# NUCLEOTIDES METABOLISM

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# Purine and pyrimidine biosynthesis

- The biosynthesis of these molecules is complex, but is vital.

**The rate of nucleotide biosynthesis depends on:**

1. Grew phase of the cells
2. Rate of growth
3. Type of cells
4. availability of intermediates including energy.

- nearly all cells can synthesize nucleotide by both *de novo* (anew) and from the degraded products of nucleic acids (salvage pathways).

***De novo*** synthesis refers to the synthesis of complex molecules from simple molecules such as sugars or amino acids which is required in growing cells.

**Salvage pathways:** recycle preformed bases and nucleosides and provide an adequate supply of nucleotides for cells at rest.

- **Purines are made separately from Pyrimidines.**
- purine ring is assembled on ribose sugar while in the Pyrimidines the ring is synthesized first and then added to the ribose.

# The *de novo* synthesis of purine ribonucleotides

- The major site of purine synthesis is in the liver.

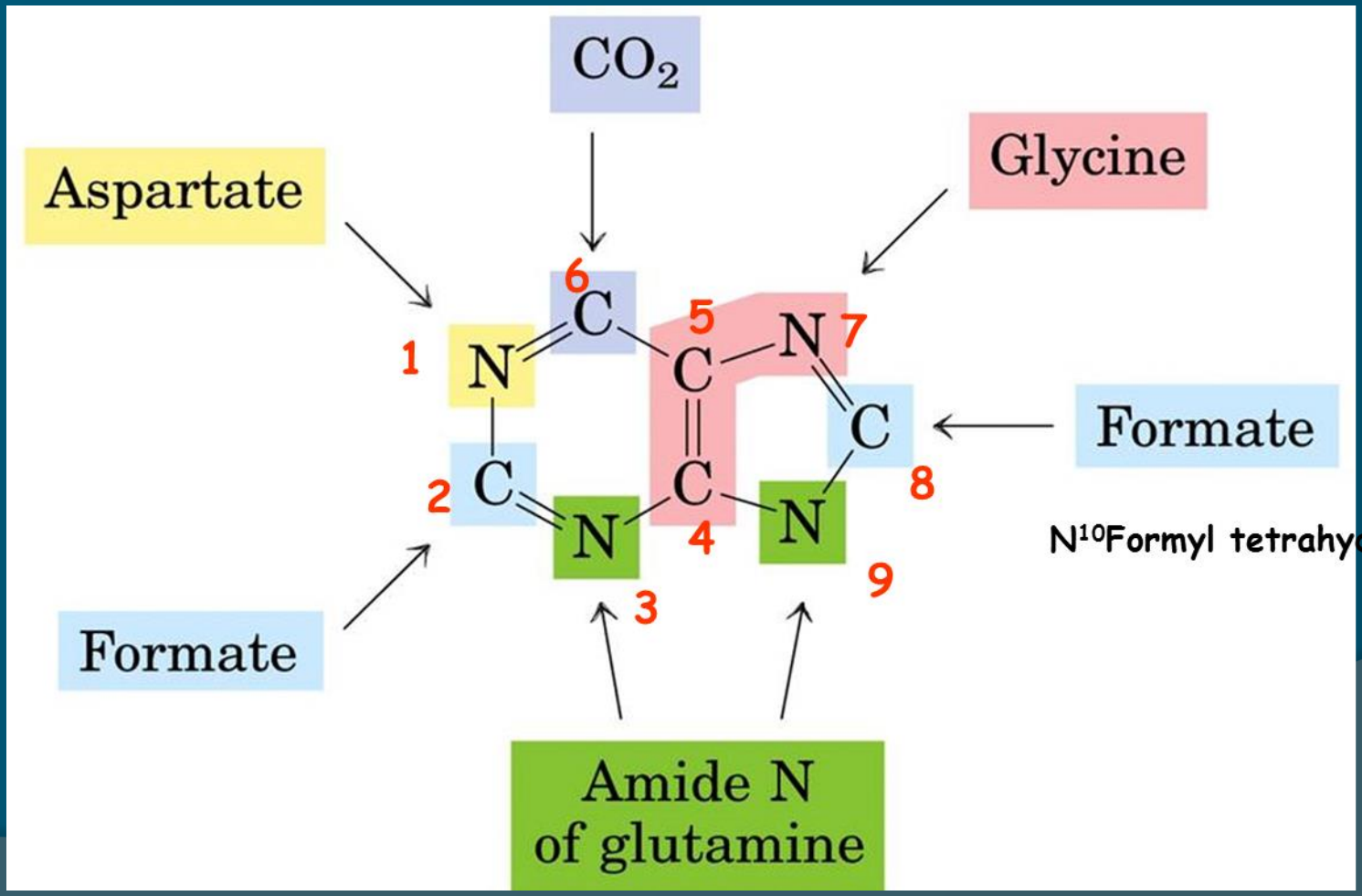
The raw materials for ***de novo*** purine synthesis are:

1. $CO_2$
2. nonessential amino acids (Asp, Glu, Gly)
3. folic acid derivatives which act as single carbon donors

- the first purine produced is **IMP** and it is the common precursor of other nucleotides.

