systematic name: medium-chain fatty acid:CoA ligase (AMP-forming)
Comments: Acts on fatty acids from C_4 to C_{11} and on the corresponding 3-hydroxy and 2,3- or 3,4-unsaturated acids. The enzyme from the bacterium *Pseudomonas putida* also acts on 4-oxo and 4-hydroxy derivatives.
References: [290, 301, 538, 339, 408]

[EC 6.2.1.2 created 1961, modified 2011, modified 2018]

EC 6.2.1.3

Accepted name: long-chain-fatty-acid—CoA ligase
Reaction: ATP + a long-chain fatty acid + CoA = AMP + diphosphate + an acyl-CoA
Other name(s): acyl-CoA synthetase; fatty acid thiokinase (long chain); acyl-activating enzyme; palmitoyl-CoA synthase; lignoceroyl-CoA synthase; arachidonyl-CoA synthetase; acyl coenzyme A synthetase; acyl-CoA ligase; palmitoyl coenzyme A synthetase; thiokinase; palmitoyl-CoA ligase; acyl-coenzyme A ligase; fatty acid CoA ligase; long-chain fatty acyl coenzyme A synthetase; oleoyl-CoA synthetase; stearoyl-CoA synthetase; long chain fatty acyl-CoA synthetase; long-chain acyl CoA synthetase; fatty acid elongase; LCFA synthetase; pristanoyl-CoA synthetase; ACS3; long-chain acyl-CoA synthetase I; long-chain acyl-CoA synthetase II; fatty acyl-coenzyme A synthetase; long-chain acyl-coenzyme A synthetase; FAA1
Systematic name: long-chain fatty acid:CoA ligase (AMP-forming)
Comments: Acts on a wide range of long-chain saturated and unsaturated fatty acids, but the enzymes from different tissues show some variation in specificity. The liver enzyme acts on acids from C_6 to C_{20}; that from brain shows high activity up to C_{24}.
References: [27, 196, 348, 496]

[EC 6.2.1.3 created 1961, modified 1989, modified 2011]

EC 6.2.1.4

Accepted name: succinate—CoA ligase (GDP-forming)
Reaction: GTP + succinate + CoA = GDP + phosphate + succinyl-CoA
Other name(s): succinyl-CoA synthetase (GDP-forming); succinyl coenzyme A synthetase (guanosine diphosphate-forming); succinate thiokinase (ambiguous); succinic thiokinase (ambiguous); succinyl coenzyme A synthetase (ambiguous); succinate-phosphorylating enzyme (ambiguous); P-enzyme; SCS (ambiguous); G-STK; succinyl coenzyme A synthetase (GDP-forming); succinyl CoA synthetase (ambiguous)
Systematic name: succinate:CoA ligase (GDP-forming)
Comments: Itaconate can act instead of succinate, and ITP instead of GTP.
References: [174, 229, 309, 439]

[EC 6.2.1.4 created 1961]

EC 6.2.1.5

Accepted name: succinate—CoA ligase (ADP-forming)
Reaction: ATP + succinate + CoA = ADP + phosphate + succinyl-CoA
Other name(s): succinyl-CoA synthetase (ADP-forming); succinic thiokinase (ambiguous); succinate thiokinase (ambiguous); succinyl-CoA synthetase (ambiguous); succinyl coenzyme A synthetase (adenosine diphosphate-forming); succinyl coenzyme A synthetase (ambiguous); A-STK (adenin nucleotide-linked succinate thiokinase); STK (ambiguous); A-SCS
Systematic name: succinate:CoA ligase (ADP-forming)
References: [174, 227, 228]

[EC 6.2.1.5 created 1961]

EC 6.2.1.6

Accepted name: glutarate—CoA ligase
Reaction: ATP + glutarate + CoA = ADP + phosphate + glutaryl-CoA
Other name(s): glutaryl-CoA synthetase; glutaryl coenzyme A synthetase
Systematic name: glutarate:CoA ligase (ADP-forming)
Comments: GTP or ITP can act instead of ATP.
References: [323]

[EC 6.2.1.6 created 1961]

EC 6.2.1.7

Accepted name: cholate—CoA ligase
Reaction: (1) ATP + cholate + CoA = AMP + diphosphate + choloyl-CoA
(2) ATP + (25*R*)-3α,7α,12α-trihydroxy-5β-cholestan-26-oate + CoA = AMP + diphosphate + (25*R*)-3α,7α,12α-trihydroxy-5β-cholestanoyl-CoA
Other name(s): BAL; bile acid CoA ligase; bile acid coenzyme A ligase; choloyl-CoA synthetase; choloyl coenzyme A synthetase; cholic thiokinase; cholate thiokinase; cholic acid:CoA ligase; 3α,7α,12α-trihydroxy-5β-cholestanoyl coenzyme A synthetase; 3α,7α,12α-trihydroxy-5β-cholestanoate-CoA ligase; 3α,7α,12α-trihydroxy-5β-cholestanoate-CoA synthetase; THCA-CoA ligase; 3α,7α,12α-trihydroxy-5β-cholestanate—CoA ligase; 3α,7α,12α-trihydroxy-5β-cholestanate:CoA ligase (AMP-forming); cholyl-CoA synthetase; trihydroxycoprostanoyl-CoA synthetase
Systematic name: cholate:CoA ligase (AMP-forming)

Comments: Requires Mg^{2+} for activity. The mammalian enzyme is membrane-bound and catalyses the first step in the conjugation of bile acids with amino acids, converting bile acids into their acyl-CoA thioesters. Chenodeoxycholate, deoxycholate, lithocholate and trihydroxycoprostanoate can also act as substrates [128]. The bacterial enzyme is soluble and participates in an anaerobic bile acid 7 α-dehydroxylation pathway [292].
References: [125, 126, 400, 446, 292, 542, 128]

[EC 6.2.1.7 created 1961 (EC 6.2.1.29 created 1992, incorporated 2005), modified 2005]

EC 6.2.1.8
Accepted name: oxalate—CoA ligase
Reaction: ATP + oxalate + CoA = AMP + diphosphate + oxalyl-CoA
Other name(s): oxalyl-CoA synthetase; oxalyl coenzyme A synthetase
Systematic name: oxalate:CoA ligase (AMP-forming)
References: [158]

[EC 6.2.1.8 created 1972]

EC 6.2.1.9
Accepted name: malate—CoA ligase
Reaction: ATP + malate + CoA = ADP + phosphate + malyl-CoA
Other name(s): malyl-CoA synthetase; malyl coenzyme A synthetase; malate thiokinase
Systematic name: malate:CoA ligase (ADP-forming)
References: [343]

[EC 6.2.1.9 created 1972]

EC 6.2.1.10
Accepted name: carboxylic acid—CoA ligase (GDP-forming)
Reaction: GTP + a carboxylate + CoA = GDP + phosphate + acyl-CoA
Other name(s): acyl-CoA synthetase (GDP-forming); acyl coenzyme A synthetase (guanosine diphosphate forming)
Systematic name: carboxylic acid:CoA ligase (GDP-forming)
References: [433]

[EC 6.2.1.10 created 1972, modified 2011]

EC 6.2.1.11
Accepted name: biotin—CoA ligase
Reaction: ATP + biotin + CoA = AMP + diphosphate + biotinyl-CoA
Other name(s): biotinyl-CoA synthetase; biotin CoA synthetase; biotinyl coenzyme A synthetase
Systematic name: biotin:CoA ligase (AMP-forming)
References: [80]

[EC 6.2.1.11 created 1972]

EC 6.2.1.12
Accepted name: 4-coumarate—CoA ligase
Reaction: ATP + 4-coumarate + CoA = AMP + diphosphate + 4-coumaroyl-CoA

Other name(s): 4-coumaroyl-CoA synthetase; *p*-coumaroyl CoA ligase; *p*-coumaryl coenzyme A synthetase; *p*-coumaryl-CoA synthetase; *p*-coumaryl-CoA ligase; feruloyl CoA ligase; hydroxycinnamoyl CoA synthetase; 4-coumarate:coenzyme A ligase; caffeolyl coenzyme A synthetase; *p*-hydroxycinnamoyl coenzyme A synthetase; feruloyl coenzyme A synthetase; sinapoyl coenzyme A synthetase; 4-coumaryl-CoA synthetase; hydroxycinnamate:CoA ligase; *p*-coumaryl-CoA ligase; *p*-hydroxycinnamic acid:CoA ligase; 4CL
Systematic name: 4-coumarate:CoA ligase (AMP-forming)
References: [167, 275]

[EC 6.2.1.12 created 1976]

EC 6.2.1.13
Accepted name: acetate—CoA ligase (ADP-forming)
Reaction: ATP + acetate + CoA = ADP + phosphate + acetyl-CoA
Other name(s): acetyl-CoA synthetase (ADP-forming); acetyl coenzyme A synthetase (adenosine diphosphate-forming); acetate thiokinase
Systematic name: acetate:CoA ligase (ADP-forming)
Comments: Also acts on propanoate and, very slowly, on butanoate.
References: [416]

[EC 6.2.1.13 created 1978]

EC 6.2.1.14
Accepted name: 6-carboxyhexanoate—CoA ligase
Reaction: ATP + 6-carboxyhexanoate + CoA = AMP + diphosphate + 6-carboxyhexanoyl-CoA
Other name(s): 6-carboxyhexanoyl-CoA synthetase; pimelyl-CoA synthetase
Systematic name: 6-carboxyhexanoate:CoA ligase (AMP-forming)
References: [211, 212]

[EC 6.2.1.14 created 1983]

EC 6.2.1.15
Accepted name: arachidonate—CoA ligase
Reaction: ATP + arachidonate + CoA = AMP + diphosphate + arachidonoyl-CoA
Other name(s): arachidonoyl-CoA synthetase
Systematic name: arachidonate:CoA ligase (AMP-forming)
Comments: Not identical with EC 6.2.1.3 long-chain-fatty-acid—CoA ligase. Icosa-8,11,14-trienoate, but not the other long-chain fatty acids, can act in place of arachidonate.
References: [546]

[EC 6.2.1.15 created 1984]

EC 6.2.1.16
Accepted name: acetoacetate—CoA ligase
Reaction: ATP + acetoacetate + CoA = AMP + diphosphate + acetoacetyl-CoA
Other name(s): acetoacetyl-CoA synthetase
Systematic name: acetoacetate:CoA ligase (AMP-forming)
Comments: Also acts, more slowly, on L-3-hydroxybutanoate.
References: [143]

[EC 6.2.1.16 created 1984]

EC 6.2.1.17

Accepted name: propionate—CoA ligase
Reaction: ATP + propanoate + CoA = AMP + diphosphate + propanoyl-CoA
Other name(s): propionyl-CoA synthetase
Systematic name: propanoate:CoA ligase (AMP-forming)
Comments: Propenoate can act instead of propanoate. Not identical with EC 6.2.1.1 (acetate—CoA ligase) or EC 6.2.1.2 (butyrate—CoA ligase).
References: [424]

[EC 6.2.1.17 created 1984]

EC 6.2.1.18

Accepted name: citrate—CoA ligase
Reaction: ATP + citrate + CoA = ADP + phosphate + (3*S*)-citryl-CoA
Other name(s): citryl-CoA synthetase; citrate:CoA ligase; citrate thiokinase
Systematic name: citrate:CoA ligase (ADP-forming)
Comments: The enzyme is a component of EC 2.3.3.8 ATP citrate synthase.
References: [273, 19]

[EC 6.2.1.18 created 1986]

EC 6.2.1.19

Accepted name: long-chain-fatty-acid—protein ligase
Reaction: ATP + a long-chain fatty acid + [protein]-L-cysteine = AMP + diphosphate + a [protein]-*S*-(long-chain-acyl)-L-cysteine
Other name(s): *luxE* (gene name); acyl-protein synthetase; long-chain-fatty-acid—luciferin-component ligase
Systematic name: long-chain-fatty-acid:protein ligase (AMP-forming)
Comments: Together with a hydrolase component (EC 3.1.2.2/EC 3.1.2.14) and a reductase component (EC 1.2.1.50), this enzyme forms a multienzyme fatty acid reductase complex that produces the long-chain aldehyde substrate of the bacterial luciferase enzyme (EC 1.14.14.3). The enzyme activates free long-chain fatty acids, generated by the action of the transferase component, forming a fatty acyl-AMP intermediate, followed by the transfer of the acyl group to an internal L-cysteine residue. It then transfers the acyl group to EC 1.2.1.50, long-chain acyl-protein thioester reductase.
References: [425, 427, 530, 468, 274]

[EC 6.2.1.19 created 1986, modified 2011, modified 2016]

EC 6.2.1.20

Accepted name: long-chain-fatty-acid—[acyl-carrier-protein] ligase
Reaction: ATP + a long-chain fatty acid + an [acyl-carrier protein] = AMP + diphosphate + a long-chain acyl-[acyl-carrier protein]
Other name(s): acyl-[acyl-carrier-protein] synthetase (ambiguous); acyl-ACP synthetase (ambiguous); stearoyl-ACP synthetase; acyl-acyl carrier protein synthetase (ambiguous); long-chain-fatty-acid:[acyl-carrier-protein] ligase (AMP-forming)
Systematic name: long-chain-fatty-acid:[acyl-carrier protein] ligase (AMP-forming)
Comments: The enzyme ligates long chain fatty acids (with aliphatic chain of 13-22 carbons) to an acyl-carrier protein. Not identical with EC 6.2.1.3 long-chain-fatty-acid—CoA ligase.
References: [505, 220]

[EC 6.2.1.20 created 1986]

[6.2.1.21 Deleted entry. phenylacetate—CoA ligase. Activity covered by EC 6.2.1.30, phenylacetate—CoA ligase]

[EC 6.2.1.21 created 1986, deleted 2001]

EC 6.2.1.22

Accepted name: [citrate (*pro*-3*S*)-lyase] ligase
Reaction: ATP + acetate + holo-[citrate (*pro*-3*S*)-lyase] = AMP + diphosphate + acetyl-[citrate (*pro*-3*S*)-lyase]
Other name(s): citrate lyase ligase; citrate lyase synthetase; acetate: SH-[acyl-carrier-protein] enzyme ligase (AMP); acetate:HS-citrate lyase ligase; acetate:citrate-(*pro*-3*S*)-lyase(thiol-form) ligase (AMP-forming); acetate:[citrate-(*pro*-3*S*)-lyase](thiol-form) ligase (AMP-forming)
Systematic name: acetate:holo-[citrate-(*pro*-3*S*)-lyase] ligase (AMP-forming)
Comments: Both this enzyme and EC 2.3.1.49,deacetyl-[citrate-(*pro*-3*S*)-lyase] *S*-acetyltransferase, acetylate and activate EC 4.1.3.6, citrate (*pro*-3*S*)-lyase.
References: [15, 16, 402, 448]

[EC 6.2.1.22 created 1989]

EC 6.2.1.23

Accepted name: dicarboxylate—CoA ligase
Reaction: ATP + an α,ω-dicarboxylate + CoA = AMP + diphosphate + an ω-carboxyacyl-CoA
Other name(s): carboxylyl-CoA synthetase; dicarboxylyl-CoA synthetase
Systematic name: ω-dicarboxylate:CoA ligase (AMP-forming)
Comments: Acts on dicarboxylic acids of chain length C_5 to C_{16}; the best substrate is dodecanedioic acid.
References: [516]

[EC 6.2.1.23 created 1989, modified 2011]

EC 6.2.1.24

Accepted name: phytanate—CoA ligase
Reaction: ATP + phytanate + CoA = AMP + diphosphate + phytanoyl-CoA
Other name(s): phytanoyl-CoA ligase
Systematic name: phytanate:CoA ligase (AMP-forming)
Comments: Not identical with EC 6.2.1.20 long-chain-fatty-acid—[acyl-carrier-protein] ligase.
References: [346]

[EC 6.2.1.24 created 1989]

EC 6.2.1.25

Accepted name: benzoate—CoA ligase
Reaction: ATP + benzoate + CoA = AMP + diphosphate + benzoyl-CoA
Other name(s): benzoate—coenzyme A ligase; benzoyl-coenzyme A synthetase; benzoyl CoA synthetase (AMP forming)
Systematic name: benzoate:CoA ligase (AMP-forming)
Comments: Also acts on 2-, 3- and 4-fluorobenzoate, but only very slowly on the corresponding chlorobenzoates.
References: [199, 445]

[EC 6.2.1.25 created 1989]

EC 6.2.1.26

Accepted name: *o*-succinylbenzoate—CoA ligase
Reaction: ATP + 2-succinylbenzoate + CoA = AMP + diphosphate + 4-(2-carboxyphenyl)-4-oxobutanoyl-CoA
Other name(s): *o*-succinylbenzoyl-coenzyme A synthetase; *o*-succinylbenzoate:CoA ligase (AMP-forming)
Systematic name: 2-succinylbenzoate:CoA ligase (AMP-forming)
References: [181, 242, 316]

[EC 6.2.1.26 created 1992]

EC 6.2.1.27

Accepted name: 4-hydroxybenzoate—CoA ligase
Reaction: ATP + 4-hydroxybenzoate + CoA = AMP + diphosphate + 4-hydroxybenzoyl-CoA
Other name(s): 4-hydroxybenzoate-CoA synthetase; 4-hydroxybenzoate—coenzyme A ligase (AMP-forming); 4-hydroxybenzoyl coenzyme A synthetase; 4-hydroxybenzoyl-CoA ligase
Systematic name: 4-hydroxybenzoate:CoA ligase (AMP-forming)
References: [324]

[EC 6.2.1.27 created 1992]

EC 6.2.1.28

Accepted name: 3α,7α-dihydroxy-5β-cholestanate—CoA ligase
Reaction: ATP + (25*R*)-3α,7α-dihydroxy-5β-cholestan-26-oate + CoA = AMP + diphosphate + (25*R*)-3α,7α-dihydroxy-5β-cholestanoyl-CoA
Other name(s): 3α,7α-dihydroxy-5β-cholestanoyl coenzyme A synthetase; DHCA-CoA ligase; 3α,7α-dihydroxy-5β-cholestanate:CoA ligase (AMP-forming)
Systematic name: (25*R*)-3α,7α-dihydroxy-5β-cholestan-26-oate:CoA ligase (AMP-forming)
References: [400]

[EC 6.2.1.28 created 1992]

[6.2.1.29 Deleted entry. 3α,7α,12α-trihydroxy-5β-cholestanate—CoA ligase. The enzyme is identical to EC 6.2.1.7, cholate—CoA ligase]

[EC 6.2.1.29 created 1992, deleted 2005]

EC 6.2.1.30

Accepted name: phenylacetate—CoA ligase
Reaction: ATP + phenylacetate + CoA = AMP + diphosphate + phenylacetyl-CoA
Other name(s): phenacyl coenzyme A synthetase; phenylacetyl-CoA ligase; PA-CoA ligase; phenylacetyl-CoA ligase (AMP-forming)
Systematic name: phenylacetate:CoA ligase (AMP-forming)
Comments: Also acts, more slowly, on acetate, propanoate and butanoate, but not on hydroxy derivatives of phenylacetate and related compounds.
References: [299]

[EC 6.2.1.30 created 1992 (EC 6.2.1.21 created 1986, incorporated 2001)]

EC 6.2.1.31

Accepted name: 2-furoate—CoA ligase
Reaction: ATP + 2-furoate + CoA = AMP + diphosphate + 2-furoyl-CoA
Other name(s): 2-furoyl coenzyme A synthetase
Systematic name: 2-furoate:CoA ligase (AMP-forming)
References: [241]

[EC 6.2.1.31 created 1992]

EC 6.2.1.32

Accepted name: anthranilate—CoA ligase
Reaction: ATP + anthranilate + CoA = AMP + diphosphate + anthraniloyl-CoA
Other name(s): anthraniloyl coenzyme A synthetase; 2-aminobenzoate—CoA ligase; 2-aminobenzoate—coenzyme A ligase; 2-aminobenzoate coenzyme A ligase
Systematic name: anthranilate:CoA ligase (AMP-forming)

References: [13]

[EC 6.2.1.32 created 1992]

EC 6.2.1.33

Accepted name: 4-chlorobenzoate—CoA ligase
Reaction: 4-chlorobenzoate + CoA + ATP = 4-chlorobenzoyl-CoA + AMP + diphosphate
Systematic name: 4-chlorobenzoate:CoA ligase
Comments: Requires Mg^{2+}. This enzyme is part of the bacterial 2,4-dichlorobenzoate degradation pathway.
References: [116, 279, 69]

[EC 6.2.1.33 created 1999]

EC 6.2.1.34

Accepted name: *trans*-feruloyl-CoA synthase
Reaction: ferulic acid + CoA + ATP = feruloyl-CoA + products of ATP breakdown
Other name(s): *trans*-feruloyl-CoA synthetase; *trans*-ferulate:CoASH ligase (ATP-hydrolysing); ferulate:CoASH ligase (ATP-hydrolysing)
Systematic name: ferulate:CoA ligase (ATP-hydrolysing)
Comments: Requires Mg^{2+}. It has not yet been established whether AMP + diphosphate or ADP + phosphate are formed in this reaction.
References: [356, 398]

[EC 6.2.1.34 created 2000]

EC 6.2.1.35

Accepted name: acetate—[acyl-carrier protein] ligase
Reaction: ATP + acetate + an [acyl-carrier protein] = AMP + diphosphate + an acetyl-[acyl-carrier protein]
Other name(s): HS-acyl-carrier protein:acetate ligase; [acyl-carrier protein]:acetate ligase; MadH; ACP-SH:acetate ligase
Systematic name: acetate:[acyl-carrier-protein] ligase (AMP-forming)
Comments: This enzyme, from the anaerobic bacterium *Malonomonas rubra*, is a component of the multienzyme complex EC 7.2.4.4, biotin-dependent malonate decarboxylase. The enzyme uses the energy from hydrolysis of ATP to convert the thiol group of the acyl-carrier-protein-bound 2′-(5-phosphoribosyl)-3′-dephospho-CoA prosthetic group into its acetyl thioester [36].
References: [185, 36, 37, 110]

[EC 6.2.1.35 created 2008, modified 2018]

EC 6.2.1.36

Accepted name: 3-hydroxypropionyl-CoA synthase
Reaction: 3-hydroxypropanoate + ATP + CoA = 3-hydroxypropanoyl-CoA + AMP + diphosphate
Other name(s): 3-hydroxypropionyl-CoA synthetase (AMP-forming); 3-hydroxypropionate—CoA ligase
Systematic name: hydroxypropanoate:CoA ligase (AMP-forming)
Comments: Catalyses a step in the 3-hydroxypropanoate/4-hydroxybutanoate cycle, an autotrophic CO_2 fixation pathway found in some thermoacidophilic archaea [35, 9].The enzymes from *Metallosphaera sedula* and *Sulfolobus tokodaii* can also use propionate, acrylate, acetate, and butanoate as substrates [9], and are thus different from EC 6.2.1.17 (propionate—CoA ligase), which does not accept acetate or butanoate.
References: [35, 9]

[EC 6.2.1.36 created 2009]

EC 6.2.1.37

Accepted name: 3-hydroxybenzoate—CoA ligase
Reaction: ATP + 3-hydroxybenzoate + CoA = AMP + diphosphate + 3-hydroxybenzoyl-CoA
Other name(s): 3-hydroxybenzoyl-CoA synthetase; 3-hydroxybenzoate—coenzyme A ligase (AMP-forming); 3-hydroxybenzoyl coenzyme A synthetase; 3-hydroxybenzoyl-CoA ligase
Systematic name: 3-hydroxybenzoate:CoA ligase (AMP-forming)
Comments: The enzyme works equally well with 4-hydroxybenzoate but shows low activity towards benzoate, 4-aminobenzoate, 3-aminobenzoate, 3-fluorobenzoate, 4-fluorobenzoate, 3-chlorobenzoate, and 4-chlorobenzoate. There is no activity with 3,4-dihydroxybenzoate, 2,3-dihydroxybenzoate, and 2-hydroxybenzoate as substrates.
References: [252]

[EC 6.2.1.37 created 2011]

EC 6.2.1.38

Accepted name: (2,2,3-trimethyl-5-oxocyclopent-3-enyl)acetyl-CoA synthase
Reaction: [(1*R*)-2,2,3-trimethyl-5-oxocyclopent-3-enyl]acetate + ATP + CoA = AMP + diphosphate + [(1*R*)-2,2,3-trimethyl-5-oxocyclopent-3-enyl]acetyl-CoA
Other name(s): 2-oxo-Δ^3-4,5,5-trimethylcyclopentenylacetyl-CoA synthetase
Systematic name: [(1*R*)-2,2,3-trimethyl-5-oxocyclopent-3-enyl]acetate:CoA ligase (AMP-forming)
Comments: Isolated from *Pseudomonas putida*. Forms part of the pathway of camphor catabolism.
References: [376]

[EC 6.2.1.38 created 2012]

EC 6.2.1.39

Accepted name: [butirosin acyl-carrier protein]—L-glutamate ligase
Reaction: (1) ATP + L-glutamate + BtrI acyl-carrier protein = ADP + phosphate + L-glutamyl-[BtrI acyl-carrier protein]
(2) ATP + L-glutamate + 4-amino butanoyl-[BtrI acyl-carrier protein] = ADP + phosphate + 4-(γ-L-glutamylamino)butanoyl-[BtrI acyl-carrier protein]
Other name(s): [BtrI acyl-carrier protein]—L-glutamate ligase; BtrJ
Systematic name: [BtrI acyl-carrier protein]:L-glutamate ligase (ADP-forming)
Comments: Catalyses two steps in the biosynthesis of the side chain of the aminoglycoside antibiotics of the butirosin family. The enzyme adds one molecule of L-glutamate to a dedicated acyl-carrier protein, and following decarboxylation of the product by EC 4.1.1.95, L-glutamyl-[BtrI acyl-carrier protein] decarboxylase, adds a second L-glutamate molecule. Requires Mg^{2+} or Mn^{2+}, and activity is enhanced in the presence of Mn^{2+}.
References: [270]

[EC 6.2.1.39 created 2012]

EC 6.2.1.40

Accepted name: 4-hydroxybutyrate—CoA ligase (AMP-forming)
Reaction: ATP + 4-hydroxybutanoate + CoA = AMP + diphosphate + 4-hydroxybutanoyl-CoA
Other name(s): 4-hydroxybutyrate-CoA synthetase (ambiguous); 4-hydroxybutyrate:CoA ligase (ambiguous); *hbs* (gene name); 4-hydroxybutyrate—CoA ligase
Systematic name: 4-hydroxybutanoate:CoA ligase (AMP-forming)
Comments: Isolated from the archaeon *Metallosphaera sedula*. Involved in the 3-hydroxypropanoate/4-hydroxybutanoate cycle. *cf.* EC 6.2.1.56, 4-hydroxybutyrate—CoA ligase (ADP-forming).
References: [407, 179]

[EC 6.2.1.40 created 2014, modified 2019]

EC 6.2.1.41

Accepted name: 3-[(3a*S*,4*S*,7a*S*)-7a-methyl-1,5-dioxo-octahydro-1*H*-inden-4-yl]propanoate—CoA ligase
Reaction: ATP + 3-[(3a*S*,4*S*,7a*S*)-7a-methyl-1,5-dioxo-octahydro-1*H*-inden-4-yl]propanoate + CoA = AMP + diphosphate + 3-[(3a*S*,4*S*,7a*S*)-7a-methyl-1,5-dioxo-octahydro-1*H*-inden-4-yl]propanoyl-CoA
Other name(s): *fadD*3 (gene name); HIP—CoA ligase
Systematic name: 3-[(3a*S*,4*S*,7a*S*)-7a-methyl-1,5-dioxo-octahydro-1*H*-inden-4-yl]propanoate:CoA ligase (AMP-forming)
Comments: The enzyme, characterized from actinobacterium *Mycobacterium tuberculosis*, catalyses a step in the degradation of cholesterol and cholate. The enzyme is very specific for its substrate, and requires that the side chain at C^{17} is completely removed.
References: [194, 60]

