Purine and Pyrimidine Biosynthesis

Biosynthesis of Nucleotides

Nucleotides have important functions in all cells.

- Precursors of DNA and RNA
- Carriers of chemical energy (ATP, GTP)
- Cofactors NAD, FAD, CoA
- Activated biosynthetic intermediates (UDP-glucose)
- Cellular second messengers (cAMP, cGMP)

Biosynthesis

Denovo pathways and the salvage pathways.

De novo synthesis of nucleotides begins with their metabolic precursors:

- amino acids
- ribose 5-phosphate,
- CO_2 and NH_3

Salvage pathways recycle the free bases and nucleosides released from nucleic acid breakdown.

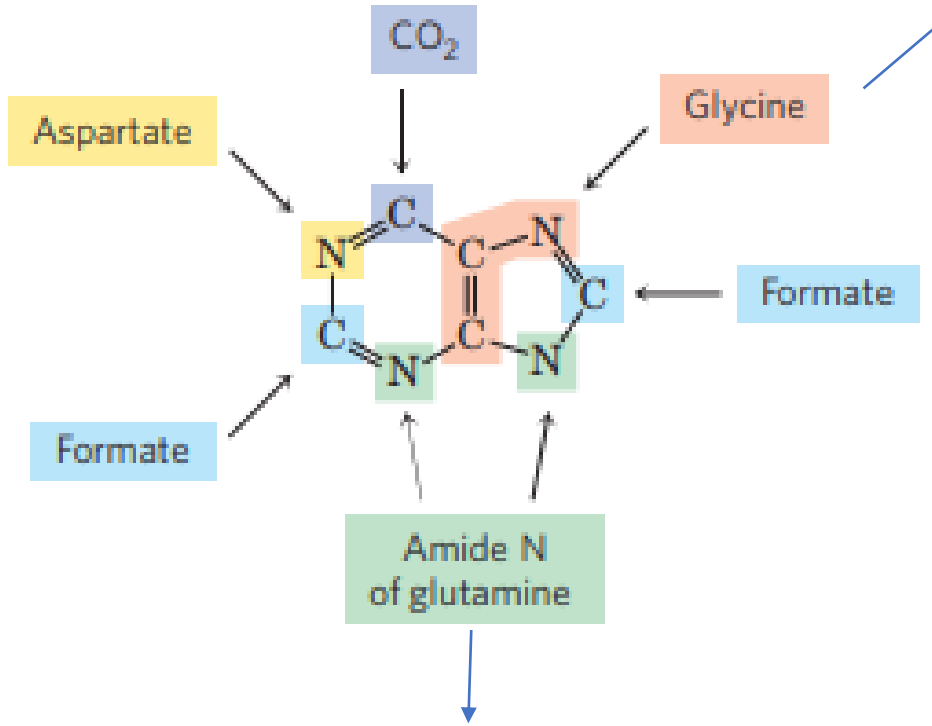
De novo synthesis of purine nucleotides: IMP, AMP and GMP

Identical in all living organisms

This process takes place mainly in the liver.

pyrimidines

purine



3 amino acids (aspartate, glycine and glutamine)

- Carbon dioxide (CO2)
- N10-formyl-THF (tetrahydropholate)

Aspartate is also used as the source of an amino group in the purine pathways

Most important source of amino group

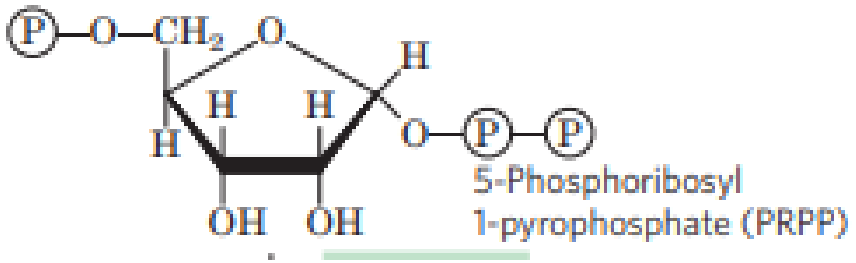
De novo synthesis of purine nucleotides: IMP, AMP and GMP

