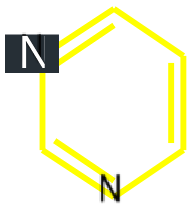
Biosynthesis of purine and pyrimidine nucleotides

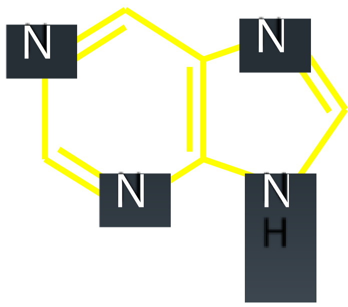
INTRODUCTION

Pyrimidine and purine are the names of the parent compounds of two types of nitrogen-containing heterocyclic aromatic compounds

Adenine and guanine are the principal purines of both DNA and RNA

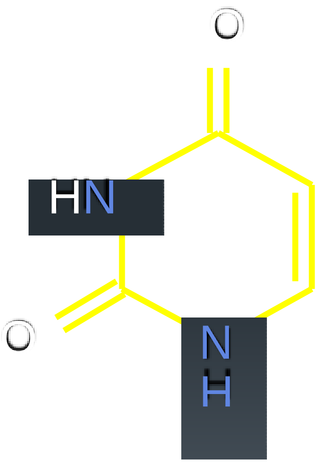
Caffeine (coffee) and theobromine (cocoa) are naturally occurring purines.



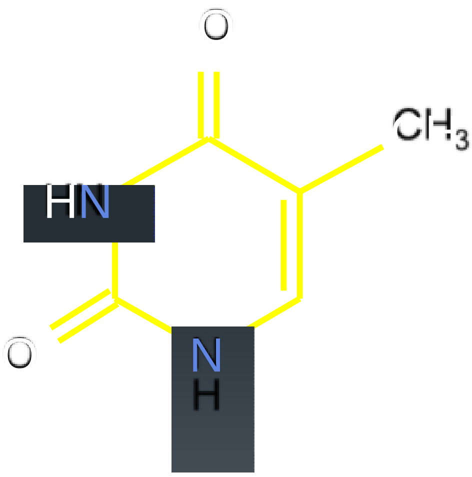


Adenine **Guanine**

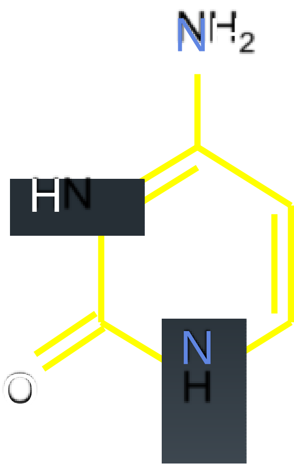
Pyrimidines that occur in DNA are cytosine and thymine. Cytosine and uracil are the pyrimidines in RNA



Uracil



Thymine



Cytosine

Nucleosides and Nucleotides :

Nucleoside is a structure formed by the combination of nitrogen base and sugar where as Nucleotides are phosphoric acid esters of nucleosides.

N2 base	Sugars	Nucleoside
Adenine	Deoxyribose/ Ribose	Adenosine
Guanine	Deoxiribose/ Ribose	Guanosine
Thymine	Deoxyribose	Thymidine
Cytosine	Deoxyribose/ Ribose	Cytidine
Uracil	Ribose	Uridine

Nucleoside	Phosphoric acid	Nucleotides
Adenosine	Phosphoric acid	Adenylate (AMP)
Guanosine	Phosphoric acid	Guanylate (GMP)
Thymidine	Phosphoric acid	Thymidylate (TMP)
Cytidine	Phosphoric acid	Cytidylate (CMP)
Uridine	Phosphoric acid	Uridylate (UMP)

In biosynthesis, simple compounds are modified, converted into other compounds, or joined together to form macromolecules.
This process often consists of metabolic pathways.

The purines are built upon a pre-existing ribose 5- phosphate.

Liver is the major site for purine nucleotide synthesis.

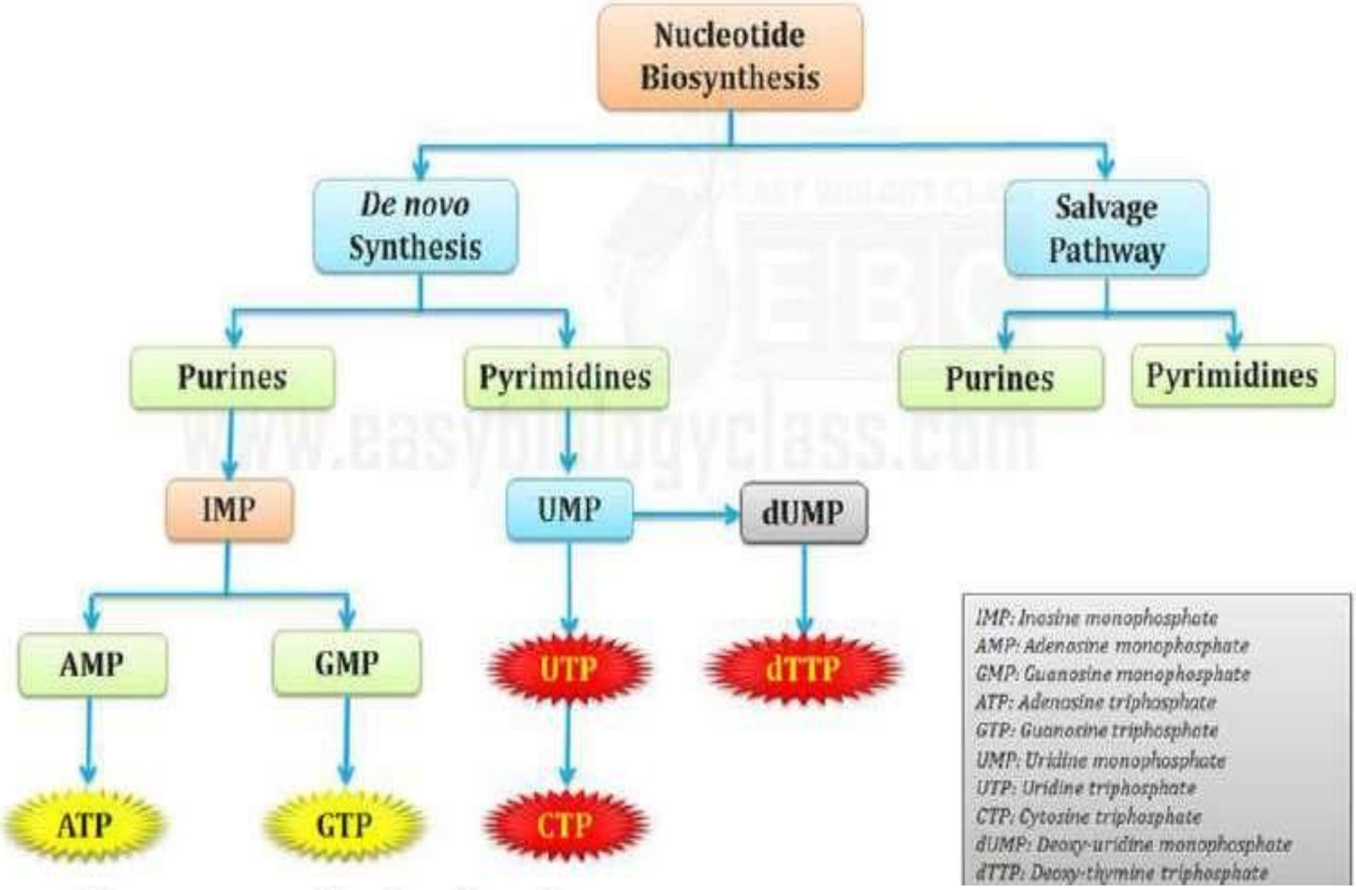
PATHWAY

There are Two pathways for the synthesis of nucleotides:

- **De-novo synthesis:** Biochemical pathway where nucleotides are synthesized from new simple precursor molecules
- **Salvage pathway:** Used to recover bases and nucleotides formed during the degradation of RNA and DNA.

