PYRIMIDINE SYNTHESIS

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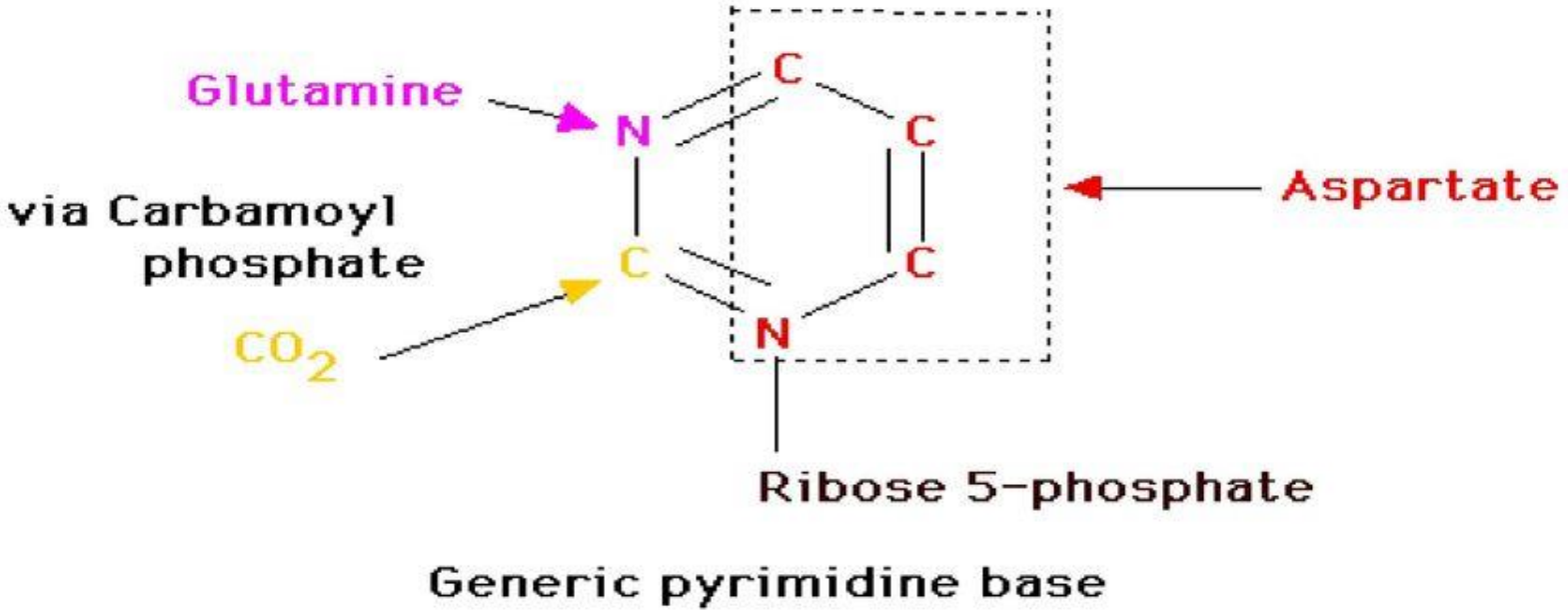
- Unlike purine ring, where the ring is constructed on a pre existing ribose-5-phosphate ring, the ring of pyrimidine is synthesized before being attached to ribose-5-phosphate which is provided by PRPP.
- Purine & pyrimidine nucleotide biosynthesis shares several common precursors

  like CO_2, Aspartate, glutamine, PRPP and tetra hydro folate.

Pyrimidine metabolism

Sources of carbon and nitrogen atoms in pyrimidine ring:

