Biosynthesis and Degradation of Nucleotides

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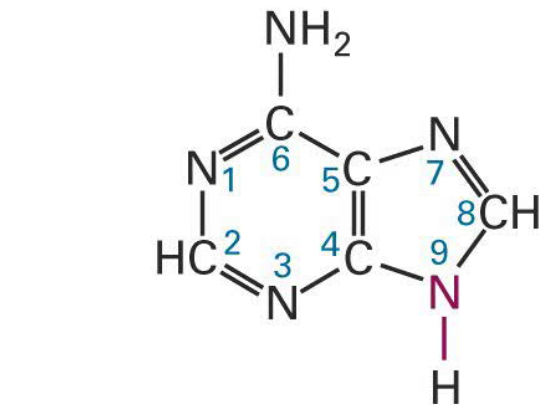
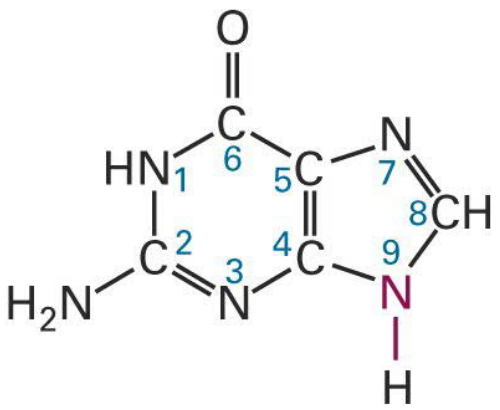
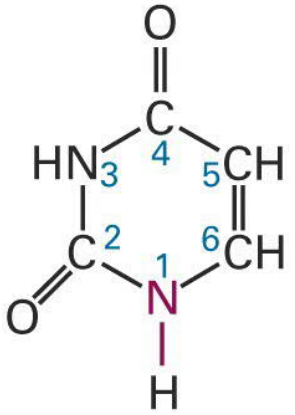
- Biosynthesis pathways of purine and pyrimidine nucleotides
  - De novo synthesis
  - Salvage pathway
- Regulation of nucleotide biosynthesis
- Formation of deoxynucleotides
- Degradation of purine/pyrimidine to Uric acid
- Chemotherapeutic agent that affect nucleotide synthesis



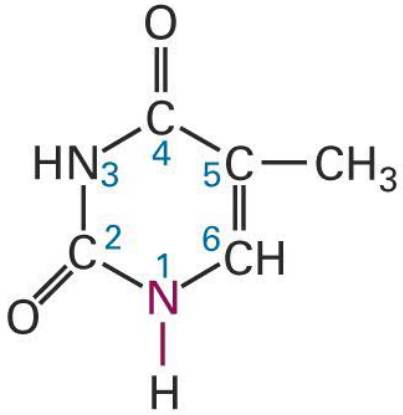
Adenine (A)



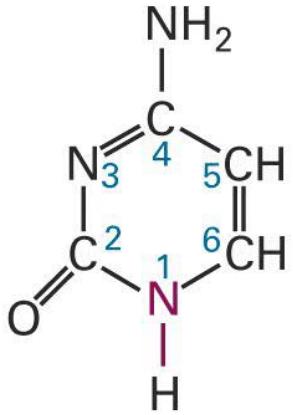
Guanine (G)



Uracil (U)



Thymine (T)



Cytosine (C)

Biological roles of nucleotides

1. Building block :

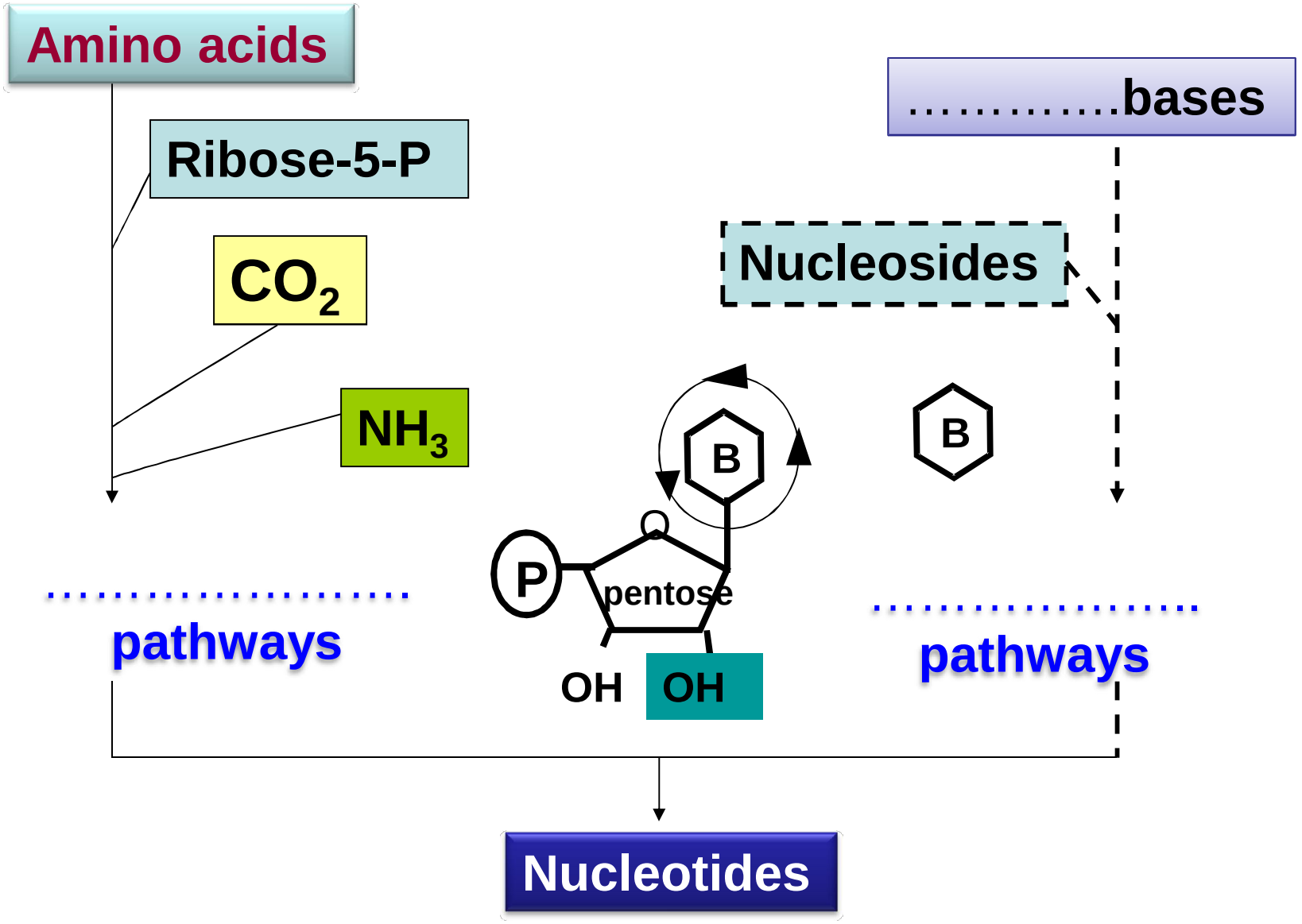
   RNA (ribonucleotide: mRNA, tRNA, rRNA, miRNA)