[EC 6.2.1.41 created 2014]

EC 6.2.1.42

Accepted name: 3-oxocholest-4-en-26-oate—CoA ligase
Reaction: ATP + (25*S*)-3-oxocholest-4-en-26-oate + CoA = AMP + diphosphate + (25*S*)-3-oxocholest-4-en-26-oyl-CoA
Other name(s): *fadD*19 (gene name)
Systematic name: (25*S*)-3-oxocholest-4-en-26-oate:CoA ligase (AMP-forming)
Comments: The enzyme, characterized from actinobacterium *Mycobacterium tuberculosis*, catalyses a step in the degradation of cholesterol. It is responsible for the activation of the C_8 side chain. 3β-hydroxycholest-5-en-26-oate can also be used as substrate.
References: [544, 61]

[EC 6.2.1.42 created 2014]

EC 6.2.1.43

Accepted name: 2-hydroxy-7-methoxy-5-methyl-1-naphthoate—CoA ligase
Reaction: ATP + 2-hydroxy-7-methoxy-5-methyl-1-naphthoate + CoA = AMP + diphosphate + 2-hydroxy-7-methoxy-5-methyl-1-naphthoyl-CoA
Other name(s): NcsB2
Systematic name: 2-hydroxy-7-methoxy-5-methyl-1-naphthoate:CoA ligase
Comments: The enzyme from the bacterium *Streptomyces carzinostaticus* is involved in the attachment of the 2-hydroxy-7-methoxy-5-methyl-1-naphthoate moiety of the antibiotic neocarzinostatin. *In vitro* the enzyme also catalyses the activation of other 1-naphthoic acid analogues, e.g. 2-hydroxy-5-methyl-1-naphthoate or 2,7-dihydroxy-5-methyl-1-naphthoate.
References: [85]

[EC 6.2.1.43 created 2014]

EC 6.2.1.44

Accepted name: 3-(methylthio)propionyl—CoA ligase
Reaction: ATP + 3-(methylsulfanyl)propanoate + CoA = AMP + diphosphate + 3-(methylsulfanyl)propanoyl-CoA
Other name(s): DmdB; MMPA-CoA ligase; methylmercaptopropionate-coenzyme A ligase; 3-methylmercaptopropionyl-CoA ligase; 3-(methylthio)propanoate:CoA ligase (AMP-forming)
Systematic name: 3-(methylsulfanyl)propanoate:CoA ligase (AMP-forming)
Comments: The enzyme is part of a dimethylsulfoniopropanoate demethylation pathway in the marine bacteria *Ruegeria pomeroyi* and *Pelagibacter ubique*. It also occurs in some nonmarine bacteria capable of metabolizing dimethylsulfoniopropionate (e.g. *Burkholderia thailandensis*, *Pseudomonas aeruginosa*, and *Silicibacter lacuscaerulensis*). It requires Mg^{2+} [57].
References: [421, 57]

[EC 6.2.1.44 created 2014]

EC 6.2.1.45

Accepted name: E1 ubiquitin-activating enzyme
Reaction: ATP + ubiquitin + [E1 ubiquitin-activating enzyme]-L-cysteine = AMP + diphosphate + *S*-ubiquitinyl-[E1 ubiquitin-activating enzyme]-L-cysteine
Other name(s): ubiquitin activating enzyme; E1; ubiquitin-activating enzyme E1
Systematic name: ubiquitin:[E1 ubiquitin-activating enzyme] ligase (AMP-forming)
Comments: Catalyses the ATP-dependent activation of ubiquitin through the formation of a thioester bond between the C-terminal glycine of ubiquitin and the sulfhydryl side group of a cysteine residue in the E1 protein. The two-step reaction consists of the ATP-dependent formation of an *E*1-ubiquitin adenylate intermediate in which the C-terminal glycine of ubiquitin is bound to AMP via an acyl-phosphate linkage, then followed by the conversion to an *E*1-ubiquitin thioester bond via the cysteine residue on E1 in the second step.
References: [173, 201, 567, 59]

[EC 6.2.1.45 created 2015]

EC 6.2.1.46

Accepted name: L-*allo*-isoleucine—holo-[CmaA peptidyl-carrier protein] ligase
Reaction: ATP + L-*allo*-isoleucine + holo-[CmaA peptidyl-carrier protein] = AMP + diphosphate + L-*allo*-isoleucyl-[CmaA peptidyl-carrier protein]
Other name(s): CmaA
Systematic name: L-*allo*-isoleucine:holo-[CmaA peptidyl-carrier protein] ligase (AMP-forming)
Comments: This two-domain protein from the bacterium *Pseudomonas syringae* contains an adenylation domain (A domain) and a thiolation domain (T domain). It catalyses the adenylation of L-*allo*-isoleucine and its attachment to the T domain. The enzyme is involved in the biosynthesis of the toxin coronatine, which mimics the plant hormone jasmonic acid isoleucine. Coronatine promotes opening of the plant stomata allowing bacterial invasion, which is followed by bacterial growth in the apoplast, systemic susceptibility, and disease.
References: [88]

[EC 6.2.1.46 created 2015]

EC 6.2.1.47

Accepted name: medium-chain-fatty-acid—[acyl-carrier-protein] ligase
Reaction: ATP + a medium-chain fatty acid + a holo-[acyl-carrier protein] = AMP + diphosphate + a medium-chain acyl-[acyl-carrier protein]
Other name(s): *jamA* (gene name)
Systematic name: medium-chain-fatty-acid:[acyl-carrier protein] ligase (AMP-forming)
Comments: The enzyme ligates medium chain fatty acids (with aliphatic chain of 6-12 carbons) to an acyl-carrier protein.
References: [120, 570]

[EC 6.2.1.47 created 2016]

EC 6.2.1.48

Accepted name: carnitine—CoA ligase
Reaction: ATP + L-carnitine + CoA = AMP + diphosphate + L-carnitinyl-CoA
Other name(s): *caiC* (gene name)
Systematic name: L-carnitine:CoA ligase (AMP-forming)

Comments: The enzyme, originally characterized from the bacterium *Escherichia coli*, can catalyse the transfer of CoA to L-carnitine, crotonobetaine and γ-butyrobetaine. *In vitro* the enzyme also exhibits the activity of EC 2.8.3.21, L-carnitine CoA-transferase.
References: [122, 40]

[EC 6.2.1.48 created 2017]

EC 6.2.1.49
Accepted name: long-chain fatty acid adenylyltransferase FadD28
Reaction: ATP + a long-chain fatty acid + holo-[mycocerosate synthase] = AMP + diphosphate + a long-chain acyl-[mycocerosate synthase] (overall reaction)
(1a) ATP + a long-chain fatty acid = diphosphate + a long-chain acyl-adenylate ester
(1b) a long-chain acyl-adenylate ester + holo-[mycocerosate synthase] = AMP + a long-chain acyl-[mycocerosate synthase]
Other name(s): *fadD*28 (gene name)
Systematic name: long-chain fatty acid:holo-[mycocerosate synthase] ligase (AMP-forming)
Comments: The enzyme, found in certain mycobacteria, activates long-chain fatty acids by adenylation and transfers them to EC 2.3.1.111, mycocerosate synthase. The enzyme participates in the biosynthesis of the virulent lipids dimycocerosates (DIM) and dimycocerosyl triglycosyl phenolphthiocerol (PGL).
References: [134, 163, 23, 321, 521]

[EC 6.2.1.49 created 2016 as EC 2.7.7.95, transferred 2017 to EC 6.2.1.49]

EC 6.2.1.50
Accepted name: 4-hydroxybenzoate adenylyltransferase FadD22
Reaction: ATP + 4-hydroxybenzoate + holo-[4-hydroxyphenylalkanoate synthase] = AMP + diphosphate + 4-hydroxybenzoyl-[4-hydroxyphenylalkanoate synthase] (overall reaction)
(1a) ATP + 4-hydroxybenzoate = 4-hydroxybenzoyl-adenylate + diphosphate
(1b) 4-hydroxybenzoyl-adenylate + holo-[4-hydroxyphenylalkanoate synthase] = AMP + 4-hydroxybenzoyl-[4-hydroxyphenylalkanoate synthase]
Other name(s): *fadD*22 (gene name); 4-hydroxybenzoate adenylase
Systematic name: 4-hydroxybenzoate:holo-[4-hydroxyphenylalkanoate synthase] ligase (AMP-forming)
Comments: This mycobacterial enzyme participates in the biosynthesis of phenolphthiocerols. Following the substrate's activation by adenylation, it is transferred to an acyl-carrier protein domain within the enzyme, from which it is transferred to EC 2.3.1.261, 4-hydroxyphenylalkanoate synthase.
References: [463, 521]

[EC 6.2.1.50 created 2017 as EC 2.7.7.98, transferred 2017 to EC 6.2.1.50]

EC 6.2.1.51
Accepted name: 4-hydroxyphenylalkanoate adenylyltransferase FadD29
Reaction: (1) ATP + 17-(4-hydroxyphenyl)heptadecanoate + holo-[(phenol)carboxyphthiodiolenone synthase] = AMP + diphosphate + 17-(4-hydroxyphenyl)heptadecanoyl-[(phenol)carboxyphthiodiolenone synthase]
(1a) ATP + 17-(4-hydroxyphenyl)heptadecanoate = diphosphate + 17-(4-hydroxyphenyl)heptadecanoyl-adenylate
(1b) 17-(4-hydroxyphenyl)heptadecanoyl-adenylate + holo-[(phenol)carboxyphthiodiolenone synthase] = AMP + 17-(4-hydroxyphenyl)heptadecanoyl-[(phenol)carboxyphthiodiolenone synthase]
(2) ATP + 19-(4-hydroxyphenyl)nonadecanoate + holo-[(phenol)carboxyphthiodiolenone synthase] = AMP + diphosphate + 19-(4-hydroxyphenyl)nonadecanoyl-[(phenol)carboxyphthiodiolenone synthase]
(2a) ATP + 19-(4-hydroxyphenyl)nonadecanoate = diphosphate + 19-(4-hydroxyphenyl)nonadecanoyl-adenylate

(2b) 19-(4-hydroxyphenyl)nonadecanoyl-adenylate + holo-[(phenol)carboxyphthiodiolenone synthase] = AMP + 19-(4-hydroxyphenyl)nonadecanoyl-[(phenol)carboxyphthiodiolenone synthase]

Other name(s): *fadD*29 (gene name); 4-hydroxyphenylalkanoate adenylase
Systematic name: 4-hydroxyphenylalkanoate:holo-[(phenol)carboxyphthiodiolenone synthase] ligase
Comments: The mycobacterial enzyme participates in the biosynthesis of phenolphthiocerols. Following the substrate's activation by adenylation, it is transferred to an acyl-carrier protein domain within the enzyme, from which it is transferred to the phenolphthiocerol/phthiocerol polyketide synthase.
References: [463, 521]

[EC 6.2.1.51 created 2016 as EC 2.7.7.94, transferred 2017 to EC 6.2.1.51]

EC 6.2.1.52

Accepted name: L-firefly luciferin—CoA ligase
Reaction: ATP + L-firefly luciferin + CoA = AMP + diphosphate + L-firefly luciferyl-CoA
Other name(s): LUC
Systematic name: (*R*)-4,5-dihydro-2-(6-hydroxy-1,3-benzothiazol-2-yl)thiazole-4-carboxylate:CoA ligase (AMP-forming)
Comments: This is an alternative activity of the firefly luciferase (EC 1.13.12.7), which the enzyme exhibits under normal conditions only when acting on the L-enantiomer of its substrate. The D-isomer can act as a substrate for the CoA—ligase activity *in vitro* only under low oxygen conditions that are not found *in vivo*. The activation of L-firefly luciferin to a CoA ester is a step in a recycling pathway that results in its epimerization to the D enantiomer, which is the only substrate whose oxygenation results in light emission.
References: [136, 352, 523, 288]

[EC 6.2.1.52 created 2017]

EC 6.2.1.53

Accepted name: L-proline—[L-prolyl-carrier protein] ligase
Reaction: ATP + L-proline + holo-[L-prolyl-carrier protein] = AMP + diphosphate + L-prolyl-[L-prolyl-carrier protein] (overall reaction)
(1a) ATP + L-proline = diphosphate + (L-prolyl)adenylate
(1b) (L-prolyl)adenylate + holo-[L-prolyl-carrier protein] = AMP + L-prolyl-[L-prolyl-carrier protein]
Other name(s): *pltF* (gene name); *bmp4* (gene name); *pigI* (gene name)
Systematic name: L-proline:[L-prolyl-carrier protein] ligase (AMP-forming)
Comments: The enzyme participates in the biosynthesis of several pyrrole-containing compounds, such as undecylprodigiosin, prodigiosin, pyoluteorin, and coumermycin A_1. It catalyses the activation of L-proline to an adenylate form, followed by its transfer to the 4′-phosphopantheine moiety of an L-prolyl-carrier protein.
References: [503, 175, 545]

[EC 6.2.1.53 created 2018]

EC 6.2.1.54

Accepted name: D-alanine—[D-alanyl-carrier protein] ligase
Reaction: ATP + D-alanine + holo-[D-alanyl-carrier protein] = AMP + diphosphate + D-alanyl-[D-alanyl-carrier protein] (overall reaction)
(1a) ATP + D-alanine = (D-alanyl)adenylate + diphosphate
(1b) (D-alanyl)adenylate + holo-[D-alanyl-carrier protein] = AMP + D-alanyl-[D-alanyl-carrier protein]
Other name(s): *dltA* (gene name); Dcl
Systematic name: D-alanine:[D-alanyl-carrier protein] ligase

Comments: The enzyme is involved in the modification of wall teichoic acids, as well as type I and IV lipoteichoic acids, with D-alanine residues. It activates D-alanine using ATP to form a high-energy (D-alanyl)adenylate intermediate and subsequently transfers the alanyl moiety to the phosphopantheinyl prosthetic group of a D-alanyl-carrier protein (DltC).
References: [388, 559, 115, 374]

[EC 6.2.1.54 created 2018]

EC 6.2.1.55
Accepted name: E1 SAMP-activating enzyme
Reaction: ATP + [SAMP]-Gly-Gly + [E1 SAMP-activating enzyme]-L-cysteine = *S*-[[SAMP]-Gly-Gly]-[[E1 SAMP-activating enzyme]-L-cysteine] + AMP + diphosphate (overall reaction)
(1a) ATP + [SAMP]-Gly-Gly = diphosphate + [SAMP]-Gly-Gly-AMP
(1b) [SAMP]-Gly-Gly-AMP + [E1 SAMP-activating enzyme]-L-cysteine = *S*-[[SAMP]-Gly-Gly]-[[E1 SAMP-activating enzyme]-L-cysteine] + AMP
Other name(s): UbaA; SAMP-activating enzyme E1
Systematic name: [SAMP]:[E1 SAMP-activating enzyme] ligase (AMP-forming)
Comments: Contains Zn^{2+}. The enzyme catalyses the activation of SAMPs (Small Archaeal Modifier Proteins), which are ubiquitin-like proteins found only in the Archaea. SAMPs are involved in protein degradation, and also act as sulfur carriers involved in thiolation of tRNA and other metabolites such as molybdopterin. The enzyme catalyses the ATP-dependent formation of a SAMP adenylate intermediate in which the C-terminal glycine of SAMP is bound to AMP via an acyl-phosphate linkage (reaction 1). This intermediate can accept a sulfur atom to form a thiocarboxylate moiety in a mechanism that is not yet understood. Alternatively, the E1 enzyme can transfer SAMP from its activated form to an internal cysteine residue, releasing AMP (reaction 2). In this case SAMP is subsequently transferred to a lysine residue in a target protein in a process termed SAMPylation. Auto-SAMPylation (attachment of SAMP to lysine residues within the E1 enzyme) has been observed. *cf.* EC 2.7.7.100, SAMP-activating enzyme.
References: [332, 306, 331, 183]

[EC 6.2.1.55 created 2018]

EC 6.2.1.56
Accepted name: 4-hydroxybutyrate—CoA ligase (ADP-forming)
Reaction: ATP + 4-hydroxybutanoate + CoA = ADP + phosphate + 4-hydroxybutanoyl-CoA
Other name(s): Nmar_0206 (locus name)
Systematic name: 4-hydroxybutanoate:CoA ligase (ADP-forming)
Comments: The enzyme, characterized from the marine ammonia-oxidizing archaeon *Nitrosopumilus maritimus*, participates in a variant of the 3-hydroxypropanoate/4-hydroxybutanate CO_2 fixation cycle. *cf.* EC 6.2.1.40, 4-hydroxybutyrate—CoA ligase (AMP-forming).
References: [243]

[EC 6.2.1.56 created 2019]

EC 6.2.1.57
Accepted name: long-chain fatty acid adenylase/transferase FadD23
Reaction: (1) ATP + stearate + a holo-[(hydroxy)phthioceranic acid synthase] = AMP + diphosphate + a stearoyl-[(hydroxy)phthioceranic acid synthase] (overall reaction)
(1a) ATP + stearate = diphosphate + (stearoyl)adenylate
(1b) (stearoyl)adenylate + a holo-[(hydroxy)phthioceranic acid synthase] = AMP + a stearoyl-[(hydroxy)phthioceranic acid synthase]
(2) ATP + palmitate + a holo-[(hydroxy)phthioceranic acid synthase] = AMP + diphosphate + a palmitoyl-[(hydroxy)phthioceranic acid synthase] (overall reaction)

(2a) ATP + palmitate = diphosphate + (palmitoyl)adenylate
(2b) (palmitoyl)adenylate + a holo-[(hydroxy)phthioceranic acid synthase] = AMP + a palmitoyl-[(hydroxy)phthioceranic acid synthase]

Other name(s): *fadD*23 (gene name); long-chain fatty acid adenylyltransferase FadD23
Systematic name: palmitate:holo-[(hydroxy)phthioceranic acid synthase] ligase
Comments: This mycobacterial enzyme activates palmitate and stearate by adenylation, followed by their loading onto the polyketide synthase EC 2.3.1.287, phthioceranic/hydroxyphthioceranic acid synthase.
References: [160, 283]

[EC 6.2.1.57 created 2019]

EC 6.2.1.58
Accepted name: isophthalate—CoA ligase
Reaction: ATP + isophthalate + CoA = AMP + diphosphate + isophthalyl-CoA
Other name(s): IPCL
Systematic name: isophthalate:CoA ligase (AMP-forming)
Comments: The enzyme, characterized from the bacterium *Syntrophorhabdus aromaticivorans*, catalyses the first step in an anaerobic isophthalate degradation pathway.
References: [219]

[EC 6.2.1.58 created 2019]

EC 6.2.1.59
Accepted name: long-chain fatty acid adenylase/transferase FadD26
Reaction: ATP + a long-chain fatty acid + holo-[(phenol)carboxyphthiodiolenone synthase] = AMP + diphosphate + a long-chain acyl-[(phenol)carboxyphthiodiolenone synthase] (overall reaction)
(1a) ATP + a long-chain fatty acid = diphosphate + a long-chain fatty-acyl adenylate ester
(1b) a long-chain fatty-acyl adenylate ester + holo-[(phenol)carboxyphthiodiolenone synthase] = AMP + a long-chain acyl-[(phenol)carboxyphthiodiolenone synthase]
Other name(s): FadD26
Systematic name: long-chain fatty acid:holo-[(phenol)carboxyphthiodiolenone synthase] ligase (AMP-forming)
Comments: The enzyme, present in pathogenic species of mycobacteria, participates in the pathway for biosynthesis of phthiocerols. It catalyses the adenylation of the long-chain fatty acids arachidate (C_{20}) or behenate (C_{22}) [24] and potentially the very-long-chain fatty acid lignocerate (C_{24}) [463]. The activated fatty acids are then loaded to EC 2.3.1.292, (phenol)carboxyphthiodiolenone synthase.
References: [24, 463, 521]

[EC 6.2.1.59 created 2019]

EC 6.2.1.60
Accepted name: marinolic acid—CoA ligase
Reaction: (1) ATP + a marinolic acid + CoA = AMP + diphosphate + a marinoloyl-CoA
(2) ATP + a pseudomonic acid + CoA = AMP + diphosphate + a pseudomonoyl-CoA
Other name(s): *tmlU* (gene name)
Systematic name: marinolic acid:CoA ligase (AMP-forming)
Comments: The enzyme, characterized from the bacterium *Pseudoalteromonas* sp. SANK 73390, catalyses the CoA acylation of pseudomonic and marinolic acids, as part of the biosynthesis of thiomarinols and related compounds.
References: [117]

[EC 6.2.1.60 created 2019]

EC 6.2.1.61

Accepted name: salicylate—[aryl-carrier protein] ligase
Reaction: ATP + salicylate + holo-[non-ribosomal peptide synthase] = AMP + diphosphate + salicyl-[non-ribosomal peptide synthase] (overall reaction)
(1a) ATP + salicylate = diphosphate + (salicyl)adenylate
(1b) (salicyl)adenylate + holo-[non-ribosomal peptide synthase] = AMP + salicyl-[non-ribosomal peptide synthase]
Other name(s): *pmsE* (gene name); *pchD* (gene name)
Systematic name: salicylate:holo-[non-ribosomal peptide synthase] ligase
Comments: The enzyme catalyses the activation of salicylate to (salicyl)adenylate, followed by the transfer of the activated compound to the free thiol of a phosphopantetheine arm of an aryl-carrier protein, which is often a domain of a larger non-ribosimal peptide synthase. The PmsE enzyme is involved in pseudomonine biosynthesis and transfers the activated salicylate first to itself, and then to a PmsG protein. The PchD enzyme is involved in pyochelin biosynthesis and transfers the activated salicylate directly to the PchE protein.
References: [401, 444]

[EC 6.2.1.61 created 2019]

EC 6.2.1.62

Accepted name: 3,4-dihydroxybenzoate—[aryl-carrier protein] ligase
Reaction: ATP + 3,4-dihydroxybenzoate + holo-[aryl-carrier protein] = AMP + diphosphate + 3,4-dihydroxybenzoyl-[aryl-carrier protein] (overall reaction)
(1a) ATP + 3,4-dihydroxybenzoate = diphosphate + (3,4-dihydroxybenzoyl)adenylate
(1b) (3,4-dihydroxybenzoyl)adenylate + holo-[aryl-carrier protein] = AMP + 3,4-dihydroxybenzoyl-[aryl-carrier protein]
Other name(s): *asbC* (gene name)
Systematic name: 3,4-dihydroxybenzoate:[aryl-carrier protein] ligase (AMP-forming)
Comments: The adenylation domain of the enzyme catalyses the activation of 3,4-dihydroxybenzoate to (3,4-dihydroxybenzoyl)adenylate, followed by the transfer of the activated compound to the free thiol of a phosphopantetheine arm of an aryl-carrier protein domain. The aryl-carrier protein domain may be part of the same protein, or of a different protein. This activity is often found as part of a larger non-ribosomal peptide synthase.
References: [394]

[EC 6.2.1.62 created 2020]

EC 6.2.1.63

Accepted name: L-arginine—[L-arginyl-carrier protein] ligase
Reaction: ATP + L-arginine + holo-[L-arginyl-carrier protein] = AMP + diphosphate + L-arginyl-[L-arginyl-carrier protein] (overall reaction)
(1a) ATP + L-arginine = diphosphate + (L-arginyl)adenylate
(1b) (L-arginyl)adenylate + holo-[L-arginyl-carrier protein] = AMP + L-arginyl-[L-arginyl-carrier protein]
Other name(s): *vabF* (gene name)
Systematic name: L-arginine:[L-arginyl-carrier protein] ligase (AMP-forming)
Comments: The adenylation domain of the enzyme catalyses the activation of L-arginine to (L-arginyl)adenylate, followed by the transfer of the activated compound to the free thiol of a phosphopantetheine arm of a peptidyl-carrier protein domain. The peptidyl-carrier protein domain may be part of the same protein, or of a different protein. This activity is often found as part of a larger non-ribosomal peptide synthase.
References: [28]

[EC 6.2.1.63 created 2020]

EC 6.2.1.64

Accepted name: E1 NEDD8-activating enzyme

Reaction: ATP + [NEDD8 protein] + [E1 NEDD8-activating enzyme]-L-cysteine = AMP + diphosphate + [E1 NEDD8-activating enzyme]-*S*-[NEDD8 protein]-yl-L-cysteine

Other name(s): NEDD-activating enzyme E1; NAE1 (gene name); UBA3 (gene name)

Systematic name: [NEDD8 protein]:[E1 NEDD8-activating enzyme] ligase (AMP-forming)

Comments: Some RING-type E3 ubiquitin transferase (EC 2.3.2.27) are not able to bind a substrate protein directly. Instead, they form complexes with a cullin scaffold protein and a substrate recognition module, which are known as CRL (Cullin-RING-Ligase) complexes. The cullin protein needs to be activated by the ubiquitin-like protein NEDD8 in a process known as neddylation. Like ubiquitin, the NEDD8 protein ends with two glycine residues. The E1 NEDD8-activating enzyme activates NEDD8 in an ATP-dependent reaction by forming a high-energy thioester intermediate between NEDD8 and one of its cysteine residues. The activated NEDD8 is subsequently transferred to a cysteine residue of EC 2.3.2.34, E2 NEDD8-conjugating enzyme, and is eventually conjugated to a lysine residue of specific substrates in the presence of the appropriate E3 transferase (EC 2.3.2.32, cullin-RING-type E3 NEDD8 transferase).

References: [372, 162]

[EC 6.2.1.64 created 2020]

EC 6.2.1.65

Accepted name: salicylate—CoA ligase

Reaction: ATP + salicylate + CoA = AMP + diphosphate + 2-hydroxybenzoyl-CoA (overall reaction)
(1a) ATP + salicylate = diphosphate + (2-hydroxybenzoyl)adenylate
(1b) (2-hydroxybenzoyl)adenylate + CoA = AMP + 2-hydroxybenzoyl-CoA

Other name(s): *sdgA* (gene name)

Systematic name: salicylate:CoA ligase (AMP-forming)

Comments: The enzyme, characterized from the bacteria *Thauera aromatica* and *Streptomyces* sp. WA46, participates in a salicylate degradation pathway. It activates salicylate by its adenylation to (2-hydroxybenzoyl)adenylate, followed by the transfer of the activated compound to coenzyme A.

References: [49, 208]

[EC 6.2.1.65 created 2020]

EC 6.2.1.66

Accepted name: glyine—[glycyl-carrier protein] ligase

Reaction: ATP + glycine + holo-[glycyl-carrier protein] = AMP + diphosphate + glycyl-[glycyl-carrier protein] (overall reaction)
(1a) ATP + glycine = diphosphate + (glycyl)adenylate
(1b) (glycyl)adenylate + holo-[glycyl-carrier protein] = AMP + glycyl-[glycyl-carrier protein]

Other name(s): *dhbF* (gene name); *sfmB* (gene name)

Systematic name: glycine:[glycyl-carrier protein] ligase (AMP-forming)

Comments: The adenylation domain of the enzyme catalyses the activation of glycine to (glycyl)adenylate, followed by the transfer of the activated compound to the free thiol of a phosphopantetheine arm of a peptidyl-carrier protein domain. The peptidyl-carrier protein domain may be part of the same protein (as in the case of DhbF in bacillibactin biosynthesis), or of a different protein. This activity is often found as part of a larger non-ribosomal peptide synthase.