Pentose phosphate pathway

↓

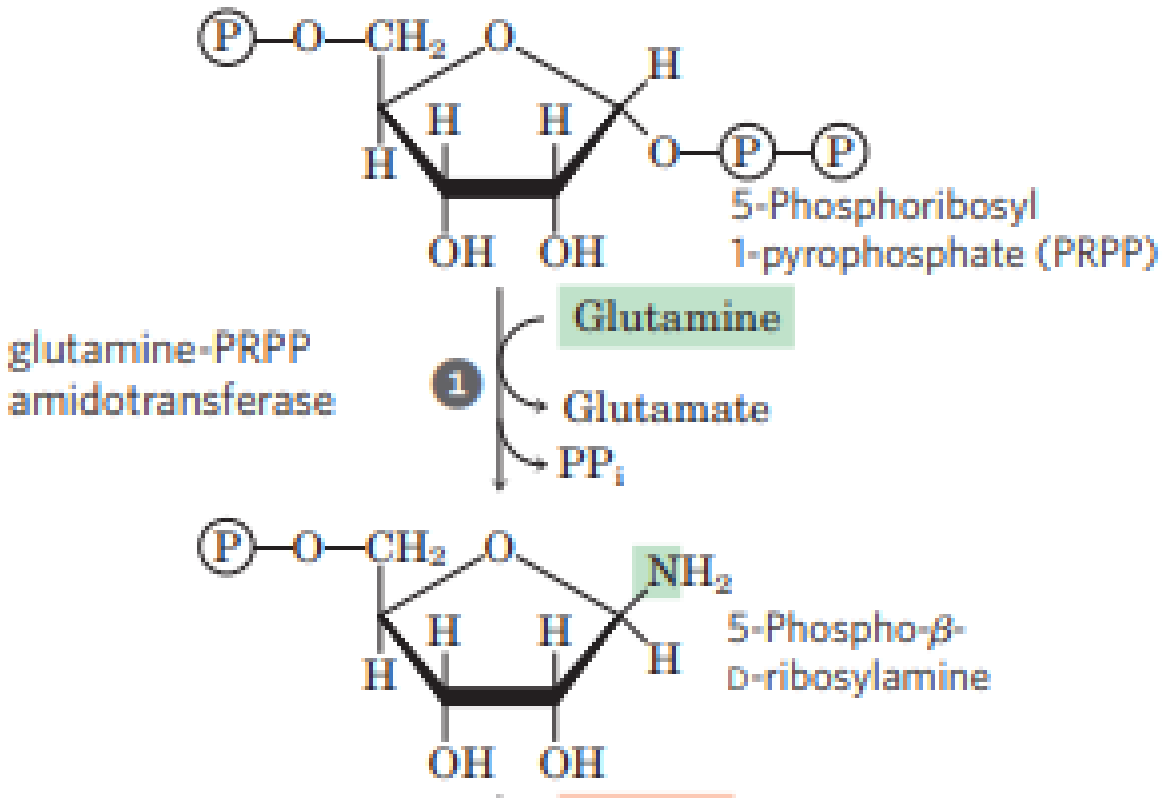
Ribose 5-phosphate + ATP

↓ Ribose phosphate pyrophospho-Kinase

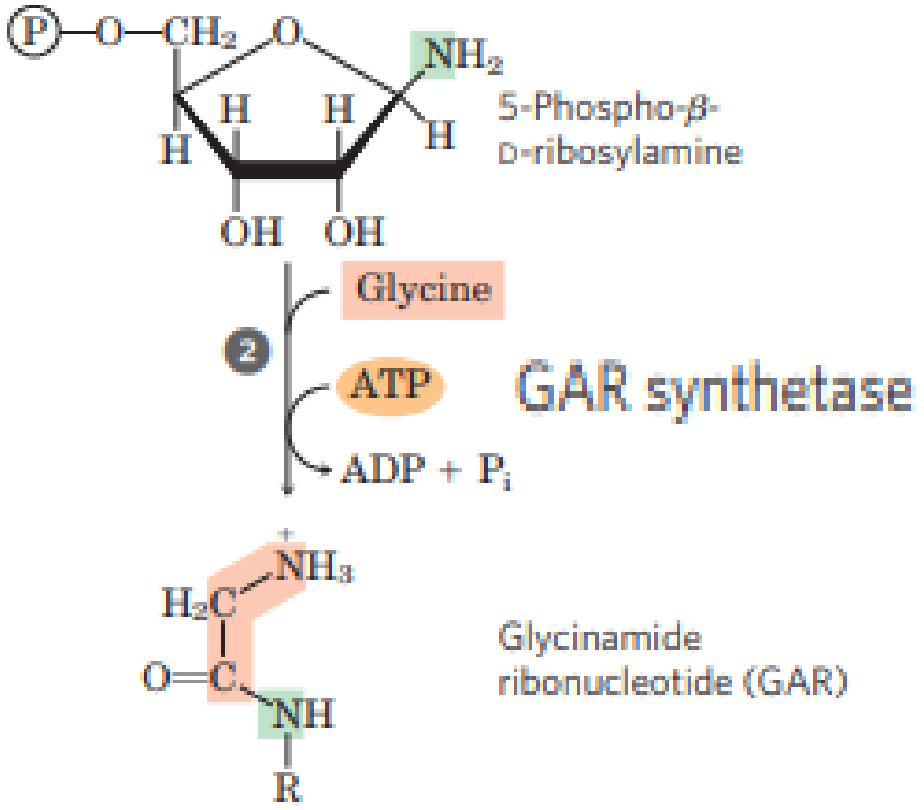


11 stage portano alla formazione di IMP

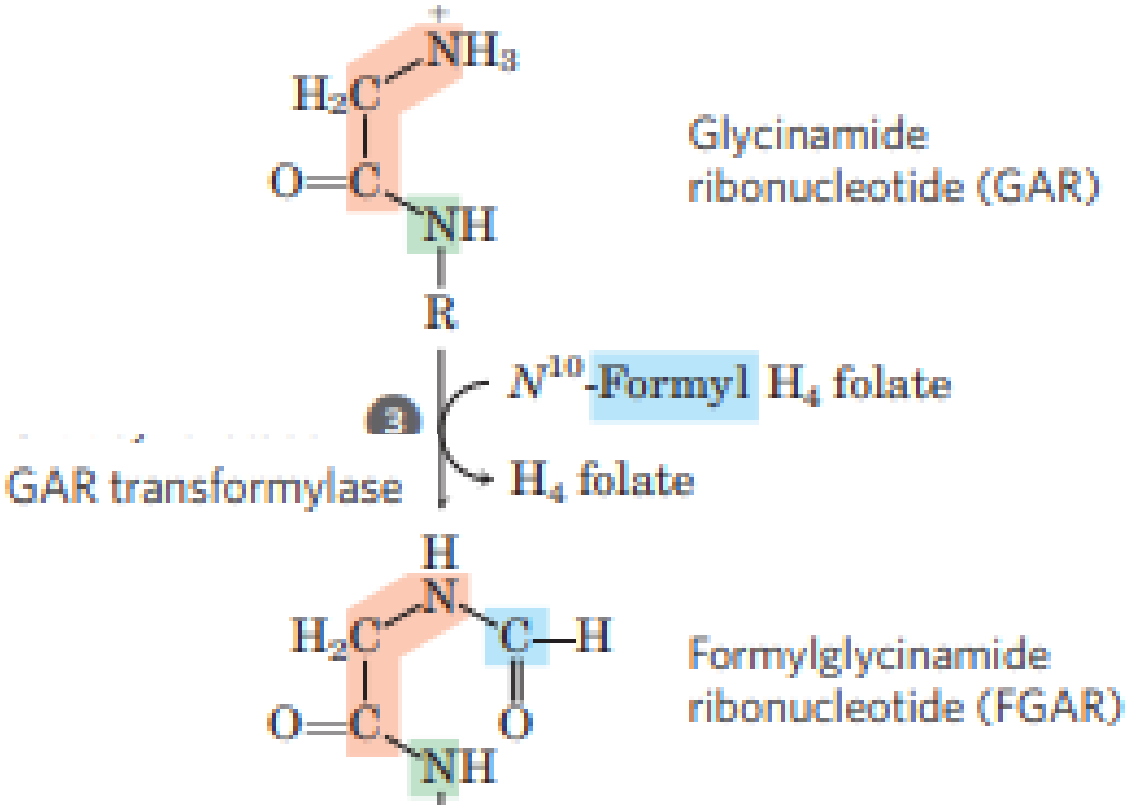
Step 1:
Glutamine donates an amino group at C-1 of PRPP
5-phosphoribosylamine is formed



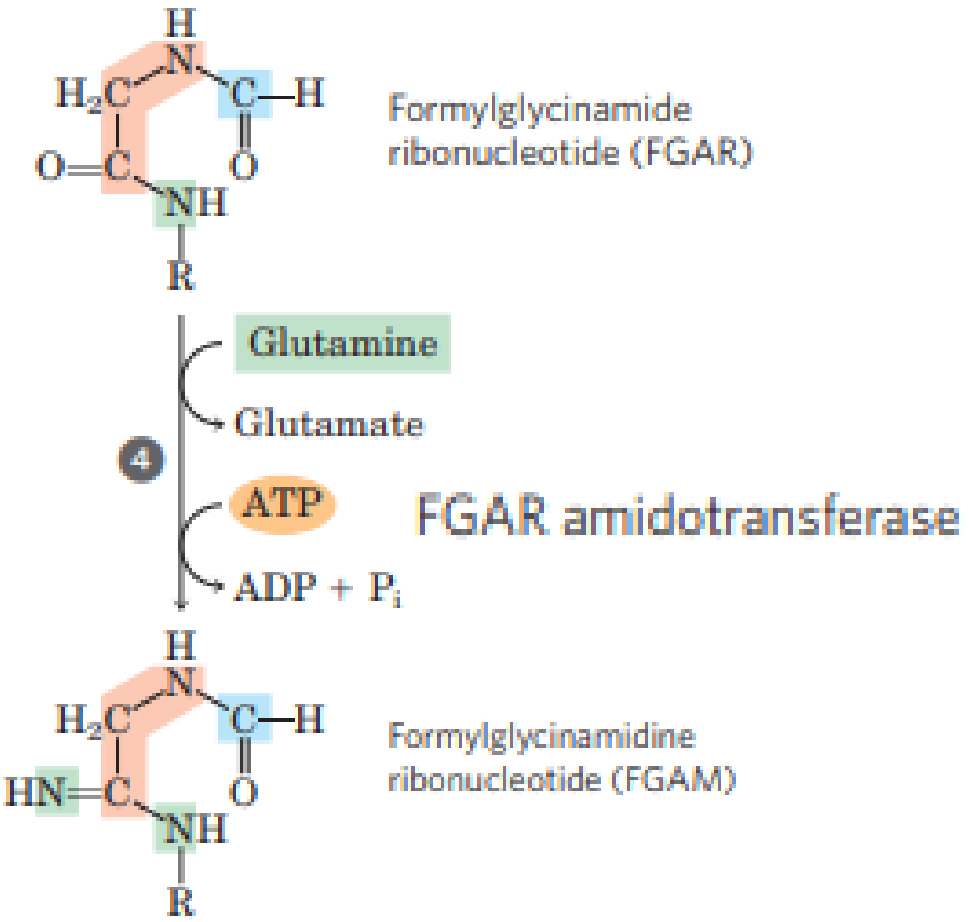
Step 2:
addition of three atoms from glycine



Step 3: addition of Formil H4 folate form FGAR

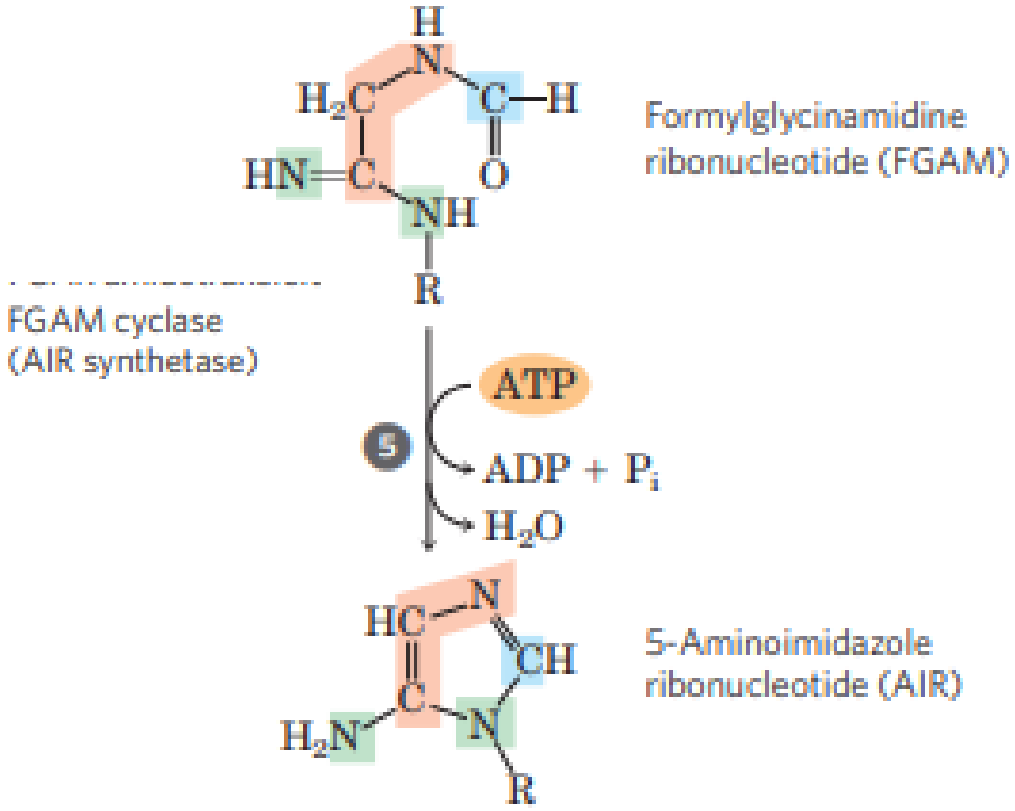


Step 4: addition of Glutamine form FGAM



Step 5:

dehydration and ring closure yield as 5-aminoimidazole ribonucleotide (AIR)