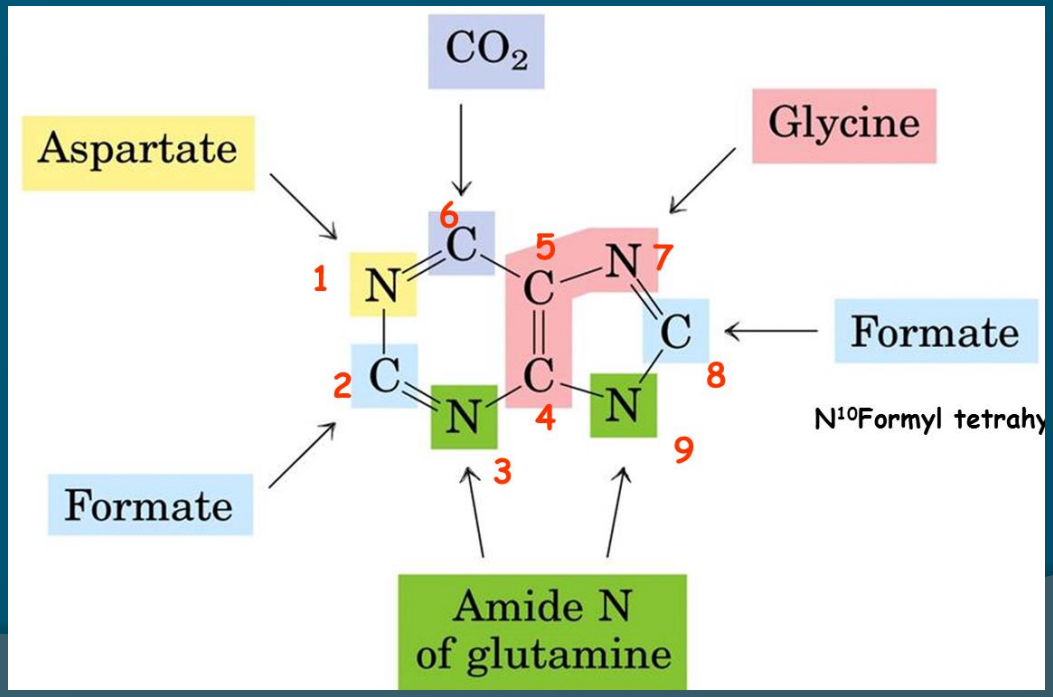
# Origin of the atoms in purine ring

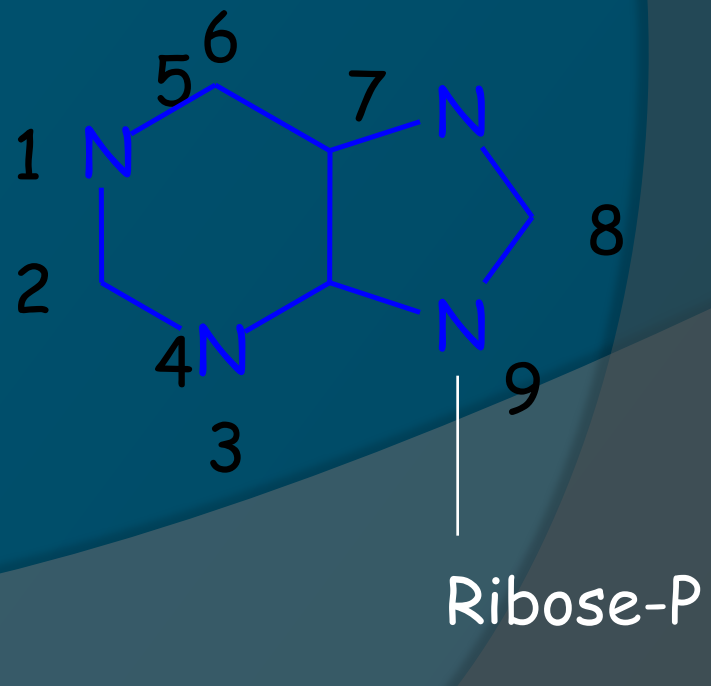
The atoms of purine ring are from amino acids (aspartic acid, glycine and glutamine), $CO_2$ and tetrahydrofolate.