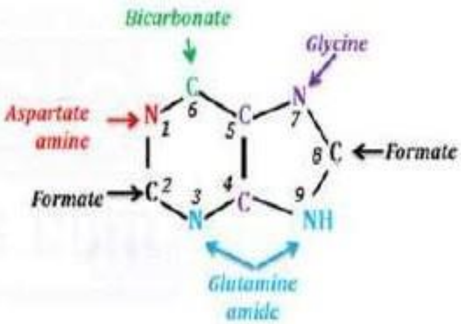
Mind-Map

(Nucleotide Biosynthesis)



De-novo synthesis of purines:

- The image shows the source of different atoms in a **purine skeleton** (identified by radio labeling studies)
  - **N1** - from amino group of **Aspartate**
  - **C2** & **C8** - from **Formate**
  - **N3** & **N9** - from amide group of **Glutamine**
  - **C4, C5** & **N7** - from **Glycine**
  - **C6** - from HCO_3^- (bicarbonate)



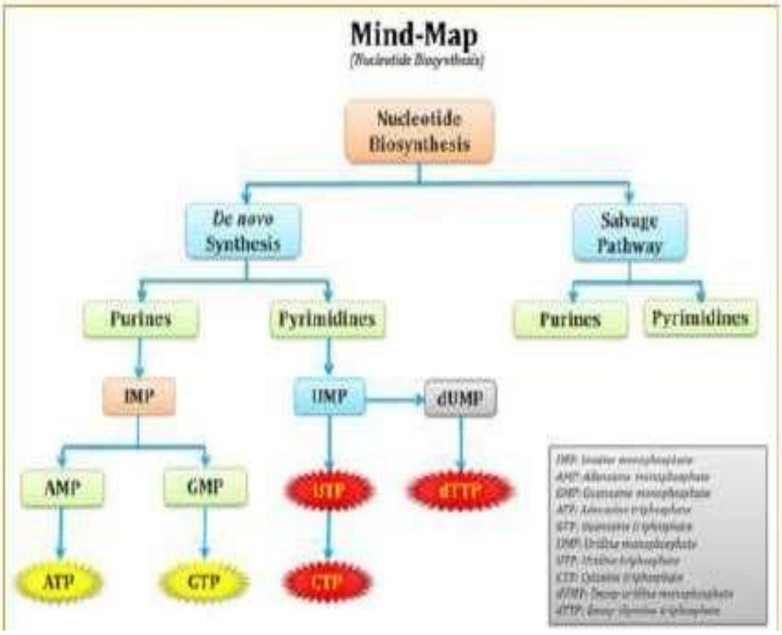
Purine Nucleus

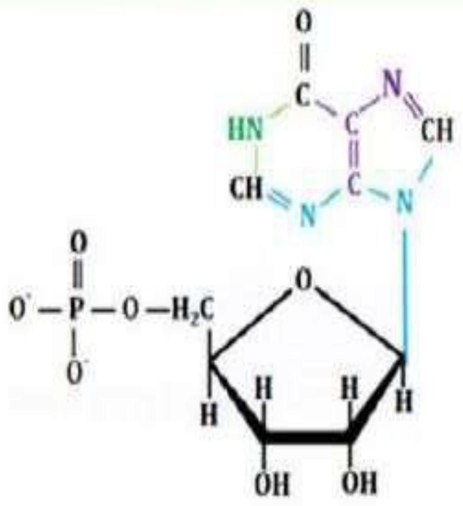
Showing the source of different atoms

- ***Thus, Aspartate, Formate, Glutamine, Glycine and Bicarbonate acts as the building blocks for purine synthesis***

- Purines (adenine and guanine) are derived from **inosine-5′-monophosphate** (IMP)

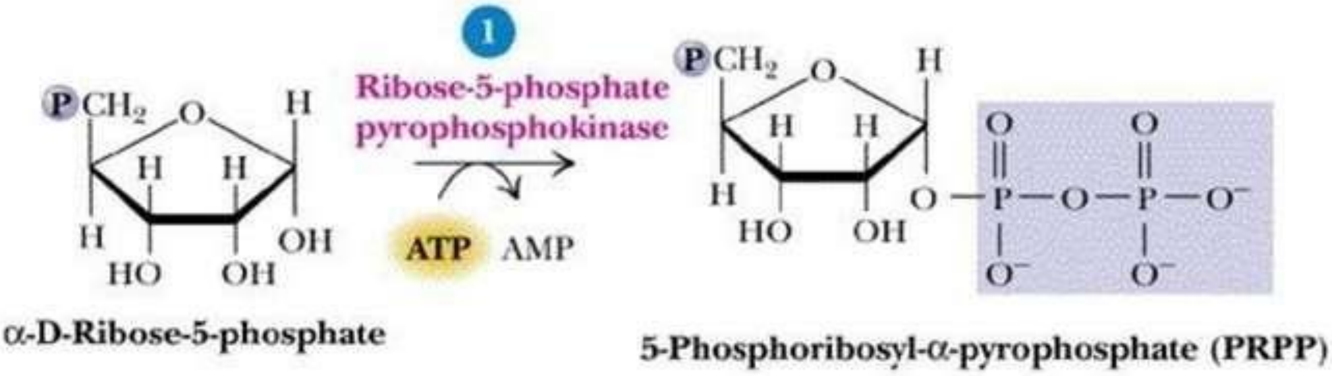
- *Thus purine synthesis starts with **IMP** synthesis (mind map)*