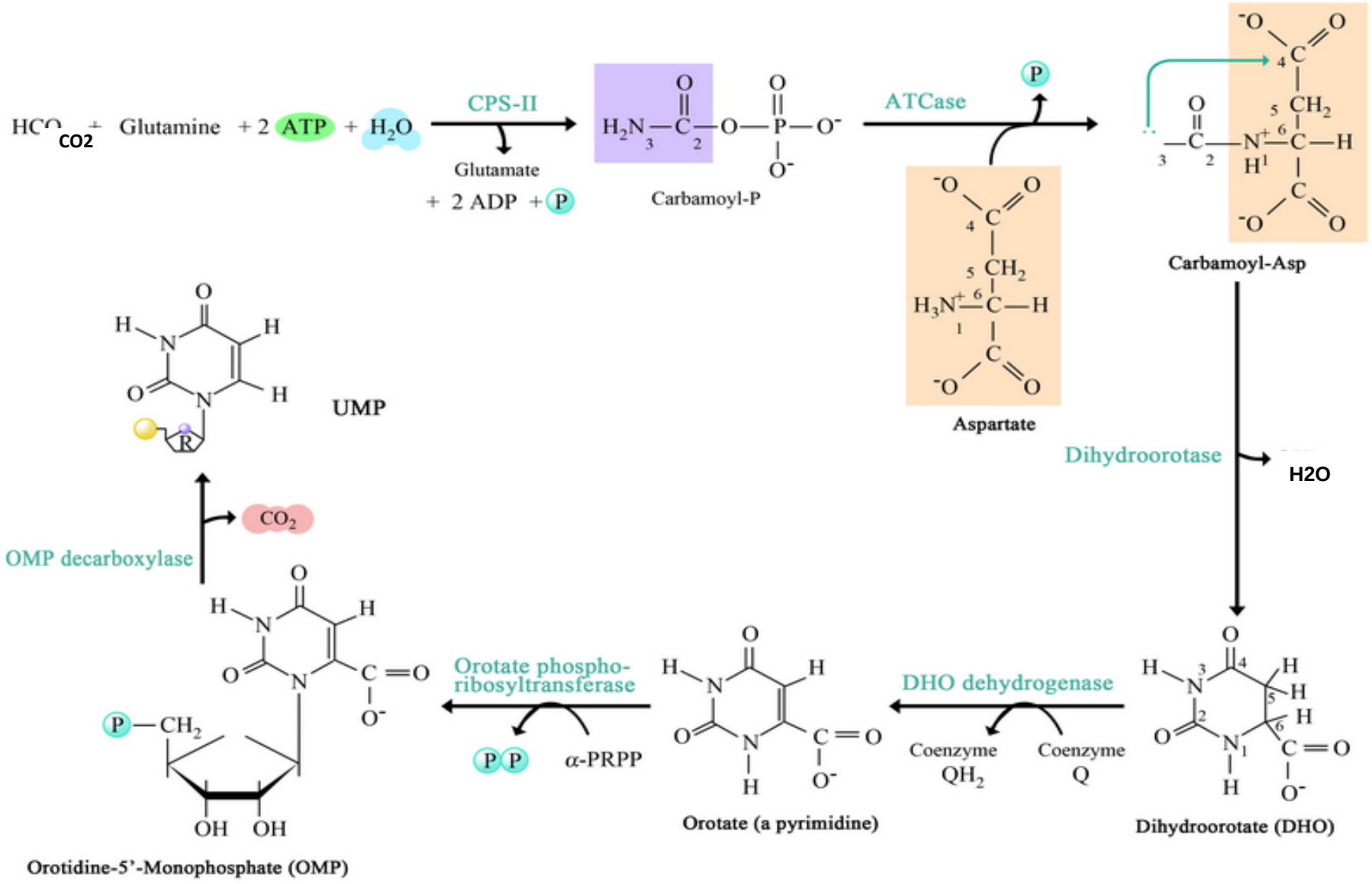


N_1, C_4, C_5 and C_6 → from aspartate

C_2 from CO_2

N_3 → from amide group of glutamine

Biosynthesis of Pyrimidine



1. The first three enzymes of the cycle are domains of single polypeptide chain (CAD).
2. Orotate phosphoribosyl Transferase and OMP decarboxylase are domains of single Polypeptide chain (Di functional enzyme).

Dihydro-orotate Dehydrogenase

- Is the only mitochondrial enzyme of the cycle .
- Contain FMN, FAD, Fe, S as Prosthetic group and require NAD as Coenzyme

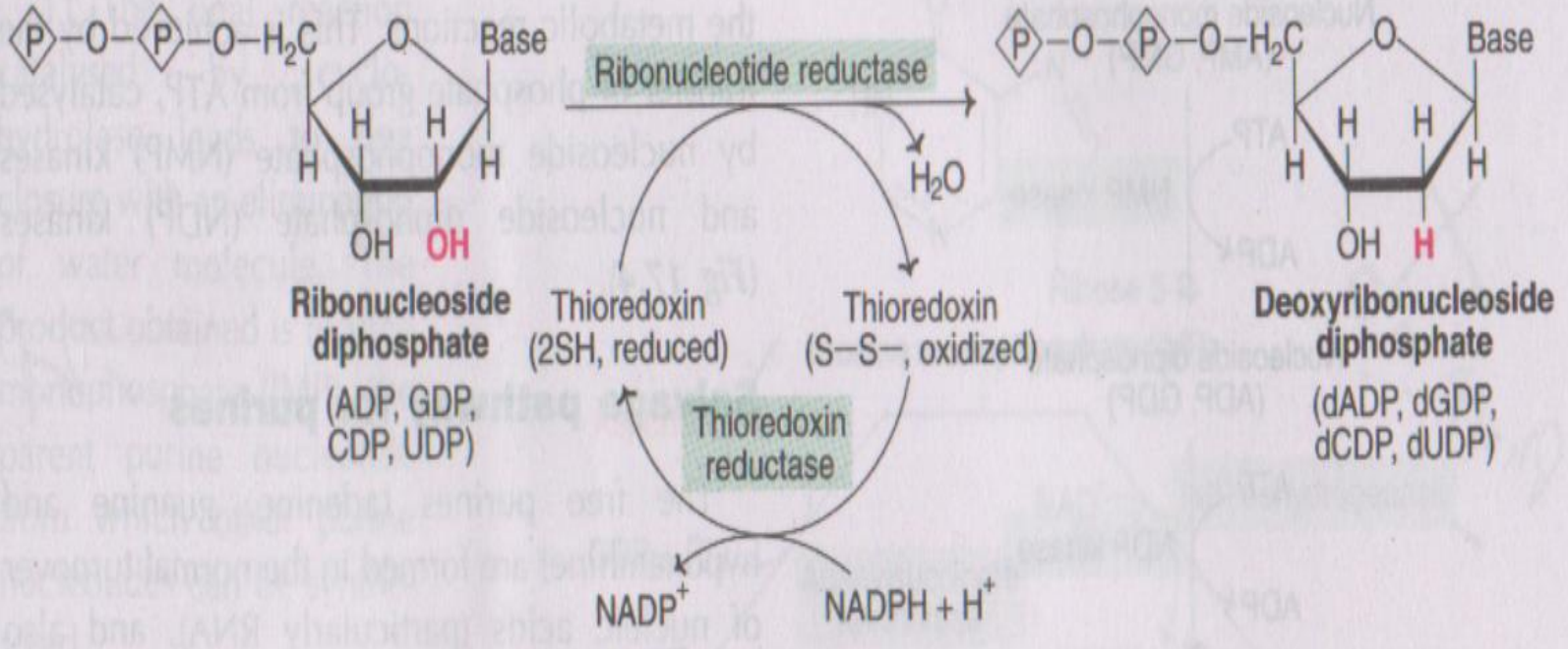
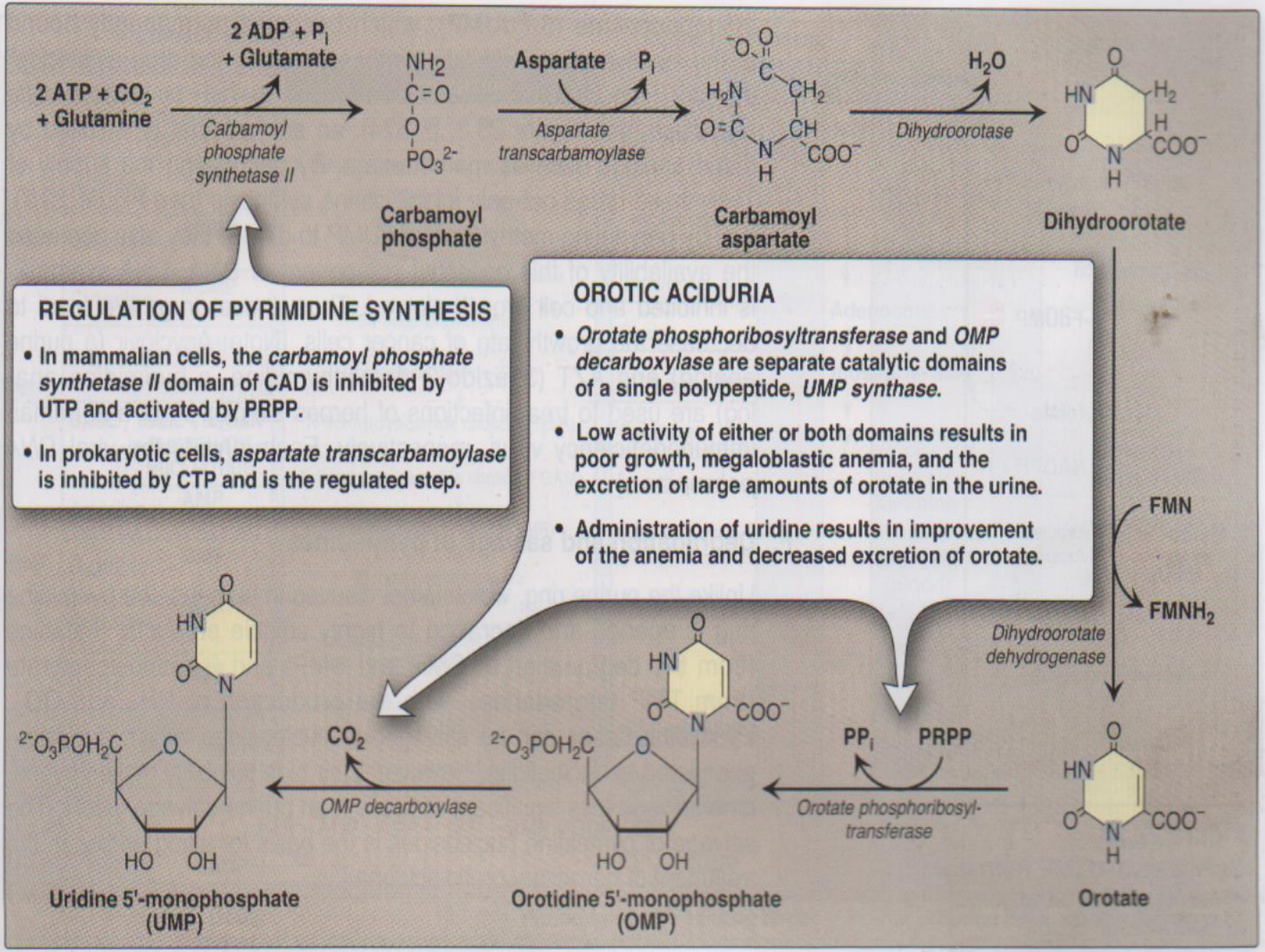