   DNA (.....ribonucleotide)

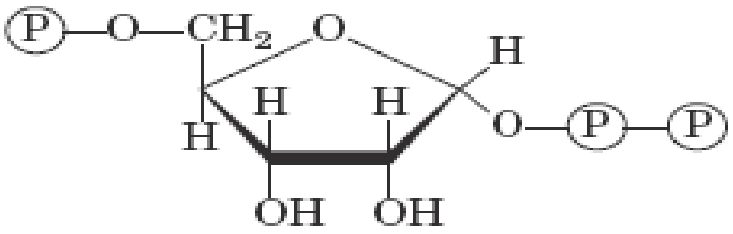
2. Metabolic energy : ATP, ...

3. Second messenger: cAMP, cGMP

4. Coenzyme: FAD^+, NAD^+,$NADP^+$

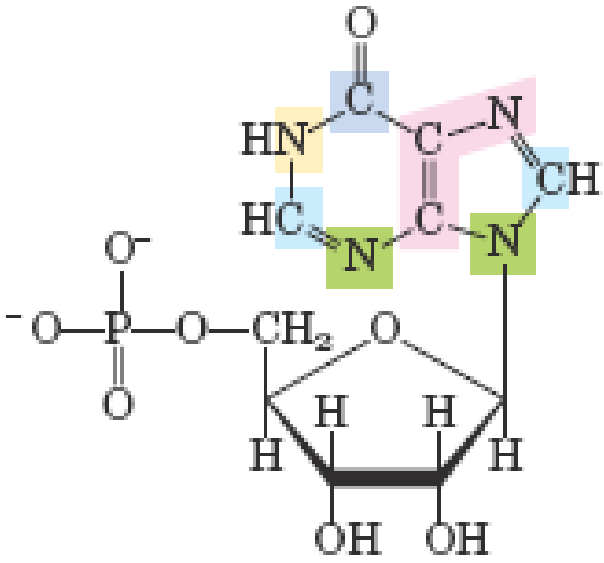

Amino acids
Ribose-5-P
CO_2
NH_3
.....bases
Nucleosides
B
B
P
pentose
OH
OH
pathways
pathways
Nucleotides

