Amino acid Biosynthesis

DISCLAIMER

ALL THE CONTENT MATERIAL PROVIDED HERE IS ONLY FOR TEACHING PURPOSE.

OUTLINE

- Introduction
- Synthesis of amino acids
  - the Glutamate family
  - Histidine biosynthesis
  - the Serine family
  - the Aromatic family
  - the Pyruvate family
  - the Aspartate family
- Regulation of amino acid biosynthesis
- Diseases of amino acid metabolism
- Conclusion
- References

INTRODUCTION

- All amino acids are derived from intermediates in glycolysis, the citric acid cycle, or pentose phosphate pathway.
- Nitrogen enters these pathways by way of glutamate and glutamine.
- Organisms vary greatly in their ability to synthesize the 20 common amino acids.
- Whereas most bacteria and plants can synthesize all 20, mammals can synthesize about half of them- generally those with simple pathways: the non-essential amino acids not needed in the diet.
- The remainder, the essential amino acids must be obtained from food.

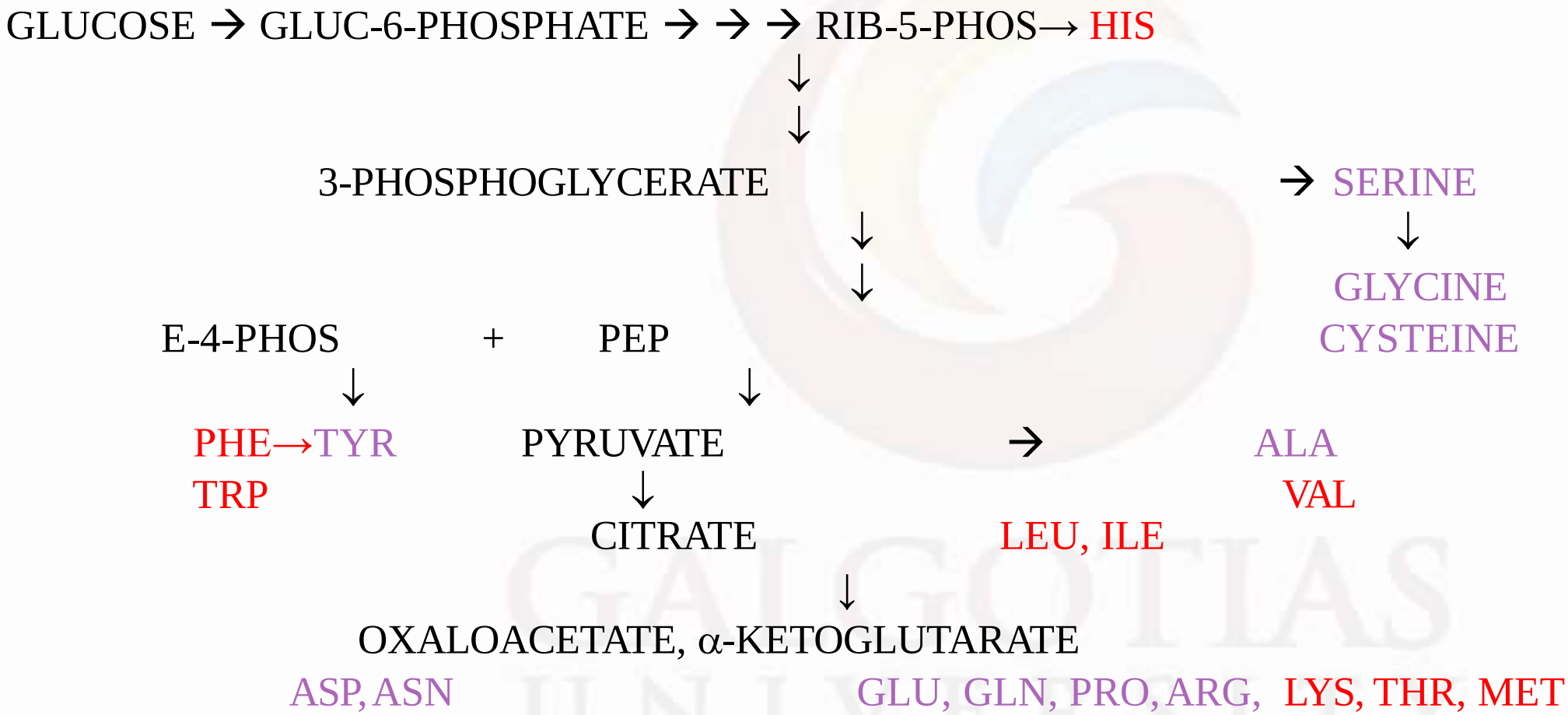
ESSENTIAL AND NON-ESSENTIAL AMINO ACIDS IN HUMANS

Essential	Nonessential
Arginine[a]	Alanine
Histidine	Asparagine
Isoleucine	Aspartate
Leucine	Cysteine
Lysine	Glutamate
Methionine	Glutamine
Phenylalanine	Glycine
Threonine	Proline
Tryptophan	Serine
Valine	Tyrosine

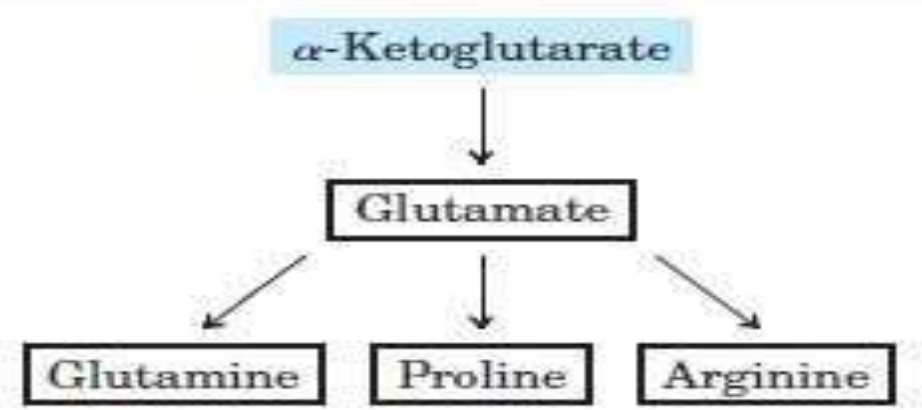
Arg is essential in infants and children
Most synthesized Arg → Ornithine and Urea via the urea cycle

Cys gets its sulfur atom from Met Tyr is hydroxylated Phe
So it's not really non-essential

AMINO ACID BIOSYNTHESIS OVERVIEW
(USE OF COMMON INTERMEDIATES)



THE GLUTAMATE FAMILY

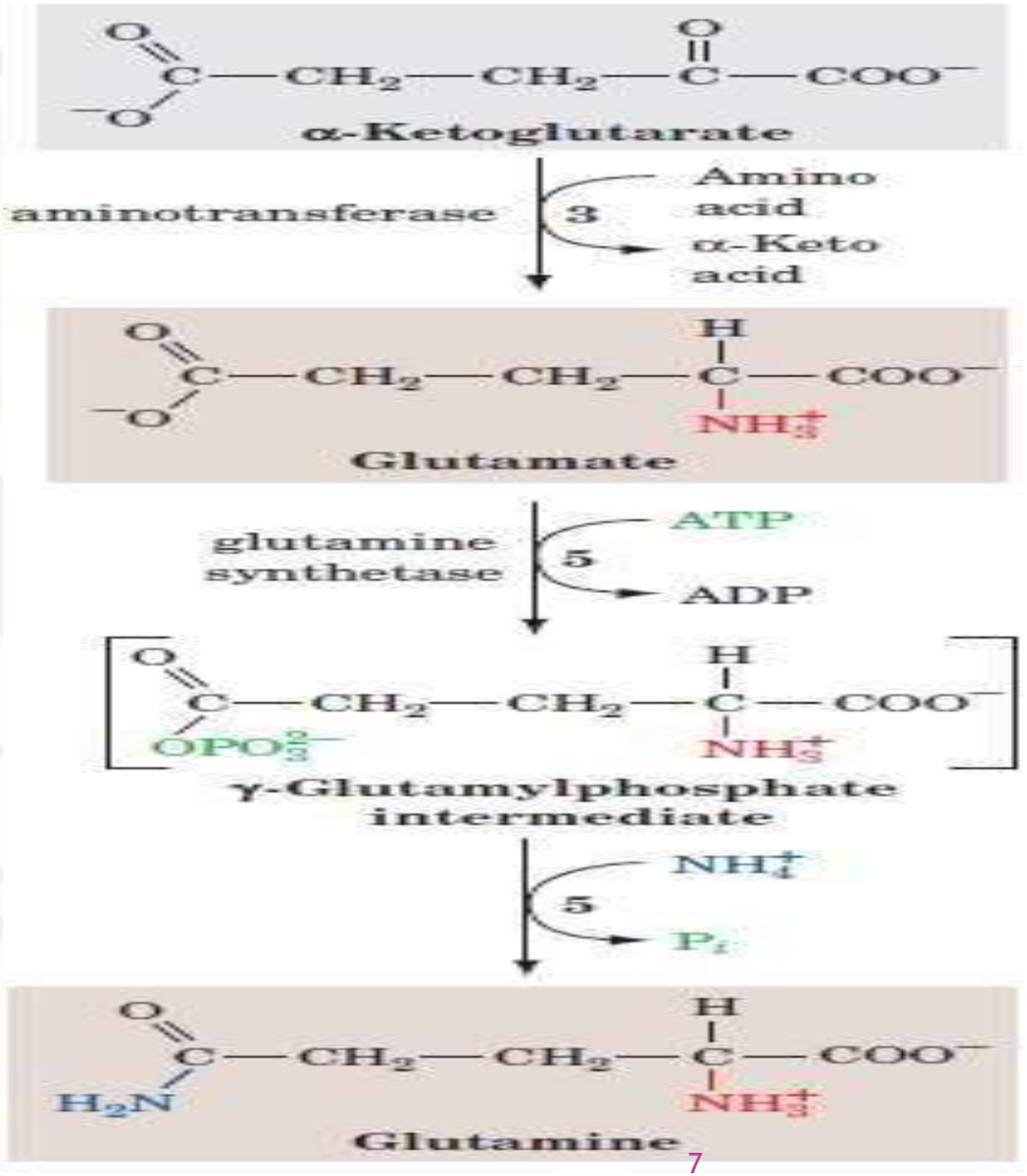


Glu

α-Ketoglutarate + AA → Glutamate + α-Ketoacid

Gln

- GLU + ATP + NH_3 → GLN + ADP + p_i
  - Glutamine synthetase
  - NH_3 is toxic; it's stored as Gln