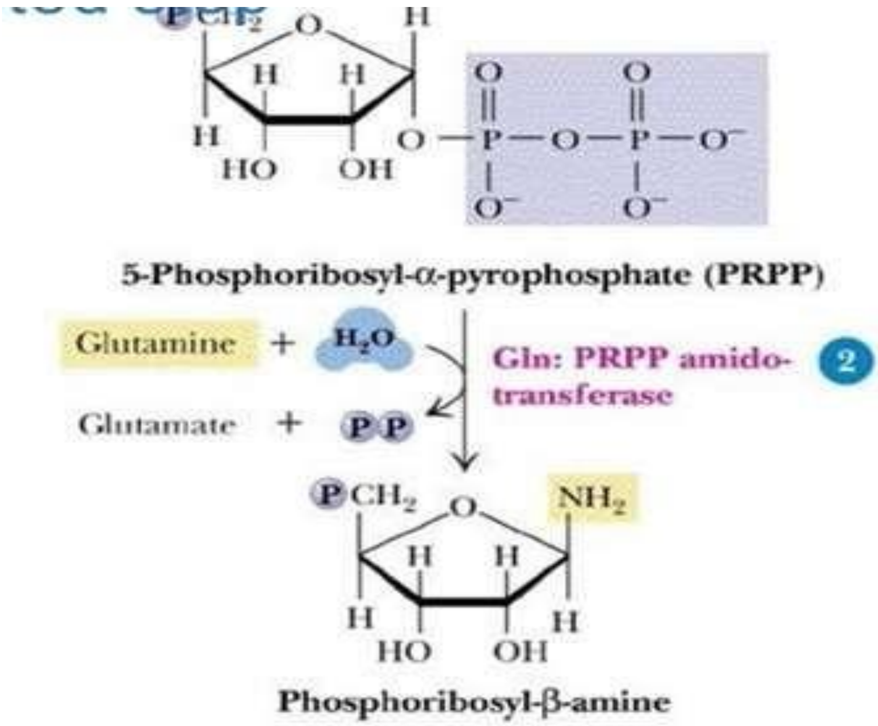


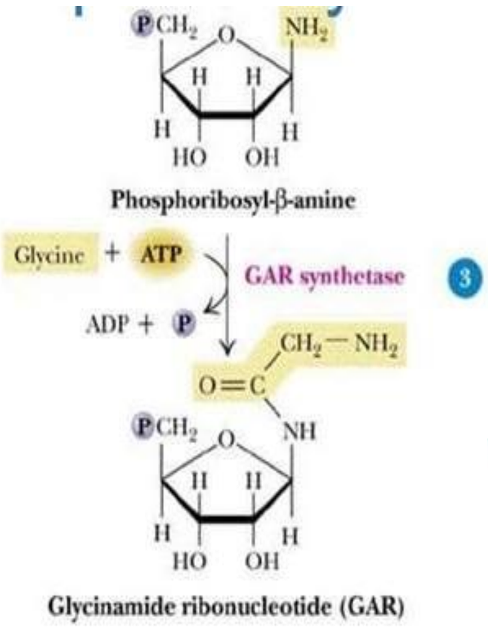
Inosine monophosphate (IMP)

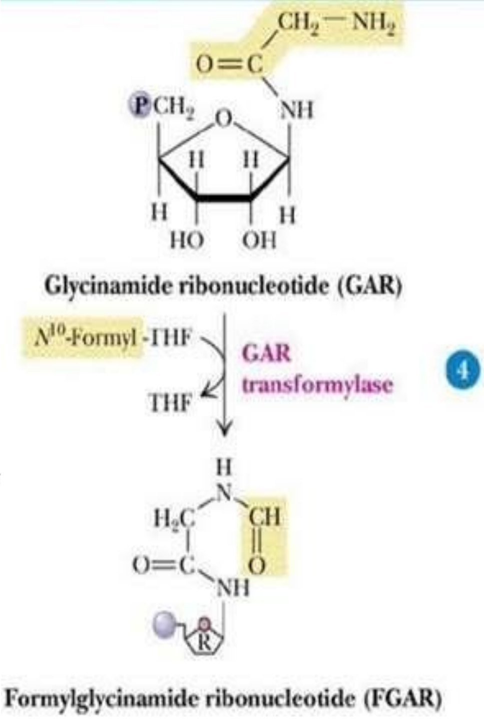
STEP 1:

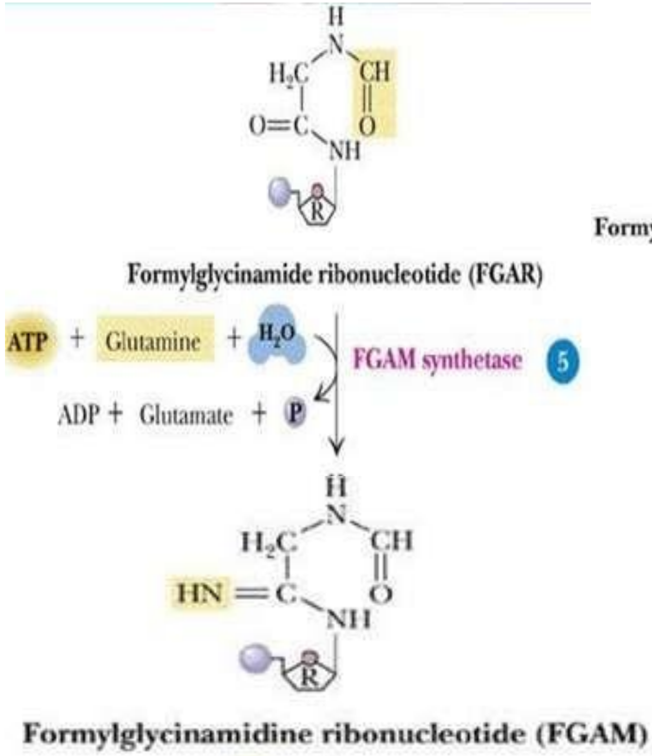

1
Ribose-5-phosphate pyrophosphokinase
ATP
AMP
α-D-Ribose-5-phosphate
5-Phosphoribosyl-α-pyrophosphate (PRPP)

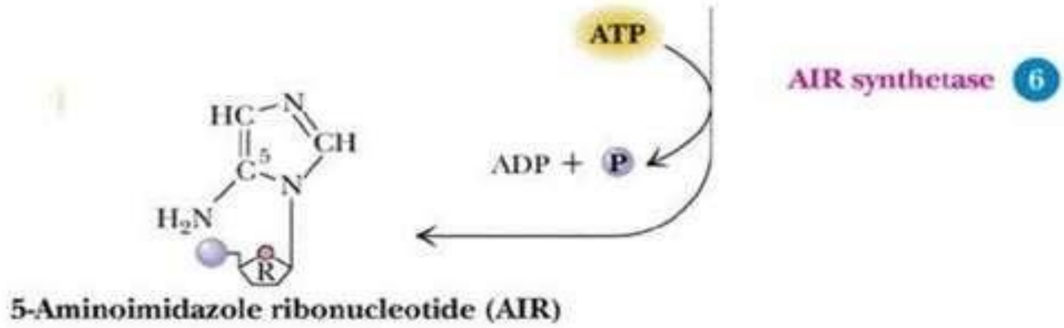
STEP 2:

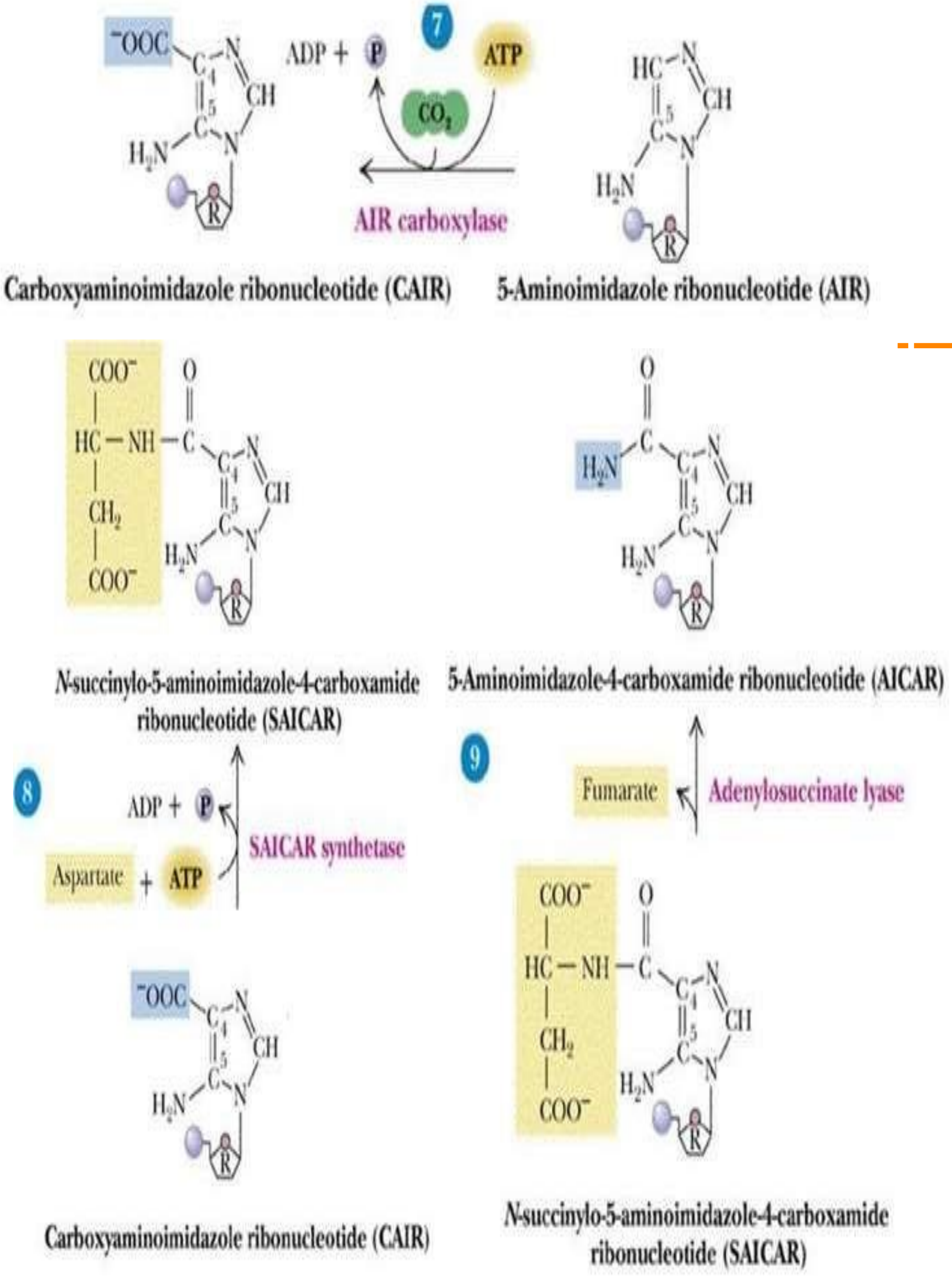

5-Phosphoribosyl-α-pyrophosphate (PRPP)
Glutamine + H₂O
Glutamate + PP
Gln: PRPP amido-transferase
2
NH₂
Phosphoribosyl-β-amine

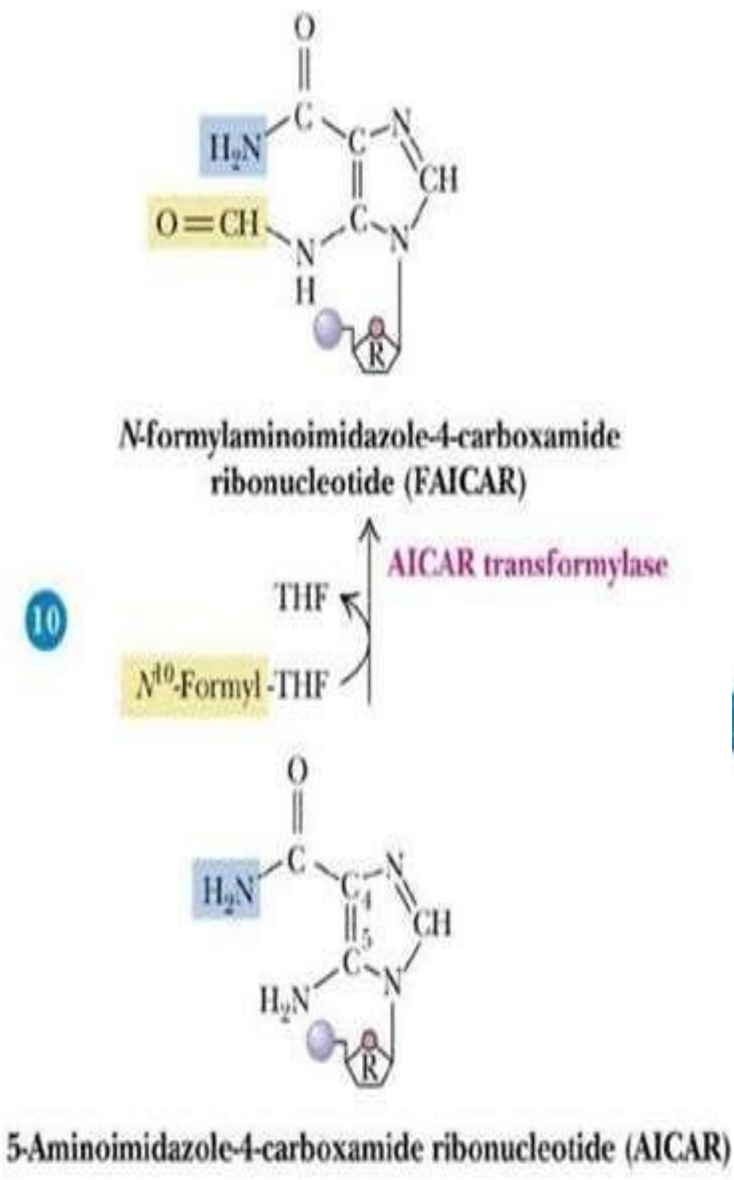

Phosphoribosyl-β-amine
Glycine + ATP
GAR synthetase
3
ADP + P
Glycinamide ribonucleotide (GAR)