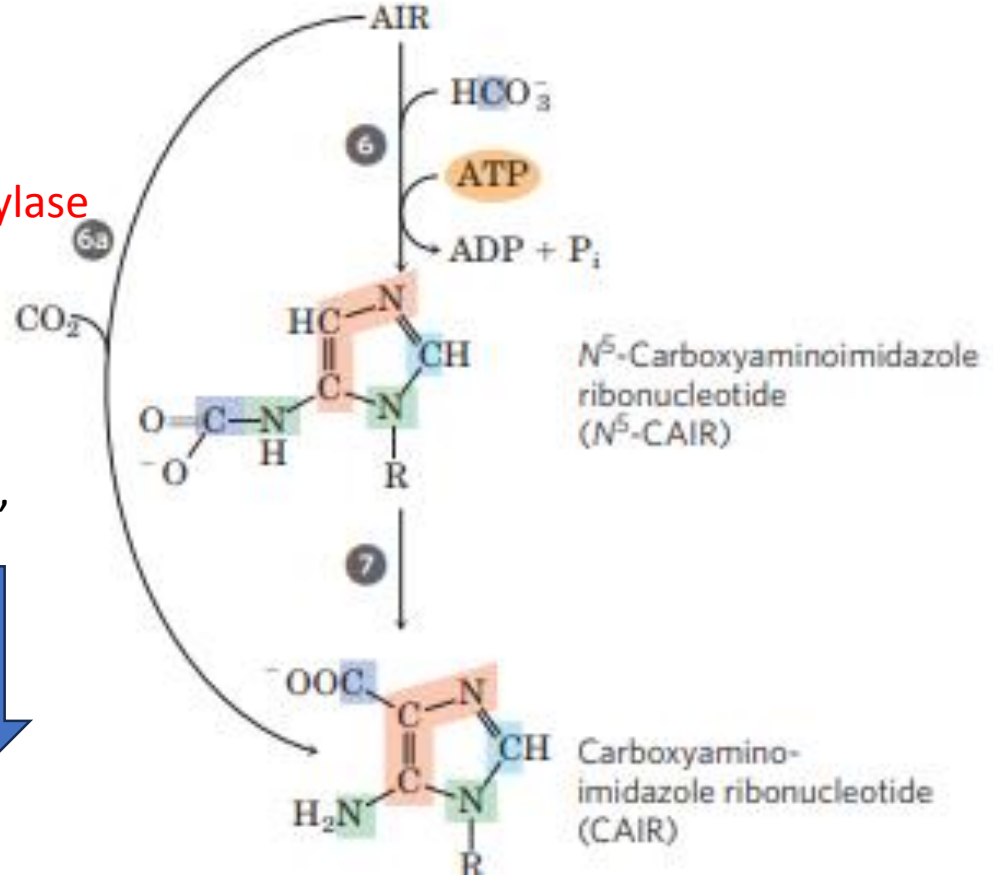


Step 6 and 7: bacteria and fungi.

carboxyl group is first added.

A rearrangement transfers the carboxylate from the exocyclic amino group to position 4 of the imidazole ring (step 7).

AIR carboxylase



Eukaryotes,

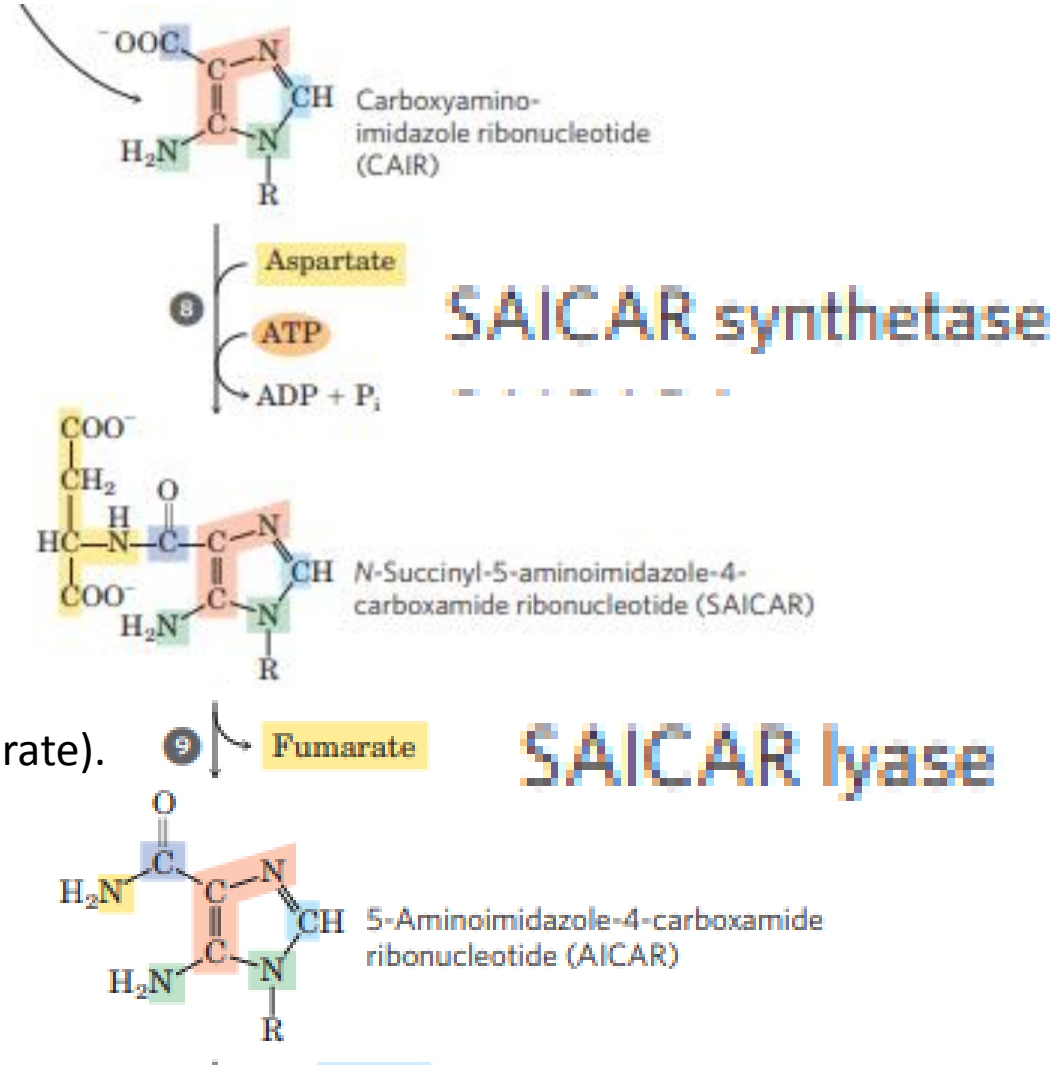
is carboxylated directly to carboxyaminoimidazole ribonucleotide

Step 8 and 9:

Aspartate donates its amino group in two steps

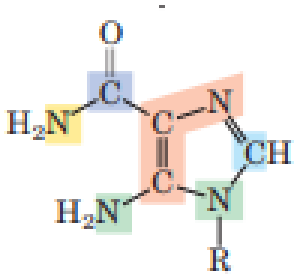
Formation of an amide bond,

Elimination of the carbon skeleton of aspartate (as fumarate).



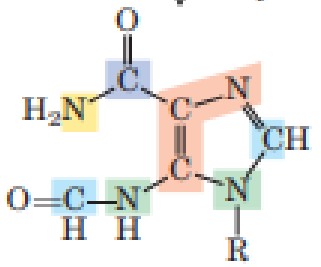
Step 10

Add N10-formyltetrahydrofoate



5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR)

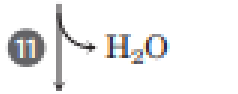
AICAR transformylase



N-Formylaminoimidazole-4-carboxamide ribonucleotide (FAICAR)

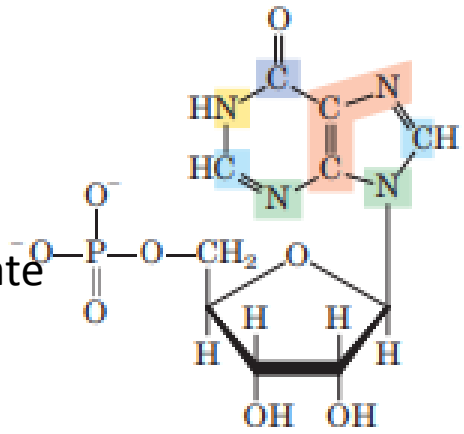
Step 11:

Closure of the second ring



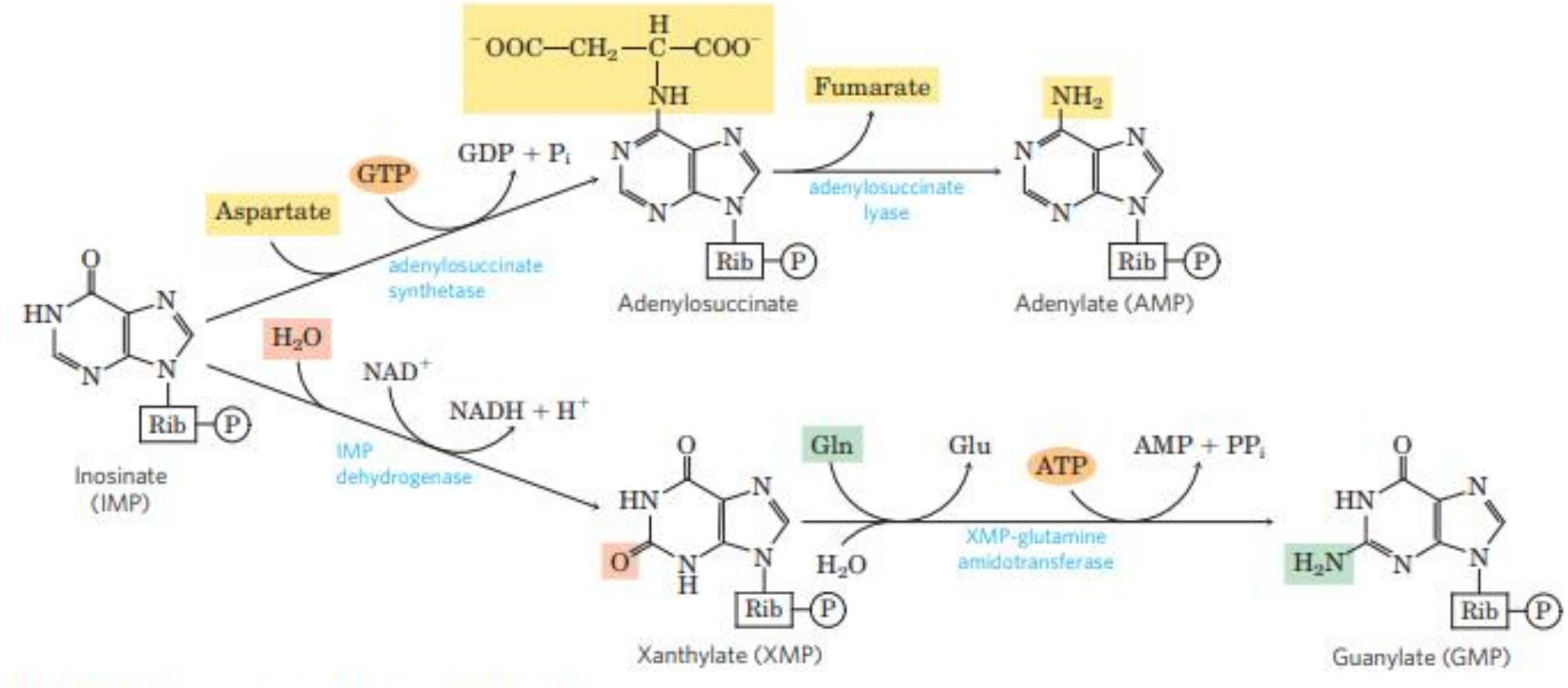
IMP synthase

The first intermediate with a complete purine ring is inosinate (IMP).