# The order in which ring atoms are added is:

| 9 | 4 5 7 | 8 | 3 | 6 | 1 | 2 |
|---|---|---|---|---|---|---|
| Glut | Glycine | For | Glut | $CO_2$ | Asp | For |



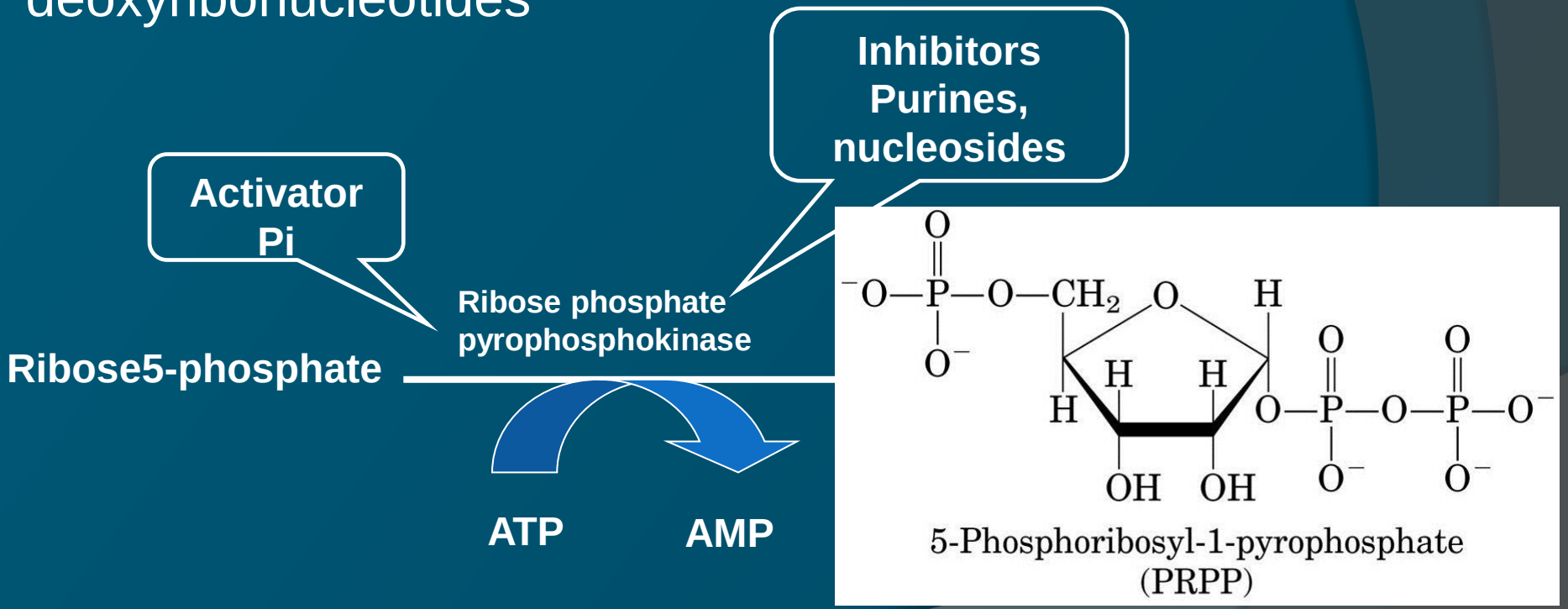



# De novo synthesis of purine nucleotides

*** Synthesis of 5-phosphoribosyl-1-pyrophosphate (PRPP)**

-Ribose 5-phosphate is synthesized from **HMP** (Hexose monophosphate pathway)