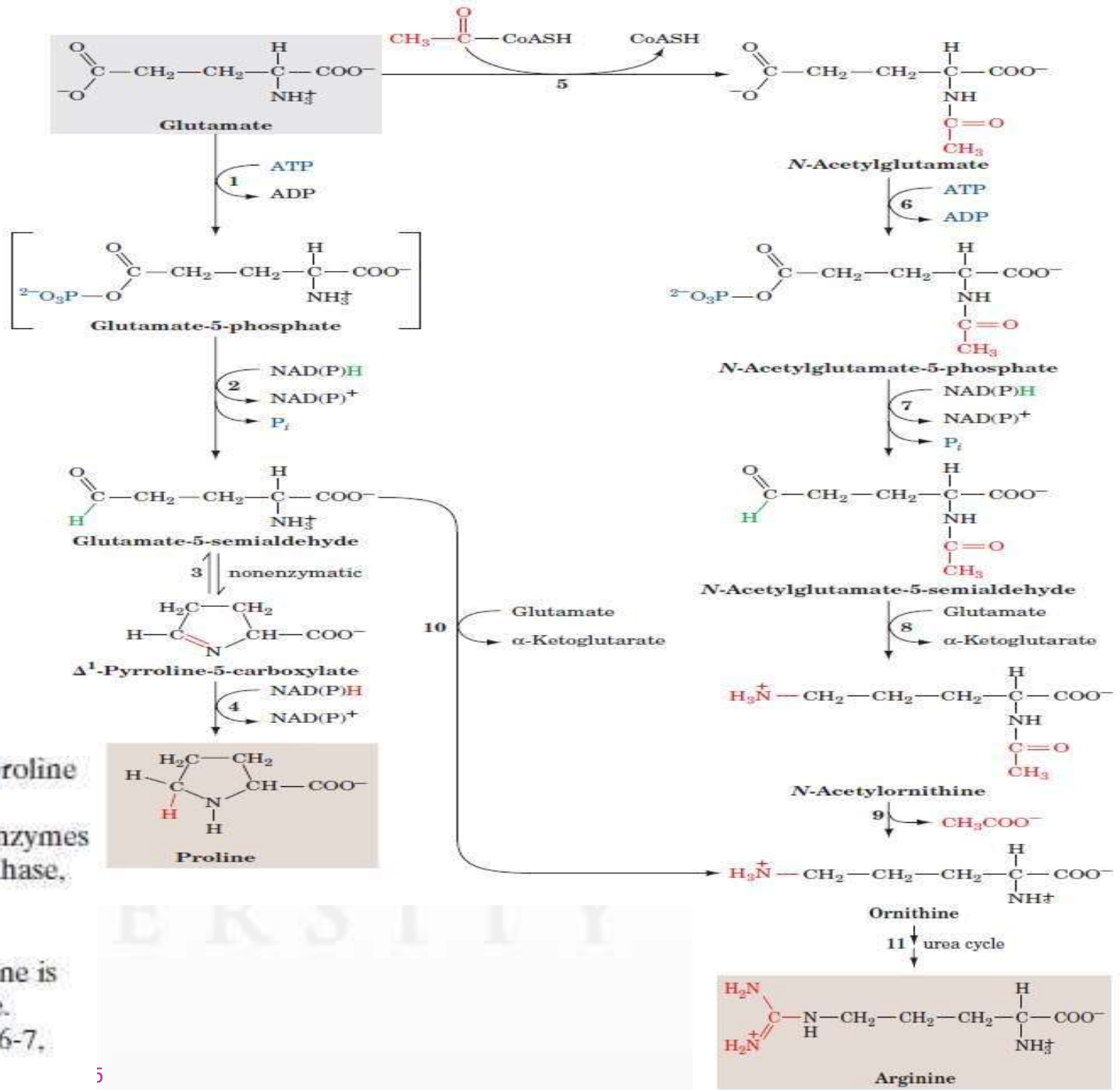
ARG, PRO

PRO, ORNITHINE, ARG ARE DERIVED FROM GLUTAMATE

Step 1: Activate Glu; a kinase

Glutamate-5-semialdehyde branch point
Spontaneous cyclization to an internal schiff base

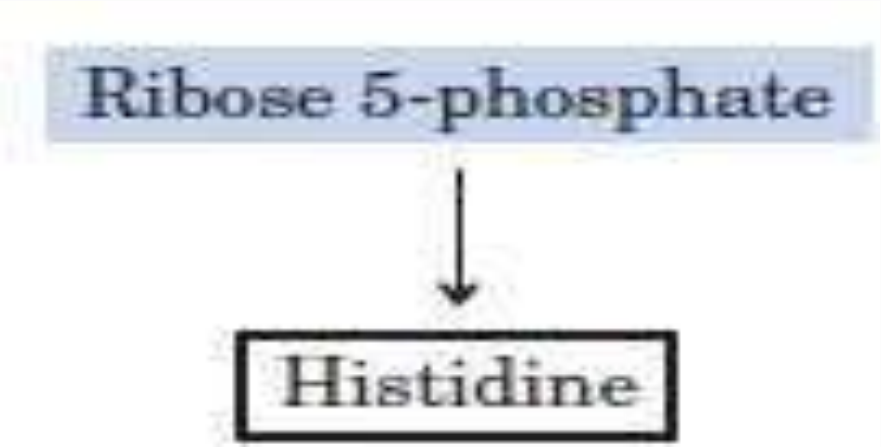
→ Pro Transamination to Ornithine
→ Arg in urea cycle



acids: arginine, ornithine, and proline. The enzymes catalyzing proline biosynthesis are **(1)** γ-glutamyl kinase, **(2)** dehydrogenase, **(3)** nonenzymatic, and **(4)** pyrroline-5-carboxylate reductase. The enzymes catalyzing ornithine biosynthesis are **(5)** *N*-acetylglutamate synthase, **(6)** acetylglutamate kinase, **(7)** *N*-acetyl-γ-glutamyl phosphate reductase, **(8)** *N*-acetylornithine-δ-aminotransferase, and **(9)** acetylornithine deacetylase. An alternate pathway to ornithine is through Reaction **10**, catalyzed by ornithine-δ-aminotransferase. Ornithine is converted to arginine **(11)** via the urea cycle (Fig. 26-7, Reactions 2–4).

HISTIDINE BIOSYNTHESIS

- Atoms derived from:
  - 5-Phosphoribosyl-α-pyrophosphate
    - Provides 5 c-atoms
    - Prpp involved in purine synthesis
    - Prpp involved in pyrimidine synthesis
    - Purine salvage pathway
    - An intermediate in trp synthesis
  - ATP provides the 6th C- atom
  - Gln supplies the second ring N