Inosinate (IMP)

Conversion of inosinate to adenylate requires the insertion of an amino group derived from aspartate



Guanylate is formed by the NAD-requiring oxidation of inosinate at C-2, followed by addition of an amino group derived from glutamine

Purine Nucleotide Biosynthesis Is Regulated by Feedback Inhibition

Three major feedback mechanisms of regulation:

1. First step of regolation

Reaction catalyzed by the allosteric enzyme glutamine-PRPP amidotransferase

transfer of an amino group to PRPP to form 5-phosphoribosylamine

Inhibited: IMP, AMP, and GMP

2. Second step of regolation

-Reaction catalyzed by IMP dehydrogenase

IMP is converted to XMP

Inhibited: High GMP

(No effect in the formation of AMP)

Reaction catalyzed by adenylosuccinate synthetase

IMP is converted to adenylosuccinate

High AMP

(No effect in the formation of GMP)

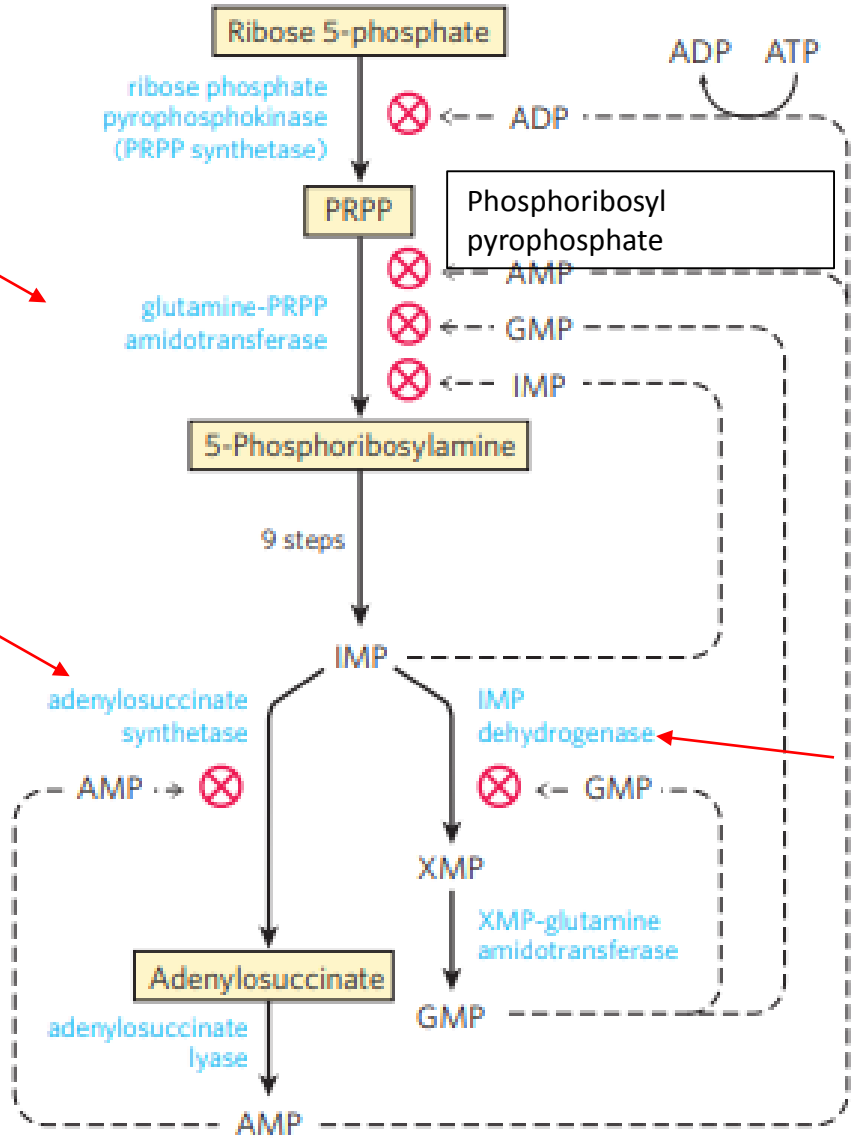


FIGURE 22–37 Regulatory mechanisms in the biosynthesis of adenine

Sequential feedback inhibition.

When AMP and GMP products are present in sufficient quantities

IMP

inhibits an earlier step in the pathway

3. Step of regolation

-Reaction catalyzed by PRPP synthase /ribose phosphate pyrophosphokinase.

Ribose 5-phosphate is converted is converted to PRPP

Inhibited: ADP and GDP

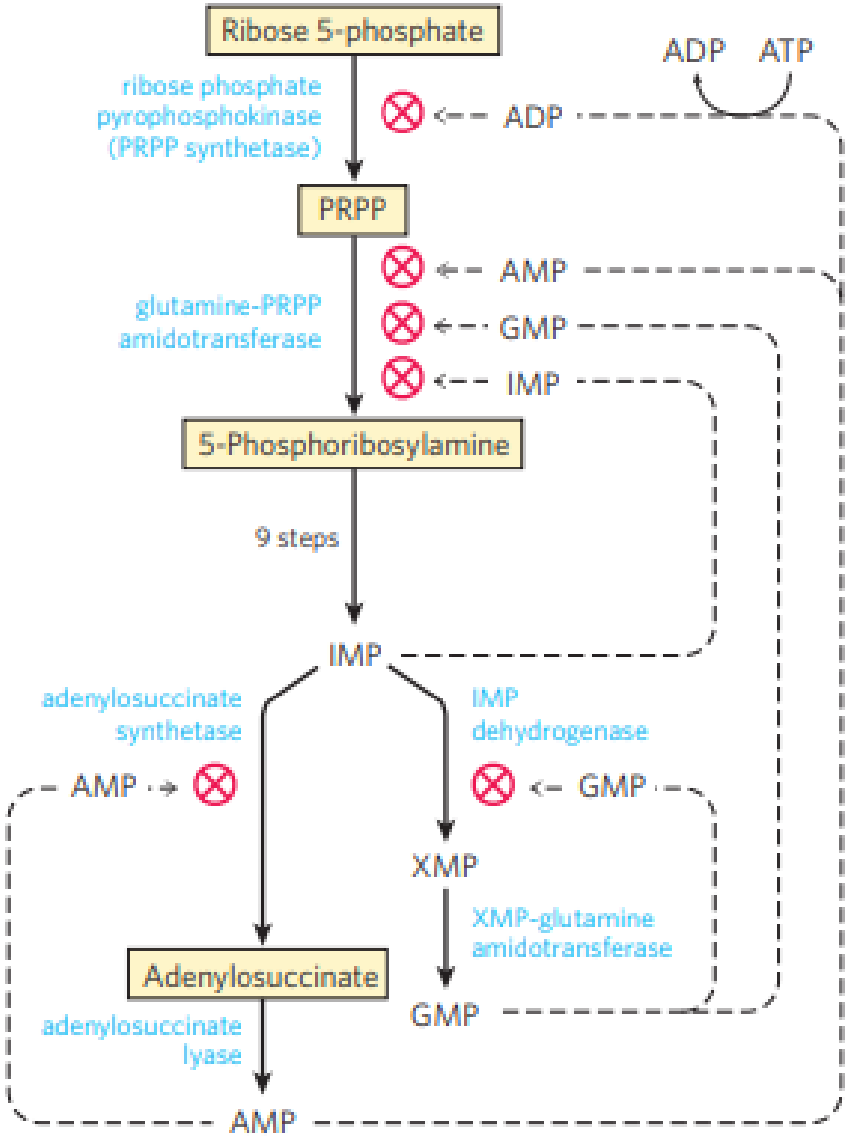


FIGURE 22–37 **Regulatory mechanisms in the biosynthesis of adenine and guanine nucleotides in *E. coli*.** Regulation of these pathways differs in other organisms.

Phosphoribosyl pyrophosphate (PRPP)

Nucleoside Monophosphates Are Converted to Nucleoside Triphosphates

AMP is phosphorylated to ADP

ATP + AMP ⟷ (adenylate kinase) 2 ADP

ADP is phosphorylated to ATP

- glycolytic enzymes
- through oxidative phosphorylation.