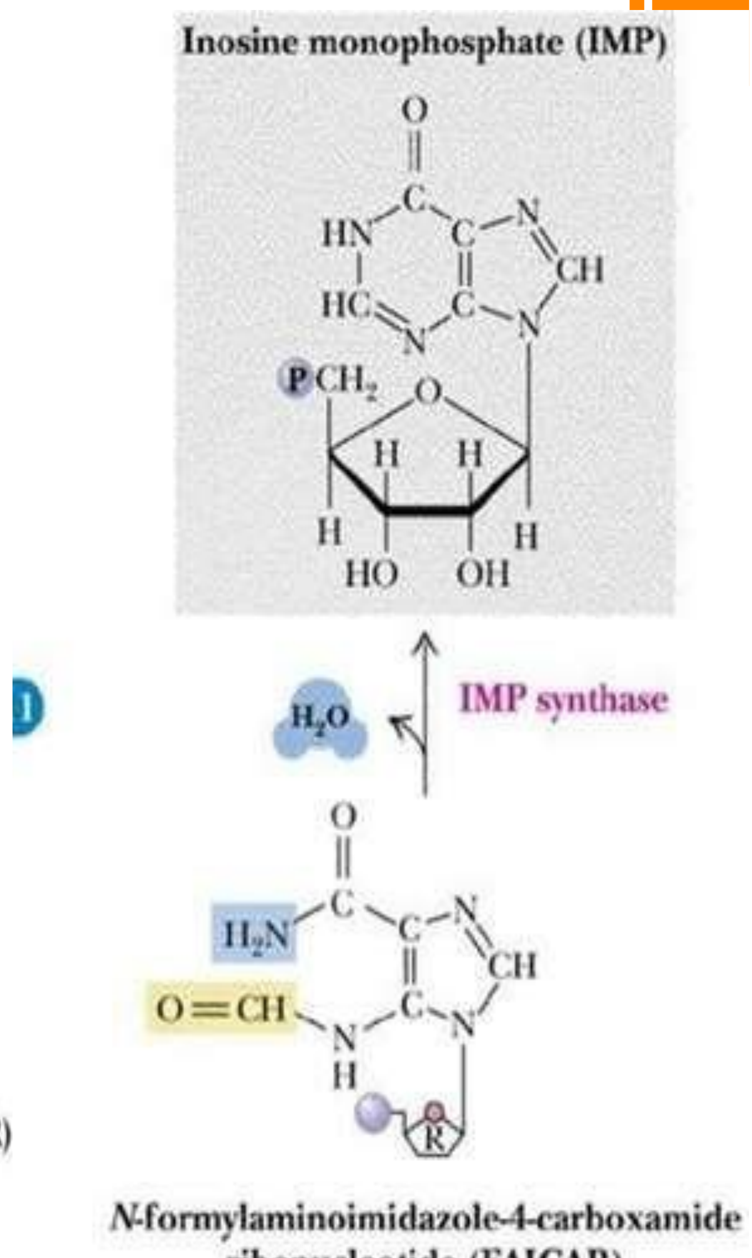

Glycinamide ribonucleotide (GAR)
N10-Formyl -THF
GAR transformylase
4
THF
Formylglycinamide ribonucleotide (FGAR)

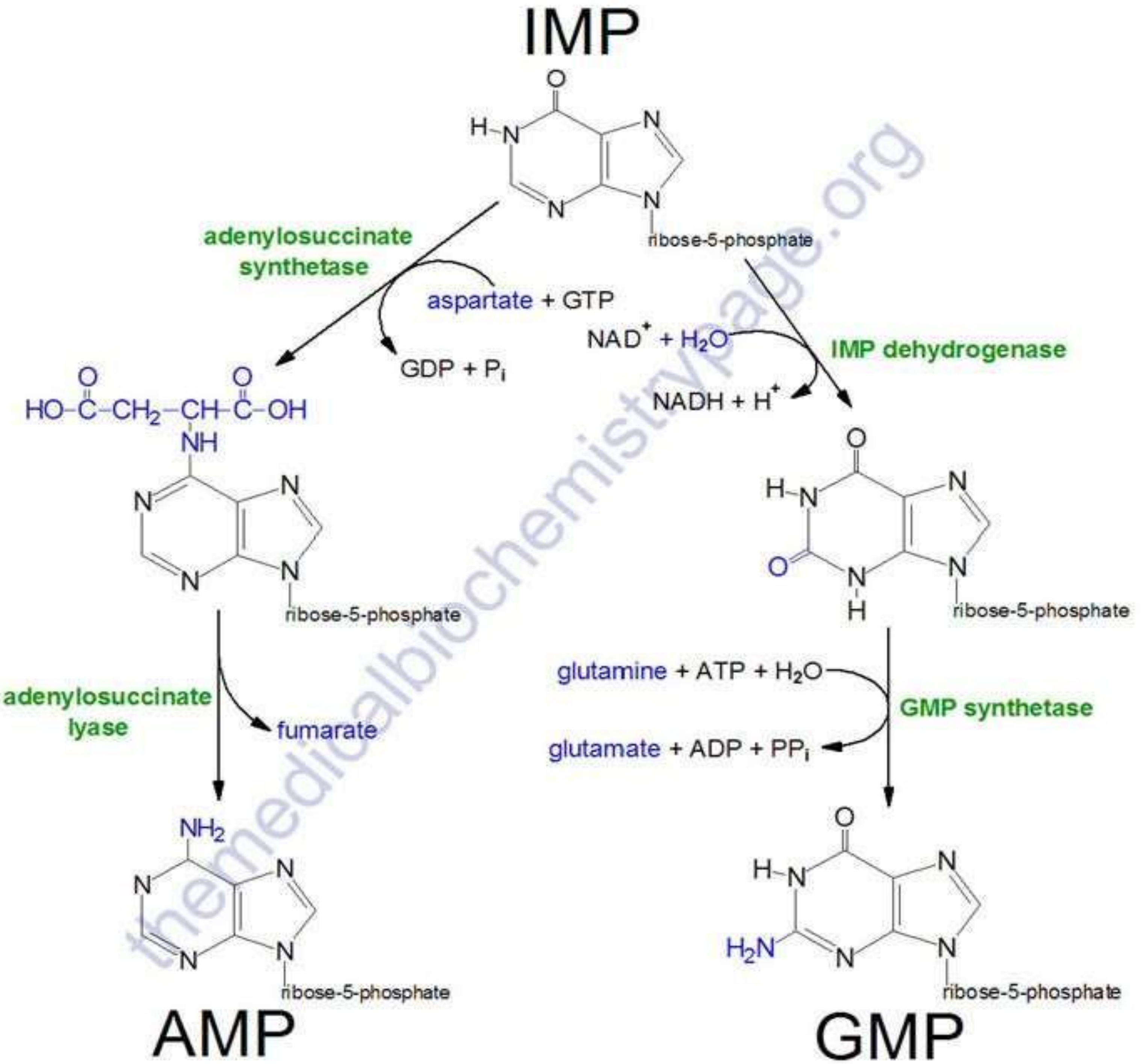

Formylglycinamide ribonucleotide (FGAR)
ATP + Glutamine + H2O
FGAM synthetase
5
ADP + Glutamate + P
Formylglycinamidine ribonucleotide (FGAM)


ATP
AIR synthetase
6
ADP + P
5-Aminoimidazole ribonucleotide (AIR)