- Ribonucleotides are first synthesized then may reduced to deoxyribonucleotides



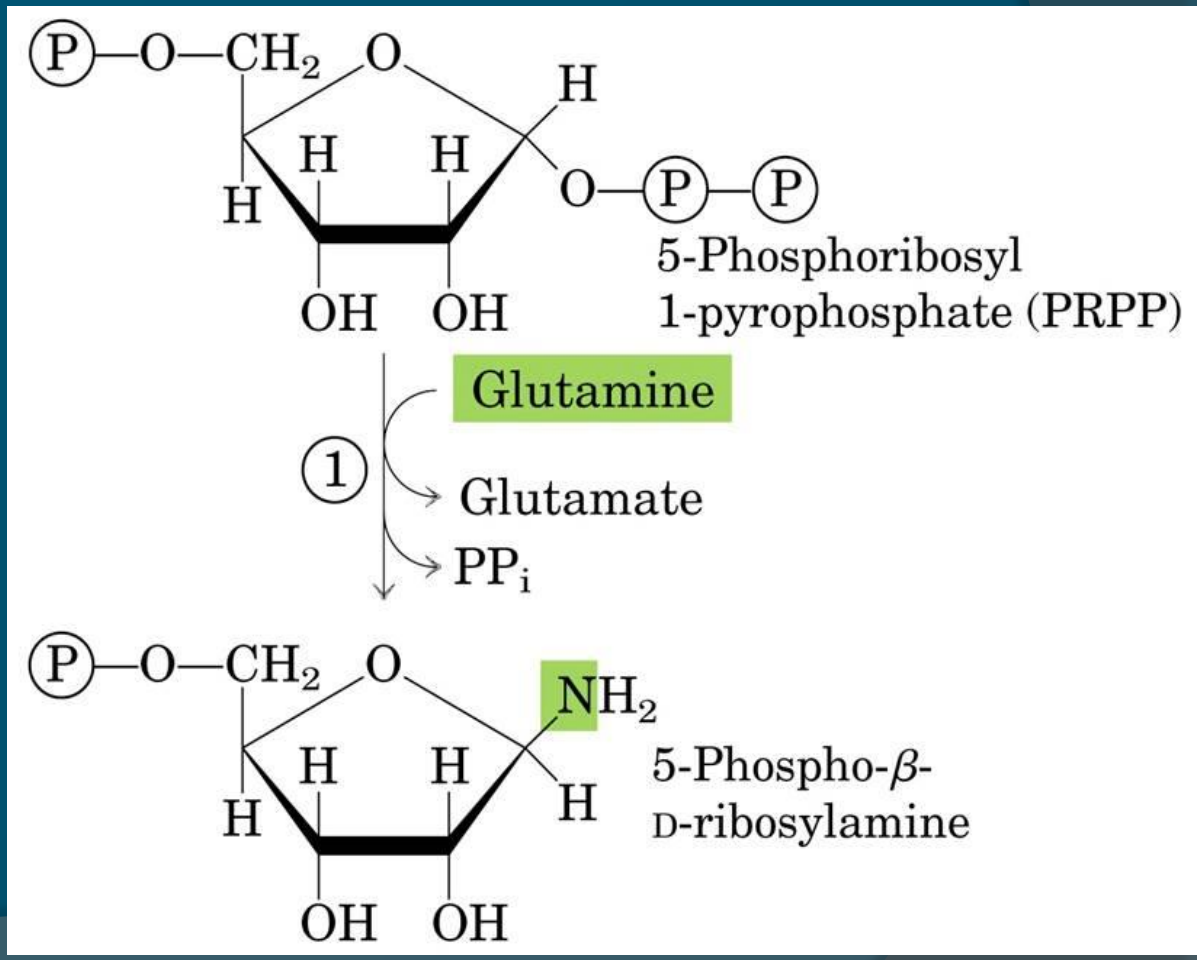
# * Synthesis of 5-phosphoribosyl-1-pyrophosphate (PRPP)

•The amide group of the glutamine replaces pyrophosphate group attached to PRPP, this reaction is mediated by

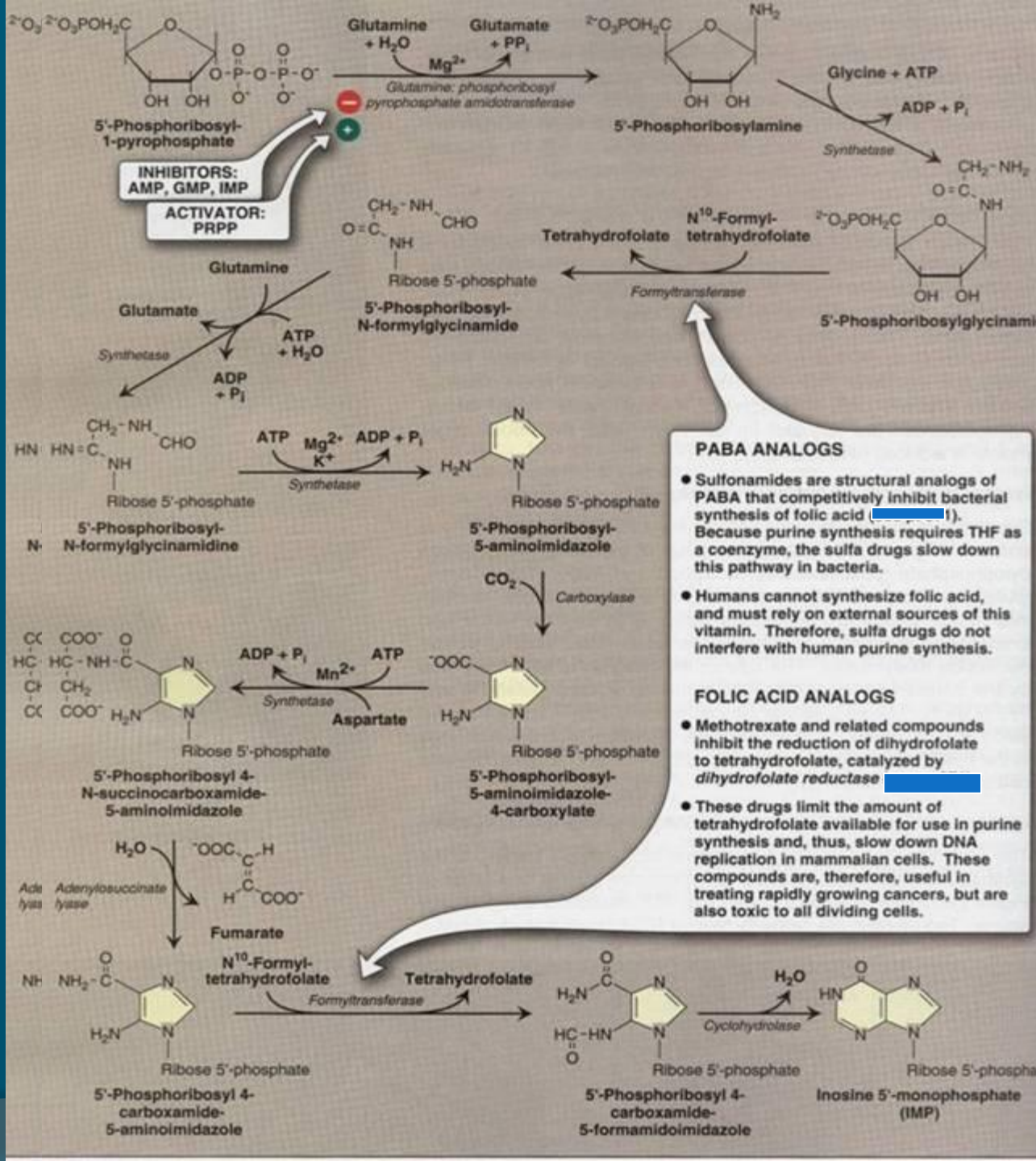
**Glutamine phosphoribosyl pyrophosphate amidotransferase.**