Fig. 17.6 : Formation of deoxyribonucleotides from ribonucleotides.

Ribonucleotide reductase catalyzes the addition of hydrogen atoms needed for reduction from the sulfhdryl groups of thioredoxin.


2 ATP + CO_2 + Glutamine
2 ADP + P_i + Glutamate
Carbamoyl phosphate synthetase II
Carbamoyl phosphate
Aspartate
P_i
Aspartate transcarbamoylase
Carbamoyl aspartate
H_2O
Dihydroorotase
Dihydroorotate
REGULATION OF PYRIMIDINE SYNTHESIS
• In mammalian cells, the carbamoyl phosphate synthetase II domain of CAD is inhibited by UTP and activated by PRPP.
• In prokaryotic cells, aspartate transcarbamoylase is inhibited by CTP and is the regulated step.
OROTIC ACIDURIA
• Orotate phosphoribosyltransferase and OMP decarboxylase are separate catalytic domains of a single polypeptide, UMP synthase.
• Low activity of either or both domains results in poor growth, megaloblastic anemia, and the excretion of large amounts of orotate in the urine.
• Administration of uridine results in improvement of the anemia and decreased excretion of orotate.
FMN
$FMNH_2$
Dihydroorotate dehydrogenase
CO_2
OMP decarboxylase
PP_i
PRPP
Orotate phosphoribosyl-transferase
Uridine 5'-monophosphate (UMP)
Orotidine 5'-monophosphate (OMP)
Orotate

Orotic Aciduria

Mainly of two types

Type-1. **Orotate phosphoribosyl transferase** and **OMP decarboxylase**(Both) are deficient.

- Results in accumulation of orotate in blood & urine causing growth retardation .Megaloblastic anaemia.

