

Table S3. List of reactions in the metabolic network we build for *S. muelleri* and the evidences used to assign the direction of the reactions. The metabolites kept in the reactions after filtering appear in bold. **M:** MetaCyc pathways evidence; **T:** topological evidence

Reaction BioCyc ID	Name	Formula	Evidence to assign the direction
PHEAMINOTRANS-RXN	Aromatic amino acid transferase	L-glutamate + phenylpyruvate → L-phenylalanine + 2-ketoglutarate	T
ACETOLACTREDUCTOISOM-RXN	Ketol-acid reductoisomerase	H ⁺ + NADPH + 2- acetolactate → 2,3-dihydroxyisovalerate + NADP ⁺	M
CARBPSYN-RXN	carbamoyl-phosphate synthetase (glutamine-hydrolysing)	L-glutamine + HCO₃⁻ + ATP + H ₂ O → carbamoyl-phosphate + ADP + phosphate + L-glutamate	M
3-ISOPROPYLMALDEHYDROG-RXN	3-isopropylmalate dehydrogenase	NAD ⁺ + 3- isopropylmalate → 2- isopropyl-3-oxosuccinate + NADH + H ⁺	M
CHORISMATEMUT-RXN	Chorismate mutase	Chorismate → prephenate	M
ASPAMINOTRANS-RXN	Aspartate aminotransferase	2-ketoglutarate + L-aspartate ↔ oxaloacetate + L-glutamate	
ASPARTATEKIN-RXN	Aspartate kinase	ATP + L-aspartate → ADP + L-aspartyl-4-phosphate	M
ACETYLORNTRANSAM-RXN	Acetylornithine aminotransferase	L-glutamate + N-acetyl-L-glutamate 5-semialdehyde → 2-ketoglutarate + N-acetyl-L-ornithine	M
ACETYLGLUTKIN-RXN	Acetylglutamate kinase	N-acetyl-L-glutamate + ATP → N-acetylglutamyl-phosphate + ADP	M
RXN-7562	Acetylornithine aminotransferase	L-ornithine + 2-ketoglutarate ↔ L-glutamate + L-glutamate gamma-semialdehyde	M
ADOMET-DMK-METHYLTRANSFER-RXN	NA	S-adenosyl-L-methionine + demethylmenaquinone-8 → menaquinone-8 + S-adenosyl-L-homocysteine	M
RXN-7800	NA	2- isopropyl-3-oxosuccinate → 2- ketoisocaproate + CO ₂	M
PRAISOM-RXN	Phosphoribosyl anthranilate isomerase	N-(5'-phosphoribosyl)-anthranilate → 1-(o-carboxyphenylamino)-1'-deoxyribulose-5'-phosphate	M
SUCCINYLDIAMINOPIMITRANS-RXN	Succinyl diaminopimelate aminotransferase	L-glutamate + N-succinyl-2-amino-6-ketopimelate → N-succinyl-L,L-2,6-diaminopimelate + 2-ketoglutarate	M
ACETOLACTSYN-RXN	Acetolactate synthase	Pyruvate → 2- acetolactate + CO ₂	M
HOMOSERDEHYDROG-RXN	Homoserine dehydrogenase	H ⁺ + NAD(P)H + L-aspartate-semialdehyde → NAD(P) ⁺ + homoserine	M
RXN-7183	NA	pyrroline 5-carboxylate + NAD(P) ⁺ + H ₂ O → L-glutamate + NAD(P)H + H ⁺	M
HOMOSERKIN-RXN	Homoserine kinase	homoserine + ATP → ADP + O-phospho-L-homoserine	M