ATP can form → other nucleoside diphosphates → Nucleoside triphosphates

- ATP can form → other nucleoside diphosphates: nucleoside monophosphate kinases
- other nucleoside diphosphates → Nucleoside triphosphates: nucleoside diphosphate kinase,

Deaseas of Purine Nucleotide Synthesis

From Adenylosuccinate to AMP

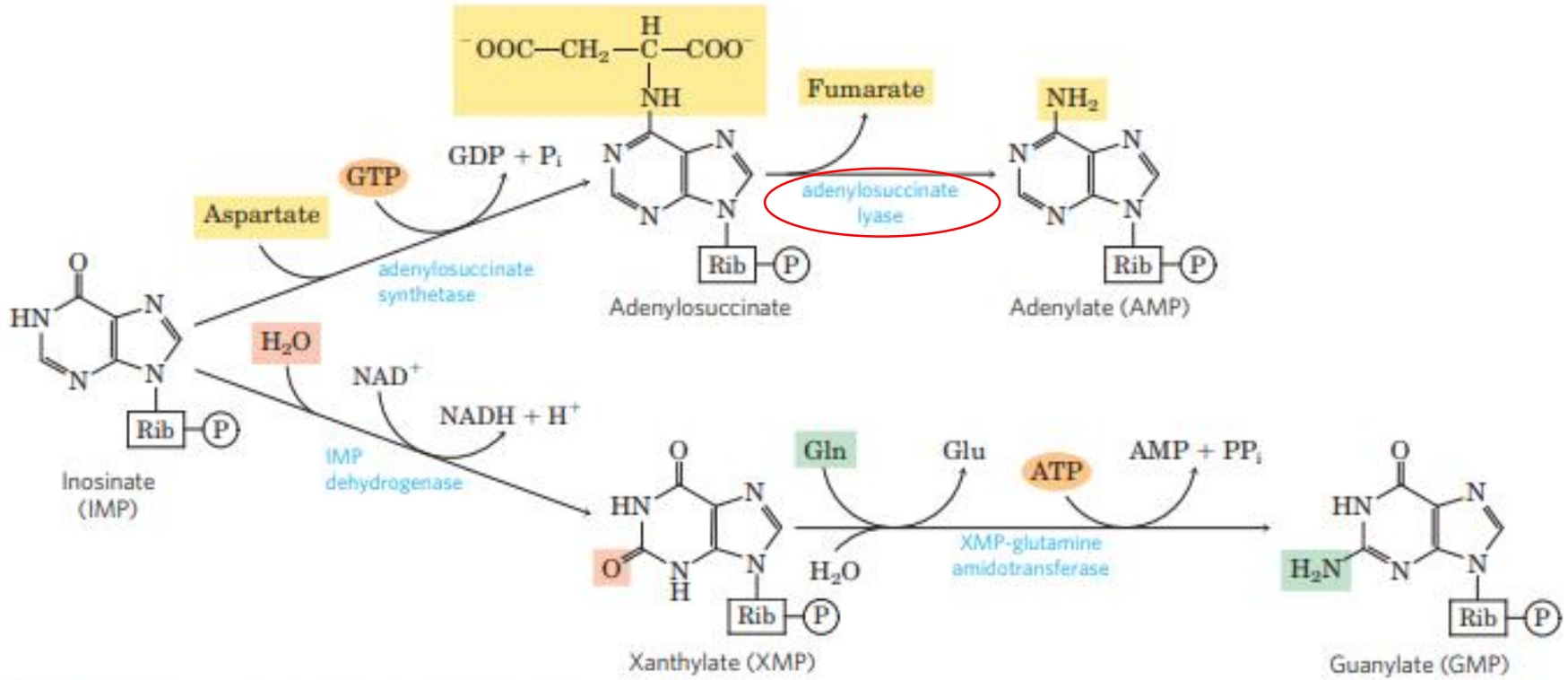


FIGURE 22–36 Biosynthesis of AMP and GMP from IMP.

Adenylosuccinate lyase deficiency is a neurological disorder that causes brain dysfunction (encephalopathy)

De novo Pyrimidine Nucleotides Biosynthesis

Byosynthesis is different from purine nucleotide synthesis.

Common pyrimidine ribonucleotides

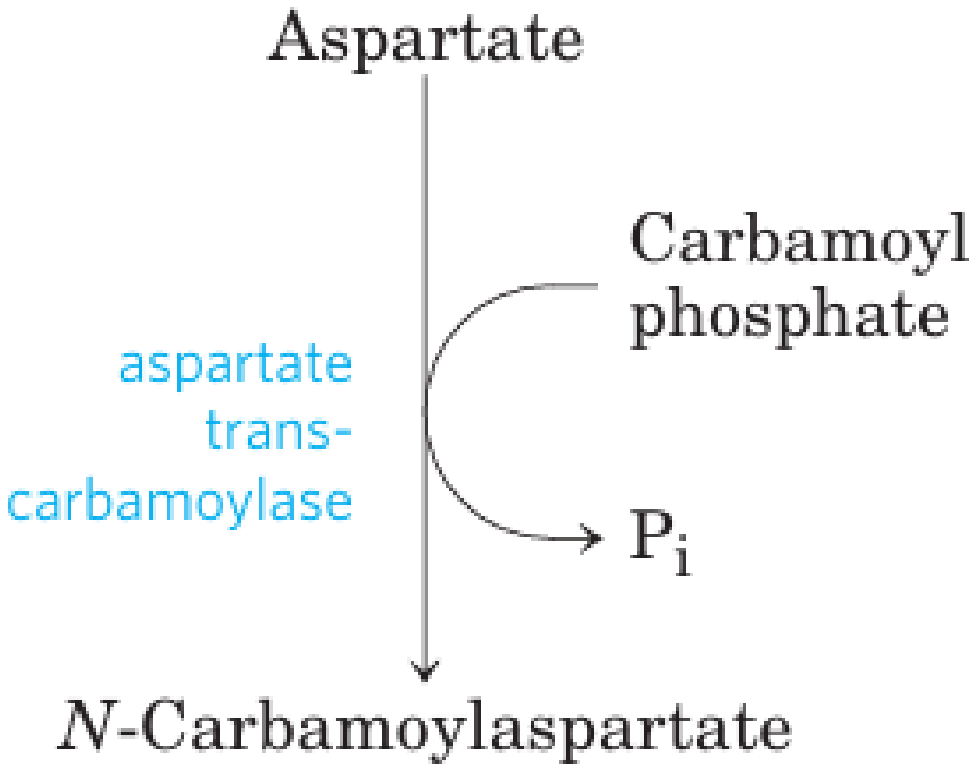
Cytidine 5’-monophosphate (CMP; cytidylate)
Uridine 5’-monophosphate (UMP; uridylate)

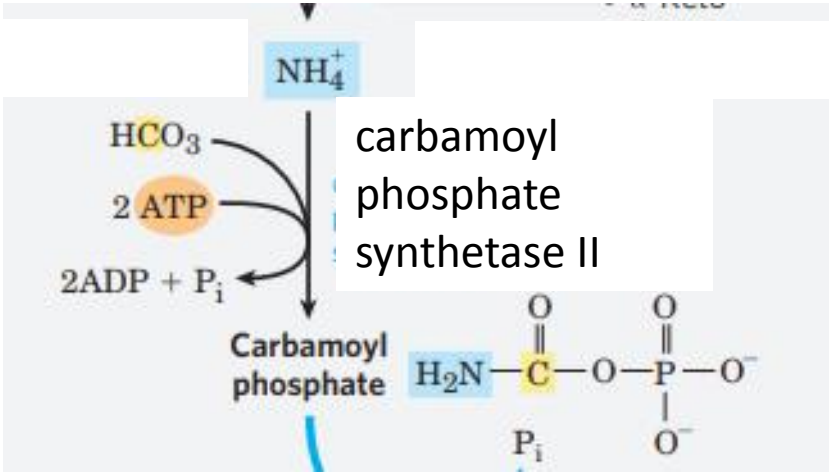
Cytosine
Uracil.

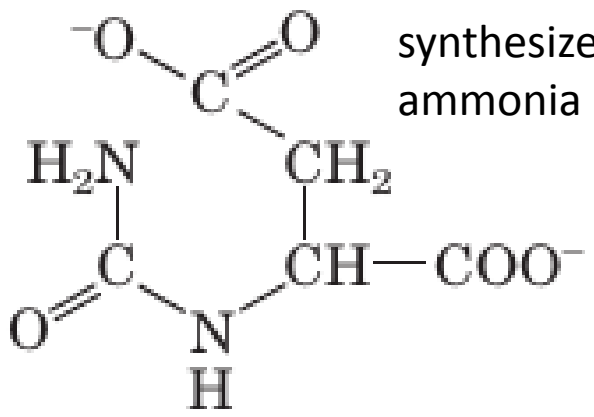
Aspartate, PRPP, and Carbamoyl Phosphate

Reaction 1:

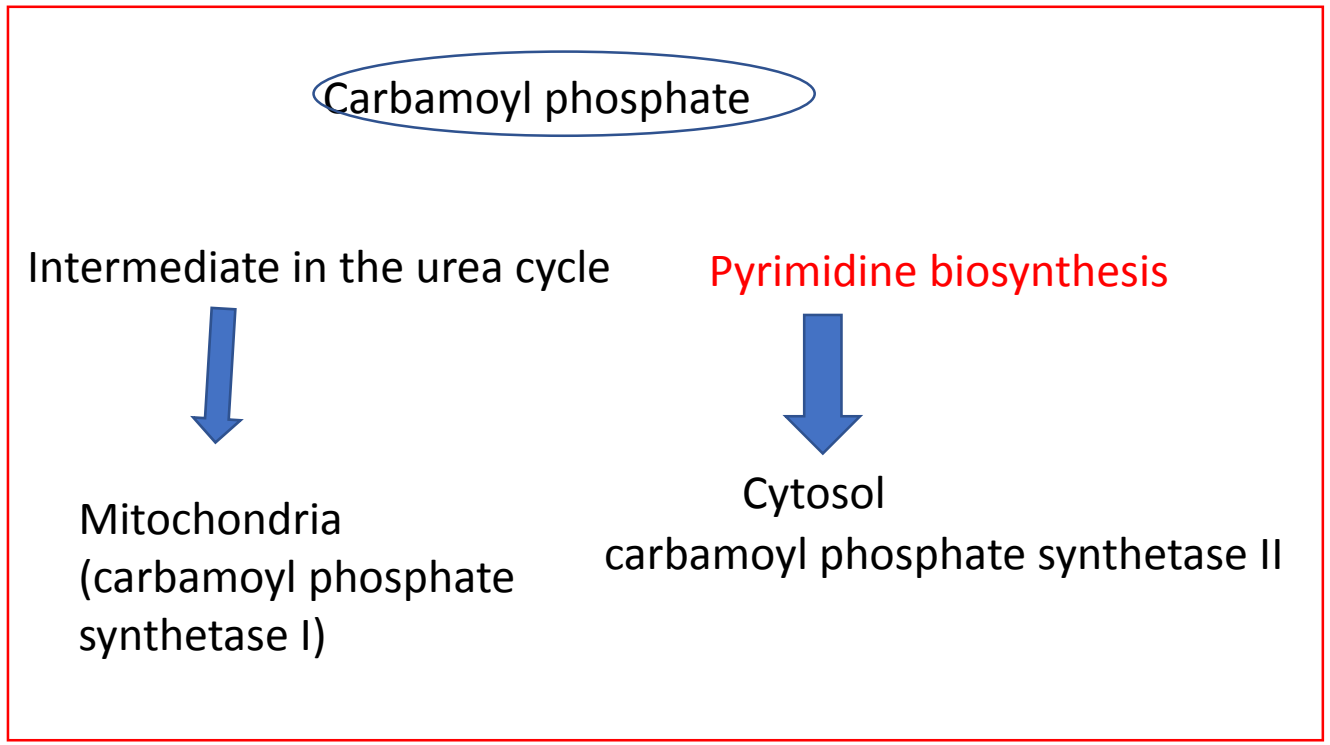
Carbamoyl phosphate reacts with aspartate to yield N-carbamoylaspartate