De novo synthesis of purine



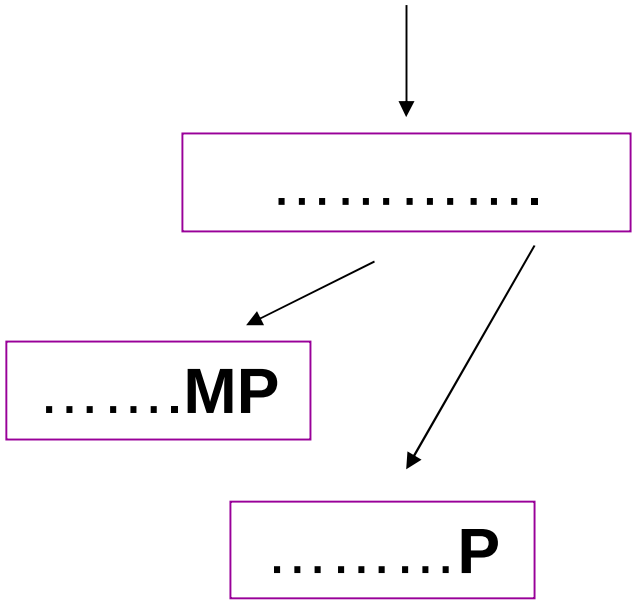
5-phosphoribosyl 1-pyrophosphate

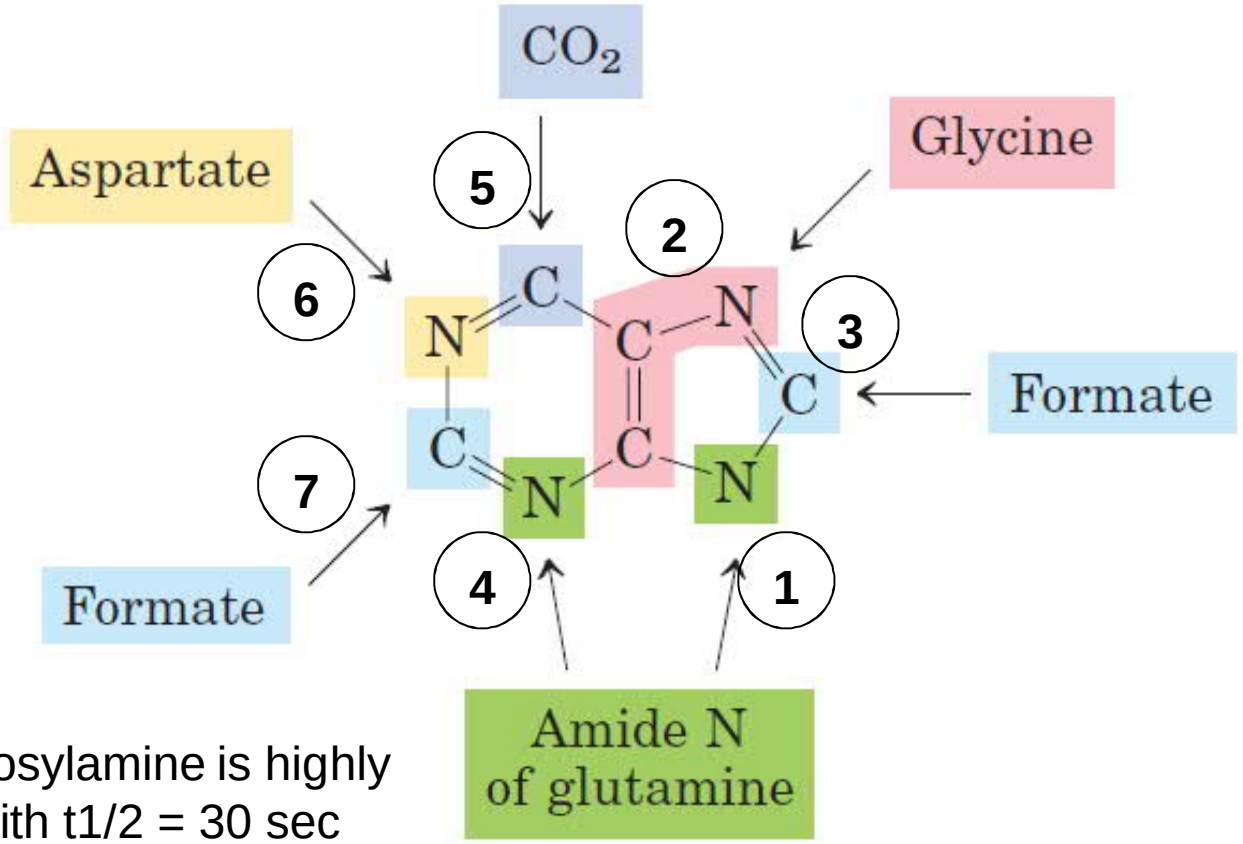
(PRPP)



Inosinate (IMP)

Each atom of base is built sequentially on ……. molecule by multi-enzyme complex





5-phosohoribosylamine is highly unstable, with t1/2 = 30 sec

FIGURE 22–32 Origin of the ring atoms of purines. This information was obtained from isotopic experiments with ^{14}C- or ^{15}N-labeled precursors. Formate is supplied in the form of N^{10}-formyltetrahydrofolate.