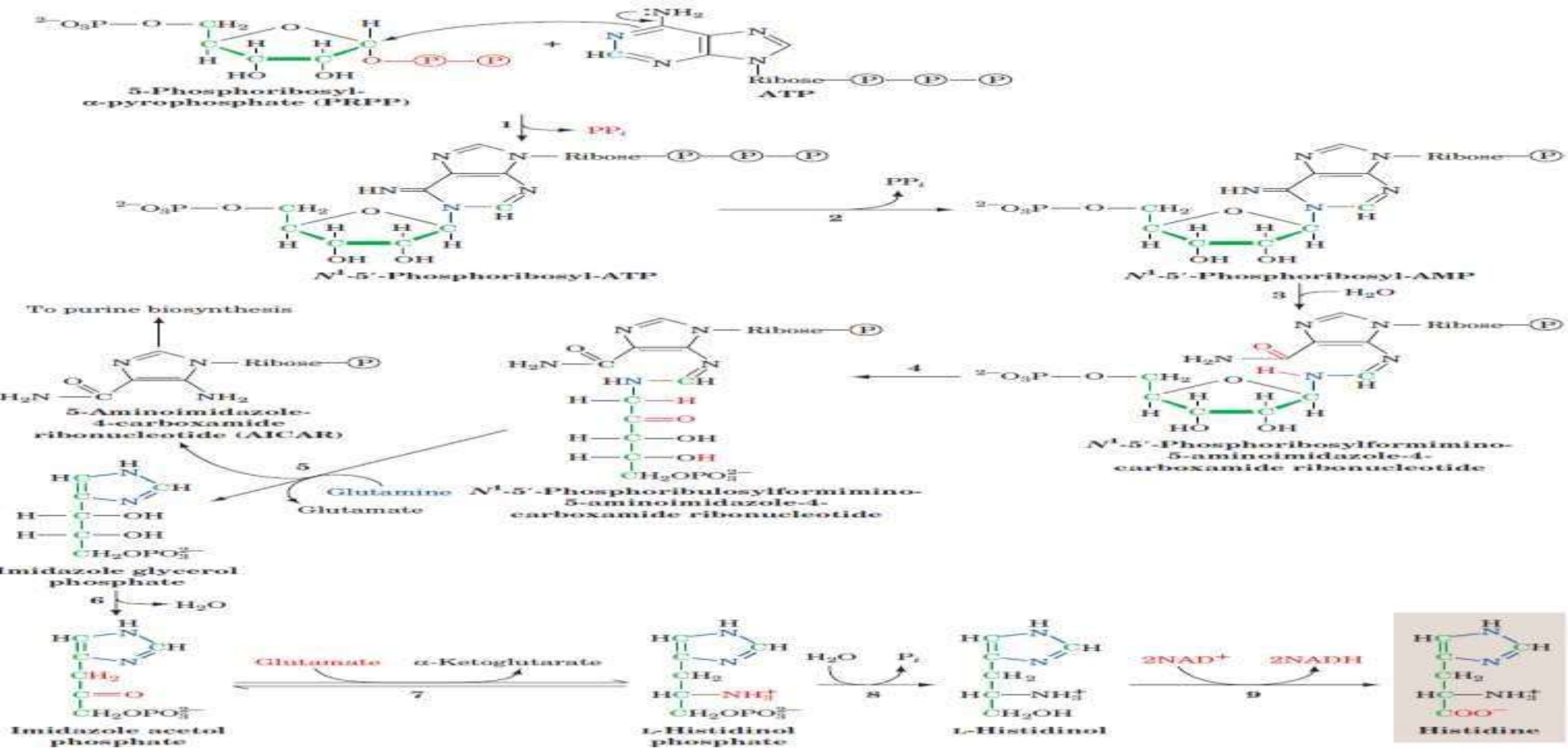


• ATP + α-D-ribose-5-phosphate → Prpp + AMP

α-D-ribose-5-phosphate from H-M shunt

▪ The products of the amido-transferase step:

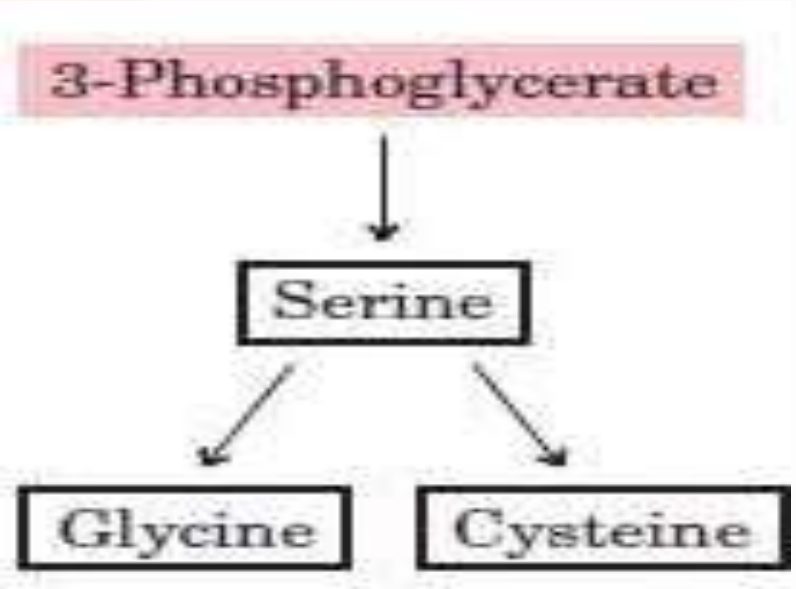
- Aicar
  An intermediate in purine biosynthesis
- Imidazole glycerol phosphate



1. ATP phosphoribosyl transferase
2. pyrophosphohydrolase
3. phosphoribosyl-AMP cyclohydrolase
4. phosphoribosylformimino-5-aminoimidazole-4-carboxamide ribonucleotide isomerase
5. glutamine amidotransferase
6. imidazole glycerol 3-phosphate dehydratase
7. L-histidinol phosphate aminotransferase
8. histidinol phosphate phosphatase
9. histidinol dehydrogenase

THE SERINE FAMILY

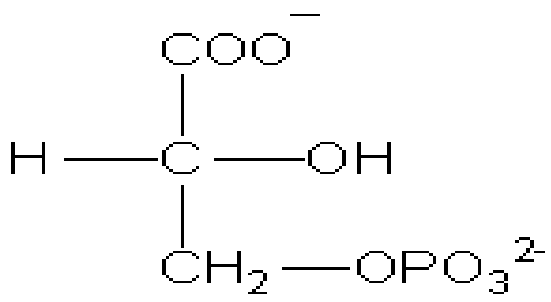
- **3-phosphoglycerate is precursor of**
  - Ser
  - Gly
  - Cys



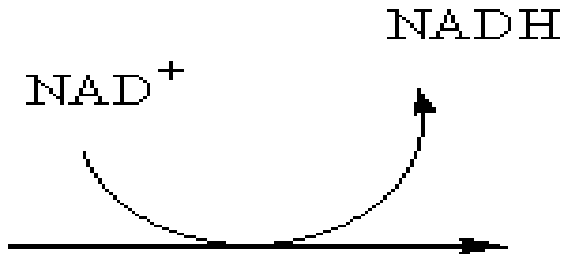
- **Ser** (a 3-step pathway) (1) 3-PG + NAD^+ → 3-phosphohydroxypyruvate + NADH+ H^+

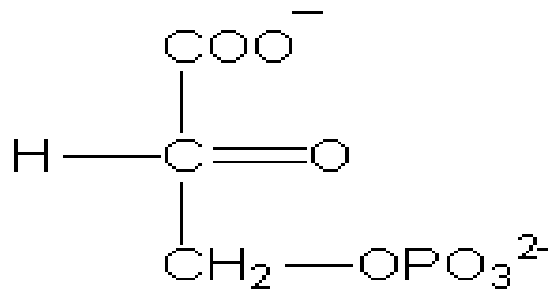
  (2) 3-PHP+ glu → 3-phosphoserine + α-KG