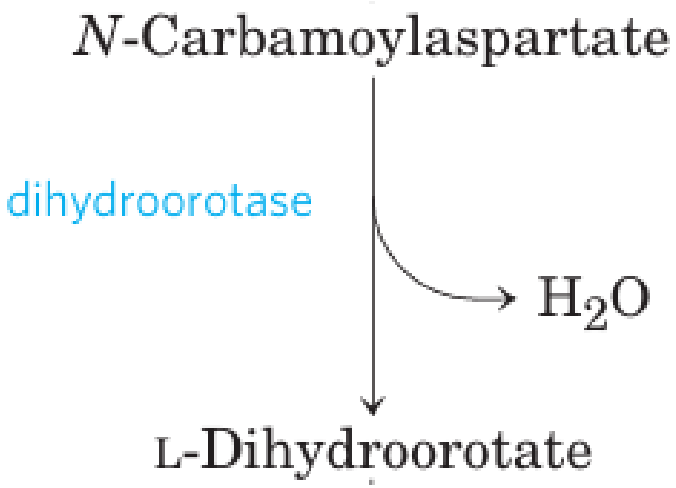


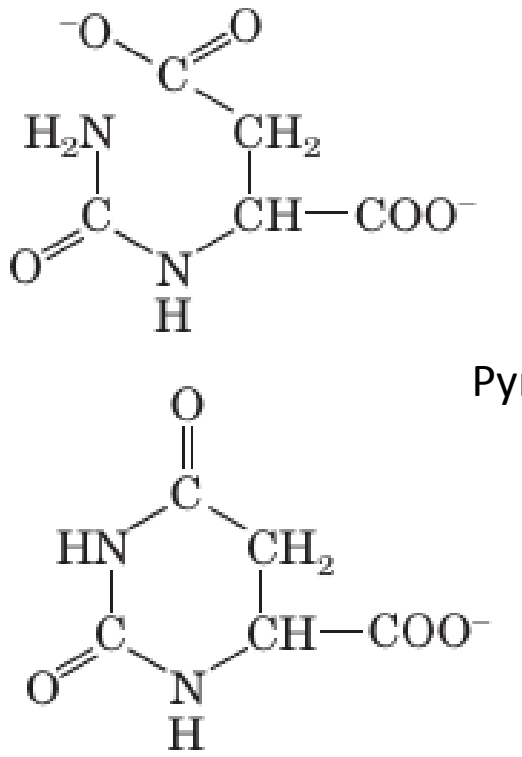


Carbarmoyl phosphate is synthesized from bacarbonate and ammonia


Carbamoyl phosphate
Intermediate in the urea cycle
Pyrimidine biosynthesis
Mitochondria
(carbamoyl phosphate
synthetase I)
Cytosol
carbamoyl phosphate synthetase II

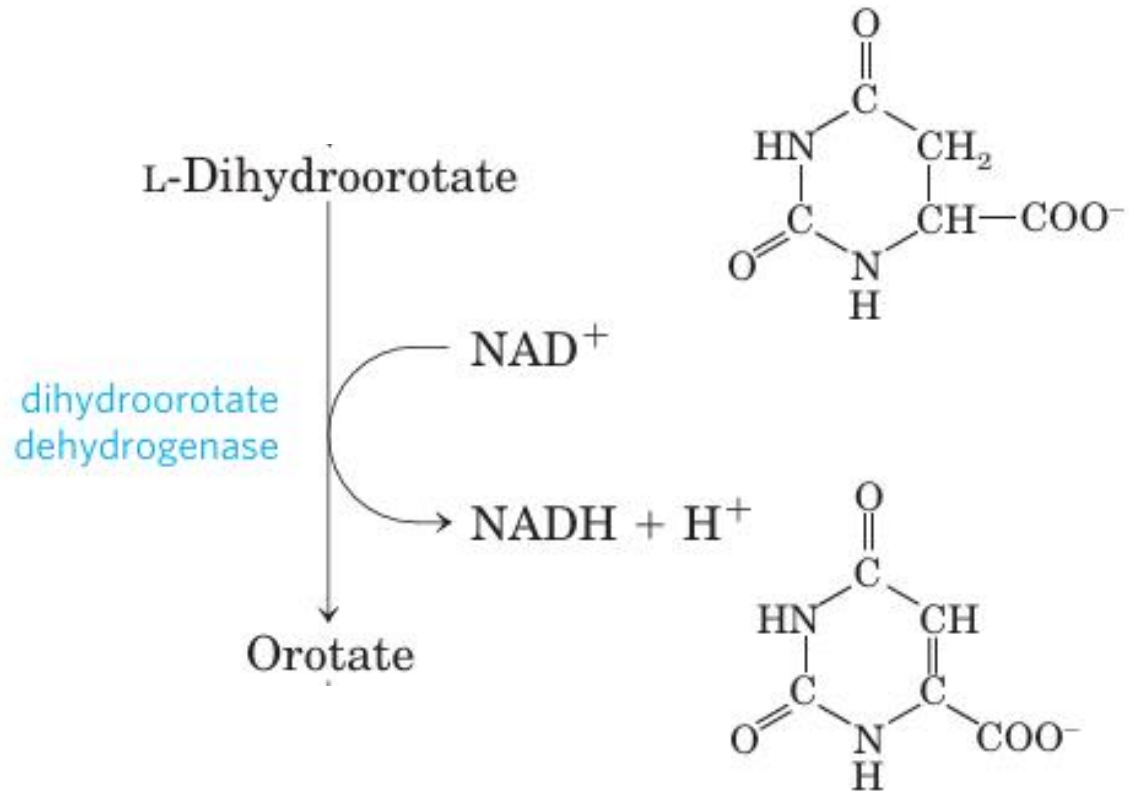
Reaction 2:
N-carbamoylaspartate, forms L-dihydroorotate by dihydroorotase,