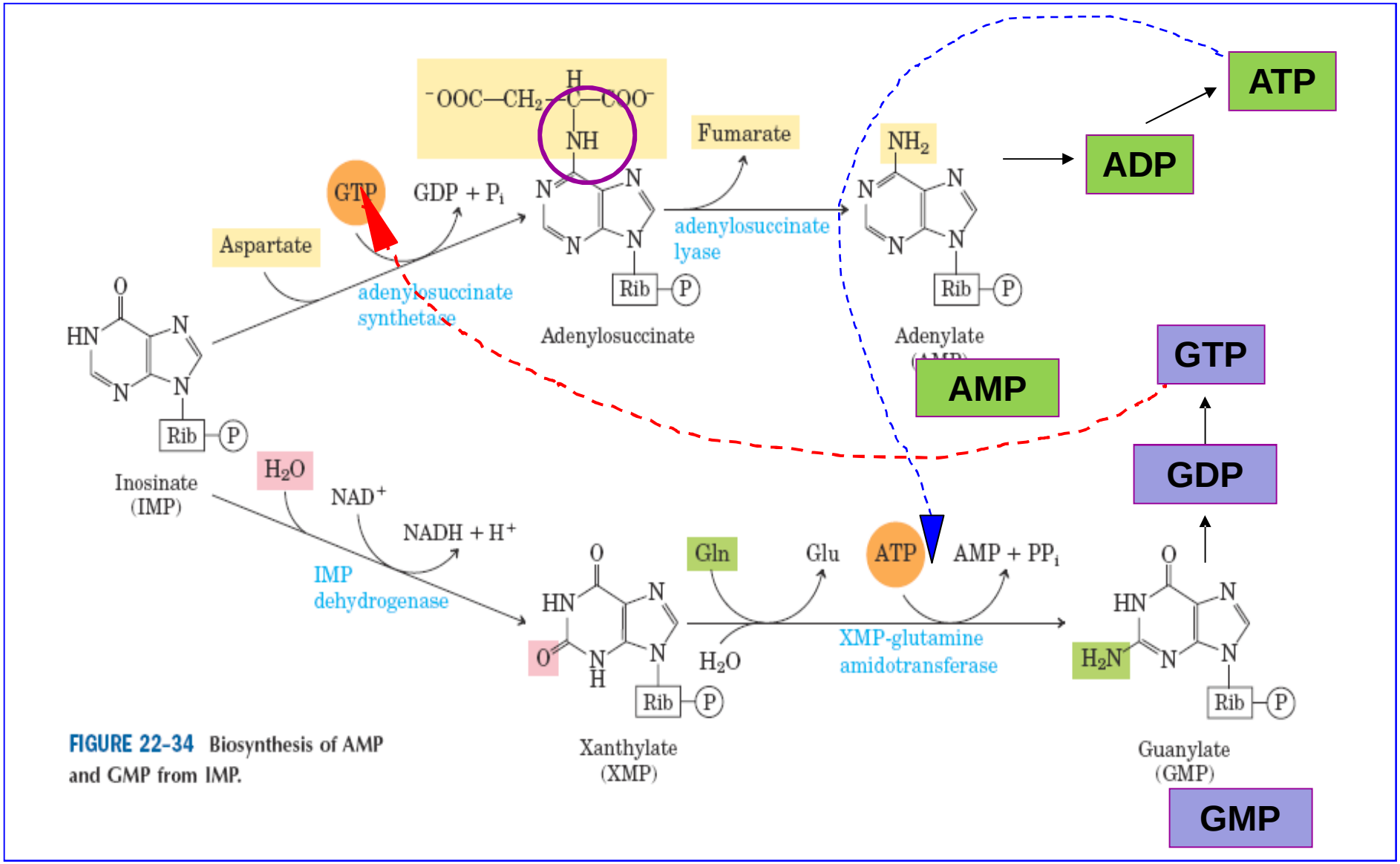
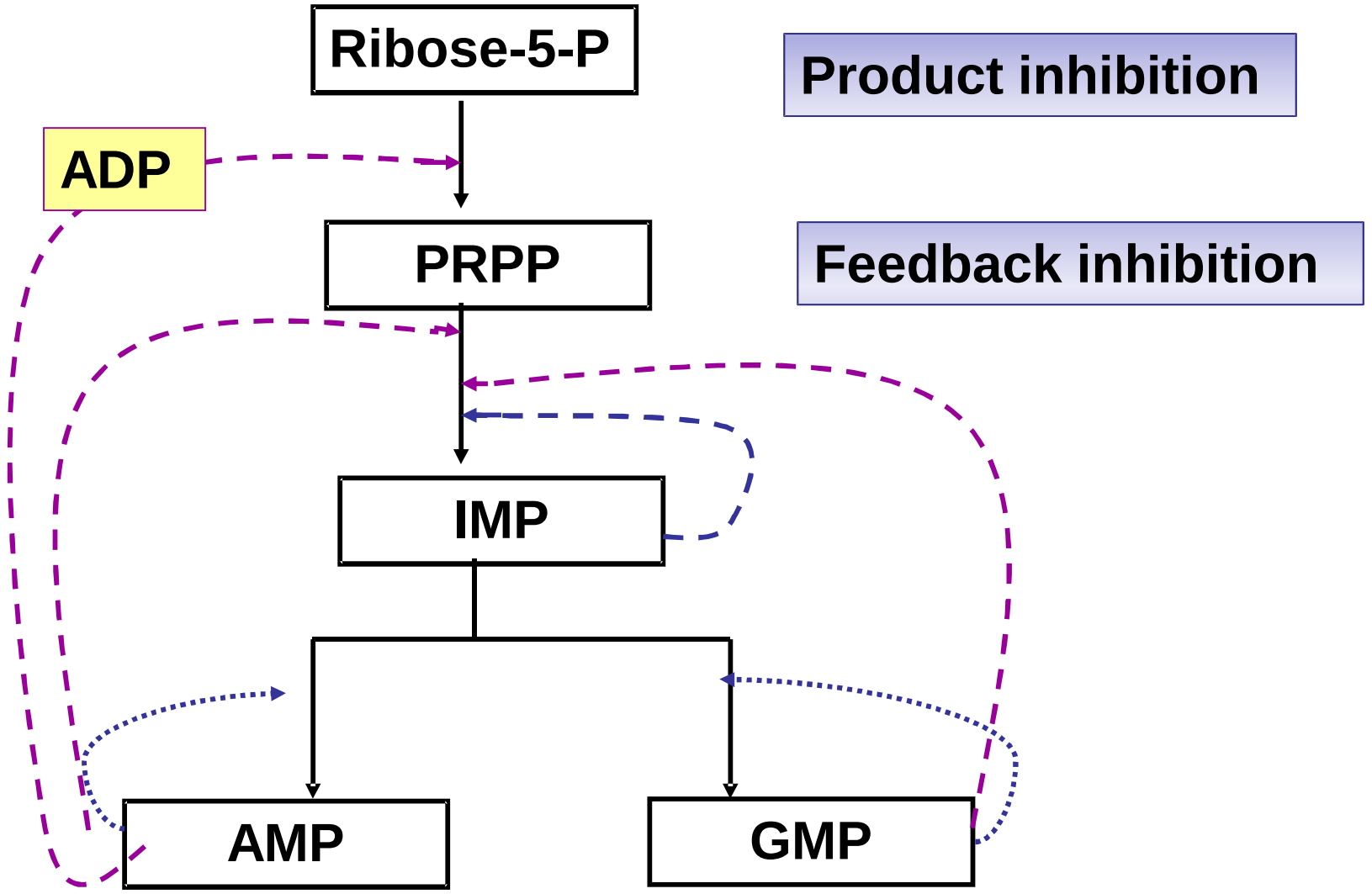


FIGURE 22-34 Biosynthesis of AMP and GMP from IMP.