References: [308, 269]

[EC 6.2.1.66 created 2021]

EC 6.2.1.67

Accepted name: L-alanine—[L-alanyl-carrier protein] ligase

Reaction: ATP + L-alanine + holo-[L-alanyl-carrier protein] = AMP + diphosphate + L-alanyl-[L-alanyl-carrier protein] (overall reaction)
(1a) ATP + L-alanine = diphosphate + (L-alanyl)adenylate
(1b) (L-alanyl)adenylate + holo-[L-alanyl-carrier protein] = AMP + L-alanyl-[L-alanyl-carrier protein]
Other name(s): *ambB* (gene name); *phsB* (gene name)
Systematic name: L-alanine:[L-alanyl-carrier protein] ligase (AMP-forming)
Comments: The adenylation domain of the enzyme catalyses the activation of L-alanine to (L-alanyl)adenylate, followed by the transfer of the activated compound to the free thiol of a phosphopantetheine arm of a peptidyl-carrier protein domain. The peptidyl-carrier protein domain may be part of the same protein, or of a different protein. This activity is often found as part of a larger non-ribosomal peptide synthase.
References: [453, 347]

[EC 6.2.1.67 created 2021]

EC 6.2.1.68
Accepted name: L-glutamate—[L-glutamyl-carrier protein] ligase
Reaction: ATP + L-glutamate + holo-[L-glutamyl-carrier protein] = AMP + diphosphate + L-glutamyl-[L-glutamyl-carrier protein] (overall reaction)
(1a) ATP + L-glutamate = diphosphate + (L-glutamyl)adenylate
(1b) (L-glutamyl)adenylate + holo-[L-glutamyl-carrier protein] = AMP + L-glutamyl-[L-glutamyl-carrier protein]
Other name(s): *ambE* (gene name)
Systematic name: L-glutamate:[L-glutamyl-carrier protein] ligase (AMP-forming)
Comments: The adenylation domain of the enzyme catalyses the activation of L-glutamate to (L-glutamyl)adenylate, followed by the transfer of the activated compound to the free thiol of a phosphopantetheine arm of a peptidyl-carrier protein domain. The peptidyl-carrier protein domain may be part of the same protein, or of a different protein. This activity is often found as part of a larger non-ribosomal peptide synthase.
References: [347]

[EC 6.2.1.68 created 2021]

EC 6.2.1.69
Accepted name: L-cysteine—[L-cysteinyl-carrier protein] ligase
Reaction: ATP + L-cysteine + holo-[L-cysteinyl-carrier protein] = AMP + diphosphate + L-cysteinyl-[L-cysteinyl-carrier protein] (overall reaction)
(1a) ATP + L-cysteine = diphosphate + (L-cysteinyl)adenylate
(1b) (L-cysteinyl)adenylate + holo-[L-cysteinyl-carrier protein] = AMP + L-cysteinyl-[L-cysteinyl-carrier protein]
Other name(s): *pchE* (gene name); *pchF* (gene name); *angR* (gene name)
Systematic name: L-cysteine:[L-cysteinyl-carrier protein] ligase (AMP-forming)
Comments: The adenylation domain of the enzyme catalyses the activation of L-cysteine to (L-cysteinyl)adenylate, followed by the transfer of the activated compound to the free thiol of a phosphopantetheine arm of a peptidyl-carrier protein domain. The peptidyl-carrier protein domain may be part of the same protein, or of a different protein. This activity is often found as part of a larger non-ribosomal peptide synthase.
References: [401]

[EC 6.2.1.69 created 2021]

EC 6.2.1.70
Accepted name: L-threonine—[L-threonyl-carrier protein] ligase

Reaction: ATP + L-threonine + holo-[L-threonyl-carrier protein] = AMP + diphosphate + L-threonyl-[L-threonyl-carrier protein] (overall reaction)
(1a) ATP + L-threonine = diphosphate + (L-threonyl)adenylate
(1b) (L-threonyl)adenylate + holo-[L-threonyl-carrier protein] = AMP + L-threonyl-[L-threonyl-carrier protein]
Other name(s): *dhbF* (gene name); *pmsD* (gene name); *syrB1* (gene name)
Systematic name: L-threonine:[L-threonyl-carrier protein] ligase (AMP-forming)
Comments: The adenylation domain of the enzyme catalyses the activation of L-threonine to (L-threonyl)adenylate, followed by the transfer of the activated compound to the free thiol of a phosphopantetheine arm of a peptidyl-carrier protein domain. The peptidyl-carrier protein domain may be part of the same protein (as in the case of DhbF in bacillibactin biosynthesis), or of a different protein (as in the case of PmsD in pseudomonine biosynthesis). This activity is often found as part of a larger non-ribosomal peptide synthase.
References: [515, 444]

[EC 6.2.1.70 created 2021]

EC 6.2.1.71
Accepted name: 2,3-dihydroxybenzoate—[aryl-carrier protein] ligase
Reaction: ATP + 2,3-dihydroxybenzoate + holo-[aryl-carrier protein] = AMP + diphosphate + 2,3-dihydroxybenzoyl-[aryl-carrier protein] (overall reaction)
(1a) ATP + 2,3-dihydroxybenzoate = diphosphate + (2,3-dihydroxybenzoyl)adenylate
(1b) (2,3-dihydroxybenzoyl)adenylate + holo-[aryl-carrier protein] = AMP + 2,3-dihydroxybenzoyl-[aryl-carrier protein]
Other name(s): *entE* (gene name); *vibE* (gene name); *dhbE* (gene name); *angE* (gene name)
Systematic name: 2,3-dihydroxybenzoate:[aryl-carrier protein] ligase (AMP-forming)
Comments: The adenylation domain of the enzyme catalyses the activation of 2,3-dihydroxybenzoate to (2,3-dihydroxybenzoyl)adenylate, followed by the transfer the activated compound to the free thiol of a phosphopantetheine arm of an aryl-carrier protein domain of a specific non-ribosomal peptide synthase. For example, the EntE enzyme of *Escherichia coli* is part of the enterobactin synthase complex, the VibE enzyme of *Vibrio cholerae* is part of the vibriobactin synthase complex, and the DhbE enzyme of *Bacillus subtilis* is part of the bacillibactin synthase complex.
References: [150, 554, 121, 231, 308, 461, 232]

[EC 6.2.1.71 created 2021 (EC 2.7.7.58 created 1992, incorporated 2021)]

EC 6.2.1.72
Accepted name: L-serine—[L-seryl-carrier protein] ligase
Reaction: ATP + L-serine + holo-[L-seryl-carrier protein] = AMP + diphosphate + L-seryl-[L-seryl-carrier protein] (overall reaction)
(1a) ATP + L-serine = diphosphate + (L-seryl)adenylate
(1b) (L-seryl)adenylate + holo-[L-seryl-carrier protein] = AMP + L-seryl-[L-seryl-carrier protein]
Other name(s): *entF* (gene name); *zmaJ* (gene name); *gdnB* (gene name); serine-activating enzyme
Systematic name: L-serine:[L-seryl-carrier protein] ligase (AMP-forming)
Comments: The adenylation domain of the enzyme catalyses the activation of L-serine to (L-seryl)adenylate, followed by the transfer of the activated compound to the free thiol of a phosphopantetheine arm of a peptidyl-carrier protein domain. The peptidyl-carrier protein domain may be part of the same protein, or of a different protein. This activity is often found as part of a larger non-ribosomal peptide synthase.
References: [392, 437, 419, 121, 68, 140]

[EC 6.2.1.72 created 2021]

EC 6.2.1.73

Accepted name: L-tryptophan—[L-tryptophyl-carrier protein] ligase
Reaction: ATP + L-tryptophan + holo-[L-tryptophyl-carrier protein] = AMP + diphosphate + -L-tryptophyl-[L-tryptophyl-carrier protein] (overall reaction)
(1a) ATP + tryptophan = diphosphate + (L-tryptophyl)adenylate
(1b) (L-tryptophyl)adenylate + holo-[L-tryptophyl-carrier protein] = AMP + L-tryptophyl-[L-tryptophyl-carrier protein]
Other name(s): ecm13 (gene name); swb11 (gene name)
Systematic name: L-tryptophan:[L-tryptophyl-carrier protein] ligase (AMP-forming)
Comments: The adenylation domain of the enzyme catalyses the activation of L-tryptophan to (L-tryptophyl)adenylate, followed by the transfer of the activated compound to the free thiol of a phosphopantetheine arm of a peptidyl-carrier protein domain. The peptidyl-carrier protein domain may be part of the same protein, or of a different protein. This activity is often found as part of a larger non-ribosomal peptide synthase.
References: [563]

[EC 6.2.1.73 created 2021]

EC 6.2.1.74

Accepted name: 3-amino-5-hydroxybenzoate—[acyl-carrier protein] ligase
Reaction: ATP + 3-amino-5-hydroxybenzoate + a holo-[acyl-carrier protein] = 3-amino-5-hydroxybenzoyl-[acyl-carrier protein] + AMP + diphosphate
Other name(s): *rifA* (gene name); *mitE* (gene name)
Systematic name: 3-amino-5-hydroxybenzoate:[acyl carrier protein] ligase (AMP-forming)
Comments: During the biosynthesis of most ansamycin antibiotics such as rifamycins, streptovaricins, naphthomycins, and chaxamycins, the activity is catalysed by the loading domain of the respective polyketide synthase (PKS), which transfers the substrate to the acyl-carrier protein domain of the first extension module of the PKS. During the biosynthesis of the mitomycins the reaction is catalysed by the MitE protein, which transfers the substrate to a dedicated acyl-carrier protein (MmcB).
References: [8, 6, 7, 67]

[EC 6.2.1.74 created 2021]

EC 6.2.1.75

Accepted name: indoleacetate—CoA ligase
Reaction: ATP + (indol-3-yl)acetate + CoA = AMP + diphosphate + (indol-3-yl)acetyl-CoA
Other name(s): *iaaB* (gene name)
Systematic name: (indol-3-yl)acetate:CoA ligase (AMP-forming)
Comments: The enzyme, characterized from the bacterium *Aromatoleum aromaticum*, is involved in degradation of (indol-3-yl)acetate. It is also active with phenylacetate and the non-physiological compound (2-naphthyl)acetate.
References: [452]

[EC 6.2.1.75 created 2022]

EC 6.2.1.76

Accepted name: malonate—CoA ligase
Reaction: ATP + malonate + CoA = AMP + diphosphate + malonyl-CoA
Other name(s): ACSF3 (gene name); AAE13 (gene name); malonyl-CoA synthetase
Systematic name: malonate:CoA ligase (AMP-forming)
Comments: The enzyme, found in mitochondria, detoxifies malonate, which is a potent inhibitor of mitochondrial respiration, and provides malonyl-CoA to the mitochondrial fatty acid biosynthesis pathway.
References: [169, 549, 70, 168, 50, 51]

[EC 6.2.1.76 created 2022]

EC 6.2.2 Amide—thiol ligases

EC 6.2.2.1

Accepted name: thioglycine synthase
Reaction: ATP + sulfide + a [methyl-coenzyme M reductase]-glycine = ADP + phosphate + a [methyl-coenzyme M reductase]-thioglycine
Other name(s): *ycaO* (gene name) (ambiguous)
Systematic name: [methyl-coenzyme M reductase]-glycine—sulfur ligase (thioglycine-forming)
Comments: Requires Mg^{2+}. The enzyme is found in anaerobic methanogenic and methanotrophic archaea, where it modifies a glycine residue in EC 2.8.4.1, coenzyme-B sulfoethylthiotransferase (methyl-CoM reductase). Upon binding to its substrate, an external source of sulfide attacks the target amide bond generating a tetrahedral intermediate. The amide oxyanion attacks the γ-phosphate of ATP, releasing ADP and forming a phosphorylated thiolate intermediate that collapses to form thioglycine and phosphate. In most organisms activity requires a second protein (TfuA) , which may allosterically activate this enzyme or assist in the delivery of sulfide to the substrate.
References: [358, 289, 112]

[EC 6.2.2.1 created 2020]

EC 6.2.2.2

Accepted name: oxazoline synthase
Reaction: (1) ATP + a [protein]-(L-amino acyl-L-serine) = ADP + phosphate + a [protein]-(*S*,*S*)-2-(C-substituted-aminomethyl)-4-acyl-2-oxazoline
(2) ATP + a [protein]-(L-amino acyl-L-threonine) = ADP + phosphate + a [protein]-(*S*,*S*)-2-(C-substituted-aminomethyl)-4-acyl-5-methyl-2-oxazoline
(3) ATP + a [protein]-(L-amino acyl-L-cysteine) = ADP + phosphate + a [protein]-(1*S*,4*R*)-2-(C-substituted-aminomethyl)-4-acyl-2-thiazoline
Other name(s): cyanobactin heterocyclase; cyanobactin cyclodehydratase; *patD* (gene name); *balhD* (gene name); *micD* (gene name)
Systematic name: [protein]-(L-amino acyl-L-serine) cyclodehydratase (2-oxazoline-forming)
Comments: Requires Mg^{2+}. The enzyme, which participates in the biosynthesis of ribosomal peptide natural products (RiPPs), converts L-cysteine, L-serine and L-threonine residues to thiazoline, oxazoline, and methyloxazoline rings, respectively. The enzyme requires two domains - a cyclodehydratase domain, known as a YcaO domain, and a substrate recognition domain (RRE domain) that controls the regiospecificity of the enzyme. The RRE domain can either be fused to the YcaO domain or occur as a separate protein; however both domains are required for activity. The enzyme can process multiple residues within the same substrate peptide, and all enzymes characterized so far follow a defined order, starting with the L-cysteine closest to the C-terminus. The reaction involves phosphorylation of the preceding ribosomal peptide backbone amide bond, forming ADP and a phosphorylated intermediate, followed by release of the phosphate group. In some cases the enzyme catalyses a side reaction in which the phosphorylated intermediate reacts with ADP to form AMP and diphosphate.
References: [314, 319, 149]

[EC 6.2.2.2 created 2020]

EC 6.2.2.3

Accepted name: thiazoline synthase
Reaction: ATP + a [protein]-(L-amino acyl-L-cysteine) = ADP + phosphate + a [protein]-(1*S*,4*R*)-2-(C-substituted-aminomethyl)-4-acyl-2-thiazoline
Systematic name: [protein]-(L-amino acyl-L-cysteine) cyclodehydratase (2-thiazoline-forming)

Comments: Requires Mg^{2+}. The enzyme, which participates in the biosynthesis of some ribosomal peptide natural products (RiPPs) such as the trunkamides, converts L-cysteine residues to thiazoline rings. The enzyme requires two domains - a cyclodehydratase domain, known as a YcaO domain, and a substrate recognition domain (RRE domain) that controls the regiospecificity of the enzyme. The RRE domain can either be fused to the YcaO domain or occur as a separate protein; however both domains are required for activity. The enzyme can process multiple L-cysteine residues within the same substrate peptide, and all enzymes characterized so far follow a defined order, starting with the L-cysteine closest to the C-terminus. The reaction involves phosphorylation of the preceding ribosomal peptide backbone amide bond, forming ADP and a phosphorylated intermediate, followed by release of the phosphate group. In some cases the enzyme catalyses a side reaction in which the phosphorylated intermediate reacts with ADP to form AMP and diphosphate. This activity is also catalysed by the related enzyme EC 6.2.2.2, oxazoline synthase. That enzyme differs by having an RRE domain that also recognizes L-serine and L-threonine residues, which are converted to oxazoline and methyloxazoline rings, respectively.
References: [315, 314, 239, 240, 149]

[EC 6.2.2.3 created 2020]

EC 6.3 Forming carbon-nitrogen bonds

This subclass contains enzymes that form carbon-nitrogen bonds. Sub-subclasses are: acid—ammonia (or amine) ligases (amide synthases; EC 6.3.1), acid—amino-acid ligases (peptide synthases; EC 6.3.2), enzymes forming heterocyclic rings (cyclo-ligases; EC 6.3.3), enzymes using glutamine as amido-N-donor (EC 6.3.5) and other carbon-nitrogen ligases (EC 6.3.4).

EC 6.3.1 Acid—ammonia (or amine) ligases (amide synthases)

EC 6.3.1.1
Accepted name: aspartate—ammonia ligase
Reaction: ATP + L-aspartate + NH_3 = AMP + diphosphate + L-asparagine
Other name(s): asparagine synthetase; L-asparagine synthetase
Systematic name: L-aspartate:ammonia ligase (AMP-forming)
References: [413, 536]

[EC 6.3.1.1 created 1961]

EC 6.3.1.2
Accepted name: glutamine synthetase
Reaction: ATP + L-glutamate + NH_3 = ADP + phosphate + L-glutamine
Other name(s): glutamate—ammonia ligase; glutamylhydroxamic synthetase; L-glutamine synthetase; GS
Systematic name: L-glutamate:ammonia ligase (ADP-forming)
Comments: Glutamine synthetase, which catalyses the incorporation of ammonium into glutamate, is a key enzyme of nitrogen metabolism found in all domains of life. Several types have been described, differing in their oligomeric structures and cofactor requirements.
References: [124, 141, 255, 318, 552, 246, 277, 300]

[EC 6.3.1.2 created 1961, modified 2016]

[6.3.1.3 Transferred entry. phosphoribosyl-glycinamide synthetase. Now EC 6.3.4.13, phosphoribosylamine—glycine ligase]

[EC 6.3.1.3 created 1961, deleted 1972]

EC 6.3.1.4

Accepted name: aspartate—ammonia ligase (ADP-forming)
Reaction: ATP + L-aspartate + NH_3 = ADP + phosphate + L-asparagine
Other name(s): asparagine synthetase (ADP-forming); asparagine synthetase (adenosine diphosphate-forming)
Systematic name: L-aspartate:ammonia ligase (ADP-forming)
References: [350]

[EC 6.3.1.4 created 1972]

EC 6.3.1.5

Accepted name: NAD^+ synthase
Reaction: ATP + deamido-NAD^+ + NH_3 = AMP + diphosphate + NAD^+
Other name(s): NAD synthetase; NAD synthase; nicotinamide adenine dinucleotide synthetase; diphosphopyridine nucleotide synthetase
Systematic name: deamido-NAD^+:ammonia ligase (AMP-forming)
Comments: L-Glutamine also acts, more slowly, as amido-donor [*cf.* EC 6.3.5.1].
References: [470]

[EC 6.3.1.5 created 1972]

EC 6.3.1.6

Accepted name: glutamate—ethylamine ligase
Reaction: ATP + L-glutamate + ethylamine = ADP + phosphate + N^5-ethyl-L-glutamine
Other name(s): N^5-ethyl-L-glutamine synthetase; theanine synthetase; N^5-ethylglutamine synthetase
Systematic name: L-glutamate:ethylamine ligase (ADP-forming)
References: [440, 441, 442]

[EC 6.3.1.6 created 1976]

EC 6.3.1.7

Accepted name: 4-methyleneglutamate—ammonia ligase
Reaction: ATP + 4-methylene-L-glutamate + NH_3 = AMP + diphosphate + 4-methylene-L-glutamine
Other name(s): 4-methyleneglutamine synthetase
Systematic name: 4-methylene-L-glutamate:ammonia ligase (AMP-forming)
Comments: Glutamine can act instead of NH_3, but more slowly.
References: [548]

[EC 6.3.1.7 created 1986]

EC 6.3.1.8

Accepted name: glutathionylspermidine synthase
Reaction: glutathione + spermidine + ATP = glutathionylspermidine + ADP + phosphate
Other name(s): glutathione:spermidine ligase (ADP-forming)
Systematic name: γ-L-glutamyl-L-cysteinyl-glycine:spermidine ligase (ADP-forming) [spermidine is numbered so that atom *N*-1 is in the amino group of the aminopropyl part of the molecule]
Comments: Requires magnesium ions. Involved in the synthesis of trypanothione in trypanosomatids. The enzyme from *Escherichia coli* is bifunctional and also catalyses the glutathionylspermidine amidase (EC 3.5.1.78) reaction, resulting in a net hydrolysis of ATP.
References: [466, 47]

[EC 6.3.1.8 created 1999]

EC 6.3.1.9

Accepted name: trypanothione synthase
Reaction: (1) glutathione + spermidine + ATP = glutathionylspermidine + ADP + phosphate
(2) glutathione + glutathionylspermidine + ATP = N^1,N^8-bis(glutathionyl)spermidine + ADP + phosphate
Other name(s): glutathionylspermidine:glutathione ligase (ADP-forming)
Systematic name: spermidine/glutathionylspermidine:glutathione ligase (ADP-forming)
Comments: The enzyme, characterized from several trypanosomatids (e.g. *Trypanosoma cruzi*) catalyses two subsequent reactions, leading to production of trypanothione from glutathione and spermidine. Some trypanosomatids (e.g. Crithidia species and some *Leishmania* species) also contain an enzyme that only carries out the first reaction (*cf.* EC 6.3.1.8, glutathionylspermidine synthase). The enzyme is bifunctional, and also catalyses the hydrolysis of glutathionylspermidine and trypanothione (*cf.* EC 3.5.1.78, glutathionylspermidine amidase).
References: [466, 380, 84, 379, 145]

[EC 6.3.1.9 created 1999, modified 2014]

EC 6.3.1.10

Accepted name: adenosylcobinamide-phosphate synthase
Reaction: (1) ATP + adenosylcobyric acid + (*R*)-1-aminopropan-2-yl phosphate = ADP + phosphate + adenosylcobinamide phosphate
(2) ATP + adenosylcobyric acid + (*R*)-1-aminopropan-2-ol = ADP + phosphate + adenosylcobinamide
Other name(s): CbiB
Systematic name: adenosylcobyric acid:(*R*)-1-aminopropan-2-yl phosphate ligase (ADP-forming)
Comments: One of the substrates for this reaction, (*R*)-1-aminopropan-2-yl phosphate, is produced by CobD (EC 4.1.1.81, threonine-phosphate decarboxylase).
References: [73, 533]

[EC 6.3.1.10 created 2004]

EC 6.3.1.11

Accepted name: glutamate—putrescine ligase
Reaction: ATP + L-glutamate + putrescine = ADP + phosphate + γ-L-glutamylputrescine
Other name(s): γ-glutamylputrescine synthetase; YcjK
Systematic name: L-glutamate:putrescine ligase (ADP-forming)
Comments: Forms part of a novel bacterial putrescine utilization pathway in *Escherichia coli*.
References: [251]

[EC 6.3.1.11 created 2005]

EC 6.3.1.12

Accepted name: D-aspartate ligase
Reaction: ATP + D-aspartate + [β-GlcNAc-(1→4)-Mur2Ac(oyl-L-Ala-γ-D-Glu-L-Lys-D-Ala-D-Ala)]$_n$ = [β-GlcNAc-(1→4)-Mur2Ac(oyl-L-Ala-γ-D-Glu-6-*N*-(β-D-Asp)-L-Lys-D-Ala-D-Ala)]$_n$ + ADP + phosphate
Other name(s): Asl$_{fm}$; UDP-MurNAc-pentapeptide:D-aspartate ligase; D-aspartic acid-activating enzyme
Systematic name: D-aspartate:[β-GlcNAc-(1→4)-Mur2Ac(oyl-L-Ala-γ-D-Glu-L-Lys-D-Ala-D-Ala)]$_n$ ligase (ADP-forming)

Comments: This enzyme forms part of the peptidoglycan assembly pathway of Gram-positive bacteria grown in medium containing D-Asp. Normally, the side chains the acylate the 6-amino group of the L-lysine residue contain L-Ala-L-Ala but these amino acids are replaced by D-Asp when D-Asp is included in the medium. Hybrid chains containing L-Ala-D-Asp, L-Ala-L-Ala-D-Asp or D-Asp-L-Ala are not formed [33]. The enzyme belongs in the ATP-grasp protein superfamily [146, 33]. The enzyme is highly specific for D-aspartate, as L-aspartate, D-glutamate, D-alanine, D-iso-asparagine and D-malic acid are not substrates [33]. In *Enterococcus faecium*, the substrate D-aspartate is produced by EC 5.1.1.13, aspartate racemase [33]
References: [473, 474, 146, 33]

[EC 6.3.1.12 created 2006]

EC 6.3.1.13

Accepted name: L-cysteine:1D-*myo*-inositol 2-amino-2-deoxy-α-D-glucopyranoside ligase
Reaction: 1-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-1D-*myo*-inositol + L-cysteine + ATP = 1-*O*-[2-(L-cysteinamido)-2-deoxy-α-D-glucopyranosyl]-1D-*myo*-inositol + AMP + diphosphate
Other name(s): MshC; MshC ligase; Cys:Glc*N*-Ins ligase; mycothiol ligase
Systematic name: L-cysteine:1-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-1D-*myo*-inositol ligase (AMP-forming)
Comments: This enzyme is a key enzyme in the biosynthesis of mycothiol, a small molecular weight thiol found in *Mycobacteria* spp. and other actinomycetes. Mycothiol plays a fundamental role in these organisms by helping to provide protection from the effects of reactive oxygen species and electrophiles, including many antibiotics. The enzyme may represent a novel target for new classes of antitubercular [172].
References: [129, 172, 507]

[EC 6.3.1.13 created 2009]

EC 6.3.1.14

Accepted name: diphthine—ammonia ligase
Reaction: ATP + diphthine-[translation elongation factor 2] + NH_3 = AMP + diphosphate + diphthamide-[translation elongation factor 2]
Other name(s): diphthamide synthase; diphthamide synthetase; DPH6 (gene name); ATPBD4 (gene name); diphthine:ammonia ligase (AMP-forming)
Systematic name: diphthine-[translation elongation factor 2]:ammonia ligase (AMP-forming)
Comments: This amidase catalyses the last step in the conversion of an L-histidine residue in the translation elongation factor EF2 to diphthamide. This factor is found in all archaea and eukaryota, but not in eubacteria, and is the target of bacterial toxins such as the diphtheria toxin and the *Pseudomonas* exotoxin A (see EC 2.4.2.36, NAD^+—diphthamide ADP-ribosyltransferase). The substrate of the enzyme, diphthine, is produced by EC 2.1.1.98, diphthine synthase.
References: [338, 337, 482]

[EC 6.3.1.14 created 1990 as EC 6.3.2.22, transferred 2010 to EC 6.3.1.14, modified 2013]

EC 6.3.1.15

Accepted name: 8-demethylnovobiocic acid synthase
Reaction: ATP + 4-hydroxy-3-prenylbenzoate + 3-amino-4,7-dihydroxycoumarin = AMP + diphosphate + 8-demethylnovobiocic acid
Other name(s): *novL* (gene name); novobiocin ligase; novobiocic acid synthetase (misleading); 8-desmethylnovobiocic acid synthetase; 8-demethylnovobiocic acid synthetase; 3-dimethylallyl-4-hydroxybenzoate:3-amino-4,7-dihydroxycoumarin ligase (AMP-forming)
Systematic name: 4-hydroxy-3-prenylbenzoate:3-amino-4,7-dihydroxycoumarin ligase (AMP-forming)
Comments: The enzyme is involved in the biosynthesis of the aminocoumarin antibiotic novobiocin.
References: [475, 395, 381]

[EC 6.3.1.15 created 2013]

[6.3.1.16 Transferred entry. carbapenam-3-carboxylate synthetase. The enzyme was discovered at the public-review stage to have been misclassified and so was withdrawn. See EC 6.3.3.6, carbapenam-3-carboxylate synthase]

[EC 6.3.1.16 created 2013, deleted 2013]