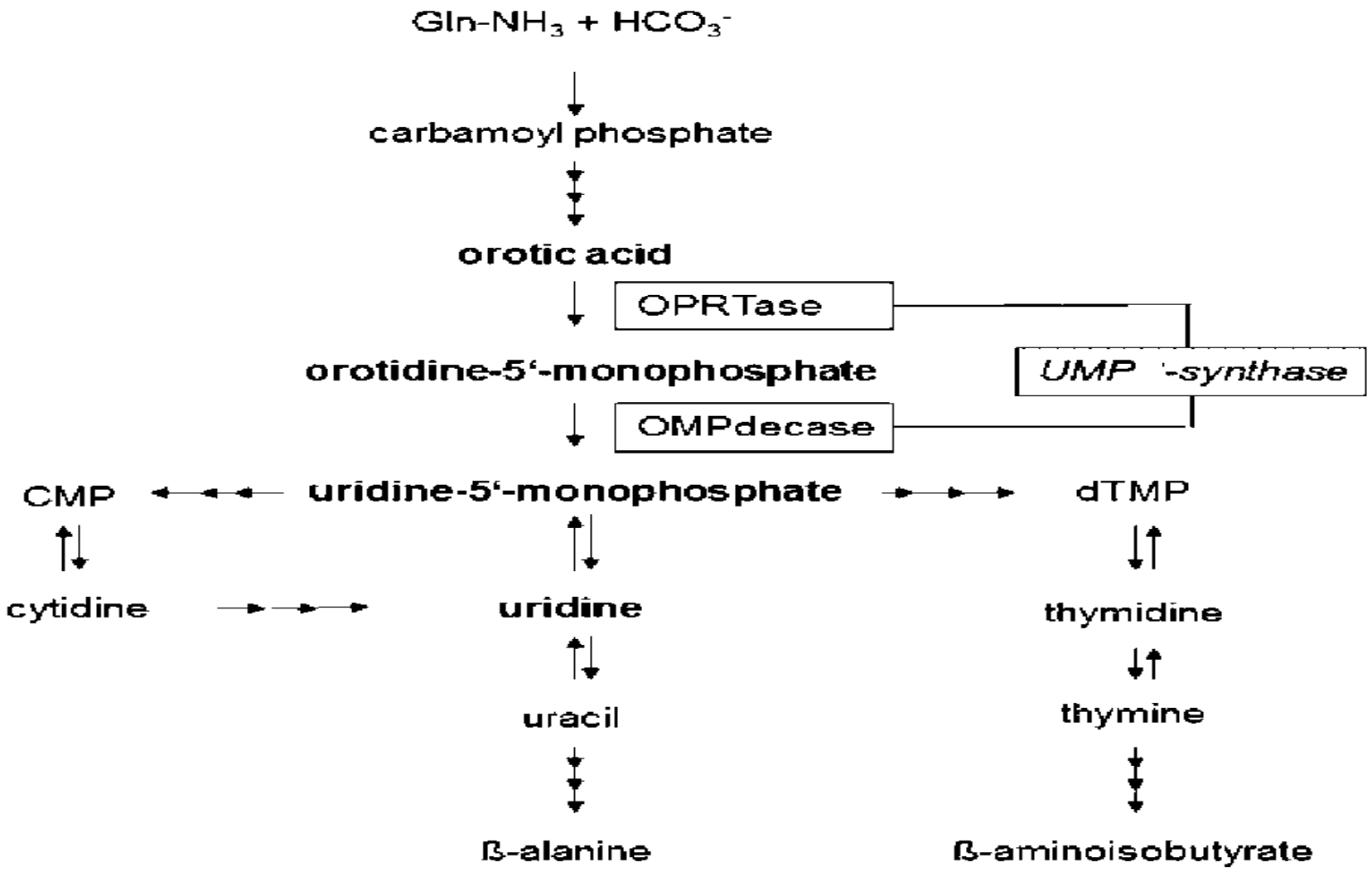
Type-2: Deficiency of **OMP decarboxylase**