  (3) 3-phosphoserine + H_2 o→ Ser + P_i

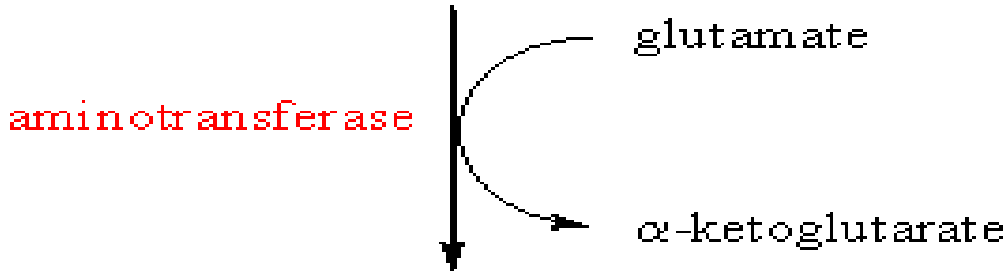


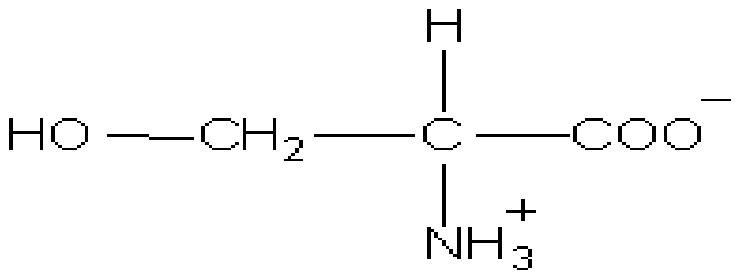
3-phosphoglycerate



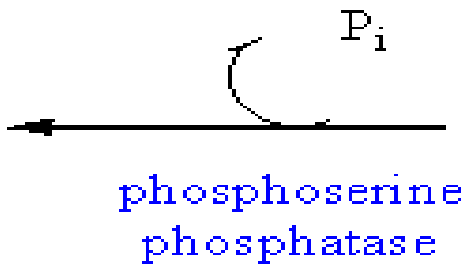


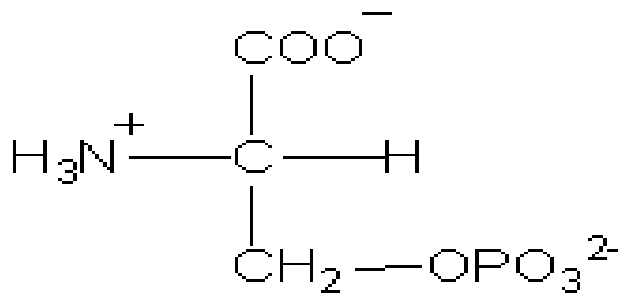
3-phosphohydroxypyruvate





Serine





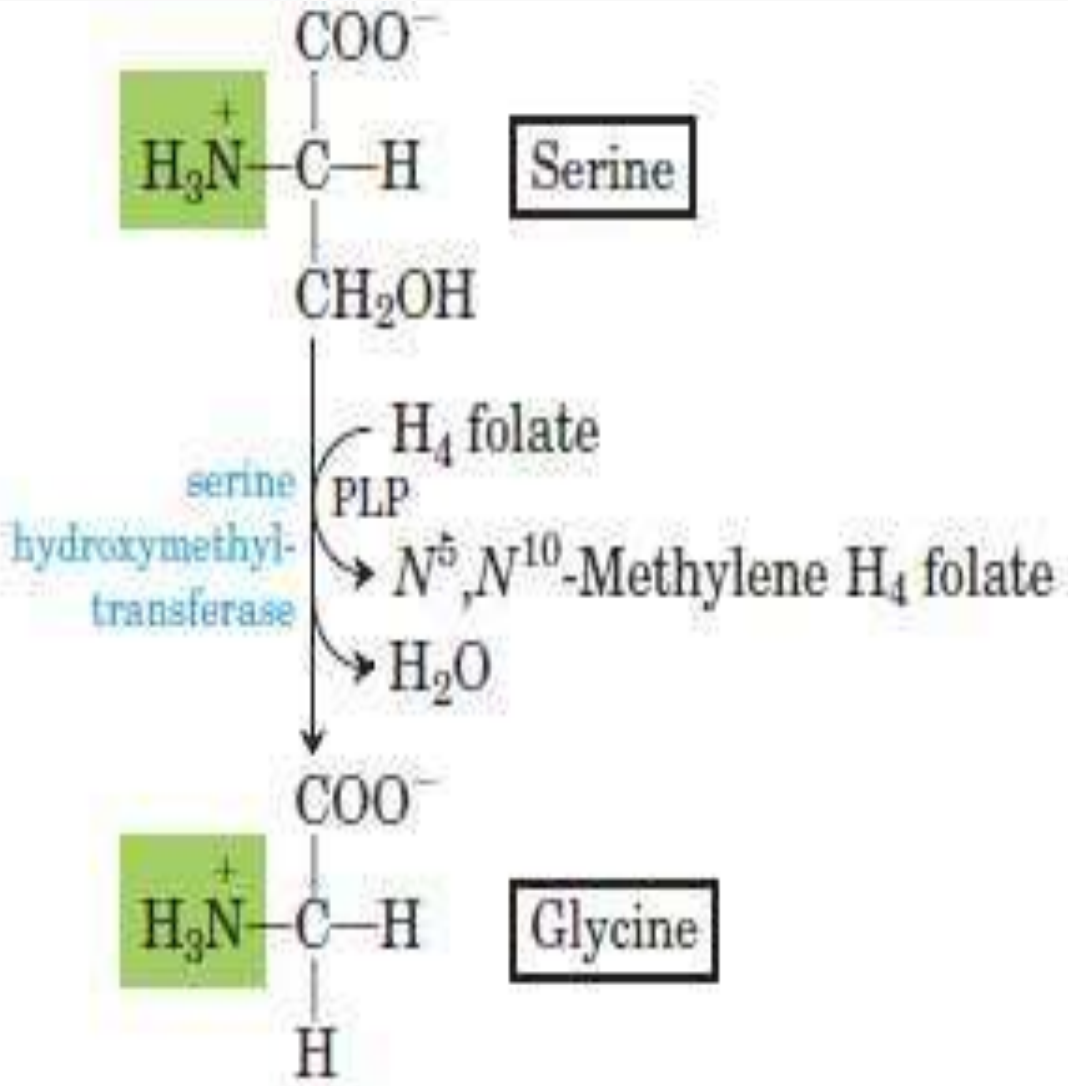
3-phosphoserine

- **Gly (2 different ways)**

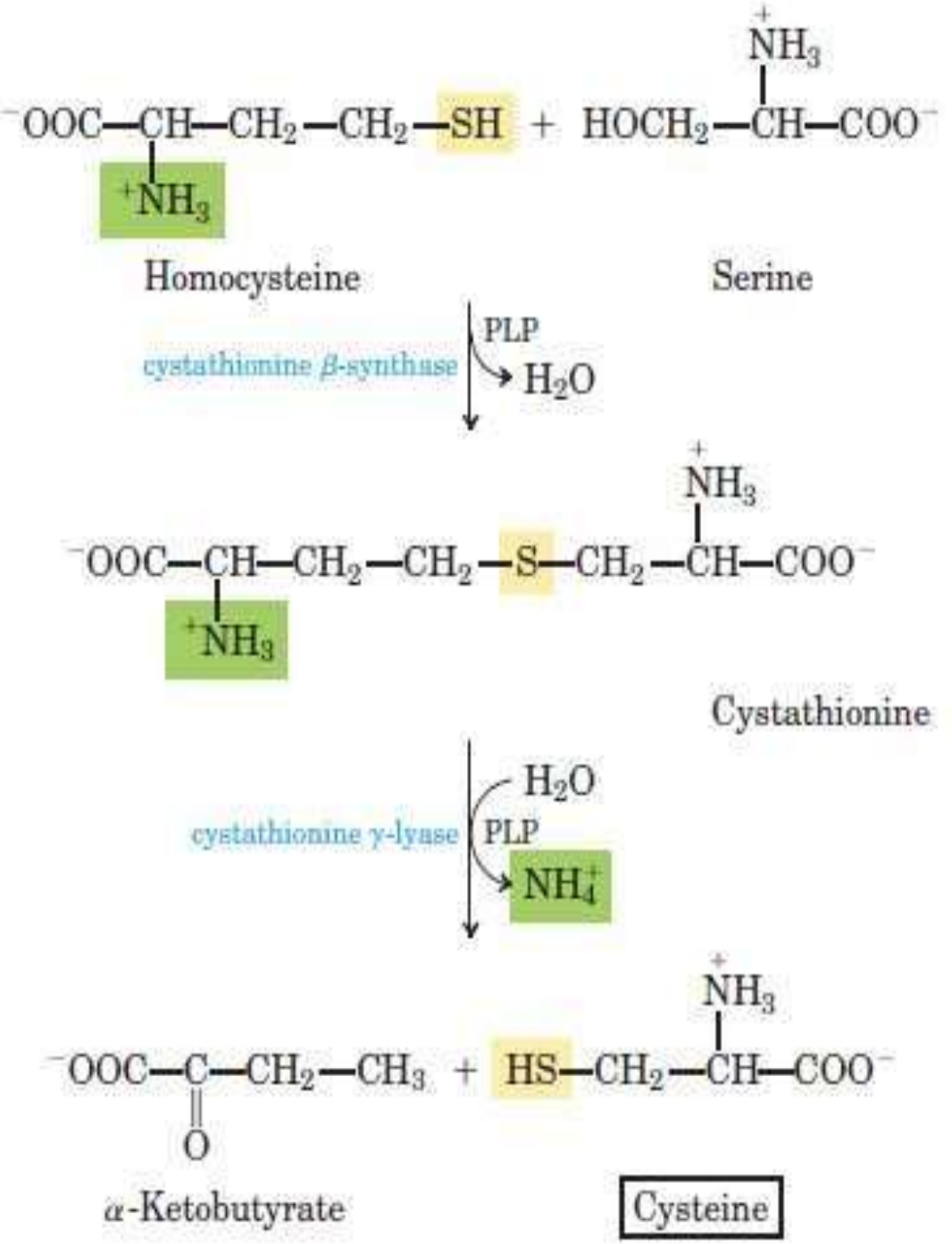
(1)Ser + THF → Gly + N^5,N^{10} – Methylene-THF (direct)

(2) N^5,N^{10} – Methylene-THF + CO_2 + NH_4^+ → Gly + THF

(CONDENSATION)