EC 6.3.1.17

Accepted name: β-citrylglutamate synthase
Reaction: ATP + citrate + L-glutamate = ADP + phosphate + β-citryl-L-glutamate
Other name(s): NAAG synthetase I; NAAGS-I; RIMKLB (gene name) (ambiguous)
Systematic name: citrate:L-glutamate ligase (ADP-forming)
Comments: The enzyme, found in animals, also has the activity of EC 6.3.2.41, *N*-acetylaspartylglutamate synthase.
References: [83]

[EC 6.3.1.17 created 2014]

EC 6.3.1.18

Accepted name: γ-glutamylanilide synthase
Reaction: ATP + L-glutamate + aniline = ADP + phosphate + N^5-phenyl-L-glutamine
Other name(s): *atdA1* (gene name); *tdnQ* (gene name); *dcaQ* (gene name)
Systematic name: L-glutamate:aniline ligase (ADP-forming)
Comments: Requires Mg^{2+}. The enzyme, characterized from the bacterium *Acinetobacter* sp. YAA, catalyses the first step in the degradation of aniline. It can also accept chlorinated and methylated forms of aniline, preferrably in the *o*- and *p*-positions.
References: [491]

[EC 6.3.1.18 created 2014]

EC 6.3.1.19

Accepted name: prokaryotic ubiquitin-like protein ligase
Reaction: ATP + [prokaryotic ubiquitin-like protein]-L-glutamate + [protein]-L-lysine = ADP + phosphate + N^6-([prokaryotic ubiquitin-like protein]-γ-L-glutamyl)-[protein]-L-lysine
Other name(s): PafA (ambiguous); Pup ligase; proteasome accessory factor A
Systematic name: [prokaryotic ubiquitin-like protein]:[protein]-L-lysine
Comments: The enzyme has been characterized from the bacteria *Mycobacterium tuberculosis* and *Corynebacterium glutamicum*. It catalyses the ligation of the prokaryotic ubiquitin-like protein (Pup) to a target protein by forming a bond between an ε-amino group of a lysine residue of the target protein and the γ-carboxylate of the C-terminal glutamate of the ubiquitin-like protein (Pup). The attachment of Pup, also known as Pupylation, marks proteins for proteasomal degradation.
References: [487, 171, 370, 29, 480]

[EC 6.3.1.19 created 2015]

EC 6.3.1.20

Accepted name: lipoate—protein ligase
Reaction: ATP + (*R*)-lipoate + a [lipoyl-carrier protein]-L-lysine = a [lipoyl-carrier protein]-N^6-(lipoyl)lysine + AMP + diphosphate (overall reaction)
(1a) ATP + (*R*)-lipoate = lipoyl-AMP + diphosphate
(1b) lipoyl-AMP + a [lipoyl-carrier protein]-L-lysine = a [lipoyl-carrier protein]-N^6-(lipoyl)lysine + AMP
Other name(s): *lplA* (gene name); *lplJ* (gene name); lipoate protein ligase; lipoate-protein ligase A; LPL; LPL-B

Systematic name: [lipoyl-carrier protein]-L-lysine:lipoate ligase (AMP-forming)
Comments: Requires Mg^{2+}. This enzyme participates in lipoate salvage, and is responsible for lipoylation in the presence of exogenous lipoic acid [389]. The enzyme attaches lipoic acid to the lipoyl domains of certain key enzymes involved in oxidative metabolism, including pyruvate dehydrogenase (E_2 domain), 2-oxoglutarate dehydrogenase (E_2 domain), the branched-chain 2-oxoacid dehydrogenases and the glycine cleavage system (H protein) [489]. Lipoylation is essential for the function of these enzymes. The enzyme can also use octanoate instead of lipoate.
References: [341, 164, 565, 111, 142, 489, 389]

[EC 6.3.1.20 created 2006 as EC 2.7.7.63, transferred 2016 to EC 6.3.1.20]

EC 6.3.1.21
Accepted name: phosphoribosylglycinamide formyltransferase 2
Reaction: ATP + formate + N^1-(5-phospho-β-D-ribosyl)glycinamide = ADP + phosphate + N^2-formyl-N^1-(5-phospho-β-D-ribosyl)glycinamide
Other name(s): *purT* (gene name); GAR transformylase 2; GART2; glycinamide ribonucleotide transformylase 2; 5′-phosphoribosylglycinamide transformylase 2; GAR transformylase T
Systematic name: formate:N^1-(5-phospho-β-D-ribosyl)glycinamide ligase (ADP-forming)
Comments: Two enzymes are known to catalyse the third step in *de novo* purine biosynthesis. This enzyme requires ATP and utilizes formate, which is provided by the hydrolysis of 10-formyltetrahydrofolate by EC 3.5.1.10, formyltetrahydrofolate deformylase. The other enzyme, EC 2.1.2.2, phosphoribosylglycinamide formyltransferase 1, utilizes 10-formyltetrahydrofolate directly. Formyl phosphate is formed during catalysis as an intermediate. The enzyme from the bacterium *Escherichia coli* can also catalyse the activity of EC 2.7.2.1, acetate kinase.
References: [349, 368, 295, 296, 500, 216]

[EC 6.3.1.21 created 2021]

EC 6.3.2 Acid—amino-acid ligases (peptide synthases)

EC 6.3.2.1
Accepted name: pantoate—β-alanine ligase (AMP-forming)
Reaction: ATP + (*R*)-pantoate + β-alanine = AMP + diphosphate + (*R*)-pantothenate
Other name(s): pantothenate synthetase; pantoate activating enzyme; pantoic-activating enzyme; D-pantoate:β-alanine ligase (AMP-forming); pantoate—β-alanine ligase (ambiguous)
Systematic name: (*R*)-pantoate:β-alanine ligase (AMP-forming)
References: [157, 284, 285]

[EC 6.3.2.1 created 1961, modified 2014]

EC 6.3.2.2
Accepted name: glutamate—cysteine ligase
Reaction: ATP + L-glutamate + L-cysteine = ADP + phosphate + γ-L-glutamyl-L-cysteine
Other name(s): γ-glutamylcysteine synthetase; γ-glutamyl-L-cysteine synthetase; γ-glutamylcysteinyl synthetase
Systematic name: L-glutamate:L-cysteine γ-ligase (ADP-forming)
Comments: Can use L-aminohexanoate in place of glutamate.
References: [286, 467, 293]

[EC 6.3.2.2 created 1961]

EC 6.3.2.3
Accepted name: glutathione synthase

Reaction: ATP + γ-L-glutamyl-L-cysteine + glycine = ADP + phosphate + glutathione
Other name(s): glutathione synthetase; GSH synthetase
Systematic name: γ-L-glutamyl-L-cysteine:glycine ligase (ADP-forming)
References: [260, 287]

[EC 6.3.2.3 created 1961]

EC 6.3.2.4
Accepted name: D-alanine—D-alanine ligase
Reaction: ATP + **2** D-alanine = ADP + phosphate + D-alanyl-D-alanine
Other name(s): MurE synthetase [ambiguous]; alanine:alanine ligase (ADP-forming); alanylalanine synthetase
Systematic name: D-alanine:D-alanine ligase (ADP-forming)
Comments: Involved with EC 6.3.2.7 (UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate—L-lysine ligase) or EC 6.3.2.13 (UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate—2,6-diaminopimelate ligase), EC 6.3.2.8 (UDP-*N*-acetylmuramate—L-alanine ligase), EC 6.3.2.9 (UDP-*N*-acetylmuramoyl-L-alanine—D-glutamate ligase) and EC 6.3.2.10 (UDP-*N*-acetylmuramoyl-tripeptide—D-alanyl-D-alanine ligase) in the synthesis of a cell-wall peptide (click here for diagram).
References: [210, 361, 519]

[EC 6.3.2.4 created 1961, modified 2002]

EC 6.3.2.5
Accepted name: phosphopantothenate—cysteine ligase (CTP)
Reaction: CTP + (*R*)-4′-phosphopantothenate + L-cysteine = CMP + diphosphate + *N*-[(*R*)-4′-phosphopantothenoyl]-L-cysteine
Other name(s): phosphopantothenoylcysteine synthetase (ambiguous); phosphopantothenate—cysteine ligase (ambiguous)
Systematic name: (*R*)-4′-phosphopantothenate:L-cysteine ligase
Comments: A key enzyme in the production of coenzyme A. The bacterial enzyme requires CTP, in contrast to the eukaryotic enzyme, EC 6.3.2.51, which requires ATP. Cysteine can be replaced by some of its derivatives.
References: [55, 479, 249]

[EC 6.3.2.5 created 1961, modified 2003, modified 2017]

EC 6.3.2.6
Accepted name: phosphoribosylaminoimidazolesuccinocarboxamide synthase
Reaction: ATP + 5-amino-1-(5-phospho-D-ribosyl)imidazole-4-carboxylate + L-aspartate = ADP + phosphate + (*S*)-2-[5-amino-1-(5-phospho-D-ribosyl)imidazole-4-carboxamido]succinate
Other name(s): phosphoribosylaminoimidazole-succinocarboxamide synthetase; PurC; SAICAR synthetase; 4-(*N*-succinocarboxamide)-5-aminoimidazole synthetase; 4-[(*N*-succinylamino)carbonyl]-5-aminoimidazole ribonucleotide synthetase; SAICARs; phosphoribosylaminoimidazolesuccinocarboxamide synthetase; 5-aminoimidazole-4-*N*-succinocarboxamide ribonucleotide synthetase
Systematic name: 5-amino-1-(5-phospho-D-ribosyl)imidazole-4-carboxylate:L-aspartate ligase (ADP-forming)
Comments: Forms part of the purine biosynthesis pathway.
References: [281, 383, 119, 71, 369, 359]

[EC 6.3.2.6 created 1961, modified 2000, modified 2006]

EC 6.3.2.7
Accepted name: UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate—L-lysine ligase
Reaction: ATP + UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-D-glutamate + L-lysine = ADP + phosphate + UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-γ-D-glutamyl-L-lysine

Other name(s): MurE synthetase; UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamyl-L-lysine synthetase; uridine diphospho-*N*-acetylmuramoylalanyl-D-glutamyllysine synthetase; UPD-MurNAc-L-Ala-D-Glu:L-Lys ligase; UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate:L-lysine γ-ligase (ADP-forming)
Systematic name: UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-D-glutamate:L-lysine γ-ligase (ADP-forming)
Comments: Involved in the synthesis of a cell-wall peptide in bacteria. This enzyme adds lysine in some Gram-positive organisms; in others and in Gram-negative organisms EC 6.3.2.13 (UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate—2,6-diaminopimelate ligase) adds 2,6-diaminopimelate instead.
References: [209, 519]

[EC 6.3.2.7 created 1961, modified 2002]

EC 6.3.2.8
Accepted name: UDP-*N*-acetylmuramate—L-alanine ligase
Reaction: ATP + UDP-*N*-acetyl-α-D-muramate + L-alanine = ADP + phosphate + UDP-*N*-acetyl-α-D-muramoyl-L-alanine
Other name(s): MurC synthetase; UDP-*N*-acetylmuramoyl-L-alanine synthetase; uridine diphospho-*N*-acetylmuramoylalanine synthetase; UDP-*N*-acetylmuramoylalanine synthetase; L-alanine-adding enzyme; UDP-acetylmuramyl-L-alanine synthetase; UDPMurNAc-L-alanine synthetase; L-Ala ligase; uridine diphosphate *N*-acetylmuramate:L-alanine ligase; uridine 5′-diphosphate-*N*-acetylmuramyl-L-alanine synthetase; uridine-diphosphate-*N*-acetylmuramate:L-alanine ligase; UDP-MurNAc:L-alanine ligase; alanine-adding enzyme; UDP-*N*-acetylmuramyl:L-alanine ligase; UDP-*N*-acetylmuramate:L-alanine ligase (ADP-forming)
Systematic name: UDP-*N*-acetyl-α-D-muramate:L-alanine ligase (ADP-forming)
Comments: Involved in the synthesis of a cell-wall peptide in bacteria.
References: [209, 357, 519]

[EC 6.3.2.8 created 1965, modified 2002]

EC 6.3.2.9
Accepted name: UDP-*N*-acetylmuramoyl-L-alanine—D-glutamate ligase
Reaction: ATP + UDP-*N*-acetyl-α-D-muramoyl-L-alanine + D-glutamate = ADP + phosphate + UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-D-glutamate
Other name(s): MurD synthetase; UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate synthetase; uridine diphospho-*N*-acetylmuramoylalanyl-D-glutamate synthetase; D-glutamate-adding enzyme; D-glutamate ligase; UDP-Mur-NAC-L-Ala:D-Glu ligase; UDP-*N*-acetylmuramoyl-L-alanine:glutamate ligase (ADP-forming); UDP-*N*-acetylmuramoylalanine—D-glutamate ligase; UDP-*N*-acetylmuramoyl-L-alanine:D-glutamate ligase (ADP-forming)
Systematic name: UDP-*N*-acetyl-α-D-muramoyl-L-alanine:D-glutamate ligase (ADP-forming)
Comments: Involved in the synthesis of a cell-wall peptide in bacteria.
References: [209, 519]

[EC 6.3.2.9 created 1965, modified 2002]

EC 6.3.2.10
Accepted name: UDP-*N*-acetylmuramoyl-tripeptide—D-alanyl-D-alanine ligase
Reaction: ATP + UDP-*N*-acetylmuramoyl-L-alanyl-γ-D-glutamyl-L-lysine + D-alanyl-D-alanine = ADP + phosphate + UDP-*N*-acetylmuramoyl-L-alanyl-γ-D-glutamyl-L-lysyl-D-alanyl-D-alanine
Other name(s): MurF synthetase; UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamyl-L-lysyl-D-alanyl-D-alanine synthetase; UDP-*N*-acetylmuramoylalanyl-D-glutamyl-lysine-D-alanyl-D-alanine ligase; uridine diphosphoacetylmuramoylpentapeptide synthetase; UDPacetylmuramoylpentapeptide synthetase; UDP-MurNAc-L-Ala-D-Glu-L-Lys:D-Ala-D-Ala ligase
Systematic name: UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamyl-L-lysine:D-alanyl-D-alanine ligase (ADP-forming)

Comments: Involved with EC 6.3.2.4 (D-alanine—D-alanine ligase), EC 6.3.2.7 (UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate—L-lysine ligase) or EC 6.3.2.13 (UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate—2,6-diaminopimelate ligase), EC 6.3.2.8 (UDP-*N*-acetylmuramate—L-alanine ligase) and EC 6.3.2.9 (UDP-*N*-acetylmuramoyl-L-alanine—D-glutamate ligase) in the synthesis of a cell-wall peptide (click here) for diagram. This enzyme also catalyses the reaction when the C-terminal residue of the tripeptide is *meso*-2,6-diaminoheptanedioate (acylated at its L-centre), linking the D-Ala-D-Ala to the carboxy group of the L-centre. This activity was previously attributed to EC 6.3.2.15, which has since been deleted.
References: [210, 519]

[EC 6.3.2.10 created 1965, modified 2002]

EC 6.3.2.11

Accepted name: carnosine synthase
Reaction: ATP + L-histidine + β-alanine = ADP + phosphate + carnosine
Other name(s): carnosine synthetase; carnosine-anserine synthetase; homocarnosine-carnosine synthetase; carnosine-homocarnosine synthetase; L-histidine:β-alanine ligase (AMP-forming) (incorrect)
Systematic name: L-histidine:β-alanine ligase (ADP-forming)
Comments: This enzyme was thought to form AMP [222, 477], but studies with highly purified enzyme proved that it forms ADP [114]. Carnosine is a dipeptide that is present at high concentrations in skeletal muscle and the olfactory bulb of vertebrates [92]. It is also found in the skeletal muscle of some invertebrates. The enzyme can also catalyse the formation of homocarnosine from 4-aminobutanoate and L-histidine, with much lower activity [114].
References: [222, 477, 92, 114]

[EC 6.3.2.11 created 1965, modified 2010]

EC 6.3.2.12

Accepted name: dihydrofolate synthase
Reaction: ATP + 7,8-dihydropteroate + L-glutamate = ADP + phosphate + 7,8-dihydropteroylglutamate
Other name(s): dihydrofolate synthetase; 7,8-dihydrofolate synthetase; H_2-folate synthetase; 7,8-dihydropteroate:L-glutamate ligase (ADP); dihydropteroate:L-glutamate ligase (ADP-forming); DHFS
Systematic name: 7,8-dihydropteroate:L-glutamate ligase (ADP-forming)
Comments: In some bacteria, a single protein catalyses both this activity and that of EC 6.3.2.17, tetrahydrofolate synthase [46], the combined activity of which leads to the formation of the coenzyme polyglutamated tetrahydropteroate ($H_4PteGlu_n$), i.e. various tetrahydrofolates. In contrast, the activities are located on separate proteins in most eukaryotes studied to date [412]. This enzyme is reponsible for attaching the first glutamate residue to dihydropteroate to form dihydrofolate and is present only in those organisms that have the ability to synthesize tetrahydrofolate *de novo*, e.g. plants, most bacteria, fungi and protozoa [412].
References: [166, 46, 412, 74, 86]

[EC 6.3.2.12 created 1972, modified 2005]

EC 6.3.2.13

Accepted name: UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate—2,6-diaminopimelate ligase
Reaction: ATP + UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-D-glutamate + *meso*-2,6-diaminoheptanedioate = ADP + phosphate + UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-γ-D-glutamyl-*meso*-2,6-diaminoheptanedioate
Other name(s): MurE synthetase [ambiguous]; UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate:*meso*-2,6-diaminoheptanedioate ligase (ADP-forming); UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamyl-*meso*-2,6-diaminopimelate synthetase; UDP-*N*-acetylmuramoylalanyl-D-glutamate—2,6-diaminopimelate ligase; UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate:*meso*-2,6-diaminoheptanedioate γ-ligase (ADP-forming)

Systematic name: UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-D-glutamate:*meso*-2,6-diaminoheptanedioate γ-ligase (ADP-forming)
Comments: Involved in the synthesis of a cell-wall peptide in bacteria. This enzyme adds diaminopimelate in Gram-negative organisms and in some Gram-positive organisms; in others EC 6.3.2.7 (UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate—L-lysine ligase) adds lysine instead. It is the amino group of the L-centre of the diaminopimelate that is acylated.
References: [334, 519]

[EC 6.3.2.13 created 1972, modified 2002, modified 2010]

EC 6.3.2.14
Accepted name: enterobactin synthase
Reaction: **6** ATP + **3** 2,3-dihydroxybenzoate + **3** L-serine = enterobactin + **6** AMP + **6** diphosphate
Other name(s): *N*-(2,3-dihydroxybenzoyl)-serine synthetase; 2,3-dihydroxybenzoylserine synthetase; 2,3-dihydroxybenzoate—serine ligase
Systematic name: 2,3-dihydroxybenzoate:L-serine ligase
Comments: This enzyme complex catalyses the conversion of three molecules each of 2,3-dihydroxybenzoate and L-serine to form the siderophore enterobactin. In *Escherichia coli* the complex is formed by EntB (an aryl carrier protein that has to be activated by 4′-phosphopantetheine), EntD (a phosphopantetheinyl transferase that activates EntB), EntE (catalyses the ATP-dependent condensation of 2,3-dihydroxybenzoate and holo-EntB to form the covalently arylated form of EntB), and EntF (a four domain protein that catalyses the activation of L-serine by ATP, the condensation of the activated L-serine with the activated 2,3-dihydroxybenzoate, and the trimerization of three such moieties to a single enterobactin molecule).
References: [53, 435, 436, 437, 151, 458]

[EC 6.3.2.14 created 1972, modified 2012]

[6.3.2.15 Deleted entry. UDP-N-acetylmuramoylalanyl-D-glutamyl-2,6-diaminopimelate-D-alanyl-D-alanine ligase. The activity observed is due to EC 6.3.2.10, UDP-N-acetylmuramoyl-tripeptide—D-alanyl-D-alanine ligase]

[EC 6.3.2.15 created 1976, deleted 2002]

EC 6.3.2.16
Accepted name: D-alanine—alanyl-poly(glycerolphosphate) ligase
Reaction: ATP + D-alanine + alanyl-poly(glycerolphosphate) = ADP + phosphate + D-alanyl-alanyl-poly(glycerolphosphate)
Other name(s): D-alanyl-alanyl-poly(glycerolphosphate) synthetase; D-alanine:membrane-acceptor ligase; D-alanylalanylpoly(phosphoglycerol) synthetase; D-alanyl-poly(phosphoglycerol) synthetase; D-alanine-membrane acceptor-ligase
Systematic name: D-alanine:alanyl-poly(glycerolphosphate) ligase (ADP-forming)
Comments: Involved in the synthesis of teichoic acids.
References: [422]

[EC 6.3.2.16 created 1976]

EC 6.3.2.17
Accepted name: tetrahydrofolate synthase
Reaction: ATP + tetrahydropteroyl-[γ-Glu]$_n$ + L-glutamate = ADP + phosphate + tetrahydropteroyl-[γ-Glu]$_{n+1}$
Other name(s): folylpolyglutamate synthase; folate polyglutamate synthetase; formyltetrahydropteroyldiglutamate synthetase; N^{10}-formyltetrahydropteroyldiglutamate synthetase; folylpoly-γ-glutamate synthase; folylpolyglutamyl synthetase; folylpoly(γ-glutamate) synthase; folylpolyglutamate synthetase; FPGS; tetrahydrofolylpolyglutamate synthase; tetrahydrofolate:L-glutamate γ-ligase (ADP-forming); tetrahydropteroyl-[γ-Glu]$_n$:L-glutamate γ-ligase (ADP-forming)

Systematic name: tetrahydropteroyl-γ-polyglutamate:L-glutamate γ-ligase (ADP-forming)
Comments: In some bacteria, a single protein catalyses both this activity and that of EC 6.3.2.12, dihydrofolate synthase [46], the combined activity of which leads to the formation of the coenzyme polyglutamated tetrahydropteroate ($H_4PteGlu_n$), i.e. various tetrahydrofolates (H_4folate). In contrast, the activities are located on separate proteins in most eukaryotes studied to date [412]. In *Arabidopsis thaliana*, this enzyme is present as distinct isoforms in the mitochondria, the cytosol and the chloroplast. Each isoform is encoded by a separate gene, a situation that is unique among eukaryotes [412]. As the affinity of folate-dependent enzymes increases markedly with the number of glutamic residues, the tetrahydropteroyl polyglutamates are the preferred coenzymes of C_1 metabolism. (reviewed in [86]). The enzymes from different sources (particularly eukaryotes versus prokaryotes) have different substrate specificities with regard to one-carbon substituents and the number of glutamate residues present on the tetrahydrofolates.
References: [81, 313, 46, 412, 86, 74]

[EC 6.3.2.17 created 1984, modified 2003, modified 2005]

EC 6.3.2.18
Accepted name: γ-glutamylhistamine synthase
Reaction: ATP + L-glutamate + histamine = products of ATP breakdown + N^{α}-γ-L-glutamylhistamine
Other name(s): γ-glutaminylhistamine synthetase; γ-GHA synthetase
Systematic name: L-glutamate:histamine ligase
References: [476]

[EC 6.3.2.18 created 1986]

[6.3.2.19 Deleted entry. ubiquitin—protein ligase. The ubiquitinylation process is now known to be performed by several enzymes in sequence, starting with EC 6.2.1.45 (ubiquitin-activating enzyme E1) and followed by several transfer reactions, including those of EC 2.3.2.23 (E2 ubiquitin-conjugating enzyme) and EC 2.3.2.27 (RING-type E3 ubiquitin transferase)]

[EC 6.3.2.19 created 1986, deleted 2015]

EC 6.3.2.20
Accepted name: indoleacetate—lysine synthetase
Reaction: ATP + (indol-3-yl)acetate + L-lysine = ADP + phosphate + N^6-[(indol-3-yl)acetyl]-L-lysine
Other name(s): indoleacetate:L-lysine ligase (ADP-forming)
Systematic name: (indol-3-yl)acetate:L-lysine ligase (ADP-forming)
References: [159, 200]

[EC 6.3.2.20 created 1989]

[6.3.2.21 Deleted entry. ubiquitin—calmodulin ligase. The reaction is performed by the sequential action of EC 6.2.1.45 (ubiquitin-activating enzyme E1), several ubiquitin transferases and finally by EC 2.3.2.27 [ubiquitin transferase RING E3 (calmodulin-selective)]]

[EC 6.3.2.21 created 1990, deleted 2015]

[6.3.2.22 Transferred entry. diphthine—ammonia ligase. Now EC 6.3.1.14, diphthine—ammonia ligase.]