- Megaloblastic aneamia.
- **Unresponsive to vitamin B12 & folic acid**

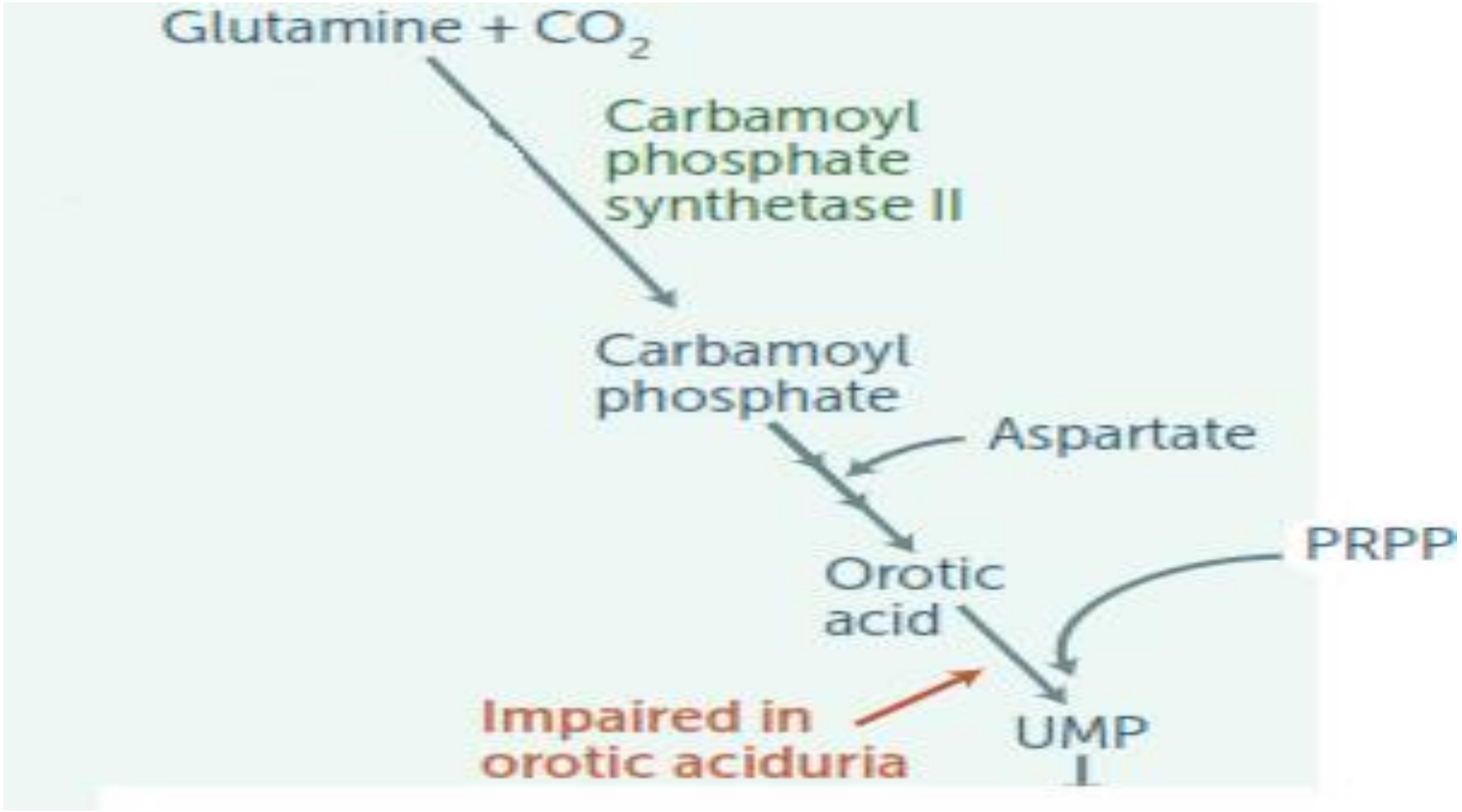
Orotic aciduria

- Mutation of one of the two enzyme activities of UMP synthase leads to orotic aciduria, characterized by accumulation of its first substrate orotic acid and insufficient levels of the product UMP,
- which reduces availability of uridine triphosphate (UTP) and cytidine triphosphate (CTP) for use in nucleic acid synthesis.
- • Patients with orotic aciduria excrete large amounts of orotic acid in their urine, and they exhibit lethargy, weakness, severe anemia, and growth retardation.
- • This autosomal recessive disorder can be treated by feeding a diet rich in uridine, which is salvaged to UMP and finally to UTP.

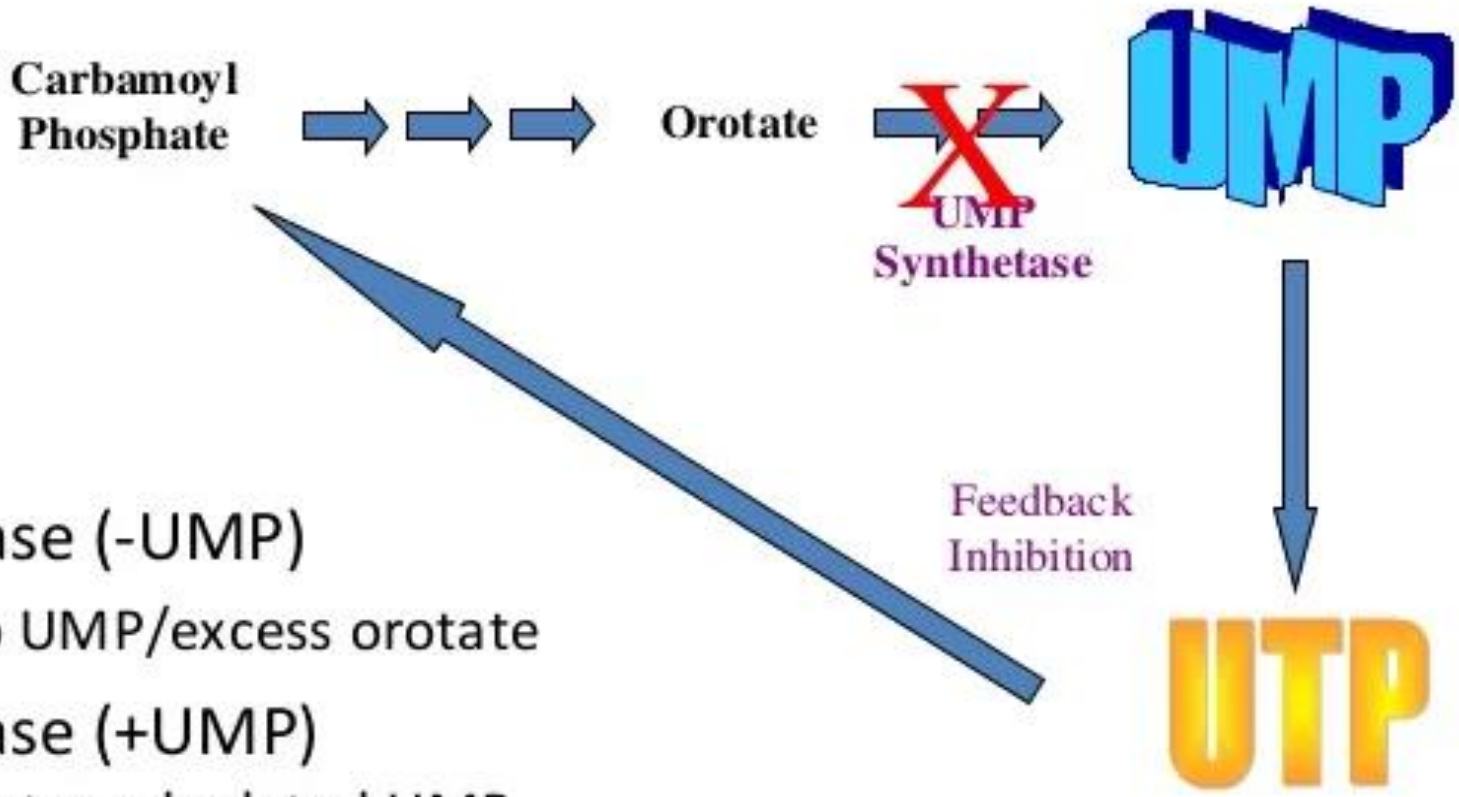
Orotic aciduria



Orotic Aciduria



Why does UMP Cure Orotic Aciduria?