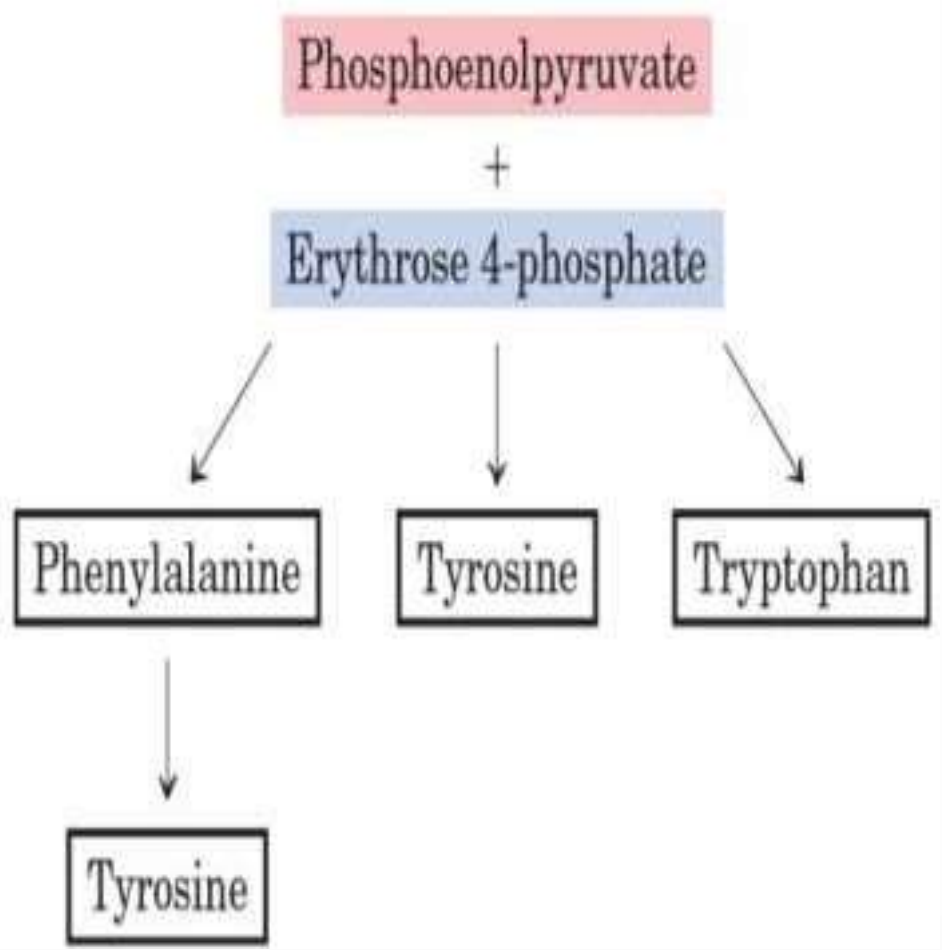


- **Cysteine (in mammals)**
  - Ser + Homocysteine → Cystathionine
    - Homocysteine is a breakdown product of methionine
  - Cystathionine → α-Ketobutyrate + Cys
- Note: -SH group comes from Met
  - So Cys is actually an essential amino acid



THE AROMATIC FAMILY

- In plants and microrganisms
  - Phe
  - Tyr
  - Trp
- Precursors are:
  - Pep
  - Erythrose-4-phosphate
  - These condense with ultimate conversion to chorismate

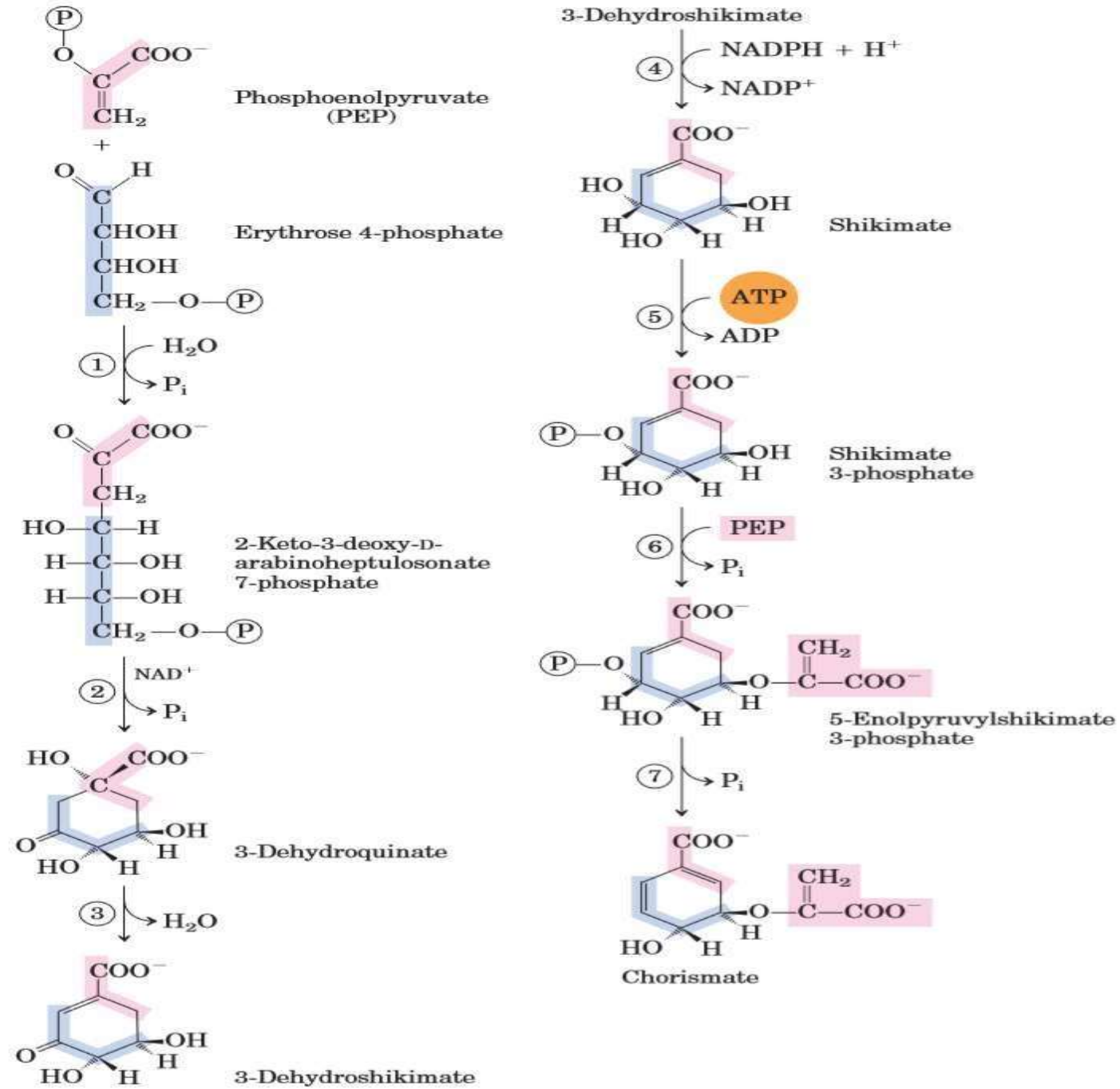


- Chorismate
  1. Shikimate formed in steps 1-4
  2. Chorismate formed in steps 5-7

Roundup

- Glycophate inhibites the enzyme that converts 5- Enolpyruvylshikimate 3–phosphate to chorismate, and hence blocks aromatic amino acid biosynthesis in plants.
- Animals lack this enz- herbicide fairly non-toxic

1. 2-keto-3-deoxy-D-arabinoheptulosonate 7-phosphate synthase
2. dehydroquinate synthase
3. 3-dehydroquinate dehydratase
4. shikimate dehydrogenase
5. shikimate kinase
6. 5-enolpyruvylshikimate 3-phosphate synthase
7. chorismate synthase



The Trp pathway

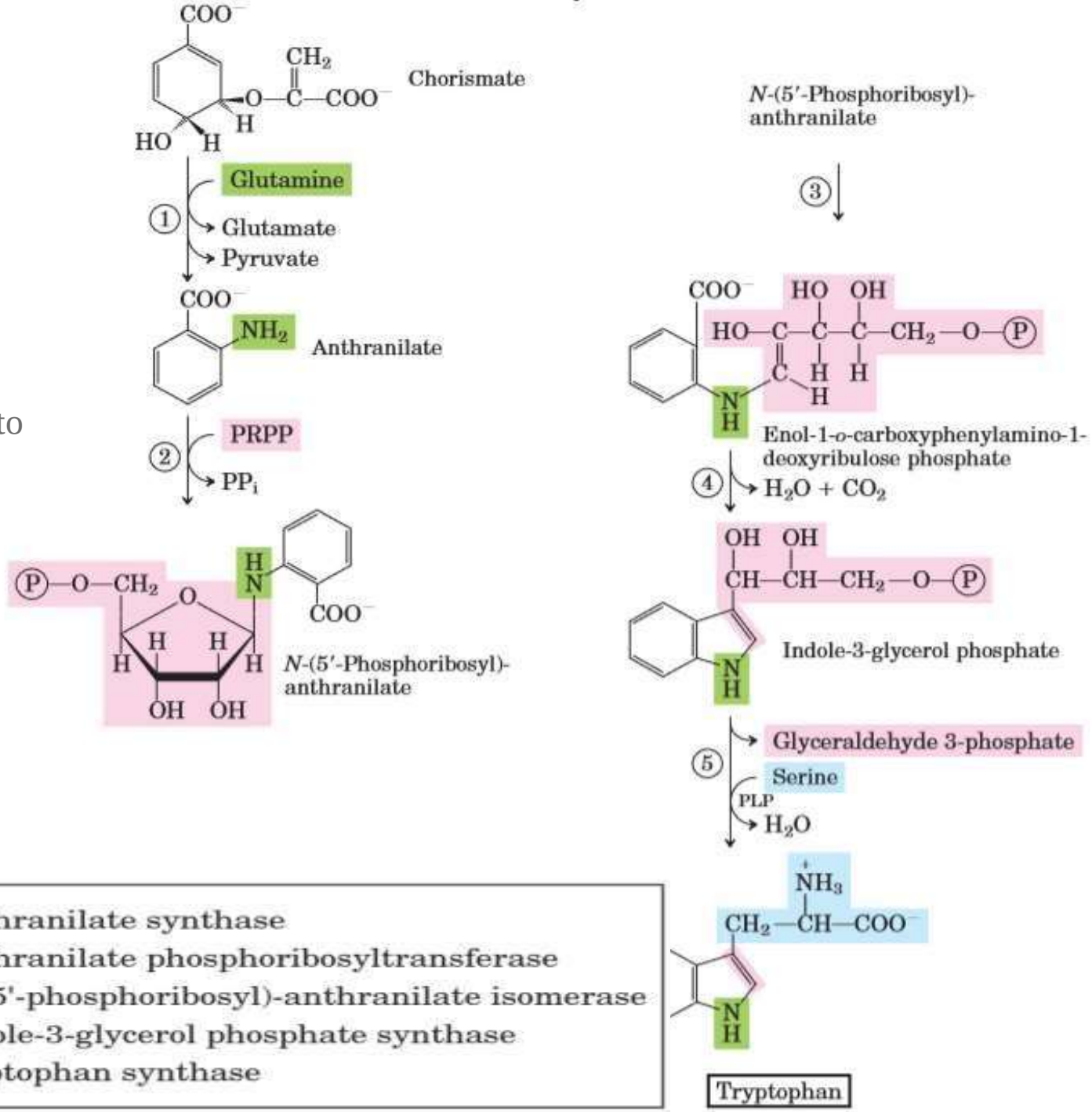
- Chorismate
  - Branch point for trp synthesis
  - Chorismate → anthranilate → trp