[EC 6.3.2.22 created 1990, deleted 2010]

EC 6.3.2.23
Accepted name: homoglutathione synthase
Reaction: ATP + γ-L-glutamyl-L-cysteine + β-alanine = ADP + phosphate + γ-L-glutamyl-L-cysteinyl-β-alanine
Other name(s): homoglutathione synthetase; β-alanine specific hGSH synthetase
Systematic name: γ-L-glutamyl-L-cysteine:β-alanine ligase (ADP-forming)

Comments: Not identical with EC 6.3.2.3 glutathione synthase.
References: [287]

[EC 6.3.2.23 created 1990]

EC 6.3.2.24
Accepted name: tyrosine—arginine ligase
Reaction: ATP + L-tyrosine + L-arginine = AMP + diphosphate + L-tyrosyl-L-arginine
Other name(s): tyrosyl-arginine synthase; kyotorphin synthase; kyotorphin-synthesizing enzyme; kyotorphin synthetase
Systematic name: L-tyrosine:L-arginine ligase (AMP-forming)
References: [511]

[EC 6.3.2.24 created 1992]

EC 6.3.2.25
Accepted name: tubulin—tyrosine ligase
Reaction: ATP + detyrosinated α-tubulin + L-tyrosine = α-tubulin + ADP + phosphate
Systematic name: α-tubulin:L-tyrosine ligase (ADP-forming)
Comments: L-Tyrosine is linked via a peptide bond to the C-terminus of de-tyrosinated α-tubulin (des-Tyr$^{\omega}$-α-tubulin). The enzyme is highly specific for α-tubulin and moderately specific for ATP and L-tyrosine. L-Phenylalanine and 3,4-dihydroxy-L-phenylalanine are transferred but with higher K_m values.
References: [539, 434]

[EC 6.3.2.25 created 1999]

EC 6.3.2.26
Accepted name: *N*-(5-amino-5-carboxypentanoyl)-L-cysteinyl-D-valine synthase
Reaction: **3** ATP + L-2-aminohexanedioate + L-cysteine + L-valine + H_2O = **3** AMP + **3** diphosphate + *N*-[L-5-amino-5-carboxypentanoyl]-L-cysteinyl-D-valine
Other name(s): L-δ-(α-aminoadipoyl)-L-cysteinyl-D-valine synthetase; ACV synthetase; L-α-aminoadipyl-cysteinyl-valine synthetase;
Systematic name: L-2-aminohexanedioate:L-cysteine:L-valine ligase (AMP-forming, valine-inverting)
Comments: Requires Mg^{2+}. The enzyme contains 4′-phosphopantetheine, which may be involved in the mechanism of the reaction. Forms part of the penicillin biosynthesis pathway (for pathway, click here).
References: [58, 499]

[EC 6.3.2.26 created 2002]

[6.3.2.27 Deleted entry. The activity is covered by two independent enzymes, EC 6.3.2.38 N^2-citryl-N^6-acetyl-N^6-hydroxylysine synthase, and EC 6.3.2.39, aerobactin synthase]

[EC 6.3.2.27 created 2002, modified 2006, deleted 2012]

[6.3.2.28 Transferred entry. L-*amino-acid* α-*ligase. Now EC 6.3.2.49,* L-*alanine*-L-*anticapsin ligase]*

[EC 6.3.2.28 created 2006, deleted 2015]

EC 6.3.2.29
Accepted name: cyanophycin synthase (L-aspartate-adding)
Reaction: ATP + [L-Asp(4-L-Arg)]$_n$ + L-Asp = ADP + phosphate + [L-Asp(4-L-Arg)]$_n$-L-Asp
Other name(s): CphA (ambiguous); CphA1 (ambiguous); CphA2 (ambiguous); cyanophycin synthetase (ambiguous); multi-L-arginyl-poly-L-aspartate synthase (ambiguous)
Systematic name: cyanophycin:L-aspartate ligase (ADP-forming)

Comments: Requires Mg^{2+} for activity. Both this enzyme and EC 6.3.2.30, cyanophycin synthase (L-arginine-adding), are required for the elongation of cyanophycin, which is a protein-like cell inclusion that is unique to cyanobacteria and acts as a temporary nitrogen store [4]. Both enzymes are found in the same protein but have different active sites [4, 34]. Both L-Asp and L-Arg must be present before either enzyme will display significant activity [4].
References: [3, 4, 11, 34, 571, 572]

[EC 6.3.2.29 created 2007]

EC 6.3.2.30
Accepted name: cyanophycin synthase (L-arginine-adding)
Reaction: ATP + [L-Asp(4-L-Arg)]$_n$-L-Asp + L-Arg = ADP + phosphate + [L-Asp(4-L-Arg)]$_{n+1}$
Other name(s): CphA (ambiguous); CphA1 (ambiguous); CphA2 (ambiguous); cyanophycin synthetase (ambiguous); multi-L-arginyl-poly-L-aspartate synthase (ambiguous)
Systematic name: cyanophycin:L-arginine ligase (ADP-forming)
Comments: Requires Mg^{2+} for activity. Both this enzyme and EC 6.3.2.29, cyanophycin synthase (L-aspartate-adding), are required for the elongation of cyanophycin, which is a protein-like cell inclusion that is unique to cyanobacteria and acts as a temporary nitrogen store [4]. Both enzymes are found in the same protein but have different active sites [4, 34]. Both L-Asp and L-Arg must be present before either enzyme will display significant activity [4]. Canavanine and lysine can be incoporated into the polymer instead of arginine [4].
References: [3, 4, 11, 34, 571, 572]

[EC 6.3.2.30 created 2007]

EC 6.3.2.31
Accepted name: coenzyme F_{420}-0:L-glutamate ligase
Reaction: GTP + coenzyme F_{420}-0 + L-glutamate = GDP + phosphate + coenzyme F_{420}-1
Other name(s): CofE-AF; MJ0768; CofE
Systematic name: L-glutamate:coenzyme F_{420}-0 ligase (GDP-forming)
Comments: This protein catalyses the successive addition of two glutamate residues to cofactor F_{420} by two distinct and independent reactions. In the reaction described here the enzyme attaches a glutamate via its α-amine group to F_{420}-0. In the second reaction (EC 6.3.2.34, coenzyme F_{420}-1—γ-L-glutamate ligase) it catalyses the addition of a second L-glutamate residue to the γ-carboxyl of the first glutamate.
References: [267, 363]

[EC 6.3.2.31 created 2010]

EC 6.3.2.32
Accepted name: coenzyme γ-F_{420}-2:α-L-glutamate ligase
Reaction: ATP + coenzyme γ-F_{420}-2 + L-glutamate = ADP + phosphate + coenzyme α-F_{420}-3
Other name(s): MJ1001; CofF protein; γ-F_{420}-2:α-L-glutamate ligase
Systematic name: L-glutamate:coenzyme γ-F_{420}-2 (ADP-forming)
Comments: The enzyme caps the γ-glutamyl tail of the hydride carrier coenzyme F_{420} [268].
References: [268]

[EC 6.3.2.32 created 2010]

EC 6.3.2.33
Accepted name: tetrahydrosarcinapterin synthase
Reaction: ATP + tetrahydromethanopterin + L-glutamate = ADP + phosphate + 5,6,7,8-tetrahydrosarcinapterin
Other name(s): H_4MPT:α-L-glutamate ligase; MJ0620; MptN protein
Systematic name: tetrahydromethanopterin:α-L-glutamate ligase (ADP-forming)

Comments: This enzyme catalyses the biosynthesis of 5,6,7,8-tetrahydrosarcinapterin, a modified form of tetrahydromethanopterin found in the Methanosarcinales. It does not require K^+, and does not discriminate between ATP and GTP [268].
References: [268]

[EC 6.3.2.33 created 2010]

EC 6.3.2.34
Accepted name: coenzyme F_{420}-1:γ-L-glutamate ligase
Reaction: GTP + coenzyme F_{420}-1 + L-glutamate = GDP + phosphate + coenzyme γ-F_{420}-2
Other name(s): F_{420}:γ-glutamyl ligase; CofE-AF; MJ0768; CofE
Systematic name: L-glutamate:coenzyme F_{420}-1 ligase (GDP-forming)
Comments: This protein catalyses the successive addition of two glutamate residues to cofactor F_{420} by two distinct and independent reactions. In the first reaction (EC 6.3.2.31, coenzyme F_{420}-0—L-glutamate ligase) the enzyme attaches a glutamate via its α-amine group to F_{420}-0. In the second reaction, which is described here, the enzyme catalyses the addition of a second L-glutamate residue to the γ-carboxyl of the first glutamate.
References: [267, 363]

[EC 6.3.2.34 created 2010]

EC 6.3.2.35
Accepted name: D-alanine—D-serine ligase
Reaction: D-alanine + D-serine + ATP = D-alanyl-D-serine + ADP + phosphate
Other name(s): VanC; VanE; VanG
Systematic name: D-alanine:D-serine ligase (ADP-forming)
Comments: The product of this enzyme, D-alanyl-D-serine, can be incorporated into the peptidoglycan pentapeptide instead of the usual D-alanyl-D-alanine dipeptide, which is formed by EC 6.3.2.4, D-alanine—D-alanine ligase. The resulting peptidoglycan does not bind the glycopeptide antibiotics vancomycin and teicoplanin, conferring resistance on the bacteria.
References: [118, 382, 133, 106, 534]

[EC 6.3.2.35 created 2010]

EC 6.3.2.36
Accepted name: 4-phosphopantoate—β-alanine ligase
Reaction: ATP + (*R*)-4-phosphopantoate + β-alanine = AMP + diphosphate + (*R*)-4′-phosphopantothenate
Other name(s): phosphopantothenate synthetase; TK1686 protein
Systematic name: (*R*)-4-phosphopantoate:β-alanine ligase (AMP-forming)
Comments: The conversion of (*R*)-pantoate to (*R*)-4′-phosphopantothenate is part of the pathway leading to biosynthesis of 4′-phosphopantetheine, an essential cofactor of coenzyme A and acyl-carrier protein. In bacteria and eukaryotes this conversion is performed by condensation with β-alanine, followed by phosphorylation (EC 6.3.2.1 [pantoate—β-alanine ligase] and EC 2.7.1.33 [pantothenate kinase], respectively). In archaea the order of these two steps is reversed, and phosphorylation precedes condensation with β-alanine. The two archaeal enzymes that catalyse this conversion are EC 2.7.1.169, pantoate kinase, and this enzyme.
References: [558]

[EC 6.3.2.36 created 2011]

EC 6.3.2.37
Accepted name: UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate—D-lysine ligase

Reaction: ATP + UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-D-glutamate + D-lysine = ADP + phosphate + UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-γ-D-glutamyl-N^{ε}-D-lysine
Other name(s): UDP-MurNAc-L-Ala-D-Glu:D-Lys ligase; D-lysine-adding enzyme
Systematic name: UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-D-glutamate:D-lysine γ-ligase (ADP-forming)
Comments: Involved in the synthesis of cell-wall peptidoglycan. The D-lysine is attached to the peptide chain at the N^6 position. The enzyme from *Thermotoga maritima* also performs the reaction of EC 6.3.2.7, UDP-*N*-acetylmuramoyl-L-alanyl-D-glutamate—L-lysine ligase.
References: [48]

[EC 6.3.2.37 created 2011, modified 2015]

EC 6.3.2.38

Accepted name: N^2-citryl-N^6-acetyl-N^6-hydroxylysine synthase
Reaction: **2** ATP + citrate + N^6-acetyl-N^6-hydroxy-L-lysine + H_2O = **2** ADP + **2** phosphate + N^6-acetyl-N^2-citryl-N^6-hydroxy-L-lysine
Other name(s): N^{α}-citryl-N^{ε}-acetyl-N^{ε}-hydroxylysine synthase; *iucA* (gene name)
Systematic name: citrate:N^6-acetyl-N^6-hydroxy-L-lysine ligase (AMP-forming)
Comments: Requires Mg^{2+}. The enzyme is involved in the biosynthesis of aerobactin, a dihydroxamate siderophore. It belongs to a class of siderophore synthases known as type A nonribosomal peptide synthase-independent synthases (NIS). Type A enzymes are responsible for the formation of amide or ester bonds between polyamines or amino alcohols and a prochiral carboxyl group of citrate. The enzyme is believed to form an adenylate intermediate prior to ligation.
References: [156, 307, 101, 20, 66, 377]

[EC 6.3.2.38 created 2012, modified 2019]

EC 6.3.2.39

Accepted name: aerobactin synthase
Reaction: ATP + N^2-citryl-N^6-acetyl-N^6-hydroxy-L-lysine + N^6-acetyl-N^6-hydroxy-L-lysine = AMP + diphosphate + aerobactin
Other name(s): *iucC* (gene name)
Systematic name: N^2-citryl-N^6-acetyl-N^6-hydroxy-L-lysine:N^6-acetyl-N^6-hydroxy-L-lysine ligase (AMP-forming)
Comments: Requires Mg^{2+}. The enzyme is involved in the biosynthesis of aerobactin, a dihydroxamate siderophore. It belongs to a class of siderophore synthases known as type C nonribosomal peptide synthase-independent synthases (NIS). Type C enzymes are responsible for the formation of amide or ester bonds between a variety of substrates and a prochiral carboxyl group of a citrate molecule that is already linked to a different moiety at its other prochiral carboxyl group. The enzyme is believed to form an adenylate intermediate prior to ligation.
References: [156, 307, 20, 101, 102, 66, 377]

[EC 6.3.2.39 created 2012, modified 2019]

EC 6.3.2.40

Accepted name: cyclopeptine synthase
Reaction: **2** ATP + *S*-adenosyl-L-methionine + anthranilate + L-phenylalanine = cyclopeptine + **2** AMP + **2** diphosphate + *S*-adenosyl-L-homocysteine
Systematic name: *S*-adenosyl-L-methionine:anthranilate:L-phenylalanine ligase (cyclopeptine-forming)
Comments: Cyclopeptine synthase is the key enzyme of benzodiazepine alkaloid biosynthesis in the fungus *Penicillium cyclopium*. The enzyme is a non-ribosomal peptide synthase.
References: [263, 154]

[EC 6.3.2.40 created 2013]

EC 6.3.2.41

Accepted name: *N*-acetylaspartylglutamate synthase
Reaction: ATP + *N*-acetyl-L-aspartate + L-glutamate = ADP + phosphate + *N*-acetyl-L-aspartyl-L-glutamate
Other name(s): *N*-acetylaspartylglutamate synthetase; NAAG synthetase; NAAGS; RIMKLA (gene name) (ambiguous); RIMKLB (gene name) (ambiguous)
Systematic name: *N*-acetyl-L-aspartate:L-glutamate ligase (ADP, *N*-acetyl-L-aspartyl-L-glutamate-forming)
Comments: The enzyme, found in animals, produces the neurotransmitter *N*-acetyl-L-aspartyl-L-glutamate. One isoform also has the activity of EC 6.3.1.17, β-citrylglutamate synthase [83], while another isoform has the activity of EC 6.3.2.42, *N*-acetylaspartylglutamylglutamate synthase [278].
References: [32, 83, 278]

[EC 6.3.2.41 created 2014]

EC 6.3.2.42

Accepted name: *N*-acetylaspartylglutamylglutamate synthase
Reaction: **2** ATP + *N*-acetyl-L-aspartate + **2** L-glutamate = **2** ADP + **2** phosphate + *N*-acetyl-L-aspartyl-L-glutamyl-L-glutamate
Other name(s): *N*-acetylaspartylglutamylglutamate synthetase; NAAG(2) synthase; NAAG synthetase II; NAAGS-II; RIMKLA (gene name) (ambiguous)
Systematic name: *N*-acetyl-L-aspartate:L-glutamate ligase (ADP, *N*-acetyl-L-aspartyl-L-glutamyl-L-glutamate-forming)
Comments: The enzyme, found in mammals, also has the activity of EC 6.3.2.41, *N*-acetylaspartylglutamate synthase.
References: [278]

[EC 6.3.2.42 created 2014]

EC 6.3.2.43

Accepted name: [amino-group carrier protein]—L-2-aminoadipate ligase
Reaction: ATP + an [amino-group carrier protein]-C-terminal-L-glutamate + L-2-aminoadipate = ADP + phosphate + an [amino-group carrier protein]-C-terminal-[*N*-(1,4-dicarboxybutyl)-L-glutamine]
Other name(s): α-aminoadipate-*lysW* ligase; *lysX* (gene name); LysX (ambiguous); AAA—LysW ligase; [lysine-biosynthesis-protein LysW]-C-terminal-L-glutamate:L-2-aminoadipate ligase (ADP-forming); [lysine-biosynthesis-protein LysW]—L-2-aminoadipate ligase
Systematic name: [amino-group carrier protein]-C-terminal-L-glutamate:L-2-aminoadipate ligase (ADP-forming)
Comments: The enzymes from the thermophilic bacterium *Thermus thermophilus* and the thermophilic archaea *Sulfolobus acidocaldarius* and *Sulfolobus tokodaii* protect the amino group of L-2-aminoadipate by conjugation to the carrier protein LysW. This reaction is part of the lysine biosynthesis pathway in these organisms.
References: [520, 193, 375]

[EC 6.3.2.43 created 2014, modified 2019]

EC 6.3.2.44

Accepted name: pantoate—β-alanine ligase (ADP-forming)
Reaction: ATP + (*R*)-pantoate + β-alanine = ADP + phosphate + (*R*)-pantothenate
Other name(s): pantothenate synthetase (ambiguous); pantoate—β-alanine ligase (ambiguous)
Systematic name: (*R*)-pantoate:β-alanine ligase (ADP-forming)
Comments: The enzyme, characterized from the archaeon *Methanosarcina mazei*, is involved in the biosynthesis of pantothenate. It is different from EC 6.3.2.1, the AMP-forming pantoate-β-alanine ligase found in bacteria and eukaryota.
References: [430]

[EC 6.3.2.44 created 2014]

EC 6.3.2.45

Accepted name: UDP-*N*-acetylmuramate—L-alanyl-γ-D-glutamyl-*meso*-2,6-diaminoheptanedioate ligase
Reaction: ATP + UDP-*N*-acetyl-α-D-muramate + L-alanyl-γ-D-glutamyl-*meso*-2,6-diaminoheptanedioate = ADP + phosphate + UDP-*N*-acetylmuramoyl-L-alanyl-γ-D-glutamyl-*meso*-2,6-diaminoheptanedioate
Other name(s): murein peptide ligase; Mpl; *yjfG* (gene name); UDP-MurNAc:L-Ala-γ-D-Glu-*meso*-A2pm ligase; UDP-*N*-acetylmuramate:L-alanyl-γ-D-glutamyl-*meso*-diaminopimelate ligase
Systematic name: UDP-*N*-acetylmuramate:L-alanyl-γ-D-glutamyl-*meso*-2,6-diaminoheptanedioate ligase2015
Comments: The enzyme catalyses the reincorporation into peptidoglycan of the tripeptide L-alanyl-γ-D-glutamyl-2,6-*meso*-diaminoheptanedioate released during the maturation and constant remodeling of this bacterial cell wall polymer that occur during cell growth and division. The enzyme can also use the tetrapeptide L-alanyl-γ-D-glutamyl-*meso*-2,6-diaminoheptanedioyl-D-alanine or the pentapeptide L-alanyl-γ-D-glutamyl-*meso*-2,6-diaminoheptanedioyl-D-alanyl-D-alanine *in vivo* and *in vitro*. Requires Mg^{2+}.
References: [322, 184]

[EC 6.3.2.45 created 2014]

EC 6.3.2.46

Accepted name: fumarate—(*S*)-2,3-diaminopropanoate ligase
Reaction: ATP + fumarate + L-2,3-diaminopropanoate = AMP + diphosphate + N^3-fumaroyl-L-2,3-diaminopropanoate
Other name(s): DdaG; fumarate:(*S*)-2,3-diaminopropanoate ligase (AMP-forming)
Systematic name: fumarate:L-2,3-diaminopropanoate ligase (AMP-forming)
Comments: The enzyme, characterized from the bacterium *Enterobacter agglomerans*, is involved in biosynthesis of dapdiamide tripeptide antibiotics, a family of fumaramoyl- and epoxysuccinamoyl-peptides named for the presence of an L-2,3-diaminopropanoate (DAP) moiety and two amide linkages in their scaffold.
References: [189]

[EC 6.3.2.46 created 2015]

EC 6.3.2.47

Accepted name: dapdiamide synthase
Reaction: (1) ATP + 3-[(2*E*)-4-amino-4-oxobut-2-enoyl]amino-L-alanine + L-valine = ADP + phosphate + 3-[(2*E*)-4-amino-4-oxobut-2-enoyl]amino-L-alanyl-L-valine
(2) ATP + 3-[(2*E*)-4-amino-4-oxobut-2-enoyl]amino-L-alanine + L-isoleucine = ADP + phosphate + 3-[(2*E*)-4-amino-4-oxobut-2-enoyl]amino-L-alanyl-L-isoleucine
(3) ATP + 3-[(2*E*)-4-amino-4-oxobut-2-enoyl]amino-L-alanine + L-leucine = ADP + phosphate + 3-[(2*E*)-4-amino-4-oxobut-2-enoyl]amino-L-alanyl-L-leucine
(4) ATP + 3-([(2*R*,3*R*)-3-carbamoyloxiran-2-yl]carbonylamino)-L-alanine + L-valine = ADP + phosphate + 3-([(2*R*,3*R*)-3-carbamoyloxiran-2-yl]carbonylamino)-L-alanyl-L-valine
Other name(s): DdaF; dapdiamide A synthase
Systematic name: 3-[(2*E*)-4-amino-4-oxobut-2-enoyl]amino-L-alanine:L-valine ligase (ADP-forming)
Comments: The enzyme, characterized from the bacterium *Pantoea agglomerans*, is involved in biosynthesis of dapdiamide tripeptide antibiotics, a family of fumaramoyl- and epoxysuccinamoyl-peptides named for the presence of an (*S*)-2,3-diaminopropanoate (DAP) moiety and two amide linkages in their scaffold.
References: [189, 188]

[EC 6.3.2.47 created 2015, modified 2016]

EC 6.3.2.48

Accepted name: L-arginine-specific L-amino acid ligase
Reaction: ATP + L-arginine + an L-amino acid = ADP + phosphate + an L-arginyl-L-amino acid

Other name(s): RizA; L-amino acid ligase RizA
Systematic name: L-arginine:L-amino acid ligase (ADP-forming)
Comments: The enzyme, characterized from the bacterium *Bacillus subtilis*, requires Mn^{2+} for activity. It shows strict substrate specificity toward L-arginine as the first (N-terminal) amino acid of the product. The second amino acid could be any standard protein-building amino acid except for L-proline.
References: [237]

[EC 6.3.2.48 created 2015]

EC 6.3.2.49
Accepted name: L-alanine—L-anticapsin ligase
Reaction: ATP + L-alanine + L-anticapsin = ADP + phosphate + bacilysin
Other name(s): BacD; alanine-anticapsin ligase; L-Ala-L-anticapsin ligase; *ywfE* (gene name)
Systematic name: L-alanine:L-anticapsin ligase (ADP-forming)
Comments: The enzyme, characterized from the bacterium *Bacillus subtilis*, is involved in the biosynthesis of the nonribosomally synthesized dipeptide antibiotic bacilysin, composed of L-alanine and L-anticapsin. The enzyme requires Mg^{2+} or Mn^{2+} for activity, and has a broad substrate specificity *in vitro* [490].
References: [490, 509, 459, 384]

[EC 6.3.2.49 created 2006 as EC 6.3.2.28, transferred 2015 to EC 6.3.2.49]

EC 6.3.2.50
Accepted name: tenuazonic acid synthetase
Reaction: ATP + L-isoleucine + acetoacetyl-CoA = AMP + diphosphate + tenuazonic acid + CoA
Other name(s): TAS1 (gene name)
Systematic name: L-isoleucine:acetoacetyl-CoA ligase (tenuazonic acid-forming)
Comments: This fungal enzyme, isolated from *Magnaporthe oryzae*, is an non-ribosomal peptide synthetase (NRPS)-polyketide synthase (PKS) hybrid protein that consists of condensation (C), adenylation (A) and peptidyl-carrier protein (PCP) domains in the NRPS portion and a ketosynthase (KS) domain in the PKS portion. ATP is required for activation of isoleucine, which is then condensed with acetoacetyl-CoA. Cyclization and release from the enzyme are catalysed by the KS domain.
References: [561]

[EC 6.3.2.50 created 2017]

EC 6.3.2.51
Accepted name: phosphopantothenate—cysteine ligase (ATP)
Reaction: ATP + (*R*)-4′-phosphopantothenate + L-cysteine = AMP + diphosphate + *N*-[(*R*)-4′-phosphopantothenoyl]-L-cysteine
Other name(s): phosphopantothenoylcysteine synthetase (ambiguous); PPCS (gene name)
Systematic name: (*R*)-4′-phosphopantothenate:L-cysteine ligase (ATP-utilizing)
Comments: A key enzyme in the production of coenzyme A. The eukaryotic enzyme requires ATP, in contrast to the bacterial enzyme, EC 6.3.2.5, phosphopantothenate—cysteine ligase, which requires CTP.
References: [97, 294, 250]

[EC 6.3.2.51 created 2017]

EC 6.3.2.52
Accepted name: jasmonoyl—L-amino acid ligase
Reaction: ATP + jasmonate + an L-amino acid = AMP + diphosphate + a jasmonoyl-L-amino acid
Other name(s): JAR1 (gene name); JAR4 (gene name); JAR6 (gene name); jasmonoyl—L-amino acid synthetase
Systematic name: jasmonate:L-amino acid ligase

Comments: Two jasmonoyl-L-amino acid synthetases have been described from *Nicotiana attenuata* [531] and one from *Arabidopsis thaliana* [472]. The *N. attenuata* enzymes generate jasmonoyl-L-isoleucine, jasmonoyl-L-leucine, and jasmonoyl-L-valine. The enzyme from *A. thaliana* could catalyse the addition of many different amino acids to jasmonate *in vitro* [1,4,5]. While the abundant form of jasmonate in plants is (–)-jasmonate, the active form of jasmonoyl-L-isoleucine is (+)-7-iso-jasmonoyl-L-isoleucine.

References: [472, 225, 531, 170, 488]

[EC 6.3.2.52 created 2018, modified 2019]

EC 6.3.2.53

Accepted name: UDP-*N*-acetylmuramoyl-L-alanine—L-glutamate ligase

Reaction: ATP + UDP-*N*-acetyl-α-D-muramoyl-L-alanine + L-glutamate = ADP + phosphate + UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-L-glutamate

Other name(s): *murD2* (gene name); UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-L-glutamate synthetase; UDP-MurNAc-L-Ala-L-Glu synthetase

Systematic name: UDP-*N*-acetylmuramoyl-L-alanine—L-glutamate ligase (ADP-forming)

Comments: The enzyme, characterized from the bacterium *Xanthomonas oryzae*, catalyses the ligation of a terminal L-glutamate to UDP-*N*-acetyl-α-D-muramoyl-L-alanine. The combined activity of this enzyme and EC 5.1.1.23, UDP-*N*-acetyl-α-D-muramoyl-L-alanyl-L-glutamate epimerase, provides an alternative route for incorporating D-glutamate into peptidoglycan, replacing the more common combination of EC 5.1.1.3, glutamate racemase, and EC 6.3.2.9, UDP-*N*-acetylmuramoyl-L-alanine—D-glutamate ligase.

References: [131]

[EC 6.3.2.53 created 2018]

EC 6.3.2.54

Accepted name: L-2,3-diaminopropanoate—citrate ligase

Reaction: ATP + L-2,3-diaminopropanoate + citrate = AMP + diphosphate + 2-[(L-alanin-3-ylcarbamoyl)methyl]-2-hydroxybutanedioate

Other name(s): *sbnE* (gene name); 2-[(L-alanin-3-ylcarbamoyl)methyl]-2-hydroxybutanedioate synthtase

Systematic name: L-2,3-diaminopropanoate:citrate ligase (2-[(L-alanin-3-ylcarbamoyl)methyl]-2-hydroxybutanedioate-forming)

Comments: Requires Mg^{2+}. The enzyme, characterized from the bacterium *Staphylococcus aureus*, is involved in the biosynthesis of the siderophore staphyloferrin B. It belongs to a class of siderophore synthases known as type A nonribosomal peptide synthase-independent synthases (NIS). Type A NIS enzymes are responsible for the formation of amide or ester bonds between polyamines or amino alcohols and a prochiral carboxyl group of citrate. The enzyme forms a citrate adenylate intermediate prior to ligation.