- Disease (-UMP)
  - No UMP/excess orotate
- Disease (+UMP)
  - Restore depleted UMP
  - Downregulate pathway via feedback inhibition (Less orotate)

Other causes of orotic Aciduria

1. Reye syndrome------
   Damaged mitochondria
2. Deficiency of urea cycle enzyme i.e
   Ornithine transcarbamyolase.
3. Drugs, e.g Allopurinol and 6-
   Azauridine.

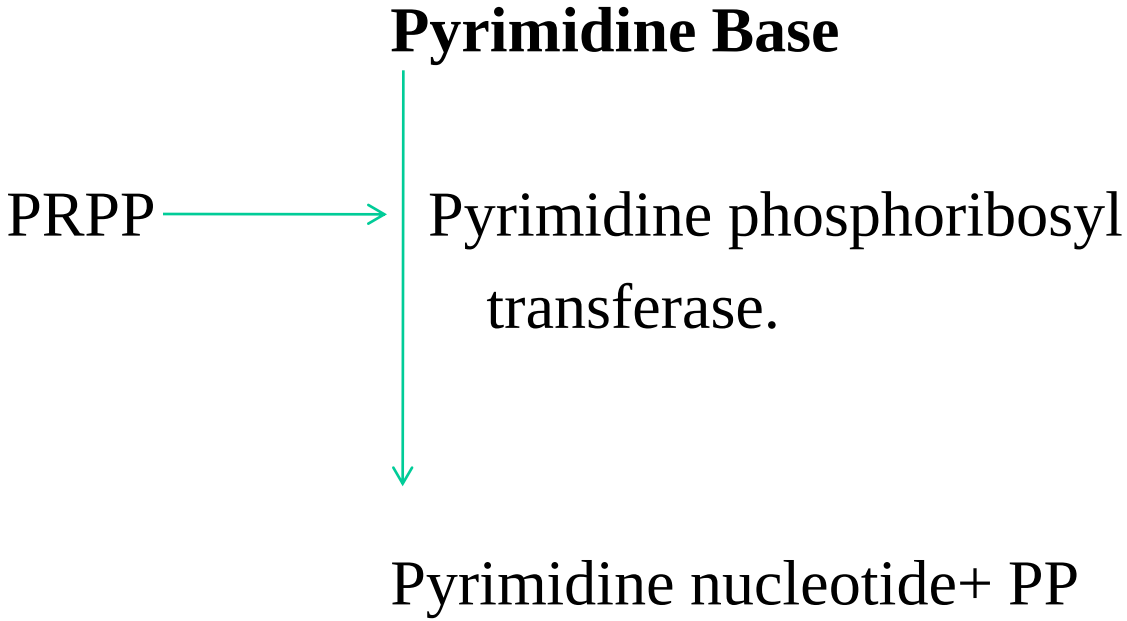
Other Causes of Orotic Aciduria

1. **Orotic aciduria that accompanies *Reye Syndrome*:** Probably is a consequence of the inability of severely damaged mitochondria to utilise carbamoyl phosphate, which then becomes available for *cytosolic overproduction of orotic acid.*
2. **Associated with deficiency of urea cycle enzyme:** Increased excretion of orotic acid, uracil and uridine, sometimes accompanies a deficiency of liver mitochondrial *ornithine transcarbamoylase.*

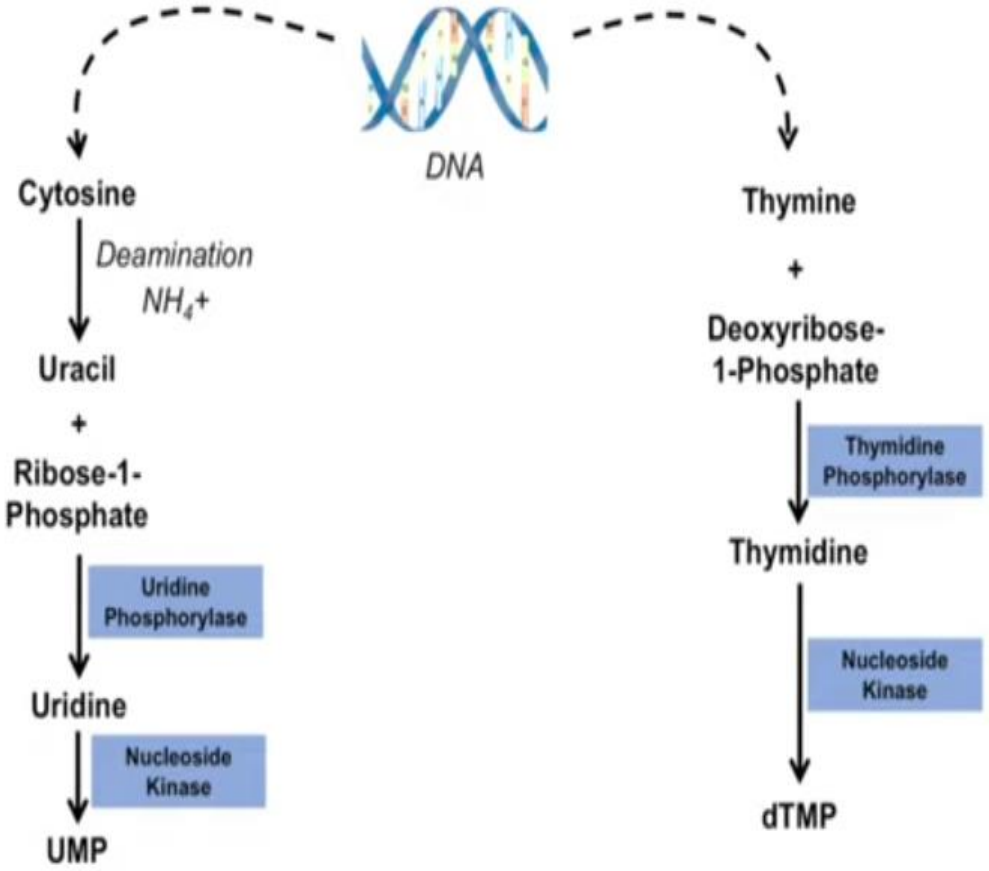
3. **Drug Related Orotic Aciduria**
   - *Allopurinol:* Allopurinol an alternative substrate for **orotate phosphoribosyl transferase** *competes with orotic acid. The resulting nucleotide product also inhibits* **orotidylate decarboxylase** *resulting in orotic aciduria and orotidinuria.*
   - *6-Azauridine:* 6-Azauridine, following its conversion to 6-azauridylate, also competively inhibits *orotidylate decarboxylase* resulting to increased excretion of orotic acid (orotic aciduria) and orotidine (orotidinuria).