- Glutamine donates the N in the indole ring
  - Condensation occurs with PRPP donating two carbons to the ring

- Tryptophan synthase
  - Catalyzes final 2 steps

Indole-3-glycerol phos → Indole + Glyc 3-p

Indole + Ser → H_2o + Trp

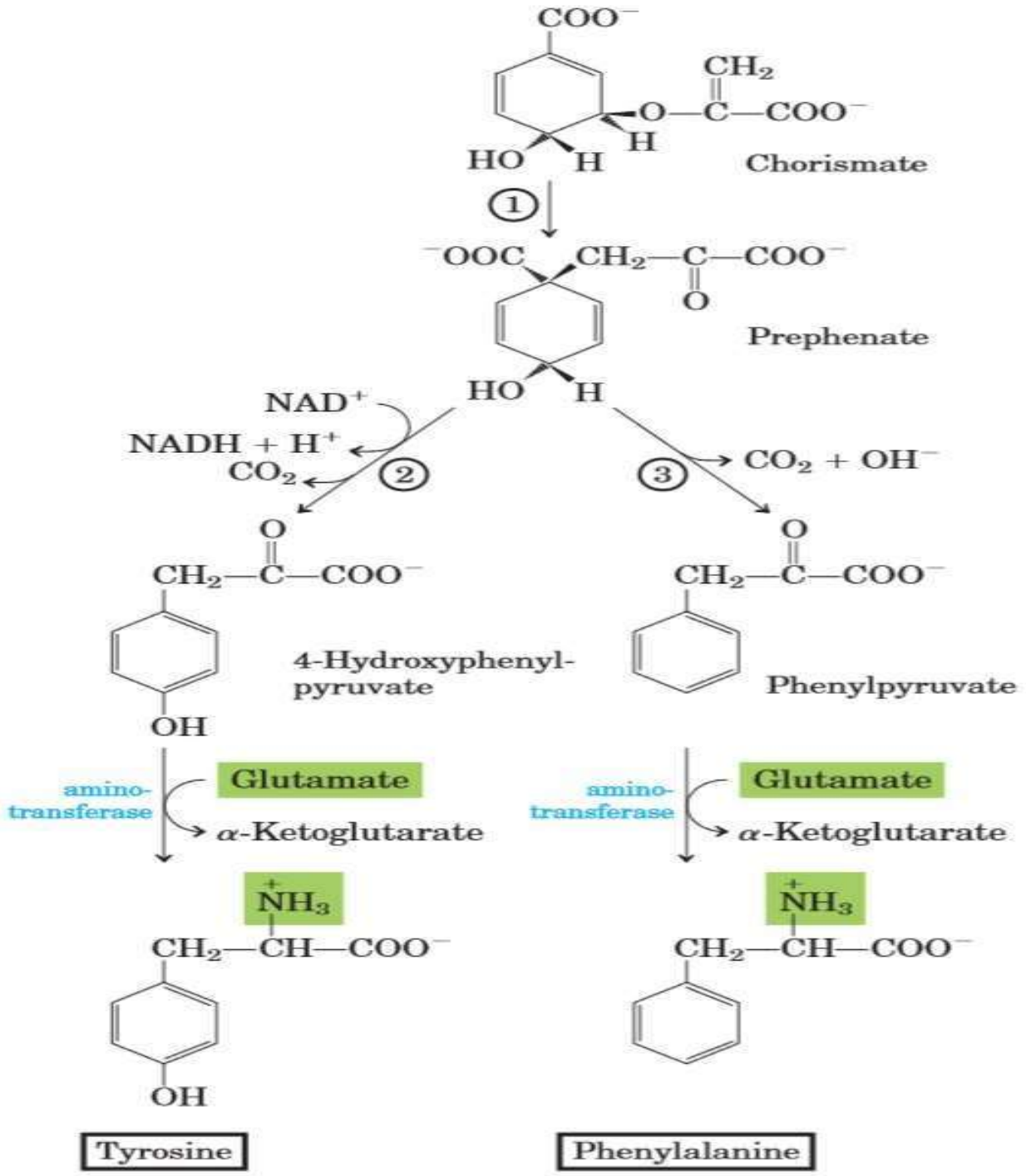


The Tyr and Phe pathway

- Chorismate → prephenate

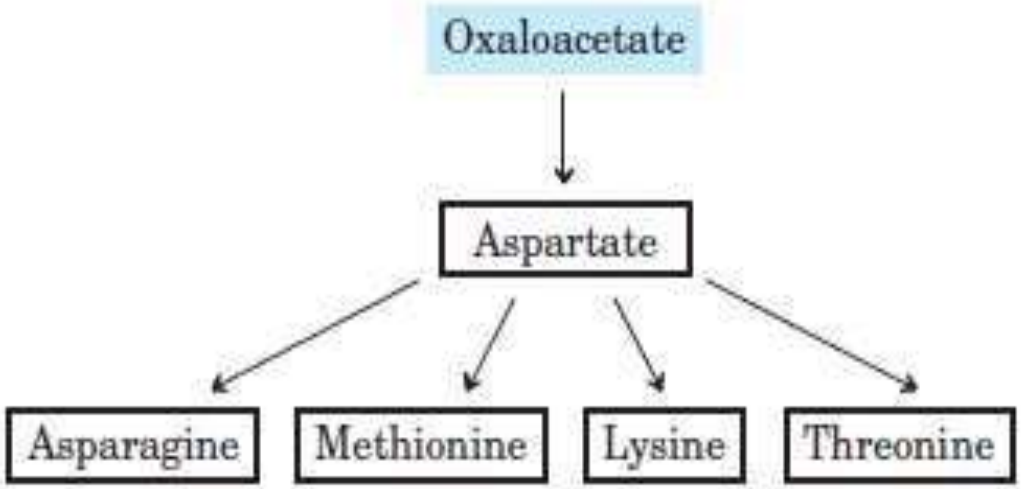
- Prephenate
  - Branch point for phe, tyr synth
    - Aminotransferases in each final step