References: [94, 75]

[EC 6.3.2.54 created 2019]

EC 6.3.2.55

Accepted name: 2-[(L-alanin-3-ylcarbamoyl)methyl]-3-(2-aminoethylcarbamoyl)-2-hydroxypropanoate synthase

Reaction: ATP + 2-[(2-aminoethylcarbamoyl)methyl]-2-hydroxybutanedioate + L-2,3-diaminopropanoate = AMP + diphosphate + 2-[(L-alanin-3-ylcarbamoyl)methyl]-3-(2-aminoethylcarbamoyl)-2-hydroxypropanoate

Other name(s): *sbnF* (gene name)

Systematic name: 2-[(2-aminoethylcarbamoyl)methyl]-2-hydroxybutanedioate:L-2,3-diaminopropanoate ligase 2-[(L-alanin-3-ylcarbamoyl)methyl]-3-(2-aminoethylcarbamoyl)-2-hydroxypropanoate-forming

Comments: Requires Mg^{2+}. The enzyme, characterized from the bacterium *Staphylococcus aureus*, is involved in the biosynthesis of the siderophore staphyloferrin B. It belongs to a class of siderophore synthases known as type C nonribosomal peptide synthase-independent synthases (NIS). Type C NIS enzymes recognize esterified or amidated derivatives of carboxylic acids. The enzyme likely forms a 2-[(2-aminoethylcarbamoyl)methyl]-2-hydroxybutanedioate adenylate intermediate prior to ligation.
References: [75]

[EC 6.3.2.55 created 2019]

EC 6.3.2.56
Accepted name: staphyloferrin B synthase
Reaction: ATP + 2-[(L-alanin-3-ylcarbamoyl)methyl]-3-(2-aminoethylcarbamoyl)-2-hydroxypropanoate + 2-oxoglutarate = AMP + diphosphate + staphyloferrin B
Other name(s): *sbnC* (gene name)
Systematic name: 2-[(L-alanin-3-ylcarbamoyl)methyl]-3-(2-aminoethylcarbamoyl)-2-hydroxypropanoate:2-oxoglutarate ligase (staphyloferrin B-forming)
Comments: Requires Mg^{2+}. The enzyme, characterized from the bacterium *Staphylococcus aureus*, catalyses the last step in the biosynthesis of the siderophore staphyloferrin B. It belongs to a class of siderophore synthases known as type B nonribosomal peptide synthase-independent synthases (NIS). Type B NIS enzymes recognize the δ-acid group of 2-oxoglutarate. The enzyme forms a 2-oxoglutarate adenylate intermediate prior to ligation.
References: [75]

[EC 6.3.2.56 created 2019]

EC 6.3.2.57
Accepted name: staphyloferrin A synthase
Reaction: ATP + N^5-[(*S*)-citryl]-D-ornithine + citrate = AMP + diphosphate + staphyloferrin A
Other name(s): *sfnaB* (gene name)
Systematic name: N^5-[(*S*)-citryl]-D-ornithine:citrate ligase (staphyloferrin A-forming)
Comments: Requires Mg^{2+}. The enzyme, characterized from the bacterium *Staphylococcus aureus*, catalyses the last step in the biosynthesis of the siderophore staphyloferrin A. It belongs to a class of siderophore synthases known as type A nonribosomal peptide synthase-independent synthases (NIS). Type A NIS enzymes are responsible for the formation of amide or ester bonds between polyamines or amino alcohols and a prochiral carboxyl group of citrate. The enzyme forms a citrate adenylate intermediate prior to ligation.
References: [87]

[EC 6.3.2.57 created 2019]

EC 6.3.2.58
Accepted name: D-ornithine—citrate ligase
Reaction: ATP + D-ornithine + citrate = AMP + diphosphate + N^5-[(*S*)-citryl]-D-ornithine
Other name(s): *sfnaD* (gene name)
Systematic name: D-ornithine:citrate ligase 3-[(2-aminopentan-5-oylcarbamoyl)methyl]-3-hydroxybutanoate-forming
Comments: Requires Mg^{2+}. The enzyme, characterized from the bacterium *Staphylococcus aureus*, is involved in the biosynthesis of the siderophore staphyloferrin A. It belongs to a class of siderophore synthases known as type A nonribosomal peptide synthase-independent synthases (NIS). Type A NIS enzymes are responsible for the formation of amide or ester bonds between polyamines or amino alcohols and a prochiral carboxyl group of citrate. The enzyme forms a citrate adenylate intermediate prior to ligation.
References: [87]

[EC 6.3.2.58 created 2019]

EC 6.3.2.59

Accepted name: 3-methyl-D-ornithine—L-lysine ligase

Reaction: ATP + (3*R*)-3-methyl-D-ornithine + L-lysine = ADP + phosphate + N^6-[(3*R*)-3-methyl-D-ornithinyl]-L-lysine

Other name(s): N^6-[(2*R*,3*R*)-3-methylornithyl]-L-lysine synthase; 3-methylornithine—L-lysine ligase; *pylC* (gene name)

Systematic name: (3*R*)-3-methyl-D-ornithine:L-lysine γ-ligase (ADP-forming)

Comments: The enzyme participates in the biosynthesis of L-pyrrolysine, a naturally occurring, genetically coded amino acid found in some methanogenic archaea and a few bacterial species. L-pyrrolysine is present in several methyltransferases that are involved in methyl transfer from methylated amine compounds to coenzyme M.

References: [148, 62, 403]

[EC 6.3.2.59 created 2021]

EC 6.3.2.60

Accepted name: glutamate—[amino group carrier protein] ligase

Reaction: ATP + L-glutamate + an [amino-group carrier protein]-C-terminal-L-glutamate = ADP + phosphate + an [amino-group carrier protein]-C-terminal-γ-(L-glutamyl)-L-glutamate

Other name(s): *argX* (gene name)

Systematic name: L-glutamate:an [amino-group carrier protein]-C-terminal-L-glutamate ligase (ADP-forming)

Comments: The enzyme, originally characterized from the archaeon *Sulfolobus acidocaldarius*, is involved in L-arginine biosynthesis. The enzyme from the archaeon *Thermococcus kodakarensis* is bifunctional and also catalyses the activity of EC 6.3.2.43, [amino-group carrier protein]—L-2-aminoadipate ligase.

References: [375, 560]

[EC 6.3.2.60 created 2021]

EC 6.3.2.61

Accepted name: tubulin-glutamate ligase

Reaction: ***n*** ATP + [tubulin]-L-glutamate + ***n*** L-glutamate = [tubulin]-(γ-(poly-α-L-glutamyl)-L-glutamyl)-L-glutamate + ***n*** ADP + ***n*** phosphate (overall reaction)
(1a) ATP + [tubulin]-L-glutamate + L-glutamate = [tubulin]-(γ-L-glutamyl)-L-glutamate + ADP + phosphate
(1b) ATP + [tubulin]-(γ-L-glutamyl)-L-glutamate + L-glutamate = [tubulin]-(α-L-glutamyl-γ-L-glutamyl)-L-glutamate + ADP + phosphate
(1c) ATP + [tubulin]-(α-L-glutamyl-γ-L-glutamyl)-L-glutamate + ***n*** L-glutamate = [tubulin]-(γ-(poly-α-L-glutamyl)-L-glutamyl)-L-glutamate + ***n*** ADP + ***n*** phosphate

Other name(s): α-tubulin-glutamate ligase; tubulin polyglutamylase; TTLL1 (ambiguous); TTLL5 (ambiguous); TTLL6 (ambiguous)

Systematic name: [tubulin]-L-glutamate:L-glutamate ligase (ADP-forming)

Comments: The eukaryotic tubulin proteins, which polymerize into microtubules, are highly modified by the addition of side-chains. The polyglutamylation reaction catalysed by this group of enzymes consists of two biochemically distinct steps: initiation and elongation. Initiation comprises the formation of an isopeptide bond with the γ-carboxyl group of the glutamate acceptor site in a glutamate-rich C-terminal region of tubulin, whereas elongation consists of the addition of glutamate residues linked by regular peptide bonds to the γ-linked residue. This entry describes enzymes that act on both α- and β-tubulins.

References: [417, 418, 541, 215, 518, 550, 517]

[EC 6.3.2.61 created 2021]

EC 6.3.2.62

Accepted name: β-tubulin-glutamate ligase
Reaction: ***n*** ATP + [β-tubulin]-L-glutamate + ***n*** L-glutamate = [β-tubulin]-(γ-(poly-α-L-glutamyl)-L-glutamyl)-L-glutamate + ***n*** ADP + ***n*** phosphate (overall reaction)
(1a) ATP + [β-tubulin]-L-glutamate + L-glutamate = [β-tubulin]-(γ-L-glutamyl)-L-glutamate + ADP + phosphate
(1b) ATP + [β-tubulin]-(γ-L-glutamyl)-L-glutamate + L-glutamate = [β-tubulin]-(α-L-glutamyl-γ-L-glutamyl)-L-glutamate + ADP + phosphate
(1c) ATP + [β-tubulin]-(α-L-glutamyl-γ-L-glutamyl)-L-glutamate + ***n*** L-glutamate = [β-tubulin]-(γ-(poly-α-L-glutamyl)-L-glutamyl)-L-glutamate + ***n*** ADP + ***n*** phosphate
Other name(s): β-tubulin polyglutamylase; TTLL4 (ambiguous); TTLL7 (ambiguous)
Systematic name: [β-tubulin]-L-glutamate:L-glutamate ligase (ADP-forming)
Comments: The eukaryotic tubulin proteins, which polymerize into microtubules, are highly modified by the addition of side-chains. The polyglutamylation reaction catalysed by this group of enzymes consists of two biochemically distinct steps: initiation and elongation. Initiation comprises the formation of an isopeptide bond with the γ-carboxyl group of the glutamate acceptor site, whereas elongation consists of the addition of glutamate residues linked by regular peptide bonds to the γ-linked residue. This entry describes enzymes that act on β-tubulins and other proteins with glutamate-rich regions but not on α-tubulins.
References: [417, 418, 203, 517]

[EC 6.3.2.62 created 2021]

EC 6.3.3 Cyclo-ligases

EC 6.3.3.1
Accepted name: phosphoribosylformylglycinamidine cyclo-ligase
Reaction: ATP + 2-(formamido)-N^1-(5-phospho-D-ribosyl)acetamidine = ADP + phosphate + 5-amino-1-(5-phospho-D-ribosyl)imidazole
Other name(s): phosphoribosylaminoimidazole synthetase; AIR synthetase; 5′-aminoimidazole ribonucleotide synthetase; 2-(formamido)-1-*N*-(5-phosphoribosyl)acetamidine cyclo-ligase (ADP-forming)
Systematic name: 2-(formamido)-N^1-(5-phosphoribosyl)acetamidine cyclo-ligase (ADP-forming)
References: [265, 264]

[EC 6.3.3.1 created 1961, modified 2000]

EC 6.3.3.2
Accepted name: 5-formyltetrahydrofolate cyclo-ligase
Reaction: ATP + 5-formyltetrahydrofolate = ADP + phosphate + 5,10-methenyltetrahydrofolate
Other name(s): 5,10-methenyltetrahydrofolate synthetase; formyltetrahydrofolic cyclodehydrase; 5-formyltetrahydrofolate cyclodehydrase
Systematic name: 5-formyltetrahydrofolate cyclo-ligase (ADP-forming)
References: [165]

[EC 6.3.3.2 created 1972]

EC 6.3.3.3
Accepted name: dethiobiotin synthase
Reaction: ATP + 7,8-diaminononanoate + CO_2 = ADP + phosphate + dethiobiotin
Other name(s): desthiobiotin synthase
Systematic name: 7,8-diaminononanoate:carbon-dioxide cyclo-ligase (ADP-forming)
Comments: CTP has half the activity of ATP.
References: [245, 555]

[EC 6.3.3.3 created 1976]

EC 6.3.3.4

Accepted name: (carboxyethyl)arginine β-lactam-synthase
Reaction: ATP + L-N^2-(2-carboxyethyl)arginine = AMP + diphosphate + deoxyamidinoproclavaminate
Other name(s): L-2-*N*-(2-carboxyethyl)arginine cyclo-ligase (AMP-forming)
Systematic name: L-N^2-(2-carboxyethyl)arginine cyclo-ligase (AMP-forming)
Comments: Forms part of the pathway for the biosynthesis of the β-lactamase inhibitor clavulanate in *Streptomyces clavuligerus*. It has been proposed [25] that L-N^2-(2-carboxyethyl)arginine is first converted into an acyl-AMP by reaction with ATP and loss of diphosphate, and that the β-lactam ring is then formed by the intramolecular attack of the β-nitrogen on the activated carboxy group.
References: [568, 506, 25]

[EC 6.3.3.4 created 2003]

EC 6.3.3.5

Accepted name: *O*-ureido-D-serine cyclo-ligase
Reaction: *O*-ureido-D-serine + ATP + H_2O = D-cycloserine + CO_2 + NH_3 + ADP + phosphate
Other name(s): *dcsG* (gene name)
Systematic name: *O*-ureido-D-serine cyclo-ligase (D-cycloserine-forming)
Comments: The enzyme participates in the biosynthetic pathway of D-cycloserine, an antibiotic substance produced by several *Streptomyces* species.
References: [247, 510]

[EC 6.3.3.5 created 2013]

EC 6.3.3.6

Accepted name: carbapenam-3-carboxylate synthase
Reaction: ATP + (2*S*,5*S*)-5-carboxymethylproline = AMP + diphosphate + (3*S*,5*S*)-carbapenam 3-carboxylate
Other name(s): CarA (ambiguous); CPS (ambiguous); carbapenam-3-carboxylate ligase; 6-methyl-(2*S*,5*S*)-5-carboxymethylproline cyclo-ligase (AMP-forming)
Systematic name: (2*S*,5*S*)-5-carboxymethylproline cyclo-ligase (AMP-forming)
Comments: The enzyme is involved in the biosynthesis of the carbapenem β-lactam antibiotic (5*R*)-carbapen-2-em-3-carboxylate in the bacterium *Pectobacterium carotovorum*.
References: [155, 328, 404, 22]

[EC 6.3.3.6 created 2013 as 6.3.1.16, transferred 2013 to EC 6.3.3.6]

EC 6.3.3.7

Accepted name: Ni-sirohydrochlorin *a*,*c*-diamide reductive cyclase
Reaction: ATP + Ni-sirohydrochlorin *a*,*c*-diamide + **3** reduced electron acceptor + H_2O = ADP + phosphate + 15,17^3-seco-F_{430}-17^3-acid + **3** electron acceptor
Other name(s): *cfbC* (gene name); *cfbD* (gene name)
Systematic name: Ni-sirohydrochlorin *a*,*c*-diamide reductive cyclo-ligase (ADP-forming)
Comments: The enzyme, studied from the methanogenic archaeon *Methanosarcina acetivorans*, participates in the biosynthesis of the nickel-containing tetrapyrrole cofactor coenzyme F_{430}, which is required by EC 2.8.4.1, coenzyme-B sulfoethylthiotransferase.
References: [393, 566]

[EC 6.3.3.7 created 2017]

EC 6.3.4 Other carbon-nitrogen ligases

[6.3.4.1 Transferred entry. GMP synthase. Now included in EC 6.3.5.2, GMP synthase (glutamine-hydrolysing)]

[EC 6.3.4.1 created 1961, deleted 2013]

EC 6.3.4.2

Accepted name: CTP synthase (glutamine hydrolysing)
Reaction: ATP + UTP + L-glutamine = ADP + phosphate + CTP + L-glutamate (overall reaction)
(1a) L-glutamine + H_2O = L-glutamate + NH_3
(1b) ATP + UTP + NH_3 = ADP + phosphate + CTP
Other name(s): UTP—ammonia ligase; cytidine triphosphate synthetase; uridine triphosphate aminase; cytidine 5′-triphosphate synthetase; CTPS (gene name); *pyrG* (gene name); CTP synthase; UTP:ammonia ligase (ADP-forming)
Systematic name: UTP:L-glutamine amido-ligase (ADP-forming)
Comments: The enzyme contains three functionally distinct sites: an allosteric GTP-binding site, a glutaminase site where glutamine hydrolysis occurs (*cf.* EC 3.5.1.2, glutaminase), and the active site where CTP synthesis takes place. The reaction proceeds via phosphorylation of UTP by ATP to give an activated intermediate 4-phosphoryl UTP and ADP [524, 266]. Ammonia then reacts with this intermediate generating CTP and a phosphate. The enzyme can also use ammonia from the surrounding solution [1, 525].
References: [271, 280, 1, 524, 266, 525]

[EC 6.3.4.2 created 1961, modified 2013]

EC 6.3.4.3

Accepted name: formate—tetrahydrofolate ligase
Reaction: ATP + formate + tetrahydrofolate = ADP + phosphate + 10-formyltetrahydrofolate
Other name(s): formyltetrahydrofolate synthetase; 10-formyltetrahydrofolate synthetase; tetrahydrofolic formylase; tetrahydrofolate formylase
Systematic name: formate:tetrahydrofolate ligase (ADP-forming)
Comments: In eukaryotes occurs as a trifunctional enzyme also having methylenetetrahydrofolate dehydrogenase ($NADP^+$) (EC 1.5.1.5) and methenyltetrahydrofolate cyclohydrolase (EC 3.5.4.9) activity.
References: [213, 280, 405, 543]

[EC 6.3.4.3 created 1961]

EC 6.3.4.4

Accepted name: adenylosuccinate synthase
Reaction: GTP + IMP + L-aspartate = GDP + phosphate + N^6-(1,2-dicarboxyethyl)-AMP
Other name(s): IMP—aspartate ligase; adenylosuccinate synthetase; succinoadenylic kinosynthetase; succino-AMP synthetase
Systematic name: IMP:L-aspartate ligase (GDP-forming)
References: [98, 272, 556]

[EC 6.3.4.4 created 1961]

EC 6.3.4.5

Accepted name: argininosuccinate synthase
Reaction: ATP + L-citrulline + L-aspartate = AMP + diphosphate + 2-(N^{ω}-L-arginino)succinate
Other name(s): citrulline—aspartate ligase; argininosuccinate synthetase; arginine succinate synthetase; argininosuccinic acid synthetase; arginosuccinate synthetase
Systematic name: L-citrulline:L-aspartate ligase (AMP-forming)

References: [409, 450]

[EC 6.3.4.5 created 1961]

EC 6.3.4.6

Accepted name: urea carboxylase
Reaction: ATP + urea + HCO_3^- = ADP + phosphate + urea-1-carboxylate
Other name(s): urease (ATP-hydrolysing); urea carboxylase (hydrolysing); ATP—urea amidolyase; urea amidolyase; UALase; UCA
Systematic name: urea:carbon-dioxide ligase (ADP-forming)
Comments: A biotinyl-protein. The yeast enzyme (but not that from green algae) also catalyses the reaction of EC 3.5.1.54 allophanate hydrolase, thus bringing about the hydrolysis of urea to CO_2 and NH_3. Previously also listed as EC 3.5.1.45. The enzyme from the prokaryotic bacterium *Oleomonas sagaranensis* can also use acetamide and formamide as substrates [223].
References: [431, 432, 485, 223]

[EC 6.3.4.6 created 1972, modified 1986 (EC 3.5.1.45 created 1978, incorporated 1986)]

EC 6.3.4.7

Accepted name: ribose-5-phosphate—ammonia ligase
Reaction: ATP + ribose 5-phosphate + NH_3 = ADP + phosphate + 5-phosphoribosylamine
Other name(s): 5-phosphoribosylamine synthetase; ribose 5-phosphate aminotransferase; ammonia-ribose 5-phosphate aminotransferase
Systematic name: ribose-5-phosphate:ammonia ligase (ADP-forming)
References: [415]

[EC 6.3.4.7 created 1972]

EC 6.3.4.8

Accepted name: imidazoleacetate—phosphoribosyldiphosphate ligase
Reaction: ATP + imidazole-4-acetate + 5-phosphoribosyl diphosphate + H_2O = ADP + phosphate + 1-(5-phosphoribosyl)imidazole-4-acetate + diphosphate
Other name(s): 5-phosphoribosylimidazoleacetate synthetase
Systematic name: imidazoleacetate:5-phosphoribosyl-diphosphate ligase (ADP- and diphosphate-forming)
References: [91]

[EC 6.3.4.8 created 1972]

EC 6.3.4.9

Accepted name: biotin—[methylmalonyl-CoA-carboxytransferase] ligase
Reaction: ATP + biotin + apo-[methylmalonyl-CoA:pyruvate carboxytransferase] = AMP + diphosphate + [methylmalonyl-CoA:pyruvate carboxytransferase]
Other name(s): biotin-[methylmalonyl-CoA-carboxyltransferase] synthetase; biotin-methylmalonyl coenzyme A carboxyltransferase synthetase; biotin-transcarboxylase synthetase; methylmalonyl coenzyme A holotranscarboxylase synthetase; biotin—[methylmalonyl-CoA-carboxyltransferase] ligase; biotin:apo[methylmalonyl-CoA:pyruvate carboxyltransferase] ligase (AMP-forming)
Systematic name: biotin:apo[methylmalonyl-CoA:pyruvate carboxytransferase] ligase (AMP-forming)
References: [258]

[EC 6.3.4.9 created 1972]

EC 6.3.4.10

Accepted name: biotin—[propionyl-CoA-carboxylase (ATP-hydrolysing)] ligase
Reaction: ATP + biotin + apo-[propionyl-CoA:carbon-dioxide ligase (ADP-forming)] = AMP + diphosphate + [propionyl-CoA:carbon-dioxide ligase (ADP-forming)]
Other name(s): biotin-[propionyl-CoA-carboxylase (ATP-hydrolysing)] synthetase; biotin-propionyl coenzyme A carboxylase synthetase; propionyl coenzyme A holocarboxylase synthetase
Systematic name: biotin:apo-[propanoyl-CoA:carbon-dioxide ligase (ADP-forming)] ligase (AMP-forming)
References: [460]

[EC 6.3.4.10 created 1972]

EC 6.3.4.11

Accepted name: biotin—[methylcrotonoyl-CoA-carboxylase] ligase
Reaction: ATP + biotin + apo-[3-methylcrotonoyl-CoA:carbon-dioxide ligase (ADP-forming)] = AMP + diphosphate + [3-methylcrotonoyl-CoA:carbon-dioxide ligase (ADP-forming)]
Other name(s): biotin-[methylcrotonoyl-CoA-carboxylase] synthetase; biotin-β-methylcrotonyl coenzyme A carboxylase synthetase; β-methylcrotonyl coenzyme A holocarboxylase synthetase; holocarboxylase-synthetase
Systematic name: biotin:apo-[3-methylcrotonoyl-CoA:carbon-dioxide ligase (ADP-forming)] ligase (AMP-forming)
References: [192]

[EC 6.3.4.11 created 1972]

EC 6.3.4.12

Accepted name: glutamate—methylamine ligase
Reaction: ATP + L-glutamate + methylamine = ADP + phosphate + N^5-methyl-L-glutamine
Other name(s): γ-glutamylmethylamide synthetase
Systematic name: L-glutamate:methylamine ligase (ADP-forming)
References: [248]

[EC 6.3.4.12 created 1972]

EC 6.3.4.13

Accepted name: phosphoribosylamine—glycine ligase
Reaction: ATP + 5-phospho-D-ribosylamine + glycine = ADP + phosphate + N^1-(5-phospho-D-ribosyl)glycinamide
Other name(s): phosphoribosylglycinamide synthetase; glycinamide ribonucleotide synthetase; phosphoribosylglycineamide synthetase; glycineamide ribonucleotide synthetase; 2-amino-*N*-ribosylacetamide 5′-phosphate kinosynthase; 5′-phosphoribosylglycinamide synthetase; GAR
Systematic name: 5-phospho-D-ribosylamine:glycine ligase (ADP-forming)
References: [161, 176]

[EC 6.3.4.13 created 1961 as EC 6.3.1.3, transferred 1972 to EC 6.3.4.13, modified 2000]

EC 6.3.4.14

Accepted name: biotin carboxylase
Reaction: ATP + [biotin carboxyl-carrier protein]-biotin-N^6-L-lysine + hydrogencarbonate- = ADP + phosphate + [biotin carboxyl-carrier protein]-carboxybiotin-N^6-L-lysine
Other name(s): *accC* (gene name); biotin-carboxyl-carrier-protein:carbon-dioxide ligase (ADP-forming)
Systematic name: [biotin carboxyl-carrier protein]-biotin-N^6-L-lysine:hydrogencarbonate ligase (ADP-forming)

Comments: This enzyme, part of an acetyl-CoA carboxylase complex, acts on a biotin carboxyl-carrier protein (BCCP) that has been biotinylated by EC 6.3.4.15, biotin—[biotin carboxyl-carrier protein] ligase. In some organisms the enzyme is part of a multi-domain polypeptide that also includes the carrier protein (e.g. mycobacteria). Yet in other organisms (e.g. mammals) this activity is included in a single polypeptide that also catalyses the transfer of the carboxyl group from biotin to acetyl-CoA (see EC 6.4.1.2, acetyl-CoA carboxylase).
References: [109, 365, 214, 77, 54]

[EC 6.3.4.14 created 1976, modified 2014, modified 2018]

EC 6.3.4.15
Accepted name: biotin—[biotin carboxyl-carrier protein] ligase
Reaction: ATP + biotin + [biotin carboxyl-carrier protein]-L-lysine = AMP + diphosphate + [biotin carboxyl-carrier protein]-N^6-biotinyl-L-lysine
Other name(s): *birA* (gene name); HLCS (gene name); HCS1 (gene name); biotin-[acetyl-CoA carboxylase] synthetase; biotin-[acetyl coenzyme A carboxylase] synthetase; acetyl coenzyme A holocarboxylase synthetase; acetyl CoA holocarboxylase synthetase; biotin:apocarboxylase ligase; Biotin holoenzyme synthetase; biotin:apo-[acetyl-CoA:carbon-dioxide ligase (ADP-forming)] ligase (AMP-forming); biotin—[acetyl-CoA-carboxylase] ligase
Systematic name: biotin:apo-[carboxyl-carrier protein] ligase (AMP-forming)
Comments: The enzyme biotinylates a biotin carboxyl-carrier protein that is part of an acetyl-CoA carboxylase complex, enabling its subsequent carboxylation by EC 6.3.4.14, biotin carboxylase. The carboxyl group is eventually transferred to acetyl-CoA by EC 2.1.3.15, acetyl-CoA carboxytransferase. In some organisms the carrier protein is part of EC 6.4.1.2, acetyl-CoA carboxylase.
References: [256, 547, 360]

[EC 6.3.4.15 created 1978, modified 2018]

EC 6.3.4.16
Accepted name: carbamoyl-phosphate synthase (ammonia)
Reaction: **2** ATP + NH_3 + hydrogencarbonate = **2** ADP + phosphate + carbamoyl phosphate (overall reaction)
(1a) ATP + hydrogencarbonate = ADP + carboxyphosphate
(1b) NH_3 + carboxyphosphate = carbamate + phosphate
(1c) ATP + carbamate = ADP + carbamoyl phosphate
Other name(s): carbon-dioxide—ammonia ligase; carbamoylphosphate synthase; carbamylphosphate synthetase; carbamoylphosphate synthase (ammonia); carbamoylphosphate synthetase; carbamylphosphate synthetase I; CPSI (gene name); carbon-dioxide:ammonia ligase (ADP-forming, carbamate-phosphorylating)
Systematic name: hydrogencarbonate:ammonia ligase (ADP-forming, carbamate-phosphorylating)
Comments: The enzyme catalyses the first committed step in the urea cycle. The reaction proceeds via three separate chemical reactions: phosphorylation of hydrogencarbonate to carboxyphosphate; a nucleophilic attack of ammonia on carboxyphosphate yielding carbamate; and the phosphorylation of carbamate forming carbamoyl phosphate. Two moles of ATP are utilized for the synthesis of one molecule of carbamyl phosphate, making the reaction essentially irreversible. The enzyme requires the allosteric activator *N*-acetyl-L-glutamate. *cf.* EC 6.3.5.5, carbamoyl-phosphate synthase (glutamine-hydrolysing).
References: [127, 218, 297, 298, 396, 387]

[EC 6.3.4.16 created 1965 as EC 2.7.2.5, transferred 1978 to EC 6.3.4.16]

EC 6.3.4.17
Accepted name: formate—dihydrofolate ligase
Reaction: ATP + formate + dihydrofolate = ADP + phosphate + 10-formyldihydrofolate

Other name(s): formyltransferase, dihydrofolate; dihydrofolate formyltransferase; formyl dihydrofolate synthase
Systematic name: formate:dihydrofolate ligase (ADP-forming)
Comments: Not identical with EC 6.3.4.3 (formate—tetrahydrofolate ligase).
References: [113]

[EC 6.3.4.17 created 1992]

EC 6.3.4.18

Accepted name: 5-(carboxyamino)imidazole ribonucleotide synthase
Reaction: ATP + 5-amino-1-(5-phospho-D-ribosyl)imidazole + HCO_3^- = ADP + phosphate + 5-carboxyamino-1-(5-phospho-D-ribosyl)imidazole
Other name(s): N^5-CAIR synthetase; N^5-carboxyaminoimidazole ribonucleotide synthetase; PurK
Systematic name: 5-amino-1-(5-phospho-D-ribosyl)imidazole:carbon-dioxide ligase (ADP-forming)
Comments: In *Escherichia coli*, this enzyme, along with EC 5.4.99.18, 5-(carboxyamino)imidazole ribonucleotide mutase, is required to carry out the single reaction catalysed by EC 4.1.1.21, phosphoribosylaminoimidazole carboxylase, in vertebrates. Belongs to the ATP grasp protein superfamily [502]. Carboxyphosphate is the putative acyl phosphate intermediate. Involved in the late stages of purine biosynthesis.
References: [325, 344, 502]

[EC 6.3.4.18 created 2006]