Regulation of purine synthesis



De novo synthesis of purine NT

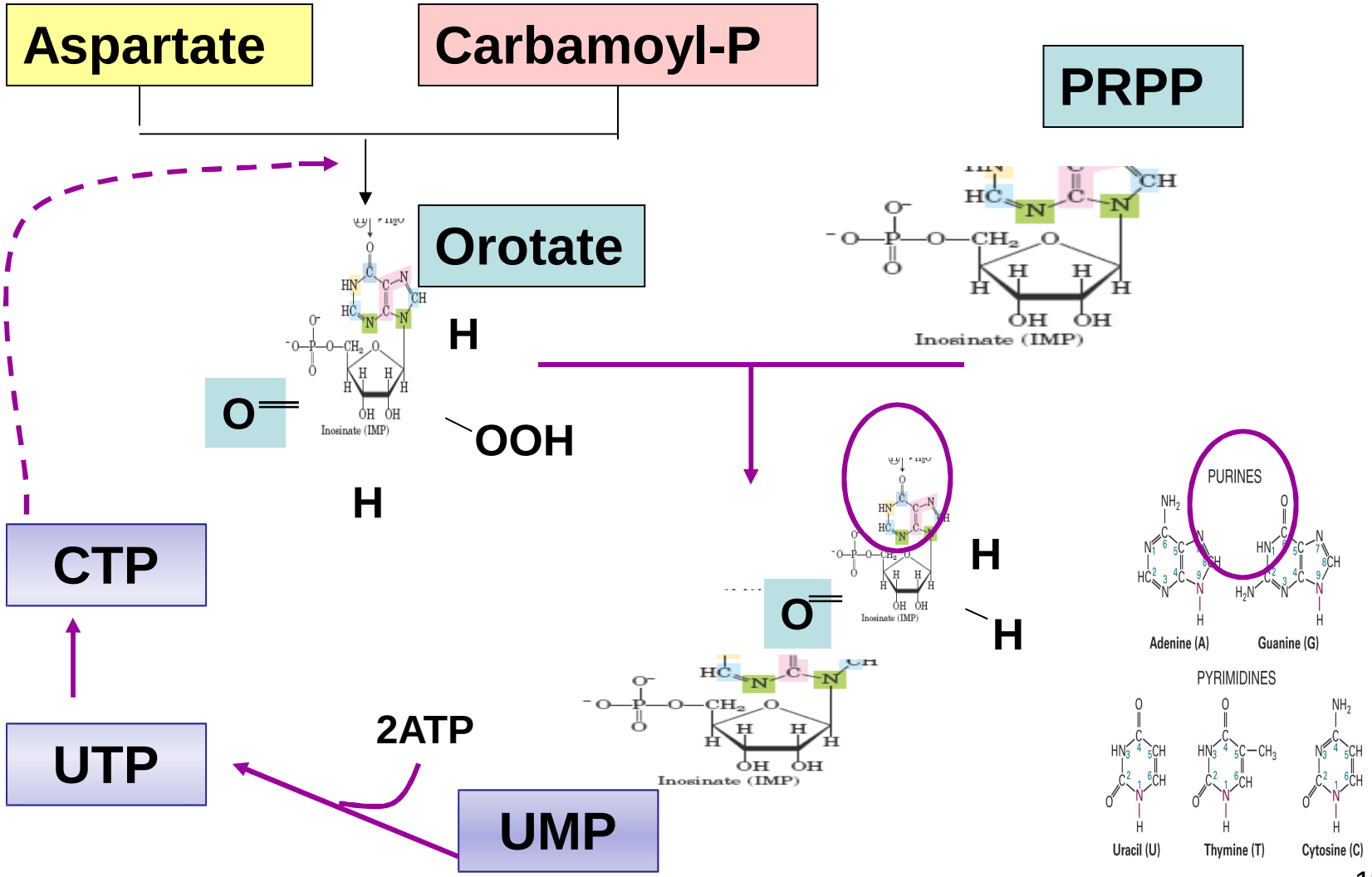
1. สร้างแต่ละส่วนของเบสบน .....
2. องค์ประกอบของเบสได้จาก กรดอะมิโน Gly,Asp,Gln; formate และ CO_2
3. โมเลกุลกลางถูกสร้างขึ้นคือ ..... ซึ่งเป็นสารตั้งต้นในการสร้าง ATP และ GTP
4. ข้อสังเกต การสังเคราะห์ ATP ต้องใช้ GTP และ

   การสังเคราะห์ GTP ต้องใช้ ATP

ซึ่งเป็นวิธีหนึ่งในการควบคุมสารทั้งสองให้มี ปริมาณ ใกล้เคียง กัน

5. เนื่องจากการสร้าง NT ต้องใช้พลังงาน จึงมีระบบการ feedback จาก product (..... inhibition) หากมีการสร้างมากเกินความจำเป็น