**•This enzyme is inhibited by end product of this pathway purine 5'-nucleotides AMP, GMP and IMP.**

**• This reaction is the committed step in purine nucleotide synthesis**



# De novo synthesis of purine nucleotides




## PABA ANALOGS

- Sulfonamides are structural analogs of PABA that competitively inhibit bacterial synthesis of folic acid ([redacted]). Because purine synthesis requires THF as a coenzyme, the sulfa drugs slow down this pathway in bacteria.
- Humans cannot synthesize folic acid, and must rely on external sources of this vitamin. Therefore, sulfa drugs do not interfere with human purine synthesis.

## FOLIC ACID ANALOGS

- Methotrexate and related compounds inhibit the reduction of dihydrofolate to tetrahydrofolate, catalyzed by *dihydrofolate reductase* [redacted]
- These drugs limit the amount of tetrahydrofolate available for use in purine synthesis and, thus, slow down DNA replication in mammalian cells. These compounds are, therefore, useful in treating rapidly growing cancers, but are also toxic to all dividing cells.

- **Synthesis Inosine monophosphate (IMP)**

- **IMP** is the parent purine nucleotide

**•Synthesis of IMP requires 4 ATP molecules**

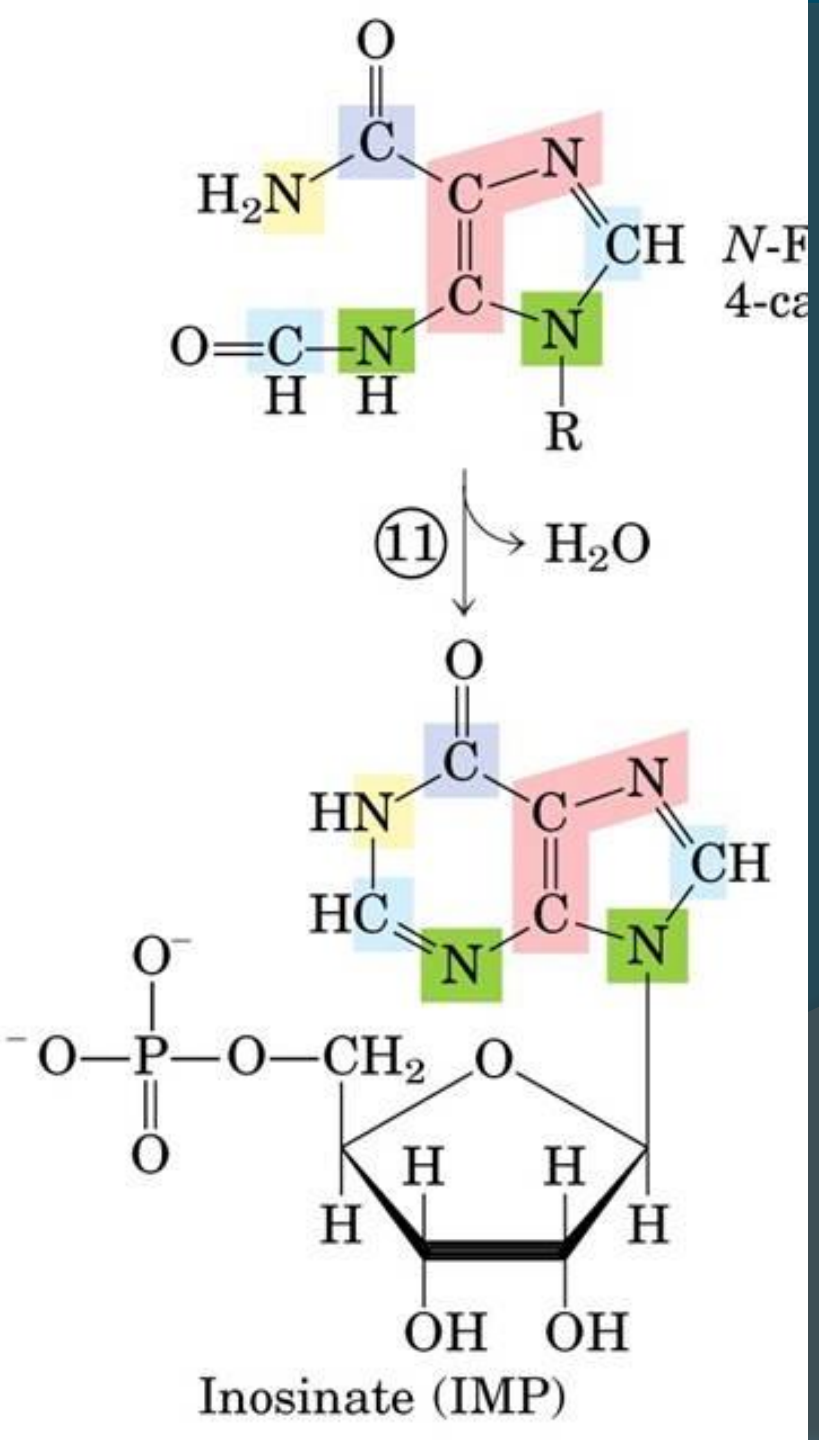
**Inhibitors of Purine synthesis**

•Specific inhibitors that inhibits the growth of rapidly growing microorganisms e.g.

**Sulfonamides**

- Structural analogues for folic acid

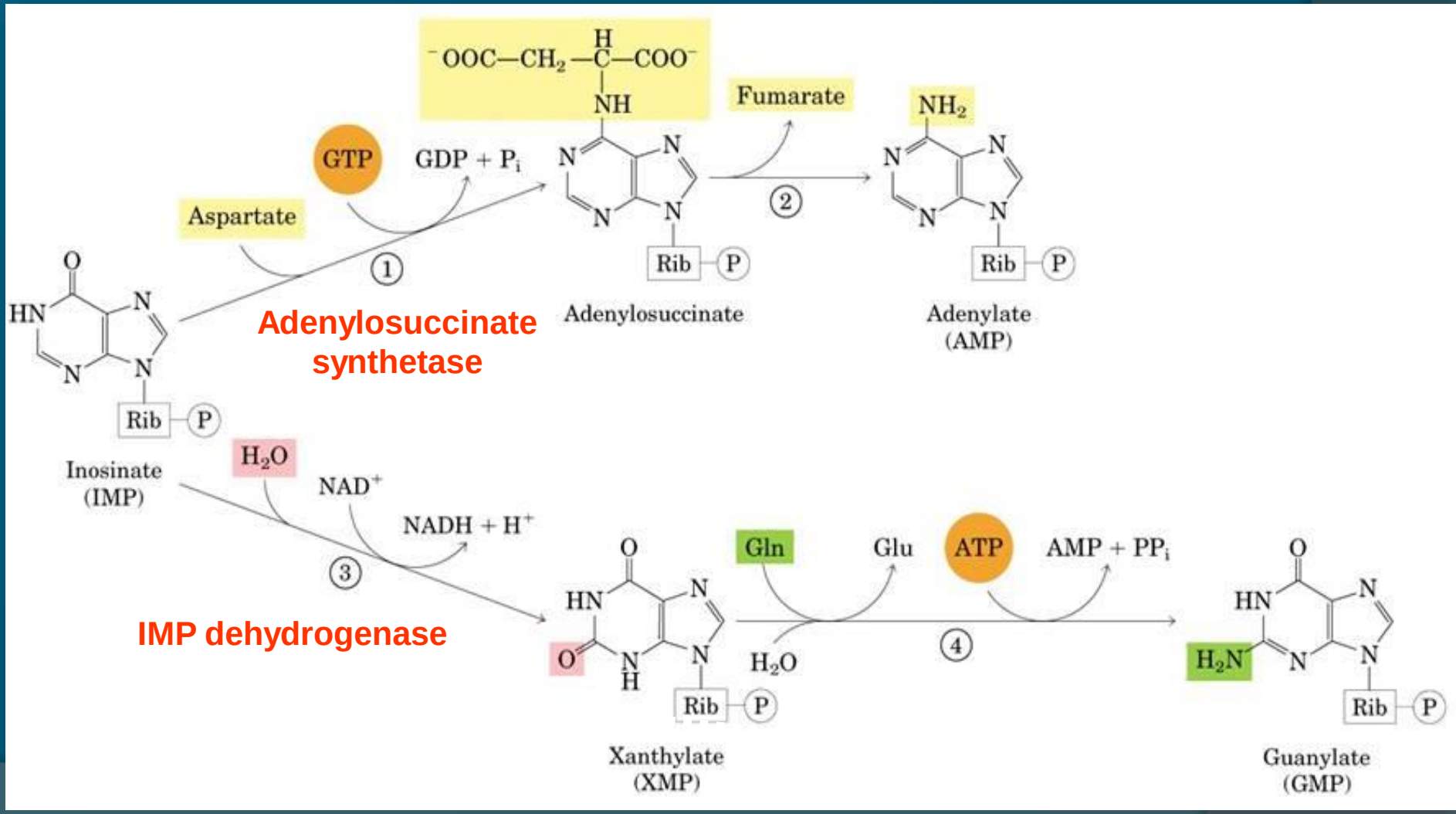
(**methotrexate**)