7
ADP + P
ATP
CO_2
AIR carboxylase
Carboxyaminoimidazole ribonucleotide (CAIR)
5-Aminoimidazole ribonucleotide (AIR)
N-succinylo-5-aminoimidazole-4-carboxamide ribonucleotide (SAICAR)
5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR)
8
ADP + P
SAICAR synthetase
Aspartate + ATP
9
Fumarate
Adenylosuccinate lyase
Carboxyaminoimidazole ribonucleotide (CAIR)
N-succinylo-5-aminoimidazole-4-carboxamide ribonucleotide (SAICAR)


N-formylaminoimidazole-4-carboxamide ribonucleotide (FAICAR)
10
AICAR transformylase
THF
N^{10}-Formyl-THF
5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR)


Inosine monophosphate (IMP)
IMP synthase
H_2O
N-formylaminoimidazole-4-carboxamide ribonucleotide (FAICAR)


IMP
ribose-5-phosphate
adenylosuccinate synthetase
aspartate + GTP
GDP + Pi
NAD+ + H2O
IMP dehydrogenase
NADH + H+
HO-C-CH2-CH-C-OH
NH
ribose-5-phosphate
ribose-5-phosphate
adenylosuccinate lyase
fumarate
glutamine + ATP + H2O
GMP synthetase
glutamate + ADP + PPi
NH2
ribose-5-phosphate
H2N
ribose-5-phosphate
AMP
GMP
themedicalbiochemistrypage.org

Synthesis of AMP & GMP from IMP

Synthesis of AMP:

Ionosine monophosphate (IMP) is the immediate precursor for the formation of AMP & GMP.

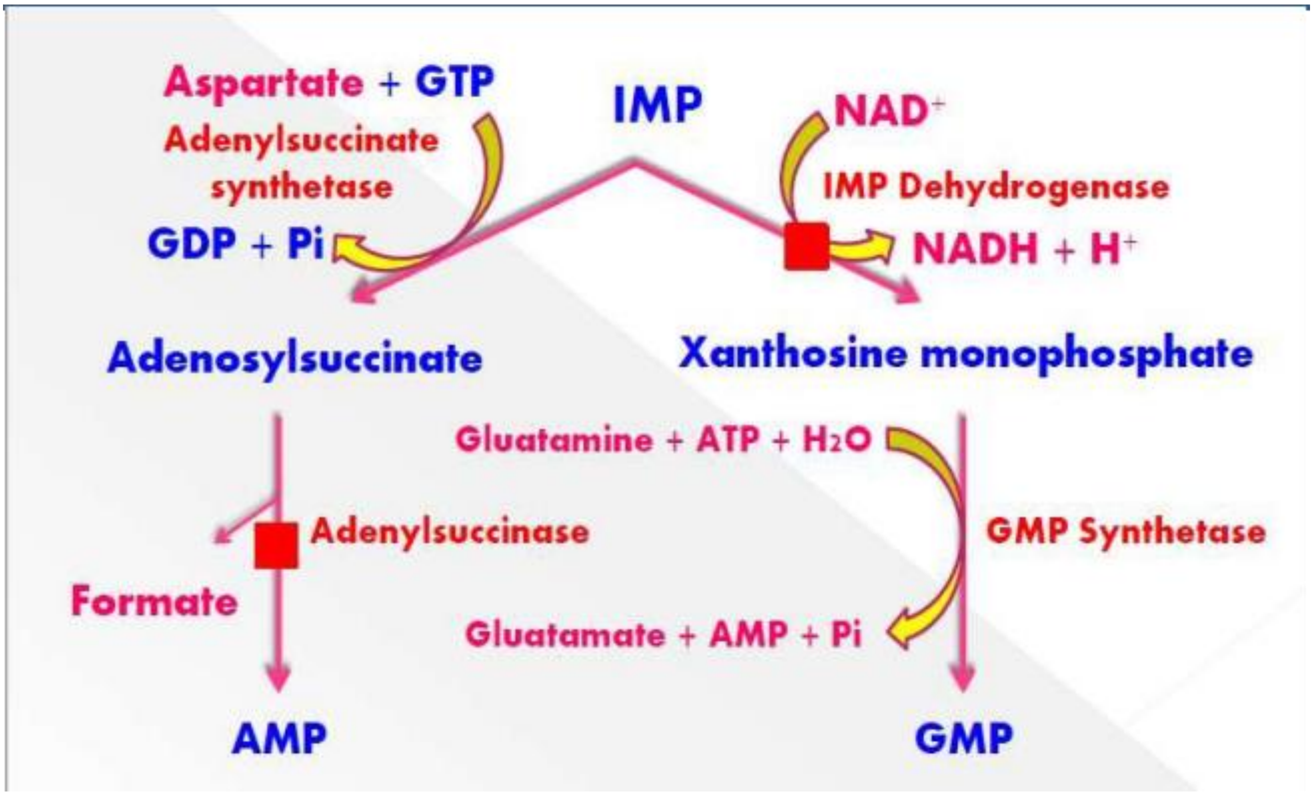
Aspartate condenses with IMP in the presence of GTP to produce adenylsuccinate which, on cleavage, forms AMP.

Synthesis of GMP:

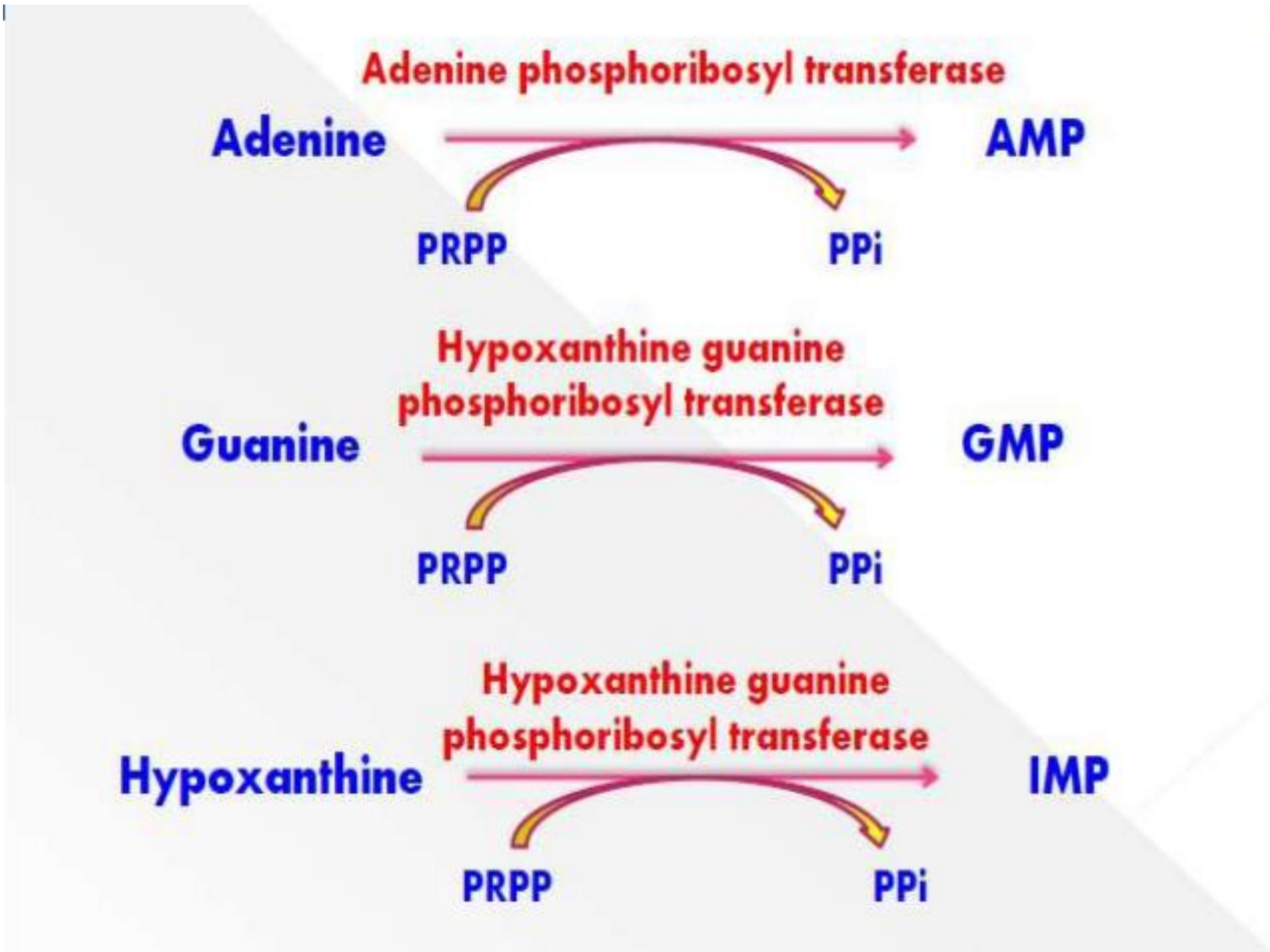
IMP undergoes NAD+ dependent dehydrogenation to form xanthosine monophosphate (XMP). Glutamine then transfers amide nitrogen to xanthosine monophosphate (XMP) to produce GMP.

6-Mercaptopurine is an inhibitor of the synthesis of AMP & GMP.

It acts on the enzyme adenylsuccinase (of AMP pathway) & IMP dehydrogenase (of GMP pathway).



SALVAGE PATHWAY



It refers to the formation of purine nucleotides by the addition of ribose phosphate (from PRPP) to the preformed purine bases.

Addition of phosphate to the preformed purine nucleosides.

Significance

Salvage pathway provide a pathway for the utilization of purine bases derived from diet (exogenous) and normal turnover of the nucleic acids.

In erythrocytes, denovo syntheis of purine nucleotides does not occur because of absence of PRPP amidotransferase. The requirement of purine nucleotides is met by the salvage pathway.

Biosynthesis of pyrimidine

(Uracil, Cytosine & Thymine)

Synthesis of pyrimidine nucleotides

- **Denovo synthesis**

Site- liver, cytosol, mitochondria

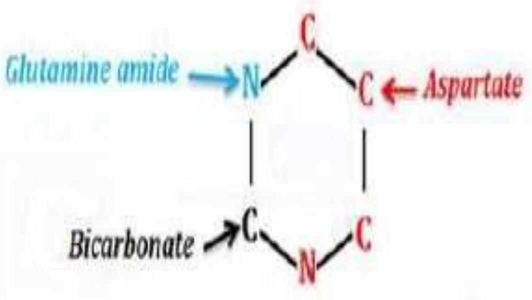
Synthesis of pyrimidine nucleotide refers to the formation of pyrimidine ring structure followed by the addition of ribose phosphate.

- **Salvage pathway**

Site - Plastid

Formation of pyrimidine nucleotides from pyrimidine bases

- Biosynthesis of pyrimidine is simple than that of purine
- Following diagram shows the source of different atoms in a pyrimidine skeleton (identified by radio labeling studies)
  - N1, C6, C5 and C4 from Aspartate
  - N3 from Glutamine
  - C2 from HCO3- (bicarbonate)

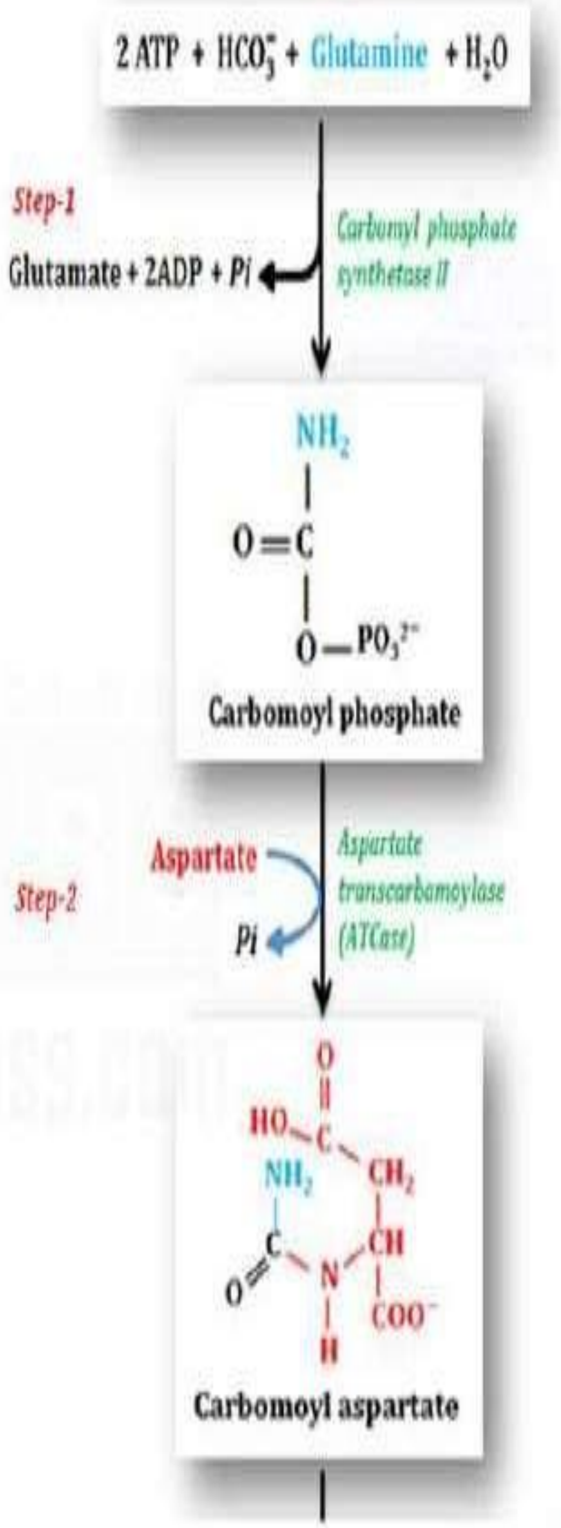


Pyrimidine Nucleus

- In pyrimidine nucleotide synthesis, the ring is completed before being linked to ribose-5-phosphate

De-novo synthesis of UMP (Uridine monophosphate)

- UMP is also act as the precursor of CMP
- UMP is synthesized in 6 steps
- **Step-1: Synthesis of carbamoyl phosphate:** With the hydrolysis of two ATPs, bicarbonate and amide nitrogen of glutamine combine to form **carbamoyl phosphate**
- **Step-2: Synthesis of carbamoyl aspartate:** Carbamoyl phosphate reacts with aspartate to yield **carbamoyl aspartate**.