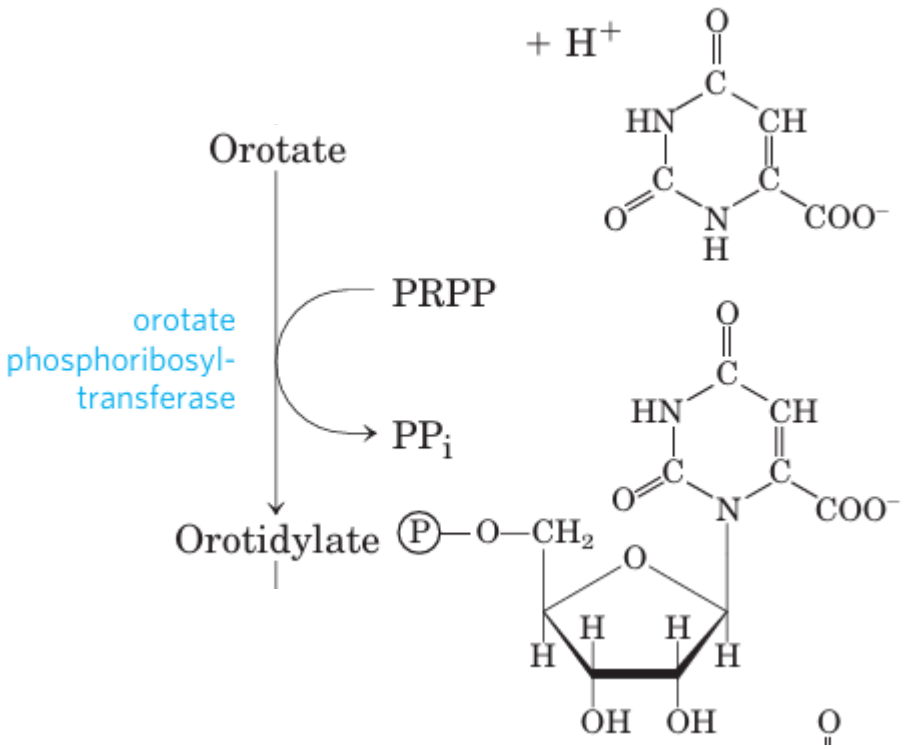
Pyrimidine ring is closed

Reraction 3:
Dihydroorotate is oxidized to the pyrimidine derivative orotate



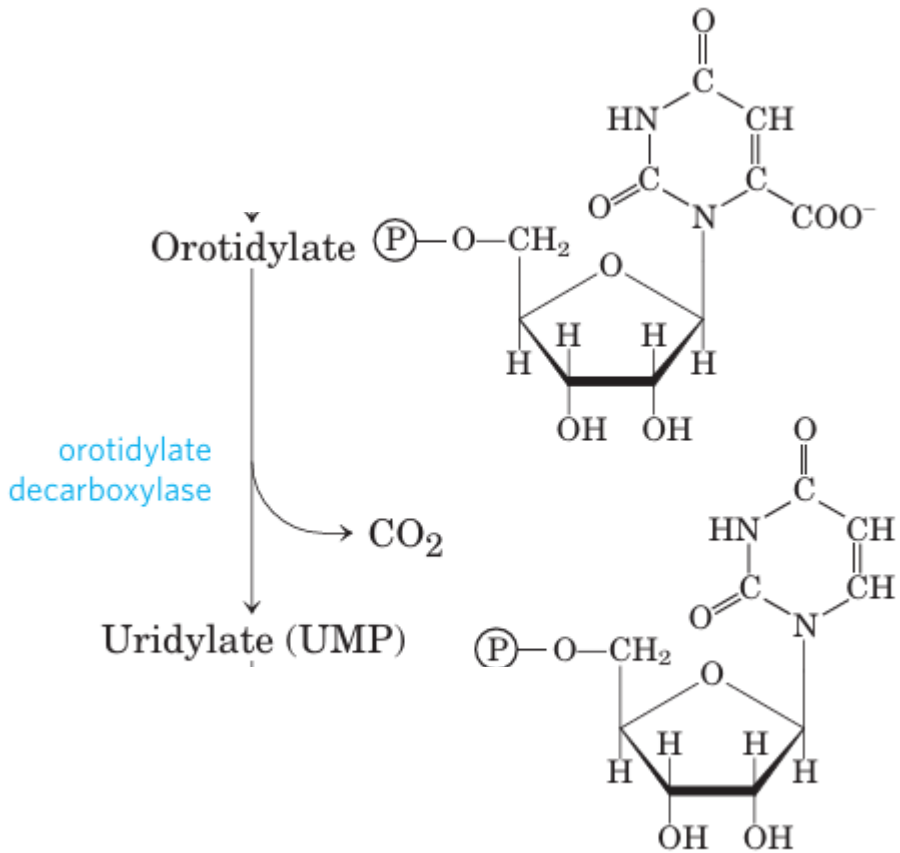
Reraction 4:

Orotate is converted to orotidylate



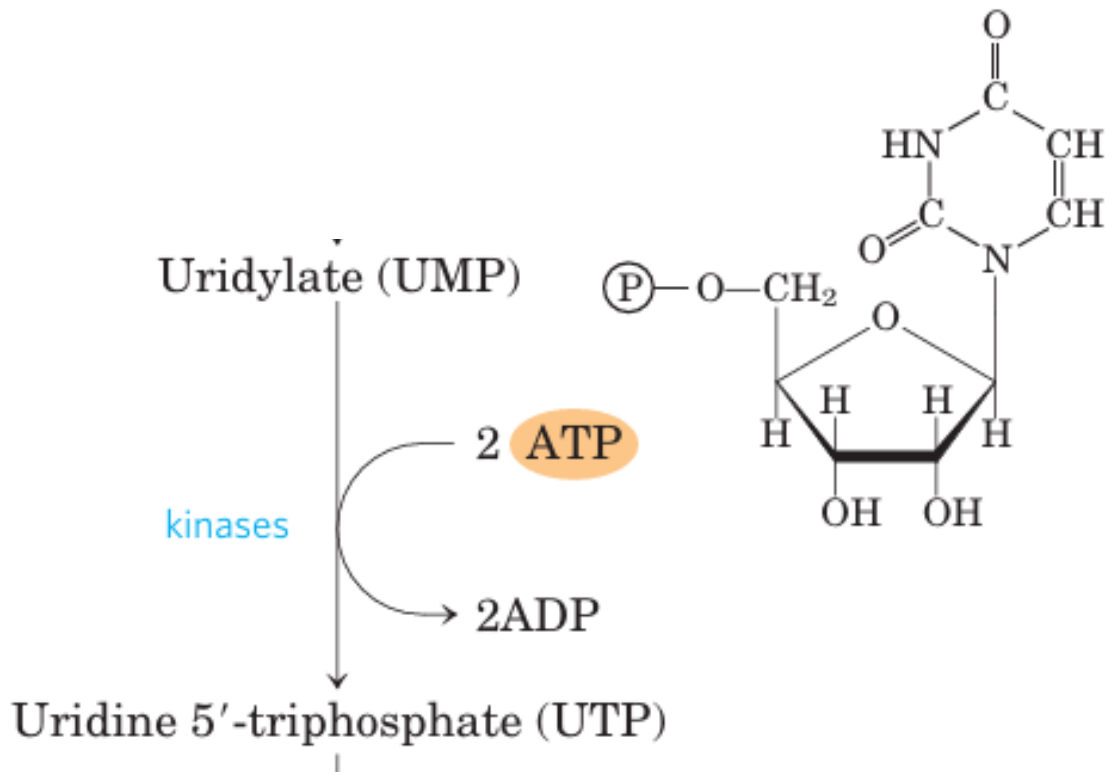
Reraction 5 :

Orotidylate is decarboxylated to uridylate by uridylate decarboxylase

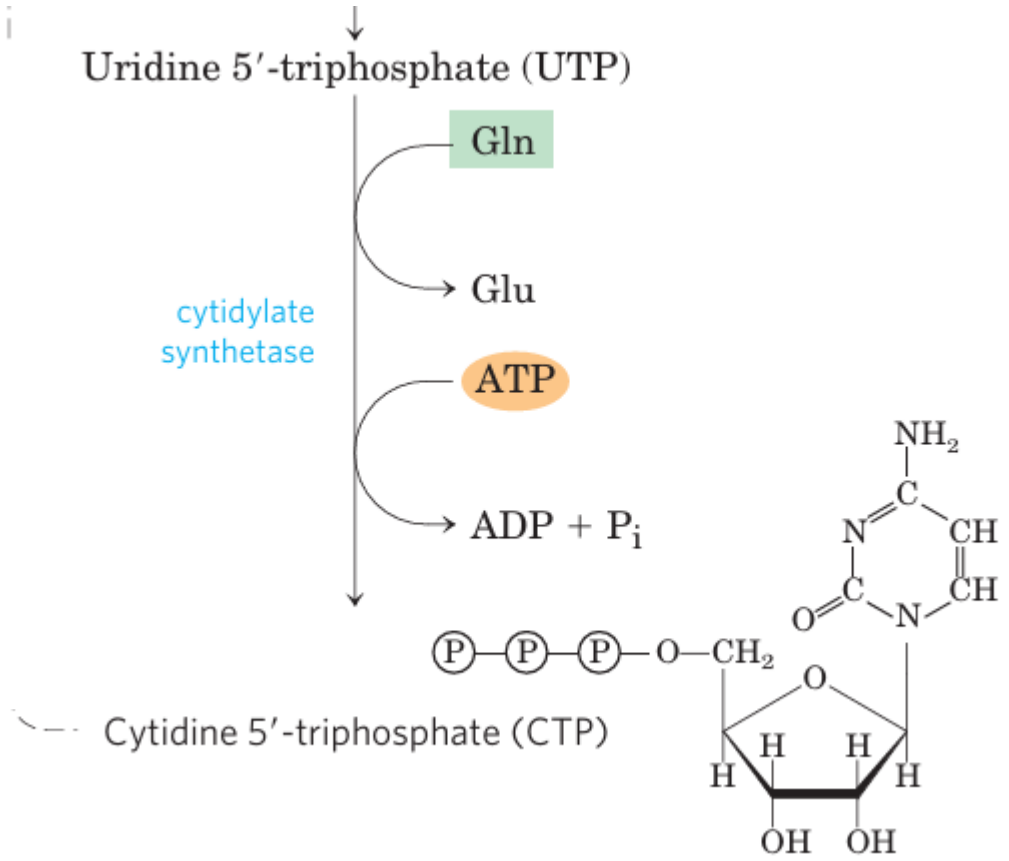


Reraction 6 :