EC 6.3.4.19

Accepted name: $tRNA^{Ile}$-lysidine synthase
Reaction: [$tRNA^{Ile2}$]-cytidine^{34} + L-lysine + ATP = [$tRNA^{Ile2}$]-lysidine^{34} + AMP + diphosphate + H_2O
Other name(s): TilS; *mesJ* (gene name); *yacA* (gene name); isoleucine-specific transfer ribonucleate lysidine synthetase; $tRNA^{Ile}$-lysidine synthetase
Systematic name: L-lysine:[$tRNA^{Ile2}$]-cytidine^{34} ligase (AMP-forming)
Comments: The bacterial enzyme modifies the wobble base of the CAU anticodon of $tRNA^{Ile}$ at the oxo group in position 2 of cytidine^{34}. This modification determines both codon and amino acid specificities of $tRNA^{Ile}$.
References: [205, 438, 354, 469, 353]

[EC 6.3.4.19 created 2011]

EC 6.3.4.20

Accepted name: 7-cyano-7-deazaguanine synthase
Reaction: 7-carboxy-7-carbaguanine + NH_3 + ATP = 7-cyano-7-carbaguanine + ADP + phosphate + H_2O
Other name(s): $preQ_0$ synthase; 7-cyano-7-carbaguanine synthase; *queC* (gene name)
Systematic name: 7-carboxy-7-carbaguanine:ammonia ligase (ADP-forming)
Comments: Binds Zn^{2+}. The reaction is part of the biosynthesis pathway of queuosine.
References: [310, 82]

[EC 6.3.4.20 created 2012]

EC 6.3.4.21

Accepted name: nicotinate phosphoribosyltransferase
Reaction: nicotinate + 5-phospho-α-D-ribose 1-diphosphate + ATP + H_2O = β-nicotinate D-ribonucleotide + diphosphate + ADP + phosphate
Other name(s): niacin ribonucleotidase; nicotinic acid mononucleotide glycohydrolase; nicotinic acid mononucleotide pyrophosphorylase; nicotinic acid phosphoribosyltransferase; nicotinate-nucleotide:diphosphate phospho-α-D-ribosyltransferase

Systematic name: 5-phospho-α-D-ribose 1-diphosphate:nicotinate ligase (ADP, diphosphate-forming)
Comments: The enzyme, which is involved in pyridine nucleotide recycling, can form β-nicotinate D-ribonucleotide and diphosphate from nicotinate and 5-phospho-α-D-ribose 1-diphosphate (PRPP) in the absence of ATP. However, when ATP is available the enzyme is phosphorylated resulting in a much lower K_m for nicotinate. The phospho-enzyme is hydrolysed during the transferase reaction, regenerating the low affinity form. The presence of ATP shifts the products/substrates equilibrium from 0.67 to 1100 [522].
References: [206, 207, 244, 522]

[EC 6.3.4.21 created 1961 as EC 2.4.2.11, transferred 2013 to EC 6.3.4.21]

EC 6.3.4.22
Accepted name: $tRNA^{Ile2}$-agmatinylcytidine synthase
Reaction: ATP + agmatine + [$tRNA^{Ile2}$]-cytidine^{34} + H_2O = [$tRNA^{Ile2}$]-2-agmatinylcytidine^{34} + AMP + **2** phosphate
Other name(s): TiaS; AF2259; $tRNA^{Ile}$-2-agmatinylcytidine synthetase; $tRNA^{Ile}$-agm^{2}C synthetase; $tRNA^{Ile}$-agmatidine synthetase
Systematic name: agmatine:[$tRNA^{Ile}$]-cytidine^{34} ligase
Comments: The enzyme from the archaeon *Archaeoglobus fulgidus* modifies the wobble base of the CAU anticodon of the archaeal $tRNA^{Ile2}$ at the oxo group in position 2 of cytidine^{34}. This modification is crucial for accurate decoding of the genetic code. In bacteria EC 6.3.4.19, $tRNA^{Ile}$-lysidine synthase, catalyses the modification of [$tRNA^{Ile2}$]-cytidine^{34} to [$tRNA^{Ile2}$]-lysidine^{34} .
References: [204, 497, 373]

[EC 6.3.4.22 created 2013]

EC 6.3.4.23
Accepted name: formate—phosphoribosylaminoimidazolecarboxamide ligase
Reaction: ATP + formate + 5-amino-1-(5-phospho-D-ribosyl)imidazole-4-carboxamide = ADP + phosphate + 5-formamido-1-(5-phospho-D-ribosyl)imidazole-4-carboxamide
Other name(s): 5-formaminoimidazole-4-carboxamide ribonucleotide synthetase; 5-formaminoimidazole-4-carboxamide-1-β-D-ribofuranosyl 5′-monophosphate synthetase; *purP* (gene name)
Systematic name: formate:5-amino-1-(5-phospho-D-ribosyl)imidazole-4-carboxamide ligase (ADP-forming)
Comments: This archaeal enzyme, characterized from the methanogen *Methanocaldococcus jannaschii*, catalyses a step in the synthesis of purine nucleotides. It differs from the orthologous bacterial/eukaryotic enzymes, which utilize 10-formyltetrahydrofolate rather than formate and ATP. *cf.* EC 2.1.2.3, phosphoribosylaminoimidazolecarboxamide formyltransferase.
References: [378, 564]

[EC 6.3.4.23 created 2013]

EC 6.3.4.24
Accepted name: tyramine—L-glutamate ligase
Reaction: ATP + tyramine + L-glutamate = ADP + phosphate + γ-glutamyltyramine
Other name(s): *mfnD* (gene name)
Systematic name: tyramine:L-glutamate γ-ligase (ADP-forming)
Comments: The enzyme, which has been characterized from the archaea *Methanocaldococcus fervens*, participates in the biosynthesis of the cofactor methanofuran. Requires a divalent cation for activity, with Mn^{2+} giving the highest activity, followed by Mg^{2+}, Co^{2+}, Zn^{2+}, and Fe^{2+}.
References: [532]

[EC 6.3.4.24 created 2014]

EC 6.3.4.25

Accepted name: 2-amino-2′-deoxyadenylo-succinate synthase
Reaction: ATP + dGMP + L-aspartate = ADP + phosphate + 2-amino-2′-deoxy-N^6-[(2*S*)-succino]adenylate
Other name(s): *purZ* (gene name)
Systematic name: dGMP:L-aspartate ligase (ADP-forming)
Comments: The enzyme, characterized from a number of bacteriophages, participates in the biosynthesis of dZTP, which replaces dATP in the genome of these phages.
References: [569, 464]

[EC 6.3.4.25 created 2021]

EC 6.3.5 Carbon-nitrogen ligases with glutamine as amido-N-donor

EC 6.3.5.1

Accepted name: NAD^+ synthase (glutamine-hydrolysing)
Reaction: ATP + deamido-NAD^+ + L-glutamine + H_2O = AMP + diphosphate + NAD^+ + L-glutamate
Other name(s): NAD synthetase (glutamine-hydrolysing); nicotinamide adenine dinucleotide synthetase (glutamine); desamidonicotinamide adenine dinucleotide amidotransferase; DPN synthetase
Systematic name: deamido-NAD^+:L-glutamine amido-ligase (AMP-forming)
Comments: NH_3 can act instead of glutamine (*cf.* EC 6.3.1.5 NAD^+ synthase).
References: [206, 207]

[EC 6.3.5.1 created 1961]

EC 6.3.5.2

Accepted name: GMP synthase (glutamine-hydrolysing)
Reaction: ATP + XMP + L-glutamine + H_2O = AMP + diphosphate + GMP + L-glutamate (overall reaction)
(1a) L-glutamine + H_2O = L-glutamate + NH_3
(1b) ATP + XMP + NH_3 = AMP + diphosphate + GMP
Other name(s): GMP synthetase (glutamine-hydrolysing); guanylate synthetase (glutamine-hydrolyzing); guanosine monophosphate synthetase (glutamine-hydrolyzing); xanthosine 5′-phosphate amidotransferase; guanosine 5′-monophosphate synthetase
Systematic name: xanthosine-5′-phosphate:L-glutamine amido-ligase (AMP-forming)
Comments: Involved in the *de novo* biosynthesis of guanosine nucleotides. An N-terminal glutaminase domain binds L-glutamine and generates ammonia, which is transferred by a substrate-protective tunnel to the ATP-pyrophosphatase domain. The enzyme can catalyse the second reaction alone in the presence of ammonia.
References: [253, 5, 562, 2]

[EC 6.3.5.2 created 1961, modified 2013]

EC 6.3.5.3

Accepted name: phosphoribosylformylglycinamidine synthase
Reaction: ATP + N^2-formyl-N^1-(5-phospho-D-ribosyl)glycinamide + L-glutamine + H_2O = ADP + phosphate + 2-(formamido)-N^1-(5-phospho-D-ribosyl)acetamidine + L-glutamate
Other name(s): phosphoribosylformylglycinamidine synthetase; formylglycinamide ribonucleotide amidotransferase; phosphoribosylformylglycineamidine synthetase; FGAM synthetase; FGAR amidotransferase; 5′-phosphoribosylformylglycinamide:L-glutamine amido-ligase (ADP-forming); 2-*N*-formyl-1-*N*-(5-phospho-D-ribosyl)glycinamide:L-glutamine amido-ligase (ADP-forming)
Systematic name: N^2-formyl-N^1-(5-phospho-D-ribosyl)glycinamide:L-glutamine amido-ligase (ADP-forming)
References: [320]

[EC 6.3.5.3 created 1961, modified 2000]

EC 6.3.5.4

Accepted name: asparagine synthase (glutamine-hydrolysing)

Reaction: ATP + L-aspartate + L-glutamine + H_2O = AMP + diphosphate + L-asparagine + L-glutamate (overall reaction)
(1a) L-glutamine + H_2O = L-glutamate + NH_3
(1b) ATP + L-aspartate + NH_3 = AMP + diphosphate + L-asparagine

Other name(s): asparagine synthetase (glutamine-hydrolysing); glutamine-dependent asparagine synthetase; asparagine synthetase B; AS; AS-B

Systematic name: L-aspartate:L-glutamine amido-ligase (AMP-forming)

Comments: The enzyme from *Escherichia coli* has two active sites [259] that are connected by an intramolecular ammonia tunnel [198, 498]. The enzyme catalyses three distinct chemical reactions: glutamine hydrolysis to yield ammonia takes place in the N-terminal domain. The C-terminal active site mediates both the synthesis of a β-aspartyl-AMP intermediate and its subsequent reaction with ammonia. The ammonia released is channeled to the other active site to yield asparagine [498].

References: [386, 45, 423, 259, 198, 498]

[EC 6.3.5.4 created 1972, modified 2006]

EC 6.3.5.5

Accepted name: carbamoyl-phosphate synthase (glutamine-hydrolysing)

Reaction: **2** ATP + L-glutamine + hydrogencarbonate + H_2O = **2** ADP + phosphate + L-glutamate + carbamoyl phosphate (overall reaction)
(1a) L-glutamine + H_2O = L-glutamate + NH_3
(1b) ATP + hydrogencarbonate = ADP + carboxyphosphate
(1c) NH_3 + carboxyphosphate = carbamate + phosphate
(1d) ATP + carbamate = ADP + carbamoyl phosphate

Other name(s): carbamoyl-phosphate synthetase (glutamine-hydrolysing); carbamyl phosphate synthetase (glutamine); carbamoylphosphate synthetase II; glutamine-dependent carbamyl phosphate synthetase; carbamoyl phosphate synthetase; CPS; carbon-dioxide:L-glutamine amido-ligase (ADP-forming, carbamate-phosphorylating); *carA* (gene name); *carB* (gene name); CAD (gene name); hydrogencarbonate:L-glutamine amido-ligase (ADP-forming, carbamate-phosphorylating)

Systematic name: hydrogencarbonate:L-glutamine amido-ligase (ADP-forming, carbamate-phosphorylating)

Comments: The product carbamoyl phosphate is an intermediate in the biosynthesis of arginine and the pyrimidine nucleotides [471]. The enzyme from *Escherichia coli* has three separate active sites, which are connected by a molecular tunnel that is almost 100 Å in length [501]. The amidotransferase domain within the small subunit of the enzyme hydrolyses glutamine to ammonia via a thioester intermediate. The ammonia migrates through the interior of the protein, where it reacts with carboxyphosphate to produce the carbamate intermediate. The carboxyphosphate intermediate is formed by the phosphorylation of hydrogencarbonate by ATP at a site contained within the N-terminal half of the large subunit. The carbamate intermediate is transported through the interior of the protein to a second site within the C-terminal half of the large subunit, where it is phosphorylated by another ATP to yield the final product, carbamoyl phosphate [411]. *cf.* EC 6.3.4.16, carbamoyl-phosphate synthase (ammonia).

References: [14, 221, 557, 471, 187, 411, 410, 501]

[EC 6.3.5.5 created 1972 as EC 2.7.2.9, transferred 1978 to EC 6.3.5.5, modified 2006]

EC 6.3.5.6

Accepted name: asparaginyl-tRNA synthase (glutamine-hydrolysing)

Reaction: ATP + L-aspartyl-$tRNA^{Asn}$ + L-glutamine + H_2O = ADP + phosphate + L-asparaginyl-$tRNA^{Asn}$ + L-glutamate
(1a) L-glutamine + H_2O = L-glutamate + NH_3
(1b) ATP + L-aspartyl-$tRNA^{Asn}$ = ADP + 4-phosphooxy-L-aspartyl-$tRNA^{Asn}$
(1c) 4-phosphooxy-L-aspartyl-$tRNA^{Asn}$ + NH_3 = L-asparaginyl-$tRNA^{Asn}$ + phosphate

Other name(s): Asp-AdT; Asp-tRNA^{Asn} amidotransferase; aspartyl-tRNA^{Asn} amidotransferase; Asn-tRNA^{Asn}:L-glutamine amido-ligase (ADP-forming); aspartyl-tRNA^{Asn}:L-glutamine amido-ligase (ADP-forming); GatCAB
Systematic name: L-aspartyl-tRNA^{Asn}:L-glutamine amido-ligase (ADP-forming)
Comments: This reaction forms part of a two-reaction system for producing asparaginyl-tRNA in *Deinococcus radiodurans* and other organisms lacking a specific enzyme for asparagine synthesis. In the first step, a non-discriminating ligase (EC 6.1.1.23, aspartate—tRNA^{Asn} ligase) mischarges tRNA^{Asn} with aspartate, leading to the formation of aspartyl-tRNA^{Asn}. The aspartyl-tRNA^{Asn} is not used in protein synthesis until the present enzyme converts it into asparaginyl-tRNA^{Asn} (aspartyl-tRNA^{Asp} is not a substrate for this enzyme). A glutaminase subunit (*cf.* EC 3.5.1.2, glutaminase) produces an ammonia molecule that is transferred by a 30 Å tunnel to a synthase subunit, where it is ligated to the carboxy group that has been activated by phosphorylation. Bacterial GatCAB complexes also has the activity of EC 6.3.5.7 (glutaminyl-tRNA synthase [glutamine-hydrolysing]).
References: [93, 202, 330]

[EC 6.3.5.6 created 2002, modified 2012, modified 2019]

EC 6.3.5.7
Accepted name: glutaminyl-tRNA synthase (glutamine-hydrolysing)
Reaction: ATP + L-glutamyl-tRNA^{Gln} + L-glutamine = ADP + phosphate + L-glutaminyl-tRNA^{Gln} + L-glutamate (overall reaction)
(1a) L-glutamine + H_2O = L-glutamate + NH_3
(1b) ATP + L-glutamyl-tRNA^{Gln} = ADP + 5-phosphooxy-L-glutamyl-tRNA^{Gln}
(1c) 5-phosphooxy-L-glutamyl-tRNA^{Gln} + NH_3 = L-glutaminyl-tRNA^{Gln} + phosphate
Other name(s): Glu-AdT; Glu-tRNA^{Gln} amidotransferase; glutamyl-tRNA^{Gln} amidotransferase; Glu-tRNA^{Gln}:L-glutamine amido-ligase (ADP-forming); GatCAB; GatFAB; GatDE
Systematic name: L-glutamyl-tRNA^{Gln}:L-glutamine amido-ligase (ADP-forming)
Comments: In systems lacking discernible glutamine—tRNA ligase (EC 6.1.1.18), glutaminyl-tRNA^{Gln} is formed by a two-enzyme system. In the first step, a nondiscriminating ligase (EC 6.1.1.24, glutamate—tRNA^{Gln} ligase) mischarges tRNA^{Gln} with glutamate, forming glutamyl-tRNA^{Gln}. The glutamyl-tRNA^{Gln} is not used in protein synthesis until the present enzyme converts it into glutaminyl-tRNA^{Gln} (glutamyl-tRNA^{Glu} is not a substrate for this enzyme). A glutaminase subunit (*cf.* EC 3.5.1.2, glutaminase) produces an ammonia molecule that is transferred by a 30 Å tunnel to a synthase subunit, where it is ligated to the carboxy group that has been activated by phosphorylation. Some bacterial GatCAB complexes also has the activity of EC 6.3.5.6 (asparaginyl-tRNA synthase [glutamine-hydrolysing]).
References: [93, 202, 406, 195, 130, 351, 553, 21]

[EC 6.3.5.7 created 2002, modified 2019]

[6.3.5.8 Transferred entry. aminodeoxychorismate synthase. Now EC 2.6.1.85, aminodeoxychorismate synthase. As ATP is not hydrolysed during the reaction, the classification of the enzyme as a ligase was incorrect]

[EC 6.3.5.8 created 2003, deleted 2007]

EC 6.3.5.9
Accepted name: hydrogenobyrinic acid *a*,*c*-diamide synthase (glutamine-hydrolysing)
Reaction: **2** ATP + hydrogenobyrinic acid + **2** L-glutamine + **2** H_2O = **2** ADP + **2** phosphate + hydrogenobyrinic acid *a*,*c*-diamide + **2** L-glutamate
Other name(s): CobB
Systematic name: hydrogenobyrinic-acid:L-glutamine amido-ligase (AMP-forming)
Comments: This enzyme, which participates in the aerobic (late cobalt insertion) cobalamin biosynthesis pathway, generates hydrogenobyrinate *a*,*c*-diamide, the substrate required by EC 6.6.1.2, cobaltochelatase, which adds cobalt to the macrocycle. The equivalent reaction in the anaerobic cobalamin biosynthesis pathway is catalysed by EC 6.3.5.11, cobyrinate *a*,*c*-diamide synthase.

References: [105, 533]

[EC 6.3.5.9 created 2004]

EC 6.3.5.10

Accepted name: adenosylcobyric acid synthase (glutamine-hydrolysing)

Reaction: **4** ATP + adenosylcobyrinic acid *a*,*c*-diamide + **4** L-glutamine + **4** H_2O = **4** ADP + **4** phosphate + adenosylcobyric acid + **4** L-glutamate

Other name(s): CobQ; cobyric acid synthase; 5′-deoxy-5′-adenosylcobyrinic-acid-*a*,*c*-diamide:L-glutamine amido-ligase; Ado-cobyric acid synthase [glutamine hydrolyzing]

Systematic name: adenosylcobyrinic-acid-*a*,*c*-diamide:L-glutamine amido-ligase (ADP-forming)

Comments: Requires Mg^{2+}. NH_3 can act instead of glutamine. This enzyme catalyses the four-step amidation sequence from cobyrinic acid *a*,*c*-diamide to cobyric acid via the formation of cobyrinic acid triamide, tetraamide and pentaamide intermediates.

References: [43, 533]

[EC 6.3.5.10 created 2004]

EC 6.3.5.11

Accepted name: cobyrinate *a*,*c*-diamide synthase

Reaction: **2** ATP + cobyrinate + **2** L-glutamine + **2** H_2O = **2** ADP + **2** phosphate + cobyrinate *a*,*c*-diamide + **2** L-glutamate (overall reaction)
(1a) ATP + cobyrinate + L-glutamine + H_2O = ADP + phosphate + cobyrinate *c*-monamide + L-glutamate
(1b) ATP + cobyrinate *c*-monamide + L-glutamine + H_2O = ADP + phosphate + cobyrinate *a*,*c*-diamide + L-glutamate

Other name(s): cobyrinic acid *a*,*c*-diamide synthetase; CbiA

Systematic name: cobyrinate:L-glutamine amido-ligase (ADP-forming)

Comments: This enzyme is the first glutamine amidotransferase that participates in the anaerobic (early cobalt insertion) biosynthetic pathway of adenosylcobalamin, and catalyses the ATP-dependent synthesis of cobyrinate *a*,*c*-diamide from cobyrinate using either L-glutamine or ammonia as the nitrogen source. It is proposed that the enzyme first catalyses the amidation of the *c*-carboxylate, and then the intermediate is released into solution and binds to the same catalytic site for the amidation of the *a*-carboxylate. The K_m for ammonia is substantially higher than that for L-glutamine. The equivalent reaction in the aerobic cobalamin biosynthesis pathway is catalysed by EC 6.3.5.9, hydrogenobyrinic acid *a*,*c*-diamide synthase (glutamine-hydrolysing).

References: [138]

[EC 6.3.5.11 created 2010]

EC 6.3.5.12

Accepted name: Ni-sirohydrochlorin *a*,*c*-diamide synthase

Reaction: **2** ATP + Ni-sirohydrochlorin + **2** L-glutamine + **2** H_2O = **2** ADP + **2** phosphate + Ni-sirohydrochlorin *a*,*c*-diamide + **2** L-glutamate

Other name(s): *cfbB* (gene name)

Systematic name: Ni-sirohydrochlorin:L-glutamine amido-ligase (ADP-forming)

Comments: The enzyme, studied from the methanogenic archaeon *Methanosarcina acetivorans*, participates in the biosynthesis of the nickel-containing tetrapyrrole cofactor coenzyme F_{430}, which is required by EC 2.8.4.1, coenzyme-B sulfoethylthiotransferase.

References: [566]

[EC 6.3.5.12 created 2017]

EC 6.3.5.13

Accepted name: lipid II isoglutaminyl synthase (glutamine-hydrolysing)

Reaction: ATP + β-D-GlcNAc-(1→4)-Mur2Ac(oyl-L-Ala-γ-D-Glu-L-Lys-D-Ala-D-Ala)-diphospho-*ditrans*,*octacis*-undecaprenol + L-glutamine + H_2O = ADP + phosphate + β-D-GlcNAc-(1→4)-MurNAc-L-Ala-D-isoglutaminyl-L-Lys-D-Ala-D-Ala-diphospho-*ditrans*,*octacis*-undecaprenol + L-glutamate (overall reaction)
(1a) L-glutamine + H_2O = L-glutamate + NH_3
(1b) ATP + β-D-GlcNAc-(1→4)-Mur2Ac(oyl-L-Ala-γ-D-Glu-L-Lys-D-Ala-D-Ala)-diphospho-*ditrans*,*octacis*-undecaprenol = ADP + β-D-GlcNAc-(1→4)-MurNAc-L-Ala-γ-D-*O*-P-Glu-L-Lys-D-Ala-D-Ala-diphospho-*ditrans*,*octacis*-undecaprenol
(1c) β-D-GlcNAc-(1→4)-Mur2Ac(oyl-L-Ala-γ-D-*O*-P-Glu-L-Lys-D-Ala-D-Ala)-diphospho-*ditrans*,*octacis*-undecaprenol + NH_3 = β-D-GlcNAc-(1→4)-MurNAc-L-Ala-D-isoglutaminyl-L-Lys-D-Ala-D-Ala-diphospho-*ditrans*,*octacis*-undecaprenol + phosphate

Other name(s): MurT/GatD; MurT/GatD complex

Systematic name: β-D-GlcNAc-(1→4)-Mur2Ac(oyl-L-Ala-γ-D-Glu-L-Lys-D-Ala-D-Ala)-diphospho-*ditrans*,*octacis*-undecaprenol:L-glutamine amidoligase (ADP-forming)

Comments: The enzyme complex, found in Gram-positive bacteria, consists of two subunits. A glutaminase subunit (*cf.* EC 3.5.1.2, glutaminase) produces an ammonia molecule that is channeled to a ligase subunit, which adds it to the activated D-glutamate residue of lipid II, converting it to an isoglutamine residue.

References: [345, 364, 340]

[EC 6.3.5.13 created 2019]

EC 6.4 Forming carbon-carbon bonds

This subclass contains a single sub-subclass (EC 6.4.1) for enzymes that form carbon-carbon bonds. These are the carboxylating enzymes, which are mostly biotinyl-proteins.

EC 6.4.1 Ligases that form carbon-carbon bonds (only sub-subclass identified to date)

EC 6.4.1.1

Accepted name: pyruvate carboxylase

Reaction: ATP + pyruvate + HCO_3^- = ADP + phosphate + oxaloacetate

Other name(s): pyruvic carboxylase

Systematic name: pyruvate:carbon-dioxide ligase (ADP-forming)

Comments: A biotinyl-protein containing manganese (animal tissues) or zinc (yeast). The animal enzyme requires acetyl-CoA.