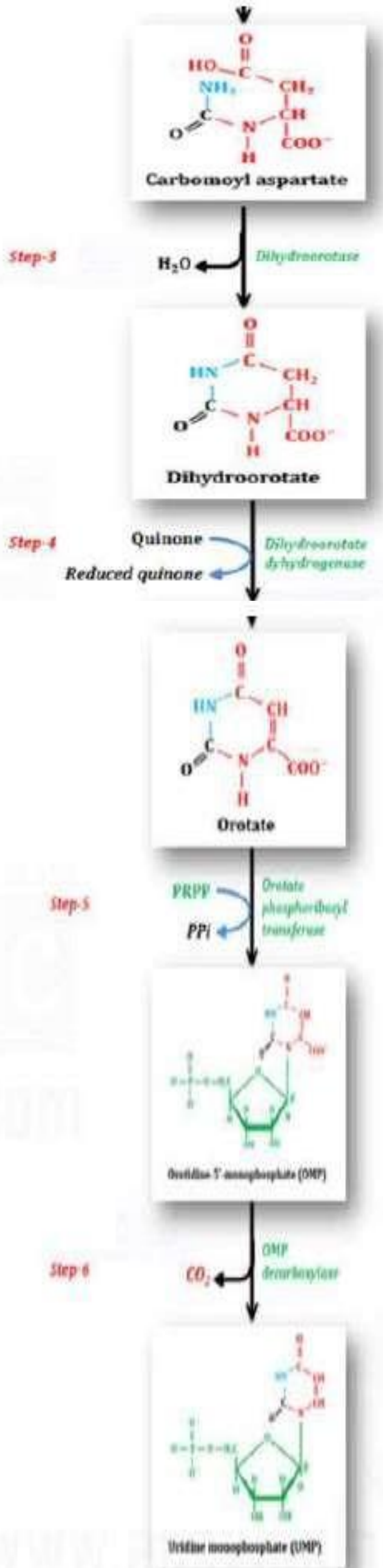


De-novo synthesis of UMP (Uridine monophosphate)

- **Step-3: Ring closure & dihydroorotate formation**: By the elimination (condensation) reaction, the carbamoyl aspartate is converted to a ring compound **dihydroorotate**
- One molecule of water is eliminated in Step-3
- **Step-4: Oxidation of dihydroorotate:** Dihydroorotate is dehydrogenated to form **orotate**

De-novo synthesis of UMP (Uridine monophosphate)

- **Step-5: Acquisition of the ribose phosphate moiety:** Orotate reacts with PRPP to produce **orotidine-5′-monophosphate** (OMP)
- **Step-6: Decarboxylation to form UMP:** OMP undergoes decarboxylation to form **UMP**



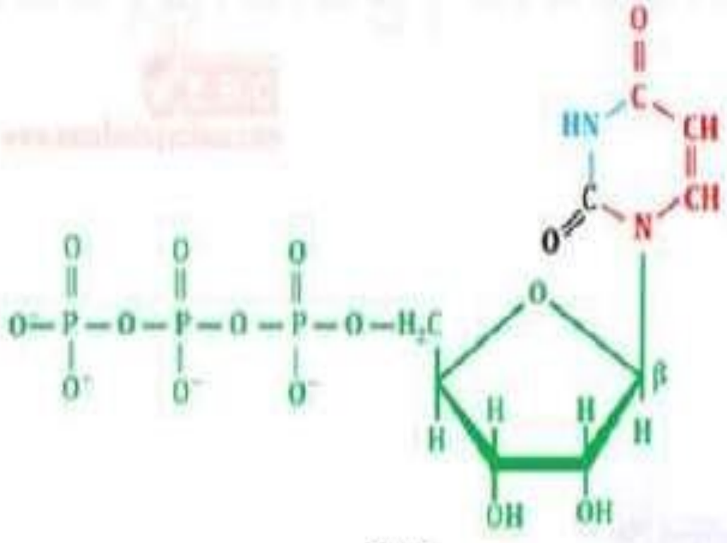
Uridine Monophosphate (UMP) Synthesis

Synthesis of UTP

- UMP is converted to UTP in two step kinase reaction
- Two ATP molecules are required

$$UMP + ATP \rightleftharpoons UDP + ADP$$

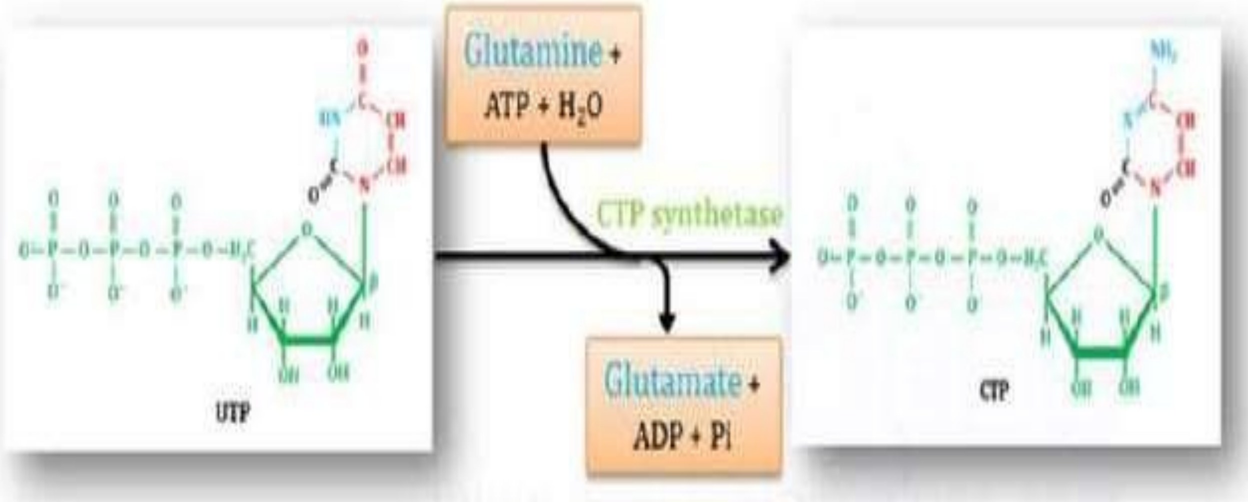
$$UDP + ATP \rightleftharpoons UTP + ADP$$



UTP

Synthesis of CTP

- CTP is synthesized by the **amination** of **UTP** by the enzyme *CTP synthase*
- In animals amino group is donated by **glutamine**
- In bacteria amino group is donated by **ammonia**



CTP is synthesized from UTP

Salvage pathway