Uridylate is phosphorylated to UTP by kinase



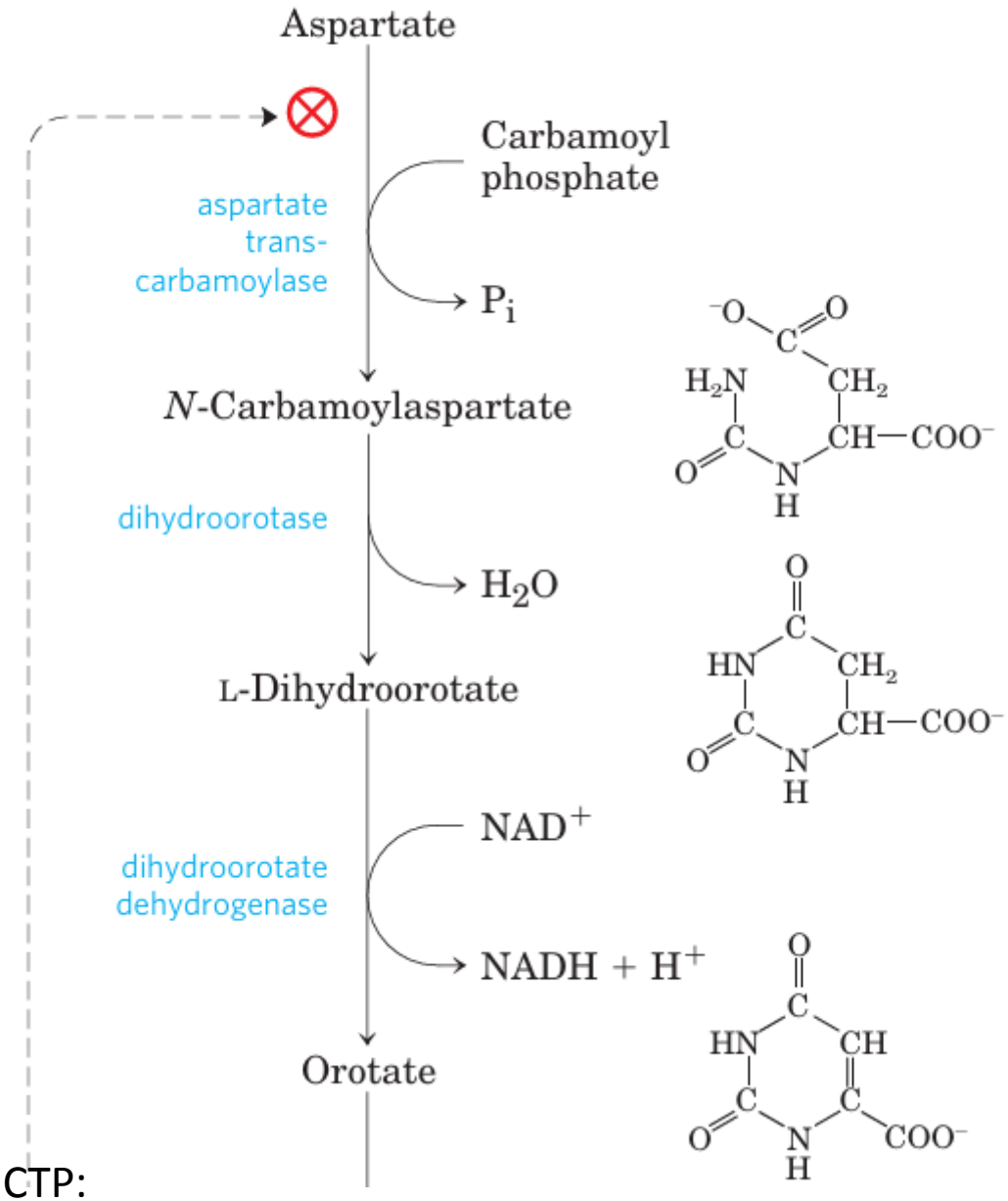
Reraction 7 : UTP is converted to CTP



In eukaryotes, the first three enzymes in this part of a single trifunctional protein.

1. Aspartate trans-carbamylase,
2. Dihydroorotase,
3. Orotase,

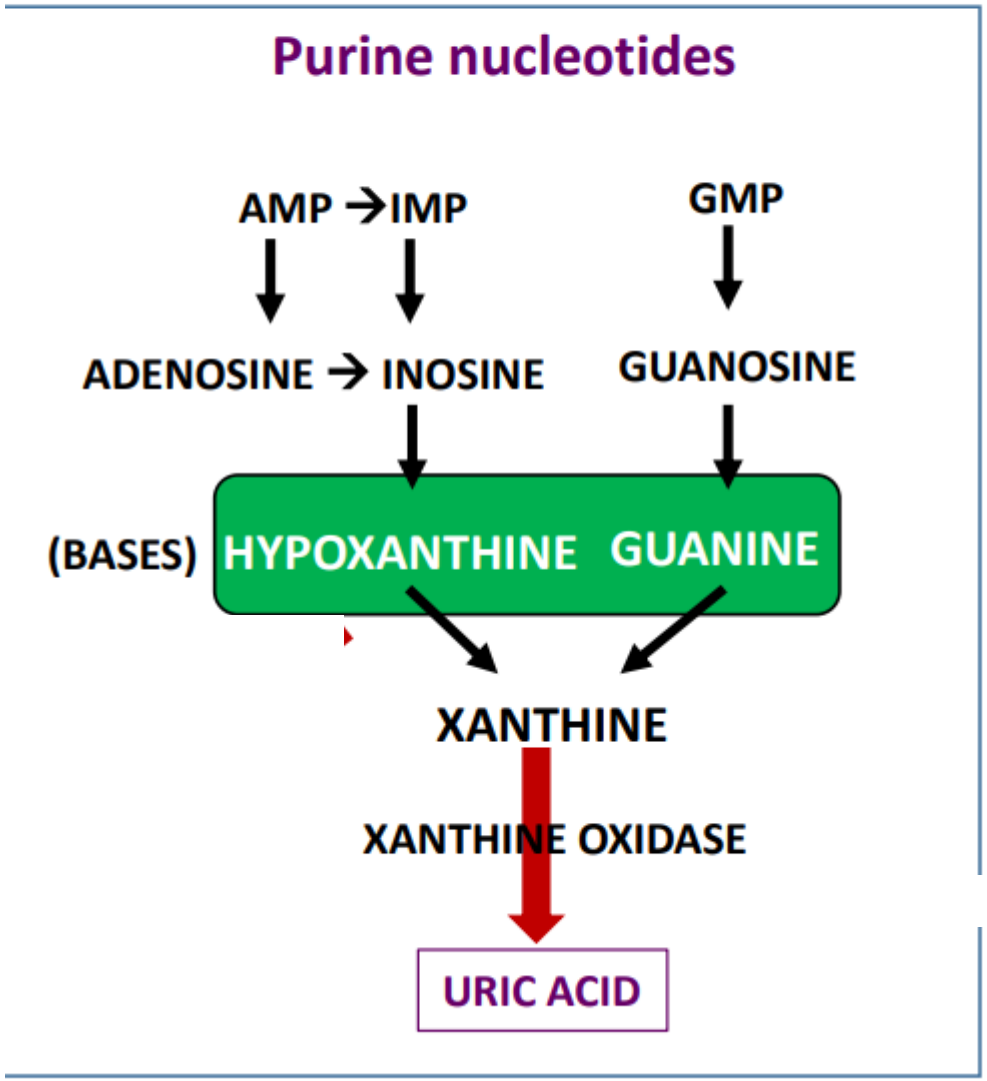
Pyrimidine Nucleotide Biosynthesis Is Regulated by Feedback Inhibition

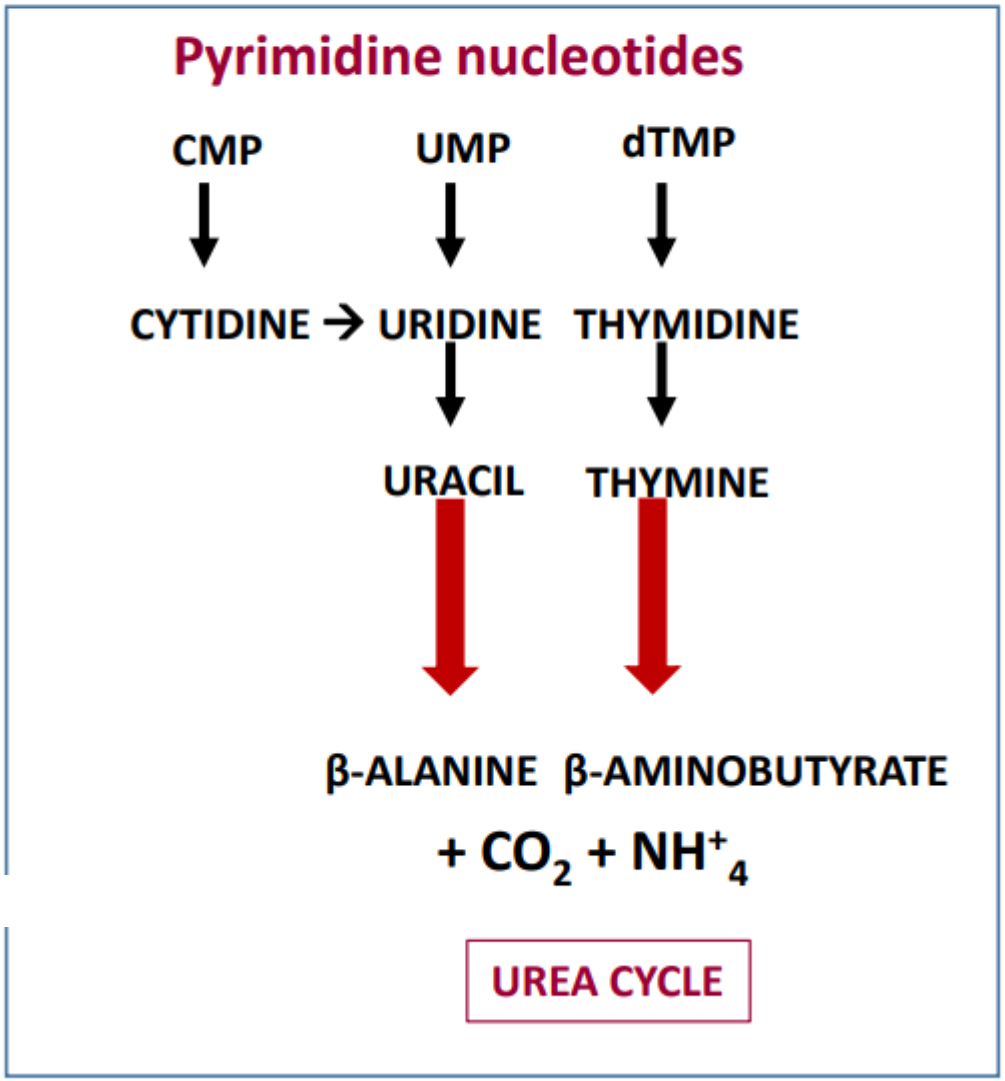


Inhibited from CTP:

Purines: These are degraded to uric acid. Uric acid is the final product of purine degradation. It enters the bloodstream and is excreted in urine.

Pyrimidines: These are completely degraded to β-alanine and β-aminobutyric acid to enter the urea cycle.





Excess of Uric Acid Causes Gout

A genetic deficiency of one or another enzyme of purine metabolism may also be a factor

Gout → elevated concentration of uric acid in the blood and tissues.

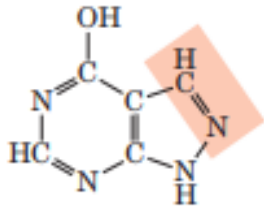
Abnormal deposition of sodium urate crystals

inflamed and arthritic joints

Kidneys → uric acid is deposited in the kidney tubules

Major incidence males. → cause is not known,

Gout is effectively treated by a combination of nutritional and drug therapies. →



Allopurinol

inhibits xanthine oxidase

(catalyzes the conversion of purines to uric acid