References: [311, 455, 457, 513]

[EC 6.4.1.1 created 1961]

EC 6.4.1.2

Accepted name: acetyl-CoA carboxylase

Reaction: ATP + acetyl-CoA + hydrogencarbonate = ADP + phosphate + malonyl-CoA

Other name(s): HFA1 (gene name); ACC1 (gene name); acetyl coenzyme A carboxylase; acetyl-CoA:carbon-dioxide ligase (ADP-forming)

Systematic name: acetyl-CoA:hydrogencarbonate ligase (ADP-forming)

Comments: This enzyme is a multi-domain polypeptide that catalyses three different activities - a biotin carboxyl-carrier protein (BCCP), a biotin carboxylase that catalyses the transfer of a carboxyl group from hydrogencarbonate to the biotin molecule carried by the carrier protein, and the transfer of the carboxyl group from biotin to acetyl-CoA, forming malonyl-CoA. In some organisms these activities are catalysed by separate enzymes (see EC 6.3.4.14, biotin carboxylase, and EC 2.1.3.15, acetyl-CoA carboxytransferase). The carboxylation of the carrier protein requires ATP, while the transfer of the carboxyl group to acetyl-CoA does not.
References: [526, 177, 303, 302, 514, 508, 72, 234]

[EC 6.4.1.2 created 1961, modified 2018]

EC 6.4.1.3
Accepted name: propionyl-CoA carboxylase
Reaction: ATP + propanoyl-CoA + HCO_3^- = ADP + phosphate + (*S*)-methylmalonyl-CoA
Other name(s): propionyl coenzyme A carboxylase
Systematic name: propanoyl-CoA:carbon-dioxide ligase (ADP-forming)
Comments: A biotinyl-protein. Also carboxylates butanoyl-CoA and catalyses transcarboxylation.
References: [230, 257, 326, 342, 514]

[EC 6.4.1.3 created 1961, modified 1983]

EC 6.4.1.4
Accepted name: methylcrotonoyl-CoA carboxylase
Reaction: ATP + 3-methylcrotonoyl-CoA + HCO_3^- = ADP + phosphate + 3-methylglutaconyl-CoA
Other name(s): methylcrotonyl coenzyme A carboxylase; β-methylcrotonyl coenzyme A carboxylase; β-methylcrotonyl CoA carboxylase; methylcrotonyl-CoA carboxylase
Systematic name: 3-methylcrotonoyl-CoA:carbon-dioxide ligase (ADP-forming)
Comments: A biotinyl-protein.
References: [238, 282, 426, 514]

[EC 6.4.1.4 created 1961]

EC 6.4.1.5
Accepted name: geranoyl-CoA carboxylase
Reaction: ATP + geranoyl-CoA + HCO_3^- = ADP + phosphate + 3-(4-methylpent-3-en-1-yl)pent-2-enedioyl-CoA
Other name(s): geranoyl coenzyme A carboxylase; geranyl-CoA carboxylase
Systematic name: geranoyl-CoA:carbon-dioxide ligase (ADP-forming)
Comments: A biotinyl-protein. Also carboxylates dimethylpropenoyl-CoA and farnesoyl-CoA.
References: [456]

[EC 6.4.1.5 created 1972]

EC 6.4.1.6
Accepted name: acetone carboxylase
Reaction: acetone + hydrogen carbonate + **2** ATP + **3** H_2O = acetoacetate + **2** AMP + **4** phosphate
Systematic name: acetone:carbon-dioxide ligase (AMP-forming)
Comments: Requires Mg^{2+} and ATP. The reaction involves separate phosphorylation of hydrogencarbonate and acetone, forming carboxyphosphate and phospho*enol*acetone, respectively, which are combined to form the final product. The enzyme from *Xanthobacter* sp. strain Py2 also carboxylates butan-2-one to 3-oxopentanoate.
References: [465, 451]

[EC 6.4.1.6 created 2001]

EC 6.4.1.7

Accepted name: 2-oxoglutarate carboxylase
Reaction: ATP + 2-oxoglutarate + HCO_3^- = ADP + phosphate + oxalosuccinate
Other name(s): oxalosuccinate synthetase; carboxylating factor for ICDH (incorrect); CFI; OGC
Comments: A biotin-containing enzyme that requires Mg^{2+} for activity. It was originally thought [18] that this enzyme was a promoting factor for the carboxylation of 2-oxoglutarate by EC 1.1.1.41, isocitrate dehydrogenase (NAD^+), but this has since been disproved [17]. The product of the reaction is unstable and is quickly converted into isocitrate by the action of EC 1.1.1.41 [17].
References: [18, 17]

[EC 6.4.1.7 created 2006]

EC 6.4.1.8

Accepted name: acetophenone carboxylase
Reaction: **2** ATP + acetophenone + HCO_3^- + H_2O + H^+ = **2** ADP + **2** phosphate + 3-oxo-3-phenylpropanoate
Systematic name: acetophenone:carbon-dioxide ligase (ADP-forming)
Comments: The enzyme is involved in anaerobic degradation of ethylbenzene. No activity with acetone, butanone, 4-hydroxy-acetophenone or 4-amino-acetophenone.
References: [217]

[EC 6.4.1.8 created 2011]

EC 6.4.1.9

Accepted name: coenzyme F_{430} synthetase
Reaction: ATP + 15,17^3-seco-F_{430}-17^3-acid = ADP + phosphate + coenzyme F_{430}
Other name(s): *cfbE* (gene name)
Systematic name: 15,17^3-seco-F_{430}-17^3-acid cyclo-ligase (ADP-forming)
Comments: The enzyme, studied from the methanogenic archaeon *Methanosarcina acetivorans*, catalyses the last step in the biosynthesis of the nickel-containing tetrapyrrole cofactor coenzyme F_{430}, which is required by EC 2.8.4.1, coenzyme-B sulfoethylthiotransferase.
References: [566]

[EC 6.4.1.9 created 2017]

EC 6.5 Forming phosphoric-ester bonds

This subclass contains enzymes that restore broken phosphodiester bonds in nucleic acids (often called repair enzymes) in a single sub-subclass (EC 6.5.1).

EC 6.5.1 Ligases that form phosphoric-ester bonds (only sub-subclass identified to date)

EC 6.5.1.1

Accepted name: DNA ligase (ATP)
Reaction: ATP + (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-phospho-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP + diphosphate (overall reaction)
(1a) ATP + [DNA ligase]-L-lysine = [DNA ligase]-N^6-(5′-adenylyl)-L-lysine + diphosphate
(1b) [DNA ligase]-N^6-(5′-adenylyl)-L-lysine + 5′-phospho-(deoxyribonucleotide)$_m$ = 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ + [DNA ligase]-L-lysine

(1c) (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP

Other name(s): polydeoxyribonucleotide synthase (ATP); polynucleotide ligase (ambiguous); sealase; DNA repair enzyme (ambiguous); DNA joinase (ambiguous); DNA ligase (ambiguous); deoxyribonucleic ligase (ambiguous); deoxyribonucleate ligase (ambiguous); DNA-joining enzyme (ambiguous); deoxyribonucleic-joining enzyme (ambiguous); deoxyribonucleic acid-joining enzyme (ambiguous); deoxyribonucleic repair enzyme (ambiguous); deoxyribonucleic joinase (ambiguous); deoxyribonucleic acid ligase (ambiguous); deoxyribonucleic acid joinase (ambiguous); deoxyribonucleic acid repair enzyme (ambiguous); poly(deoxyribonucleotide):poly(deoxyribonucleotide) ligase (AMP-forming)

Systematic name: poly(deoxyribonucleotide)-3′-hydroxyl:5′-phospho-poly(deoxyribonucleotide) ligase (ATP)

Comments: The enzyme catalyses the ligation of DNA strands with 3′-hydroxyl and 5′-phosphate termini, forming a phosphodiester and sealing certain types of single-strand breaks in duplex DNA. Catalysis occurs by a three-step mechanism, starting with the activation of the enzyme by ATP, forming a phosphoramide bond between adenylate and a lysine residue. The adenylate group is then transferred to the 5′-phosphate terminus of the substrate, forming the capped structure 5′-(5′-diphosphoadenosine)-[DNA]. Finally, the enzyme catalyses a nucleophilic attack of the 3′-OH terminus on the capped terminus, which results in formation of the phosphodiester bond and release of the adenylate. RNA can also act as substrate, to some extent. *cf.* EC 6.5.1.2, DNA ligase (NAD$^+$), EC 6.5.1.6, DNA ligase (ATP or NAD$^+$), and EC 6.5.1.7, DNA ligase (ATP, ADP or GTP).

References: [30, 41, 540, 197]

[EC 6.5.1.1 created 1972, modified 1976, modified 2016]

EC 6.5.1.2

Accepted name: DNA ligase (NAD$^+$)

Reaction: NAD$^+$ + (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-phospho-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP + β-nicotinamide D-nucleotide (overall reaction)
(1a) NAD$^+$ + [DNA ligase]-L-lysine = [DNA ligase]-N^6-(5′-adenylyl)-L-lysine + β-nicotinamide D-nucleotide
(1b) [DNA ligase]-N^6-(5′-adenylyl)-L-lysine + 5′-phospho-(deoxyribonucleotide)$_m$ = 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ + [DNA ligase]-L-lysine
(1c) (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP

Other name(s): polydeoxyribonucleotide synthase (NAD$^+$); polynucleotide ligase (NAD$^+$); DNA repair enzyme (ambiguous); DNA joinase (ambiguous); polynucleotide synthetase (nicotinamide adenine dinucleotide); deoxyribonucleic-joining enzyme (ambiguous); deoxyribonucleic ligase (ambiguous); deoxyribonucleic repair enzyme (ambiguous); deoxyribonucleic joinase (ambiguous); DNA ligase (ambiguous); deoxyribonucleate ligase (ambiguous); polynucleotide ligase (ambiguous); deoxyribonucleic acid ligase (ambiguous); polynucleotide synthetase (ambiguous); deoxyribonucleic acid joinase (ambiguous); DNA-joining enzyme (ambiguous); polynucleotide ligase (nicotinamide adenine dinucleotide); poly(deoxyribonucleotide):poly(deoxyribonucleotide) ligase (AMP-forming, NMN-forming)

Systematic name: poly(deoxyribonucleotide)-3′-hydroxyl:5′-phospho-poly(deoxyribonucleotide) ligase (NAD$^+$)

Comments: The enzyme, typically found in bacteria, catalyses the ligation of DNA strands with 3′-hydroxyl and 5′-phosphate termini, forming a phosphodiester and sealing certain types of single-strand breaks in duplex DNA. Catalysis occurs by a three-step mechanism, starting with the activation of the enzyme by NAD$^+$, forming a phosphoramide bond between adenylate and a lysine residue. The adenylate group is then transferred to the 5′-phosphate terminus of the substrate, forming the capped structure 5′-(5′-diphosphoadenosine)-[DNA]. Finally, the enzyme catalyses a nucleophilic attack of the 3′-OH terminus on the capped terminus, which results in formation of the phosphodiester bond and release of the adenylate. RNA can also act as substrate, to some extent. *cf.* EC 6.5.1.1, DNA ligase (ATP), EC 6.5.1.6, DNA ligase (ATP or NAD$^+$), and EC 6.5.1.7, DNA ligase (ATP, ADP or GTP).

References: [573, 276, 335, 336, 512]

[EC 6.5.1.2 created 1972, modified 1976, modified 2016]

EC 6.5.1.3

Accepted name: RNA ligase (ATP)

Reaction: ATP + (ribonucleotide)$_n$-3′-hydroxyl + 5′-phospho-(ribonucleotide)$_m$ = (ribonucleotide)$_{n+m}$ + AMP + diphosphate (overall reaction)
(1a) ATP + [RNA ligase]-L-lysine = [RNA ligase]-N^6-(5′-adenylyl)-L-lysine + diphosphate
(1b) [RNA ligase]-N^6-(5′-adenylyl)-L-lysine + 5′-phospho-(ribonucleotide)$_m$ = 5′-(5′-diphosphoadenosine)-(ribonucleotide)$_m$ + [RNA ligase]-L-lysine
(1c) (ribonucleotide)$_n$-3′-hydroxyl + 5′-(5′-diphosphoadenosine)-(ribonucleotide)$_m$ = (ribonucleotide)$_{n+m}$ + AMP

Other name(s): polyribonucleotide synthase (ATP); RNA ligase; polyribonucleotide ligase; ribonucleic ligase; poly(ribonucleotide):poly(ribonucleotide) ligase (AMP-forming)

Systematic name: poly(ribonucleotide)-3′-hydroxyl:5′-phospho-poly(ribonucleotide) ligase (ATP)

Comments: The enzyme catalyses the ligation of RNA strands with 3′-hydroxyl and 5′-phosphate termini, forming a phosphodiester and sealing certain types of single-strand breaks in RNA. Catalysis occurs by a three-step mechanism, starting with the activation of the enzyme by ATP, forming a phosphoramide bond between adenylate and a lysine residue. The adenylate group is then transferred to the 5′-phosphate terminus of the substrate, forming the capped structure 5′-(5′-diphosphoadenosine)-[RNA]. Finally, the enzyme catalyses a nucleophilic attack of the 3′-OH terminus on the capped terminus, which results in formation of the phosphodiester bond and release of the adenylate.

References: [462, 90, 483, 429, 186, 355]

[EC 6.5.1.3 created 1976, modified 2016]

EC 6.5.1.4

Accepted name: RNA 3′-terminal-phosphate cyclase (ATP)

Reaction: ATP + [RNA]-3′-(3′-phospho-ribonucleoside) = AMP + diphosphate + [RNA]-3′-(2′,3′-cyclophospho)-ribonucleoside (overall reaction)
(1a) ATP + [RNA 3′-phosphate cyclase]-L-histidine = [RNA 3′-phosphate cyclase]-N^τ-(5′-adenylyl)-L-histidine + diphosphate
(1b) [RNA 3′-phosphate cyclase]-N^τ-(5′-adenylyl)-L-histidine + [RNA]-3′-(3′-phospho-ribonucleoside) = [RNA 3′-phosphate cyclase]-L-histidine + [RNA]-3′-ribonucleoside-3′-(5′-diphosphoadenosine)
(1c) [RNA]-3′-ribonucleoside-3′-(5′-diphosphoadenosine) = [RNA]-3′-(2′,3′-cyclophospho)-ribonucleoside + AMP

Other name(s): *rtcA* (gene name); RNA cyclase (ambiguous); RNA-3′-phosphate cyclase (ambiguous)

Systematic name: RNA-3′-phosphate:RNA ligase (cyclizing, AMP-forming)

Comments: The enzyme converts the 3′-terminal phosphate of various RNA substrates into the 2′,3′-cyclic phosphodiester in an ATP-dependent reaction. Catalysis occurs by a three-step mechanism, starting with the activation of the enzyme by ATP, forming a phosphoramide bond between adenylate and a histidine residue [42, 494]. The adenylate group is then transferred to the 3′-phosphate terminus of the substrate, forming the capped structure [RNA]-3′-(5′-diphosphoadenosine). Finally, the enzyme catalyses an attack of the vicinal O-2′ on the 3′-phosphorus, which results in formation of cyclic phosphate and release of the adenylate. The enzyme also has a polynucleotide 5′ adenylylation activity [63]. *cf.* EC 6.5.1.5, RNA 3′-terminal-phosphate cyclase (GTP).

References: [132, 420, 152, 153, 42, 494, 63, 96]

[EC 6.5.1.4 created 1986, modified 1989, modified 2013, modified 2016]

EC 6.5.1.5

Accepted name: RNA 3′-terminal-phosphate cyclase (GTP)

Reaction: GTP + [RNA]-3′-(3′-phospho-ribonucleoside) = GMP + diphosphate + [RNA]-3′-(2′,3′-cyclophospho)-ribonucleoside (overall reaction)
(1a) GTP + [RNA 3′-phosphate cyclase]-L-histidine = 5′-guanosyl [RNA 3′-phosphate cyclase]-N^τ-phosphono-L-histidine + diphosphate

(1b) 5′-guanosyl [RNA 3′-phosphate cyclase]-N^{τ}-phosphono-L-histidine + [RNA]-3′-(3′-phosphoribonucleoside) = [RNA 3′-phosphate cyclase]-L-histidine + [RNA]-3′-ribonucleoside-3′-(5′-diphosphoguanosine)
(1c) [RNA]-3′-ribonucleoside-3′-(5′-diphosphoguanosine) = [RNA]-3′-(2′,3′-cyclophospho)-ribonucleoside + GMP

Other name(s): Pf-Rtc; RNA-3′-phosphate cyclase (GTP)

Systematic name: RNA-3′-phosphate:RNA ligase (cyclizing, GMP-forming)

Comments: The enzyme, which is specific for GTP, was characterized from the archaeon *Pyrococcus furiosus*. The enzyme converts the 3′-terminal phosphate of various RNA substrates into the 2′,3′-cyclic phosphodiester in a GTP-dependent reaction. Catalysis occurs by a three-step mechanism, starting with the activation of the enzyme by GTP, forming a phosphoramide bond between guanylate and a histidine residue. The guanylate group is then transferred to the 3′-phosphate terminus of the substrate, forming the capped structure [RNA]-3′-(5′-diphosphoguanosine). Finally, the enzyme catalyses an attack of the vicinal O-2′ on the 3′-phosphorus, which results in formation of cyclic phosphate and release of the guanylate. *cf.* EC 6.5.1.4, RNA-3′-phosphate cyclase (ATP).

References: [443]

[EC 6.5.1.5 created 2013, modified 2016]

EC 6.5.1.6

Accepted name: DNA ligase (ATP or NAD^+)

Reaction: (1) ATP + (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-phospho-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP + diphosphate (overall reaction)
(1a) ATP + [DNA ligase]-L-lysine = 5′-adenosyl [DNA ligase]-N^{ϵ}-phosphono-L-lysine + diphosphate
(1b) 5′-adenosyl [DNA ligase]-N^{ϵ}-phosphono-L-lysine + 5′-phospho-(deoxyribonucleotide)$_m$ = 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ + [DNA ligase]-L-lysine
(1c) (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP
(2) NAD^+ + (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-phospho-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP + β-nicotinamide D-nucleotide (overall reaction)
(2a) NAD^+ + [DNA ligase]-L-lysine = 5′-adenosyl [DNA ligase]-N^{ϵ}-phosphono-L-lysine + β-nicotinamide D-nucleotide
(2b) 5′-adenosyl [DNA ligase]-N^{ϵ}-phosphono-L-lysine + 5′-phospho-(deoxyribonucleotide)$_m$ = 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ + [DNA ligase]-L-lysine
(2c) (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP

Systematic name: poly(deoxyribonucleotide)-3′-hydroxyl:5′-phospho-poly(deoxyribonucleotide) ligase (ATP or NAD^+)

Comments: The enzymes from the archaea *Thermococcus fumicolans* and *Thermococcus onnurineus* show high activity with either ATP or NAD^+, and significantly lower activity with TTP, GTP, and CTP. The enzyme catalyses the ligation of DNA strands with 3′-hydroxyl and 5′-phosphate termini, forming a phosphodiester and sealing certain types of single-strand breaks in duplex DNA. Catalysis occurs by a three-step mechanism, starting with the activation of the enzyme by ATP or NAD^+, forming a phosphoramide bond between adenylate and a lysine residue. The adenylate group is then transferred to the 5′-phosphate terminus of the substrate, forming the capped structure 5′-(5′-diphosphoadenosine)-[DNA]. Finally, the enzyme catalyses a nucleophilic attack of the 3′-OH terminus on the capped terminus, which results in formation of the phosphodiester bond and release of the adenylate. Different from EC 6.5.1.1, DNA ligase (ATP), EC 6.5.1.2, DNA ligase (NAD^+) and EC 6.5.1.7, DNA ligase (ATP, ADP or GTP).

References: [428, 236]

[EC 6.5.1.6 created 2014, modified 2016]

EC 6.5.1.7

Accepted name: DNA ligase (ATP, ADP or GTP)

Reaction: (1) ATP + (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-phospho-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP + diphosphate (overall reaction)
(1a) ATP + [DNA ligase]-L-lysine = 5′-adenosyl [DNA ligase]-N^{ε}-phosphono-L-lysine + diphosphate
(1b) 5′-adenosyl [DNA ligase]-N^{ε}-phosphono-L-lysine + 5′-phospho-(deoxyribonucleotide)$_m$ = 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ + [DNA ligase]-L-lysine
(1c) (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP
(2) ADP + (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-phospho-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP + phosphate (overall reaction)
(2a) ADP + [DNA ligase]-L-lysine = 5′-adenosyl [DNA ligase]-N^{ε}-phosphono-L-lysine + phosphate
(2b) 5′-adenosyl [DNA ligase]-N^{ε}-phosphono-L-lysine + 5′-phospho-(deoxyribonucleotide)$_m$ = 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ + [DNA ligase]-L-lysine
(2c) (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-(5′-diphosphoadenosine)-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + AMP
(3) GTP + (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-phospho-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + GMP + diphosphate (overall reaction)
(3a) GTP + [DNA ligase]-L-lysine = 5′-guanosyl [DNA ligase]-N^{ε}-phosphono-L-lysine + diphosphate
(3b) 5′-guanosyl [DNA ligase]-N^{ε}-phosphono-L-lysine + 5′-phospho-(deoxyribonucleotide)$_m$ = 5′-(5′-diphosphoguanosine)-(deoxyribonucleotide)$_m$ + [DNA ligase]-L-lysine
(3c) (deoxyribonucleotide)$_n$-3′-hydroxyl + 5′-(5′-diphosphoguanosine)-(deoxyribonucleotide)$_m$ = (deoxyribonucleotide)$_{n+m}$ + GMP
Other name(s): poly(deoxyribonucleotide):poly(deoxyribonucleotide) ligase (ATP, ADP or GTP)
Systematic name: poly(deoxyribonucleotide)-3′-hydroxyl:5′-phospho-poly(deoxyribonucleotide) ligase (ATP, ADP or GTP)
Comments: The enzymes from the archaea *Hyperthermus butylicus* and *Sulfophobococcus zilligii* are active with ATP, ADP or GTP. They show no activity with NAD^+. The enzyme catalyses the ligation of DNA strands with 3′-hydroxyl and 5′-phosphate termini, forming a phosphodiester and sealing certain types of single-strand breaks in duplex DNA. Catalysis occurs by a three-step mechanism, starting with the activation of the enzyme by ATP, ADP, or GTP, forming a phosphoramide bond between adenylate/guanylate and a lysine residue. The nucleotide is then transferred to the 5′-phosphate terminus of the substrate, forming the capped structure 5′-(5′-diphosphoadenosine/guanosine)-[DNA]. Finally, the enzyme catalyses a nucleophilic attack of the 3′-OH terminus on the capped terminus, which results in formation of the phosphodiester bond and release of the nucleotide. Different from EC 6.5.1.1, DNA ligase (ATP), and EC 6.5.1.6, DNA ligase (ATP or NAD^+), which cannot utilize GTP.
References: [486, 233]

[EC 6.5.1.7 created 2014, modified 2016]

EC 6.5.1.8

Accepted name: 3′-phosphate/5′-hydroxy nucleic acid ligase
Reaction: (1) (ribonucleotide)$_n$-3′-phosphate + 5′-hydroxy-(ribonucleotide)$_m$ + GTP = (ribonucleotide)$_{n+m}$ + GMP + diphosphate (overall reaction)
(1a) GTP + [RNA ligase]-L-histidine = [RNA ligase]-N^{τ}-(5′-guanosyl-phosphono)-L-histidine + diphosphate
(1b) [RNA ligase]-N^{τ}-(5′-guanosyl-phosphono)-L-histidine + (ribonucleotide)$_n$-3′-phosphate = (ribonucleotide)$_n$-3′-(5′-diphosphoguanosine) + [RNA ligase]-L-histidine
(1c) (ribonucleotide)$_n$-3′-(5′-diphosphoguanosine) + 5′-hydroxy-(ribonucleotide)$_m$ = (ribonucleotide)$_{n+m}$ + GMP
(2) (ribonucleotide)$_n$-2′,3′-cyclophosphate + 5′-hydroxy-(ribonucleotide)$_m$ + GTP + H_2O = (ribonucleotide)$_{n+m}$ + GMP + diphosphate (overall reaction)
(2a) (ribonucleotide)$_n$-2′,3′-cyclophosphate + H_2O = (ribonucleotide)$_n$-3′-phosphate
(2b) GTP + [RNA ligase]-L-histidine = [RNA ligase]-N^{τ}-(5′-guanosyl-phosphono)-L-histidine + diphosphate
(2c) [RNA ligase]-N^{τ}-(5′-guanosyl-phosphono)-L-histidine + (ribonucleotide)$_n$-3′-phosphate = (ribonucleotide)$_n$-3′-(5′-diphosphoguanosine) + [RNA ligase]-L-histidine

(2d) (ribonucleotide)$_n$-3′-(5′-diphosphoguanosine) + 5′-hydroxy-(ribonucleotide)$_m$ = (ribonucleotide)$_{n+m}$ + GMP

Other name(s): *rtcB* (gene name)

Systematic name: poly(ribonucleotide)-3′-phosphate:5′-hydroxy-poly(ribonucleotide) ligase (GMP-forming)

Comments: The enzyme is a GTP- and Mn^{2+}-dependent 3′-5′ nucleic acid ligase with the ability to join RNA with 3′-phosphate or 2′,3′-cyclic-phosphate ends to RNA with 5′-hydroxy ends. It can also join DNA with 3′-phosphate ends to DNA with 5′-hydroxy ends, provided the DNA termini are unpaired [64]. The enzyme is found in members of all three kingdoms of life, and is essential in metazoa for the splicing of intron-containing tRNAs. The reaction follows a three-step mechanism with initial activation of the enzyme by GTP hydrolysis, forming a phosphoramide bond between the guanylate and a histidine residue. The guanylate group is transferred to the 3′-phosphate terminus of the substrate, forming the capped structure [DNA/RNA]-3′-(5′-diphosphoguanosine). When a suitable 5′-OH end is available, the enzyme catalyses an attack of the 5′-OH on the capped end to form a 3′-5′ phosphodiester splice junction, releasing the guanylate. When acting on an RNA 2′,3′-cyclic-phosphate, the enzyme catalyses an additional reaction, hydrolysing the cyclic phosphate to a 3′-phosphate [305]. The metazoan enzyme requires activating cofactors in order to achieve multiple turnover catalysis [107].

References: [493, 495, 492, 108, 65, 64, 95, 107, 305]

[EC 6.5.1.8 created 2017]

EC 6.5.1.9

Accepted name: cyclic 2,3-diphosphoglycerate synthase

Reaction: ATP + 2,3-diphospho-D-glycerate = ADP + phosphate + cyclic 2,3-bisphosphoglycerate

Other name(s): *cpgS* (gene name)

Systematic name: (2*R*)-2,3-bisphosphoglycerate ligase (cyclizing)

Comments: The enzyme is present in a number of methanogenic archaeal genera that accumulate cyclic 2,3-bisphosphoglycerate as a thermoprotectant. Activity is stimulated by potassium ions.

References: [262, 304]

[EC 6.5.1.9 created 2020]

EC 6.6 Forming nitrogen-metal bonds

This subclass contains a single sub-subclass for enzymes that form coordination complexes, i.e. form nitrogen—metal bonds (EC 6.6.1).

EC 6.6.1 Forming coordination complexes

EC 6.6.1.1

Accepted name: magnesium chelatase

Reaction: ATP + protoporphyrin IX + Mg^{2+} + H_2O = ADP + phosphate + Mg-protoporphyrin IX + **2** H^+

Other name(s): protoporphyrin IX magnesium-chelatase; protoporphyrin IX Mg-chelatase; magnesium-protoporphyrin IX chelatase; magnesium-protoporphyrin chelatase; magnesium-chelatase; Mg-chelatase; Mg-protoporphyrin IX magnesio-lyase

Systematic name: Mg-protoporphyrin IX magnesium-lyase

Comments: This is the first committed step of chlorophyll biosynthesis and is a branchpoint of two major routes in the tetrapyrrole pathway.

References: [528, 529, 135]

[EC 6.6.1.1 created 2003]

EC 6.6.1.2

Accepted name: cobaltochelatase

Reaction: ATP + hydrogenobyrinate *a*,*c*-diamide + Co^{2+} + H_2O = ADP + phosphate + cob(II)yrinate *a*,*c*-diamide + H^+

Other name(s): hydrogenobyrinic acid *a*,*c*-diamide cobaltochelatase; CobNST; CobNCobST; hydrogenobyrinic-acid-*a*,*c*-diamide:cobalt cobalt-ligase (ADP-forming)

Systematic name: hydrogenobyrinate-*a*,*c*-diamide:cobalt cobalt-ligase (ADP-forming)

Comments: This enzyme, which forms part of the aerobic (late cobalt insertion) cobalamin biosynthesis pathway, is a type I chelatase, being heterotrimeric and ATP-dependent. It comprises two components, one of which corresponds to CobN and the other is composed of two polypeptides, specified by *cobS* and *cobT* in *Pseudomonas denitrificans*, and named CobST [104]. Hydrogenobyrinate is a very poor substrate. ATP can be replaced by dATP or CTP but the reaction proceeds more slowly. CobN exhibits a high affinity for hydrogenobyrinate *a*,*c*-diamide. The oligomeric protein CobST possesses at least one sulfhydryl group that is essential for ATP-binding. See EC 4.99.1.3, sirohydrochlorin cobaltochelatase, for the cobaltochelatase that participates in the anaerobic cobalamin biosynthesis pathway.

References: [104, 533]

[EC 6.6.1.2 created 2004]

EC 6.7 Forming nitrogen-nitrogen bonds

This subclass contains a single sub-subclass for enzymes that form diazo bonds (EC 6.7.1).

EC 6.7.1 Forming diazo bonds

EC 6.7.1.1

Accepted name: 3-amino-2-hydroxy-4-methoxybenzoate diazotase

Reaction: ATP + 3-amino-2-hydroxy-4-methoxybenzoate + nitrite = AMP + diphosphate + cremeomycin + H_2O

Other name(s): *creM* (gene name)

Systematic name: 3-amino-2-hydroxy-4-methoxybenzoate:nitrite ligase (AMP-forming)

Comments: The enzyme, characterized from *Streptomyces cremeus*, catalyses the last step in the biosynthesis of the *ortho*-diazoquinone cremeomycin.

References: [527]

[EC 6.7.1.1 created 2021]

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