De novo synthesis of pyrimidine



De novo synthesis of pyrimidine NT

1. สร้างเบสเรียบร้อยก่อนจึงต่อเข้ากับ PRPP
2. องค์ประกอบของเบสได้จาก Asp และ carbamoyl-P
3. โมเลกุลกลางถูกสร้างขึ้นคือ UMP ซึ่งเป็นสารตั้งต้นในการสร้าง UTP และ CTP สำหรับสร้าง RNA ต่อไป
4. ข้อสังเกต การสังเคราะห์ ATP ต้องใช้ GTP และ

   การสังเคราะห์ GTP ต้องใช้ ATP

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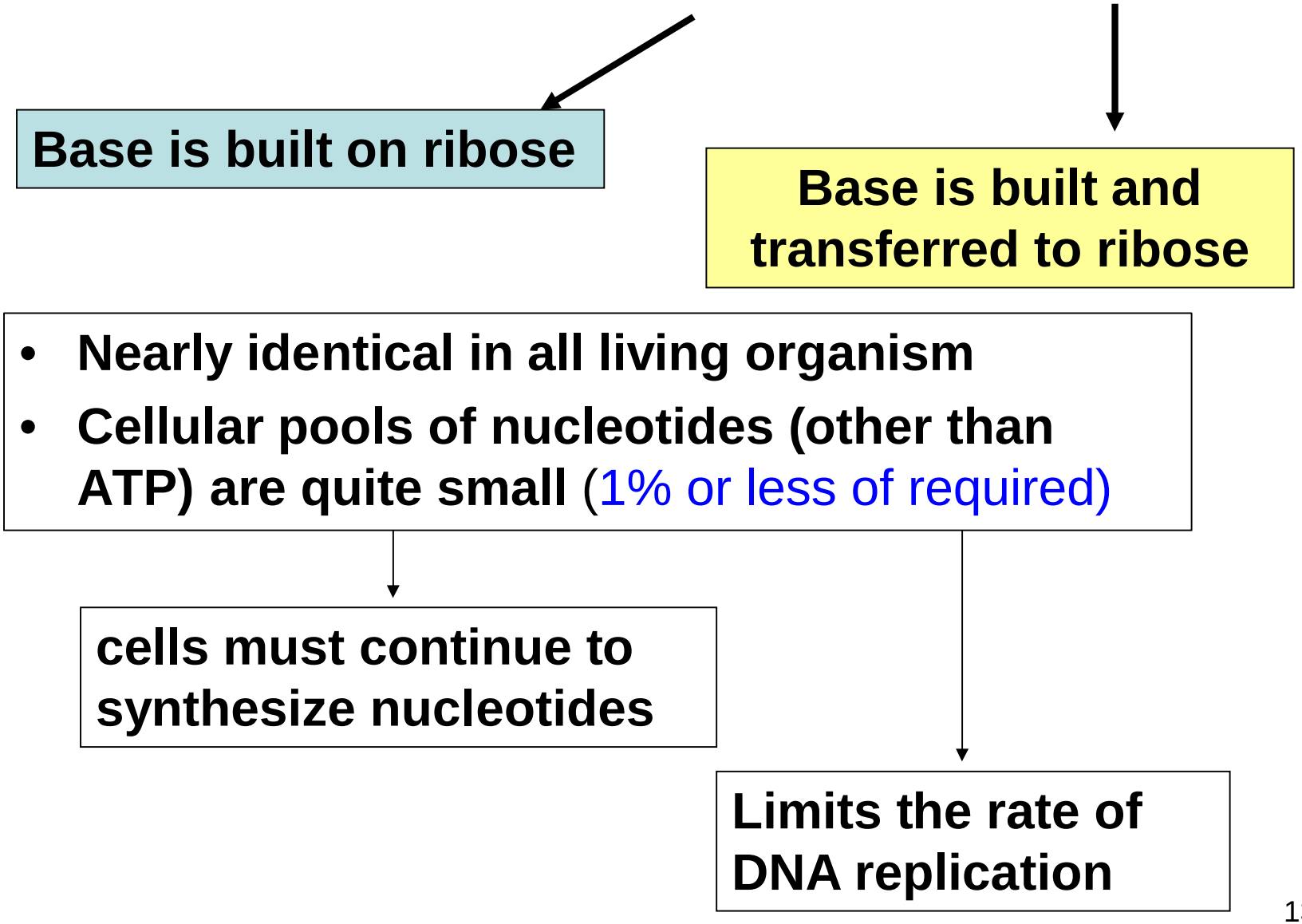
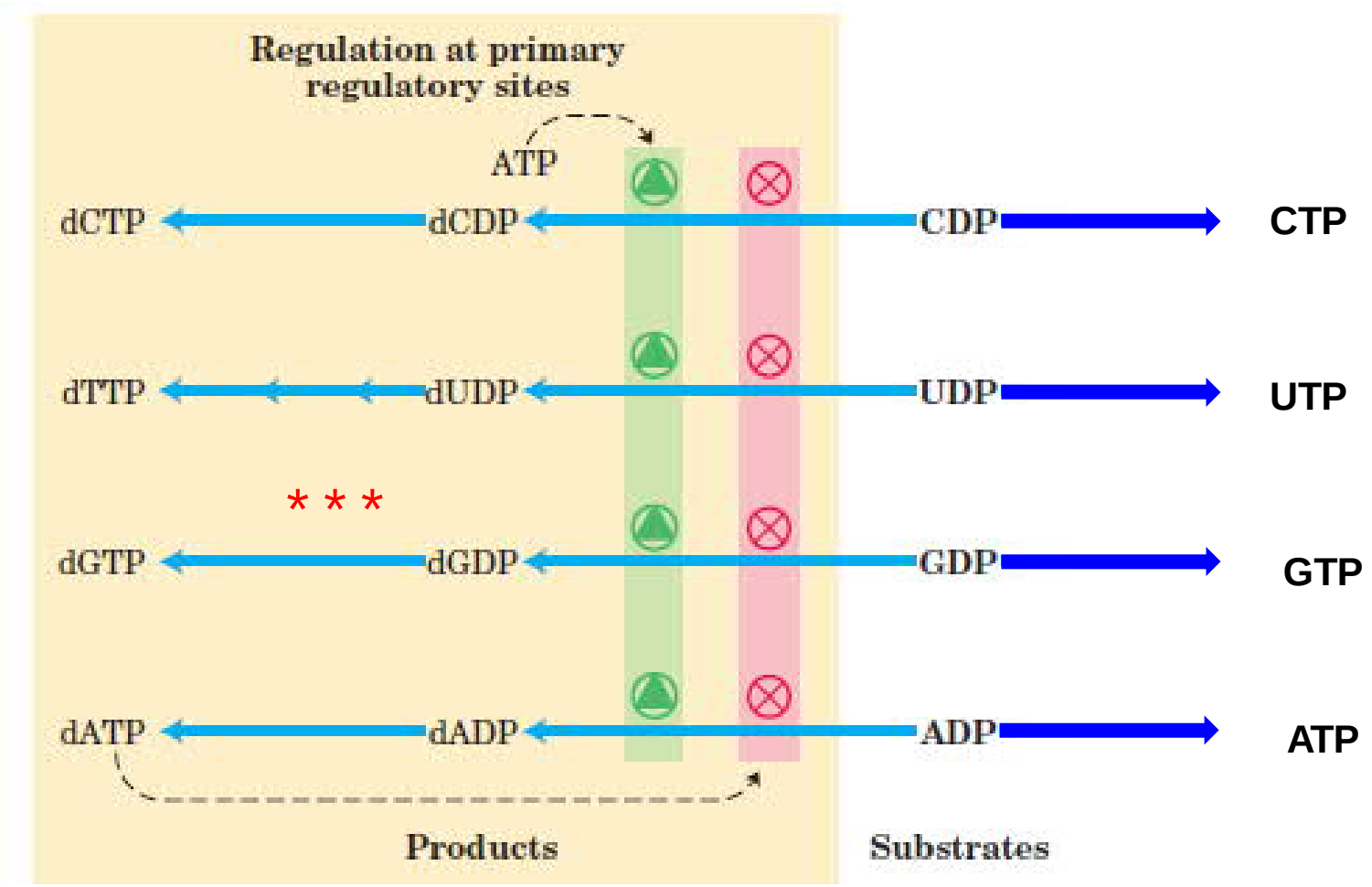
De novo pathways of purine and pyrimidine