PYRIMIDINE BASE SALVAGE

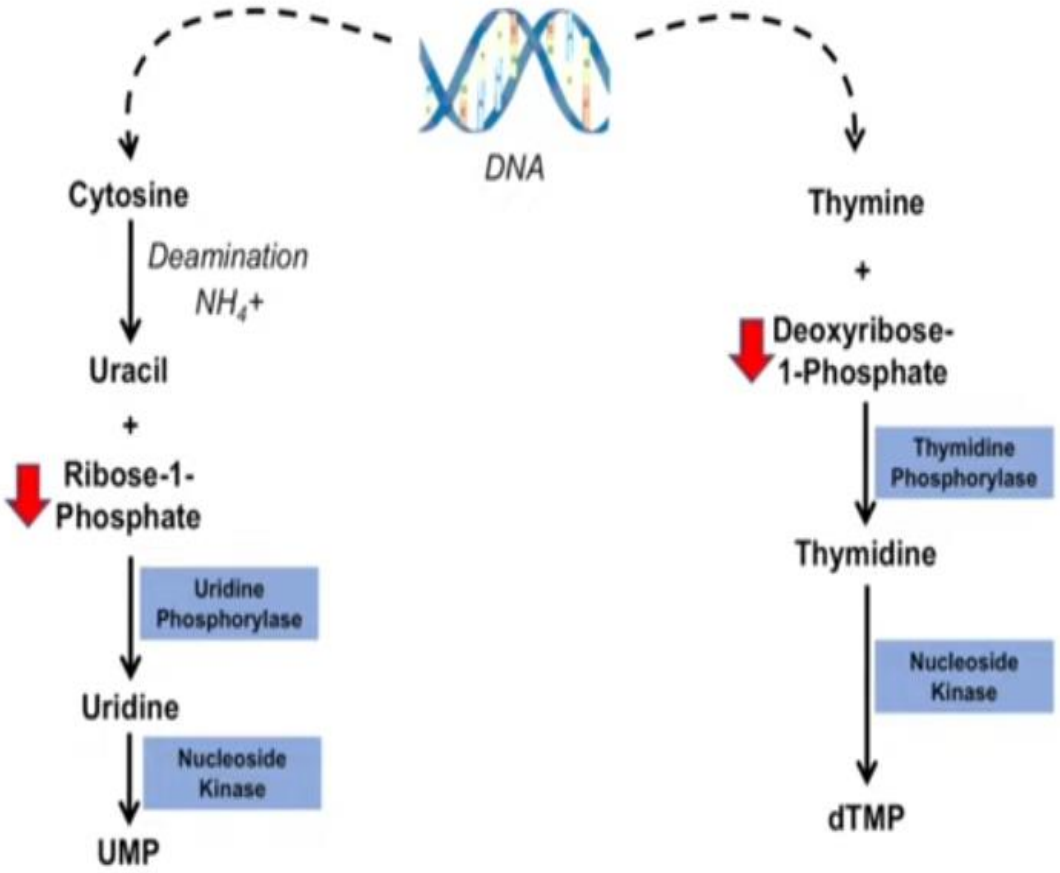
- The enzyme pyrimidine phosphoribosyl transferase catalyzes the formation of pyrimidine nucleotide, using PRPP as the donor of ribosyl moiety.