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ACETOOHBUTREDUCTO ISOM-RXN	Ketol-acid reducto isomerase	$\text{NADPH} + 2\text{-aceto-2-hydroxy-butyrate} \rightarrow 2,3\text{-dihydroxy-3-methylvalerate} + \text{NADP}^+$	M
TETHYDPICSUCC-RXN	2,3,4,5-tetrahydropyridine-2-carboxylate N-succinyltransferase	$\text{H}_2\text{O} + \text{tetrahydrodipicolinate} + \text{succinyl-CoA} \rightarrow \text{coenzyme A} + \text{N-succinyl-2-amino-6-ketopimelate}$	M
N-ACETYLGLUTPREDUCT-RXN	N-acetyl-gamma-glutamyl-phosphate reductase	$\text{N-acetylglutamyl-phosphate} + \text{NADPH} \rightarrow \text{N-acetyl-L-glutamate 5-semialdehyde} + \text{NADP}^+ + \text{phosphate}$	M
2461463469-RXN	NA	$\text{carbamoyl-phosphate} + \text{N-acetyl-L-ornithine} \rightarrow \text{N-acetyl-L-citrulline} + \text{phosphate}$	M
3-DEHYDROQUINATE-DEHYDRATASE-RXN	3-dehydroquinate dehydratase	$3\text{-dehydroquinate} \rightarrow 3\text{-dehydro-shikimate} + \text{H}_2\text{O}$	M
THRESYN-RXN	Threonine synthase	$\text{H}_2\text{O} + \text{O-phospho-L-homoserine} \rightarrow \text{L-threonine} + \text{phosphate}$	M
RXN0-2381	NA	$\text{indole-3-glycerol-phosphate} \rightarrow \text{D-glyceraldehyde-3-phosphate} + \text{indole}$	M
SHIKIMATE-5-DEHYDROGENASE-RXN	Shikimate 5-dehydrogenase	$3\text{-dehydro-shikimate} + \text{NADPH} \rightarrow \text{shikimate} + \text{NADP}^+$	M
N-ACETYLTRANSFER-RXN	Amino-acid N-acetyltransferase	$\text{L-glutamate} + \text{acetyl-CoA} \rightarrow \text{coenzyme A} + \text{N-acetyl-L-glutamate}$	M
2-ISOPROPYLMALATESYN-RXN	2-isopropylmalate synthase	$\text{H}_2\text{O} + \text{acetyl-CoA} + 2\text{-keto-isovalerate} \rightarrow \text{coenzyme A} + 2\text{-isopropylmalate}$	M
CHORISMATE-SYNTHASE-RXN	Chorismate synthase	$5\text{-enolpyruvyl-shikimate-3-phosphate} \rightarrow \text{phosphate} + \text{chorismate}$	M
TRYPSYN-RXN	Tryptophan synthase	$\text{L-serine} + \text{indole-3-glycerol-phosphate} \rightarrow \text{L-tryptophan} + \text{D-glyceraldehyde-3-phosphate} + \text{H}_2\text{O}$	T
RXN-8991	3-isopropylmalate dehydratase	$\text{Isopropylmaleate} + \text{H}_2\text{O} \rightarrow 3\text{-isopropylmalate}$	M
DIAMINOPIMEPIM-RXN	Diamino pimelate epimerase	$\text{L,L-diaminopimelate} \rightarrow \text{meso-diaminopimelate}$	M
BRANCHED-CHAINAMINOTRANSFERVAL-RXN	Branched-chain amino acid aminotransferase	$\text{L-valine} + 2\text{-ketoglutarate} \leftarrow \text{L-glutamate} + 2\text{-keto-isovalerate}$	T
DMK-RXN	NA	$\text{all-trans-octaprenyl diphosphate} + 1,4\text{-dihydroxy-2-naphthoate} \rightarrow \text{demethylmenaquinone-8} + \text{diphosphate} + \text{CO}_2$	M
DAHPSYN-RXN	2-dehydro-3-deoxy phosphoheptonate aldolase	$\text{H}_2\text{O} + \text{phosphoenolpyruvate} + \text{D-erythrose-4-phosphate} \rightarrow 3\text{-deoxy-D-arabino-heptulosonate-7-phosphate} + \text{phosphate}$	M
3-ISOPROPYLMALISOM-RXN	3-isopropylmalate dehydratase	$\text{H}_2\text{O} + 2\text{-isopropylmalate} \rightarrow \text{isopropylmaleate} + \text{H}_2\text{O}$	M