  - In mammals, tyr is a product of:
    - Phe hydroxylation

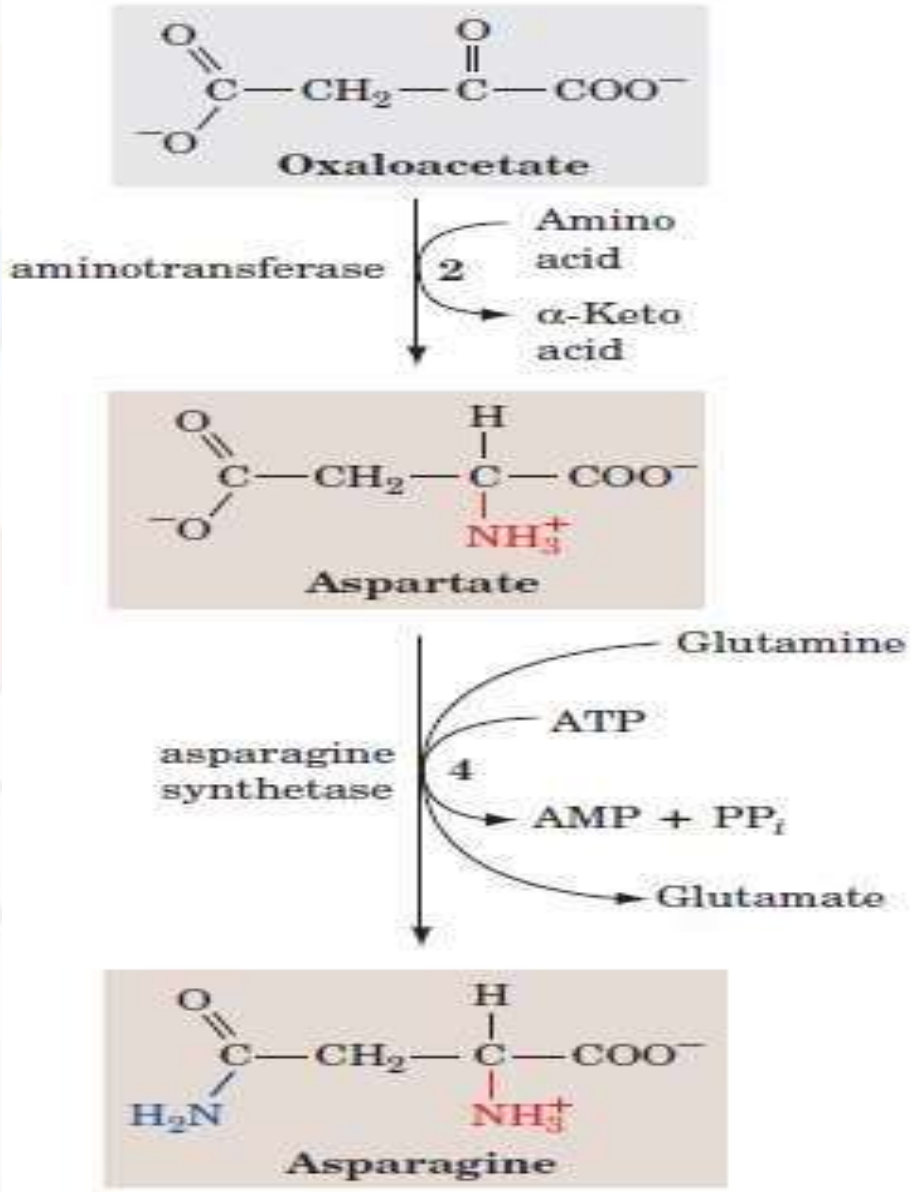


① chorismate mutase
② prephenate dehydrogenase
③ prephenate dehydratase

THE ASPARTATE FAMILY

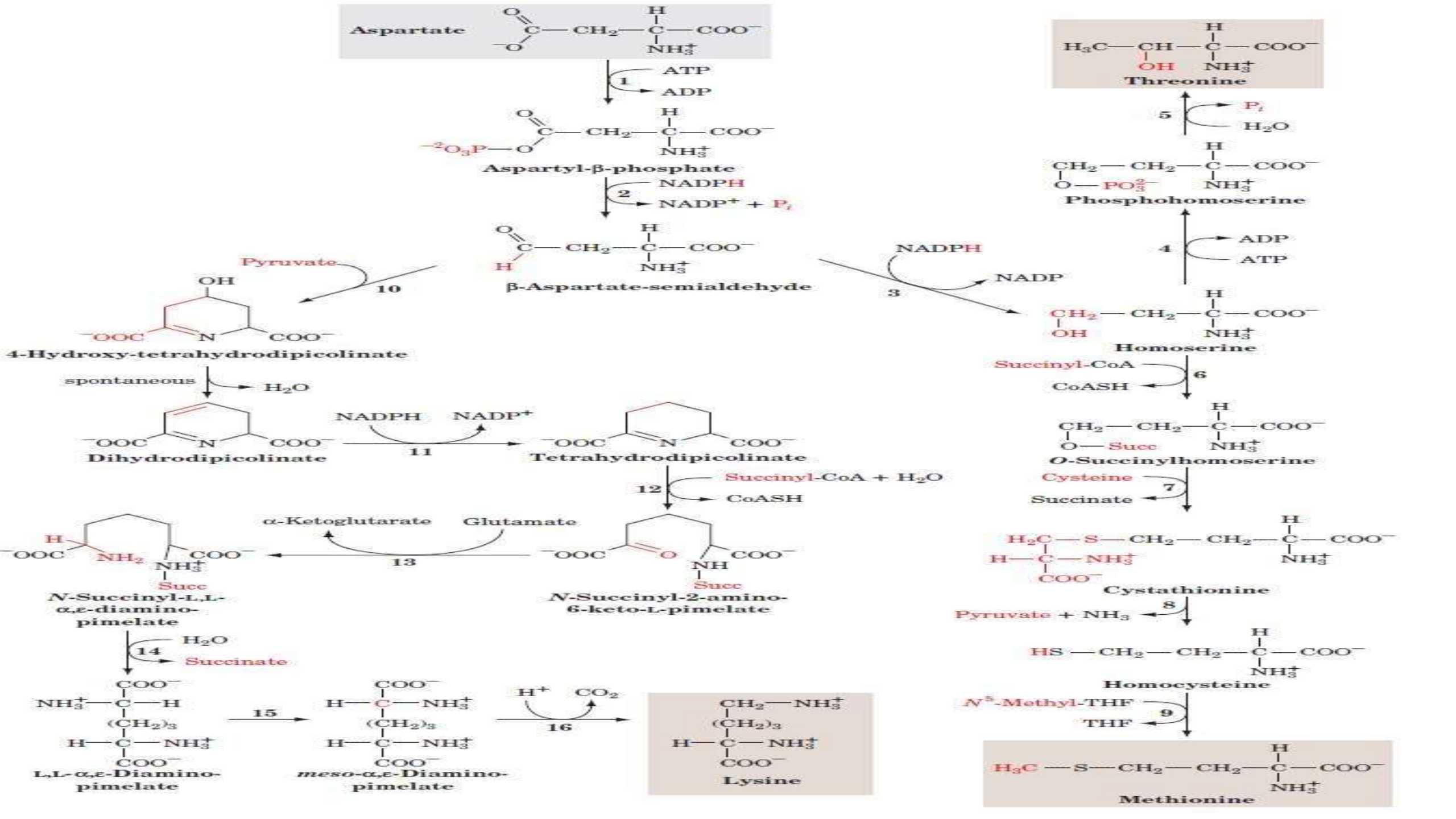


- Asp: non-essential amino acid
- one-step transamination reaction from oxaloacetate
- glu is the amino donor
- Asn: synthesized from Asp
- gln is the amino donor

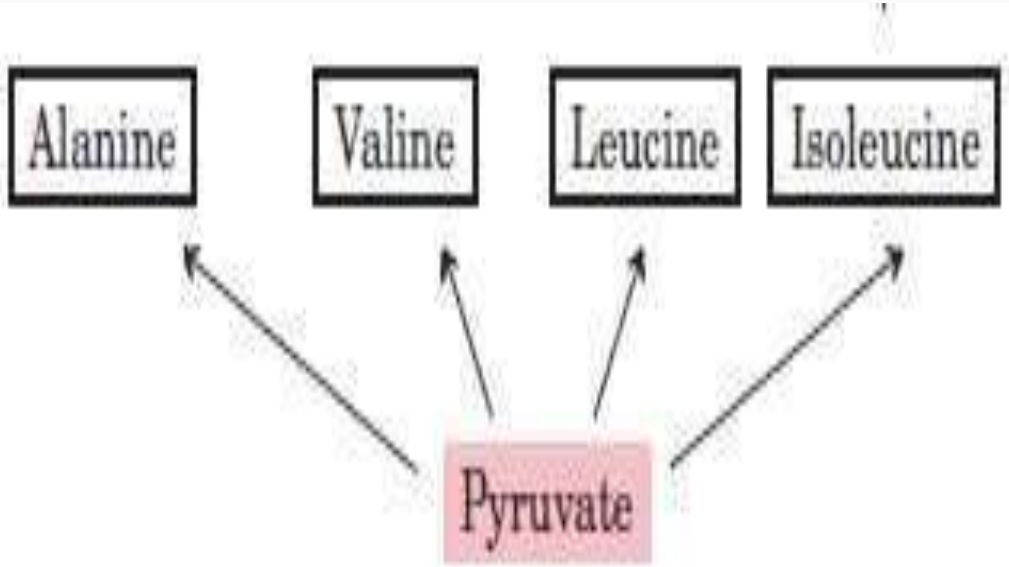


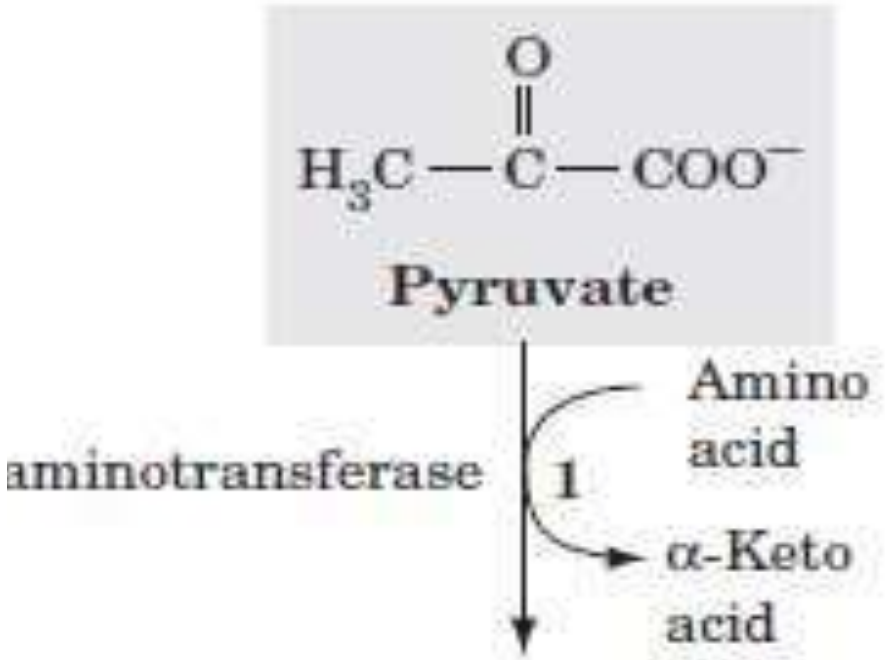
MET, THR AND LYS

- Asp- commom precursor of these essential amino acids
  - Met
  - Thr
  - Lys
- First committed step is
  - Asp + ATP → Aspartyl-β-phosphate +ADP
- Branch points occur at
  - aspartate β-semialdehyde- an intermediate in all three pathways, and
  - homoserine,- a precursor of thr and met