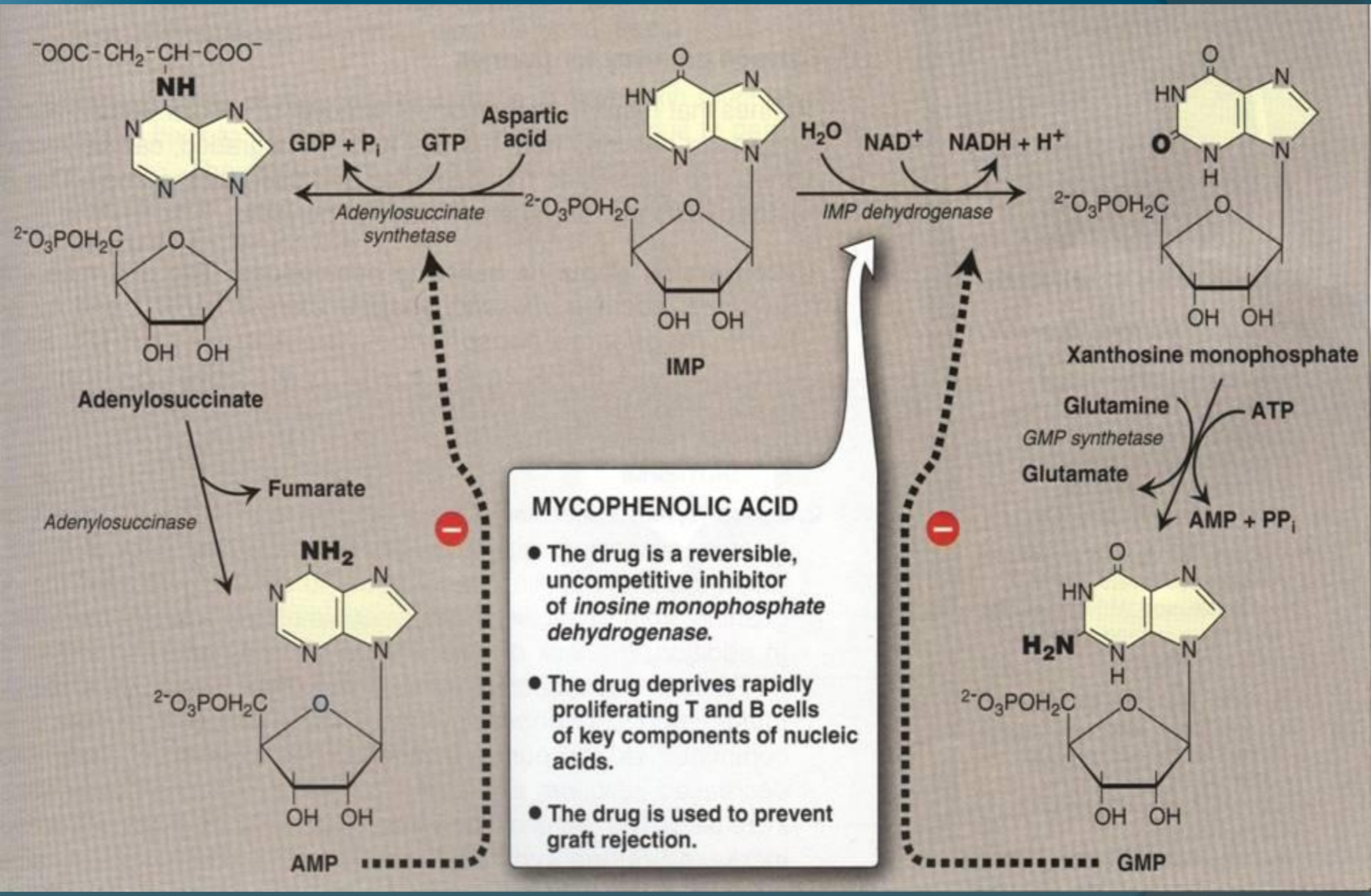
Inosinate (IMP)