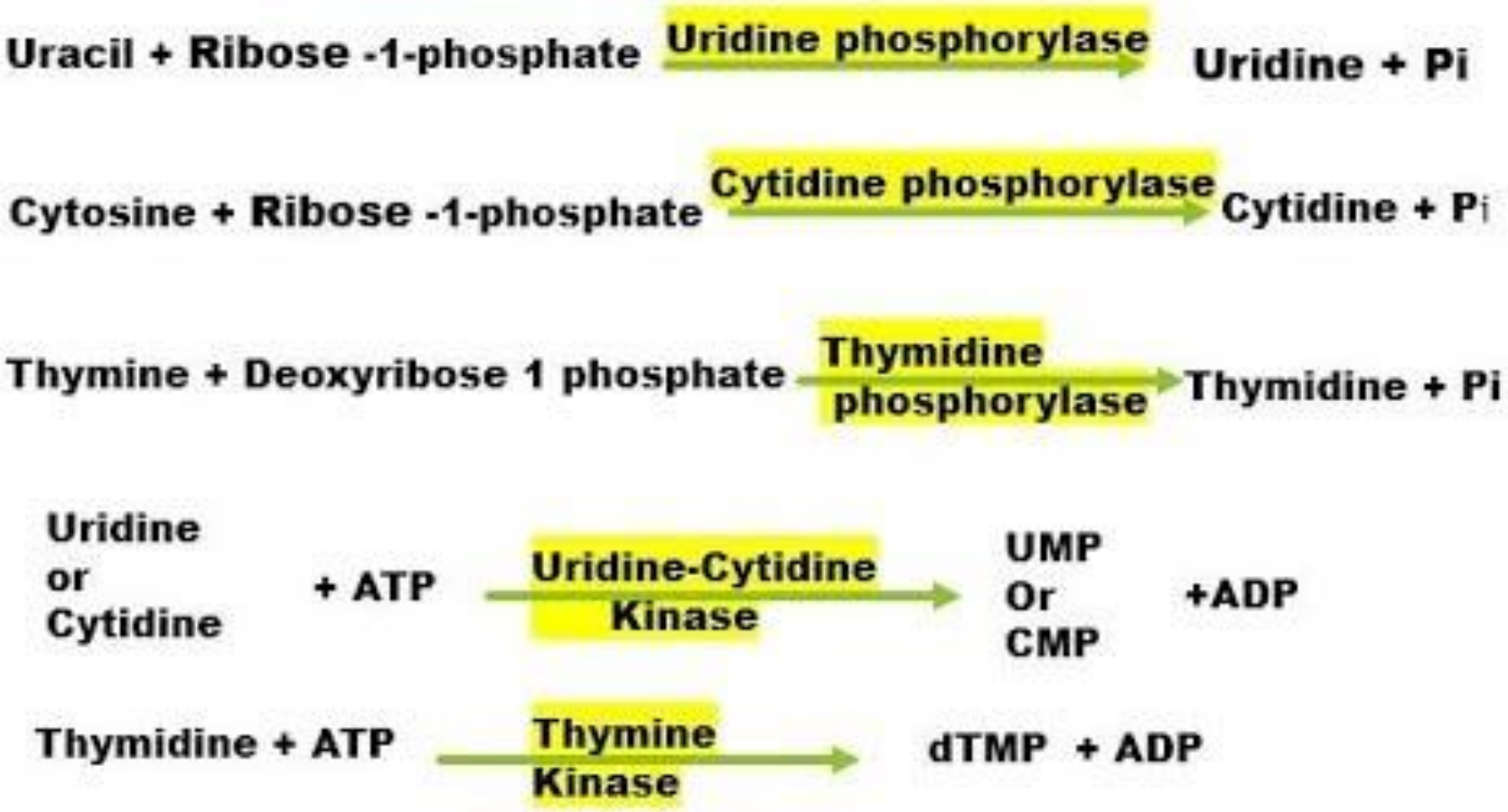
Pyrimidine Salvage Pathway



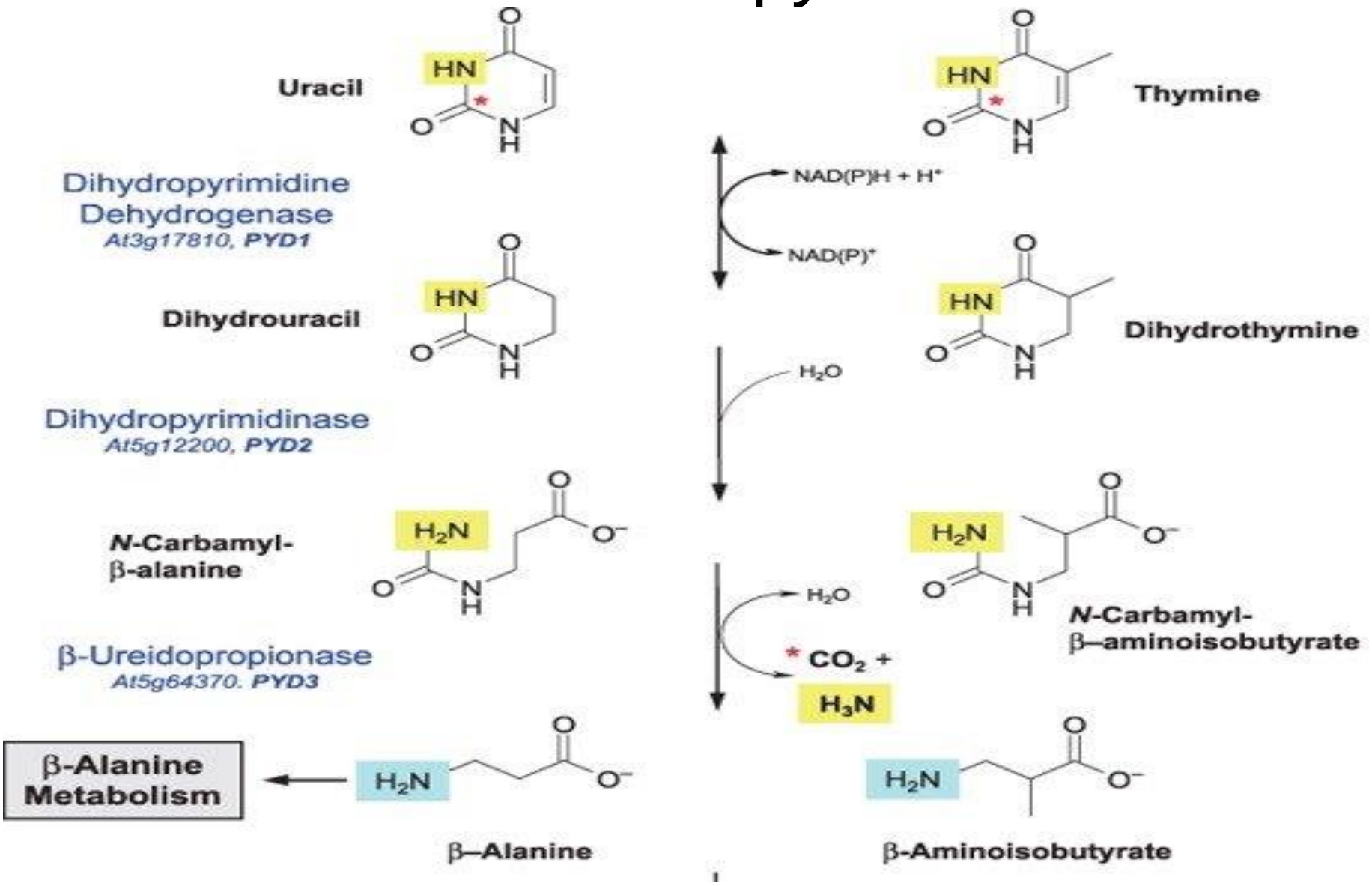
Pyrimidine Salvage Pathway



SALVAGE OF PYRIMIDINES



Catabolism of pyrimidine



Thank you