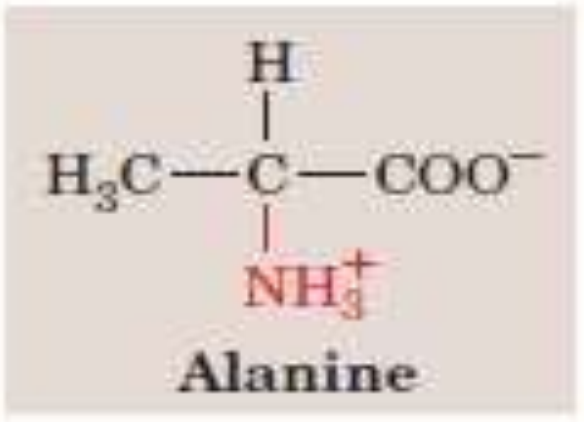

Aspartate
ATP
1
ADP
Aspartyl-β-phosphate
NADPH
2
NADP+ + Pi
β-Aspartate-semialdehyde
Pyruvate
10
4-Hydroxy-tetrahydrodipicolinate
spontaneous
H2O
Dihydrodipicolinate
NADPH
NADP+
11
Tetrahydrodipicolinate
Succinyl-CoA + H2O
12
CoASH
α-Ketoglutarate
Glutamate
13
N-Succinyl-L,L-α,ε-diamino-pimelate
N-Succinyl-2-amino-6-keto-L-pimelate
H2O
14
Succinate
L,L-α,ε-Diamino-pimelate
15
meso-α,ε-Diamino-pimelate
H+
CO2
16
Lysine
NADPH
3
NADP
β-Aspartate-semialdehyde
Homoserine
Succinyl-CoA
6
CoASH
O-Succinylhomoserine
Cysteine
7
Succinate
Cystathionine
8
Pyruvate + NH3
Homocysteine
N5-Methyl-THF
9
THF
Methionine
4
ADP
ATP
Phosphohomoserine
5
Pi
H2O
Threonine

THE PYRUVATE FAMILY





- Ala: non-essential amino acid
- One-step transamination reaction from pyruvate.
- glu is the amino donor



LEU, ILE AND VAL

- "branched chain essential amino acids"
  - leu
  - ile
  - val
- Val, Ile: same pathway after 1st step
- Leu pathway branches from val pathway
- final steps all catalyzed by amino-transferases
  - glu is the amino donor

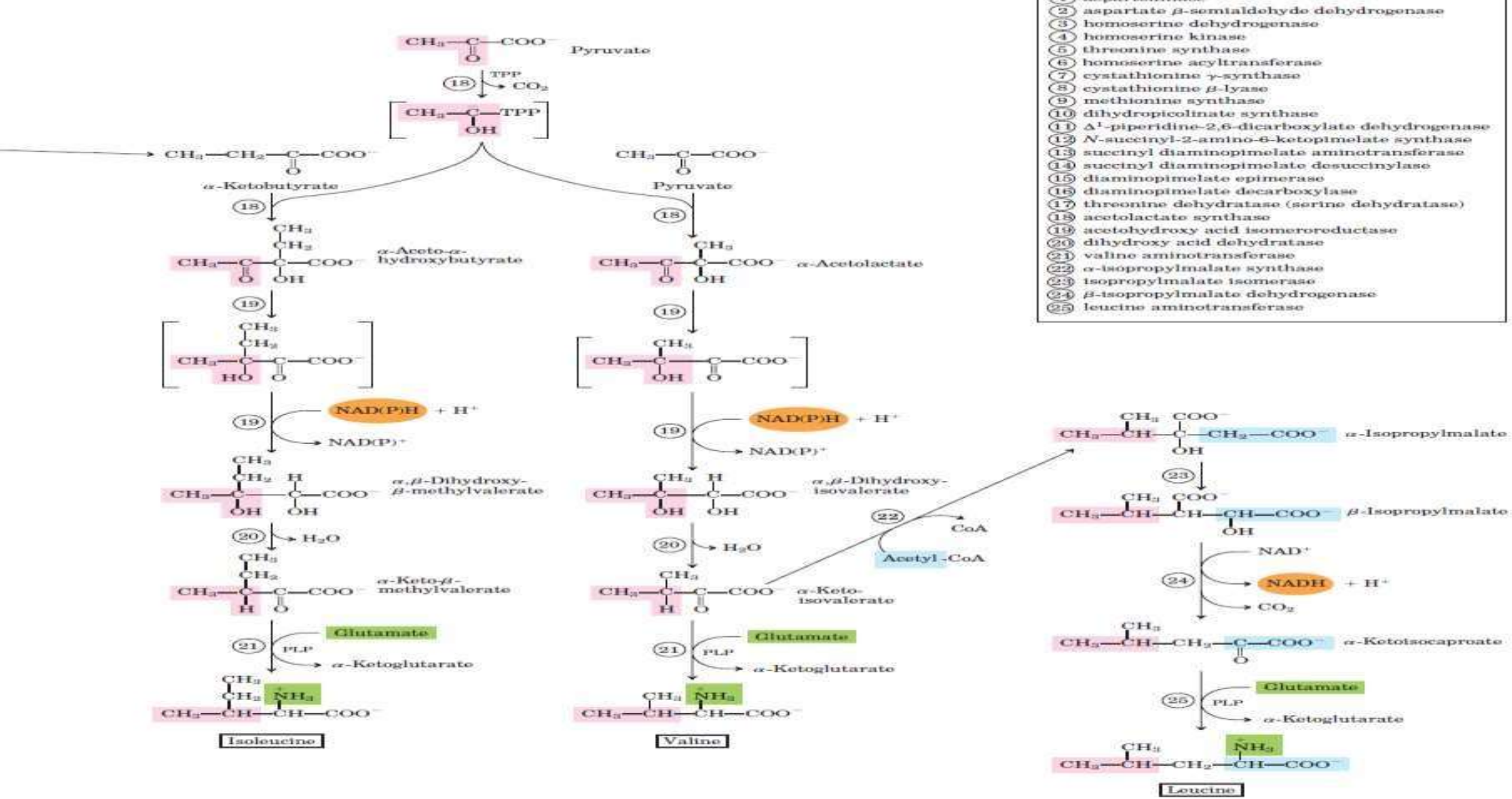
• the first step:

Pyr + Tpp → hydroxyethyl-tpp

•first pyr and tpp form an adduct then decarboxylated to He-tpp

•adds to keto group of

pyruvate → val, leu
α-ketobutyrate → ile


Pyruvate
TPP
CO2
α-Ketobutyrate
Pyruvate
α-Aceto-α-hydroxybutyrate
α-Acetolactate
NAD(P)H + H+
NAD(P)+
α,β-Dihydroxy-β-methylvalerate
α,β-Dihydroxy-isovalerate
H2O
α-Keto-β-methylvalerate
α-Keto-isovalerate
CoA
Acetyl-CoA
Glutamate
PLP
α-Ketoglutarate
Isoleucine
Valine
α-Isopropylmalate
β-Isopropylmalate
NAD+
NADH + H+
α-Ketoisocaproate
Leucine
1 aspartokinase
2 aspartate β-semialdehyde dehydrogenase
3 homoserine dehydrogenase
4 homoserine kinase
5 threonine synthase
6 homoserine acyltransferase
7 cystathionine γ-synthase
8 cystathionine β-lyase
9 methionine synthase
10 dihydropicolinate synthase
11 Δ1-piperidine-2,6-dicarboxylate dehydrogenase
12 N-succinyl-2-amino-6-ketopimelate synthase
13 succinyl diaminopimelate aminotransferase
14 succinyl diaminopimelate desuccinylase
15 diaminopimelate epimerase
16 diaminopimelate decarboxylase
17 threonine dehydratase (serine dehydratase)
18 acetolactate synthase
19 acetohydroxy acid isomeroreductase
20 dihydroxy acid dehydratase
21 valine aminotransferase
22 α-isopropylmalate synthase
23 isopropylmalate isomerase
24 β-isopropylmalate dehydrogenase
25 leucine aminotransferase

References :

1. https://www.biochemden.com/citric-acid-cycle.
2. Weinstein, L. H.; Porter, C. A.; Laurencot, H. J. (1962). "Role of the Shikimic Acid Pathway in the Formation of Tryptophan in Higher Plants : Evidence for an Alternative Pathway in the Bean". Nature. 194 (4824): 205–206.
3. Brown, Stewart A.; Neish, A. C. (1955). "Shikimic Acid as a Precursor in Lignin Biosynthesis". Nature. 175 (4459): 688–689
4. https://www.sciencedirect.com/topics/biochemistry-genetics-and- molecular-biology/shikimic-acid-pathway
5. https://www.sciencedirect.com/topics/biochemistry-genetics-and- molecular-biology/mevalonate-pathway
6. Banerjee A, Sharkey TD. (2014) Methylerythritol 4-phosphate (MEP) pathway metabolic regulation. Nat Prod Rep 31:10431055