# * Conversion of IMP into AMP and GMP

-this reaction is energy-requiring pathway



# Conversion of IMP into AMP and GMP



# Control of purine biosynthesis

- Purine Nucleotide Biosynthesis Is Regulated by Feedback Control

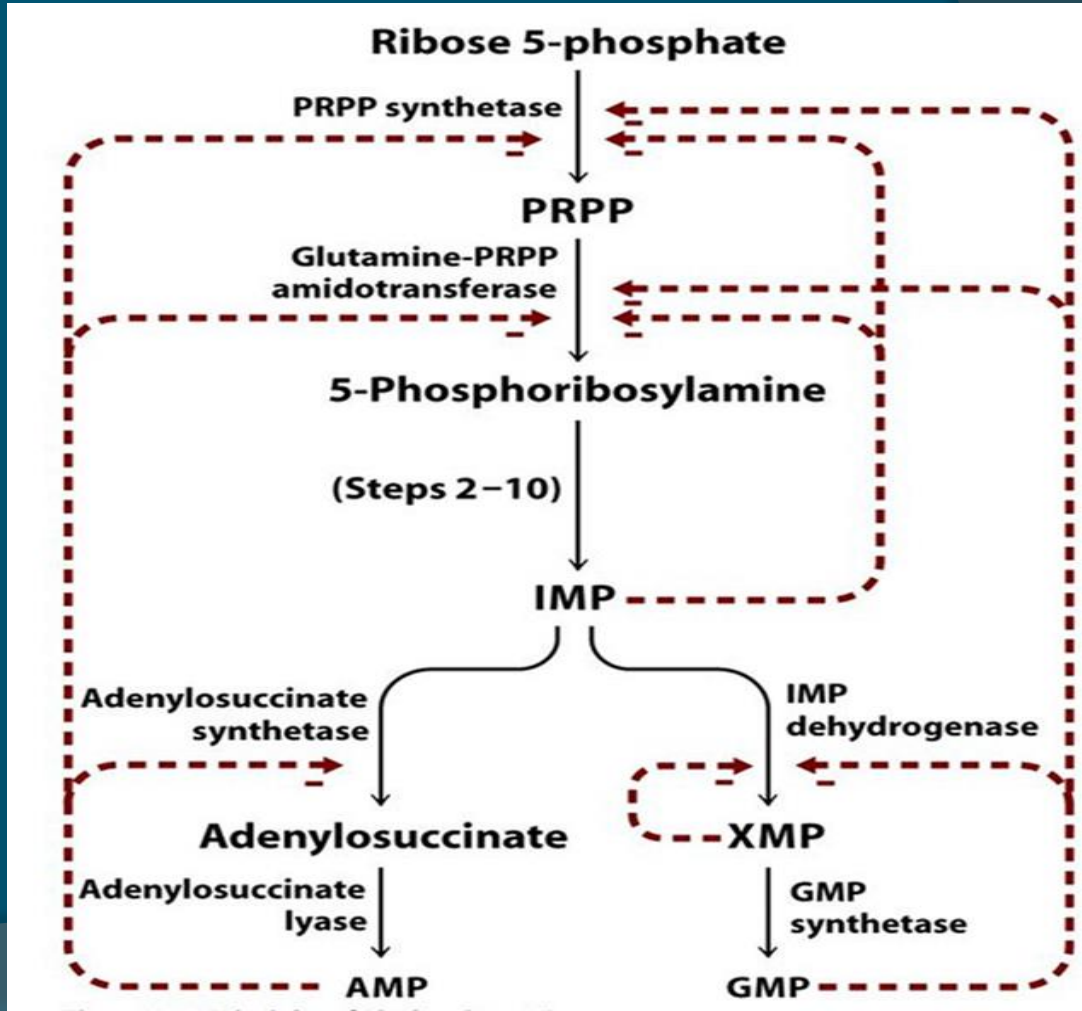
Three major feedback mechanisms are regulating the rate of de novo purine synthesis:

1. first reaction that is the transfer of an amino group to PRPP to form 5-phosphoribosylamine. allosteric enzyme glutamine-PRPP amidotransferase, which is inhibited by the end products IMP, AMP, and GMP

2. an excess of GMP in the cell inhibits formation of xanthine from inosinate by IMP dehydrogenase

3. GTP is required in the conversion of IMP to AMP, whereas ATP is required to form GMP from IMP, a reciprocal arrangement

balance synthesis of the two ribonucleotides.



# Thank You