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SPONTPRO-RXN	NA	L-glutamate gamma-semialdehyde → pyrroline 5-carboxylate + H ₂ O	T
ORNCARBAMTRANSFERR-RXN	Ornithine carbamoyl transferase	carbamoyl-phosphate + L-ornithine → citrulline + phosphate	T
DIHYDROXYISOVALDEHYDRAT-RXN	Dihydroxy-acid dehydratase	2,3-dihydroxy-isovalerate → 2-keto-isovalerate + H ₂ O	M
PREPHENATEDEHYDRAT-RXN	Prephenate dehydratase	Prephenate → phenylpyruvate + H ₂ O + CO ₂	M
ARGSUCCINSYN-RXN	Arginino succinate synthetase	citrulline + ATP + L-aspartate → L-arginino-succinate + AMP + diphosphate	M
3-DEHYDROQUINATE-SYNTHASE-RXN	3-dehydroquinate synthase	3-deoxy-D-arabino-heptulosonate-7-phosphate → 3-dehydroquinate + phosphate	M
PRTRANS-RXN	Anthranilate phosphoribosyl transferase	anthranilate + 5-phosphoribosyl 1-pyrophosphate → N-(5'-phosphoribosyl)-anthranilate + diphosphate	M
DIHYDROPICRED-RXN	Dihydrodipicolinate reductase	NAD(P)H + L-2,3-dihydrodipicolinate → NAD(P) ⁺ + tetrahydrodipicolinate	M
ASPARTATE-SEMIALDEHYDE-DEHYDROGENASE-RXN	Aspartate-semialdehyde dehydrogenase	H ⁺ + NADPH + L-aspartyl-4-phosphate → L-aspartate-semialdehyde + NADP ⁺ + phosphate	M
ANTHRANSYN-RXN	Anthranilate synthase	L-glutamine + chorismate → anthranilate + pyruvate + L-glutamate	M
DIAMINOPIMDECARB-RXN	Diaminopimelate decarboxylase	Meso-diaminopimelate → L-lysine + CO ₂	M
RXN0-2382	NA	L-serine + indole → L-tryptophan + H ₂ O	M
PRPPSYN-RXN	ribose-phosphate diphosphokinase	D-ribose-5-phosphate + ATP → 5-phosphoribosyl 1-pyrophosphate + AMP	M
IGPSYN-RXN	indole-3-glycerol-phosphate synthase	1-(o-carboxyphenylamino)-1'-deoxyribulose-5'-phosphate → indole-3-glycerol-phosphate + H ₂ O + CO ₂	M
SUCCDIAMINOPIMDESUCC-RXN	Succinyl-diaminopimelate desuccinylase	N-succinyl-L,L-2,6-diaminopimelate + H ₂ O → succinate + L,L-diaminopimelate	M
24654614619-RXN	3-phosphoshikimate 1-carboxy vinyltransferase	phosphoenolpyruvate + shikimate-3-phosphate → 5-enolpyruvyl-shikimate-3-phosphate + phosphate	M
BRANCHED-CHAINAMINOTRANSFER-RLEU-RXN	Branched-chain amino acid aminotransferase	2-ketoglutarate + L-leucine ← L-glutamate + 2-ketoisocaproate	T
BRANCHED-CHAINAMINOTRANSFER-RILEU-RXN	Branched-chain amino acid aminotransferase	2-ketoglutarate + L-isoleucine ← L-glutamate + 2-keto-3-methyl-valerate	T

Reaction BioCyc ID	Name	Formula	Evidence to assign the direction
DIHYDRODIPICSYN-RXN	Dihydro dipicolinate synthase	pyruvate + L-aspartate-semialdehyde → L-2,3-dihydrodipicolinate + H2O	M
DIHYDROXYMETVALDEHYDRAT-RXN	Dihydroxy-acid dehydratase	2,3-dihydroxy-3-methylvalerate → 2-keto-3-methylvalerate + H2O	M
THREDEHYD-RXN	Threonine dehydratase	L-threonine → ammonia + 2-oxobutanoate	M
SHIKIMATE-KINASE-RXN	shikimate-kinase	ATP + shikimate → ADP + shikimate-3-phosphate	M
ARGSUCCINLYA-RXN	Arginino succinate lyase	L-arginino-succinate → L-arginine + fumarate	M
GAPOXNPHOSPHN-RXN	Glyceraldehyde 3-phosphate dehydrogenase (phosphorylating)	NAD ⁺ + D-glyceraldehyde-3-phosphate + phosphate → NADH + 1,3-diphosphateglycerate	T
ACETOOHBUTSYN-RXN	Acetolactate synthase	pyruvate + 2-oxobutanoate → 2-aceto-2-hydroxybutyrate + CO2	M
PYRROLINECARBDEHYDROG-RXN	1-pyrroline-5-carboxylate dehydrogenase	pyrroline 5-carboxylate + NAD⁺ + H2O → NADH + L-glutamate	M
RXN-7933	NA	N-acetyl-L-citrulline + H2O → acetate + citrulline	M
ACETYLORNDEACET-RXN	Acetylmithine deacetylase	N-acetyl-L-ornithine + H2O → acetate + L-ornithine	M