Deoxyribonucleotides are synthesized from ribonucleotides

Ribonuclotide reductase

Deoxyribonucleotides ⟵ **Ribonucleotides**



Deoxyribonucleotides ⟸ ribonucleotides

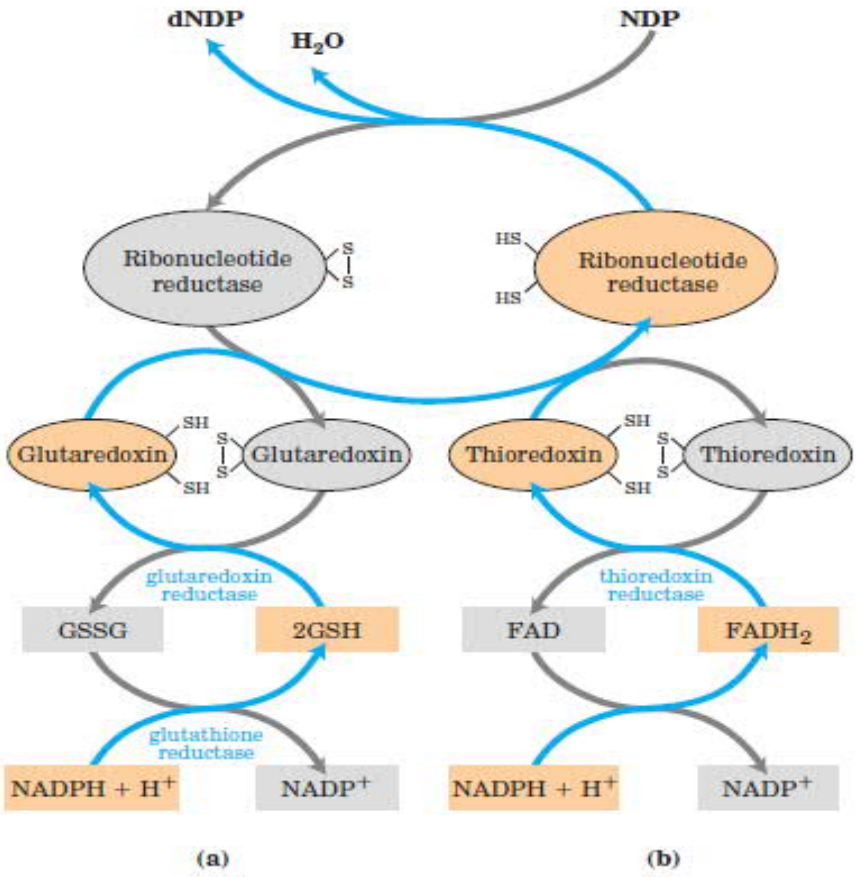
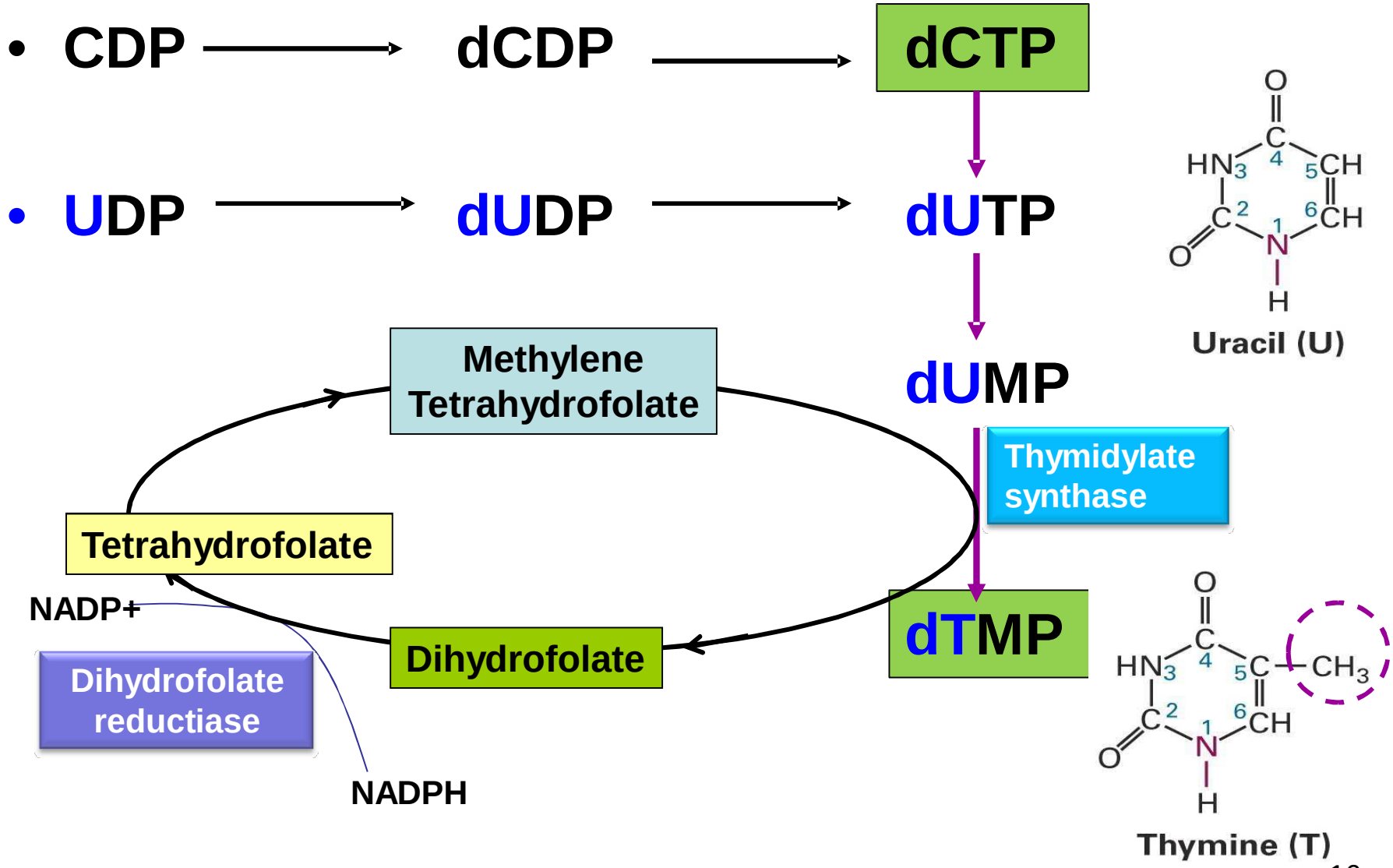
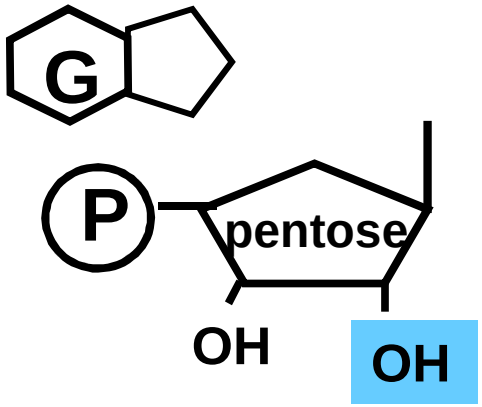


FIGURE 22–39 Reduction of ribonucleotides to deoxyribonucleotides by ribonucleotide reductase. Electrons are transmitted (blue arrows) to the enzyme from NADPH via **(a)** glutaredoxin or **(b)** thioredoxin. The sulfide groups in glutaredoxin reductase are contributed by two molecules of bound glutathione (GSH; GSSG indicates oxidized glutathione). Note that thioredoxin reductase is a flavoenzyme, with FAD as prosthetic group.


CDP
dCDP
dCTP
UDP
dUDP
dUTP
dUMP
Methylene Tetrahydrofolate
Thymidylate synthase
Tetrahydrofolate
NADP+
Dihydrofolate
dTMP
Dihydrofolate reductiase
NADPH
Uracil (U)
Thymine (T)

Salvage Pathway

Free purine bases



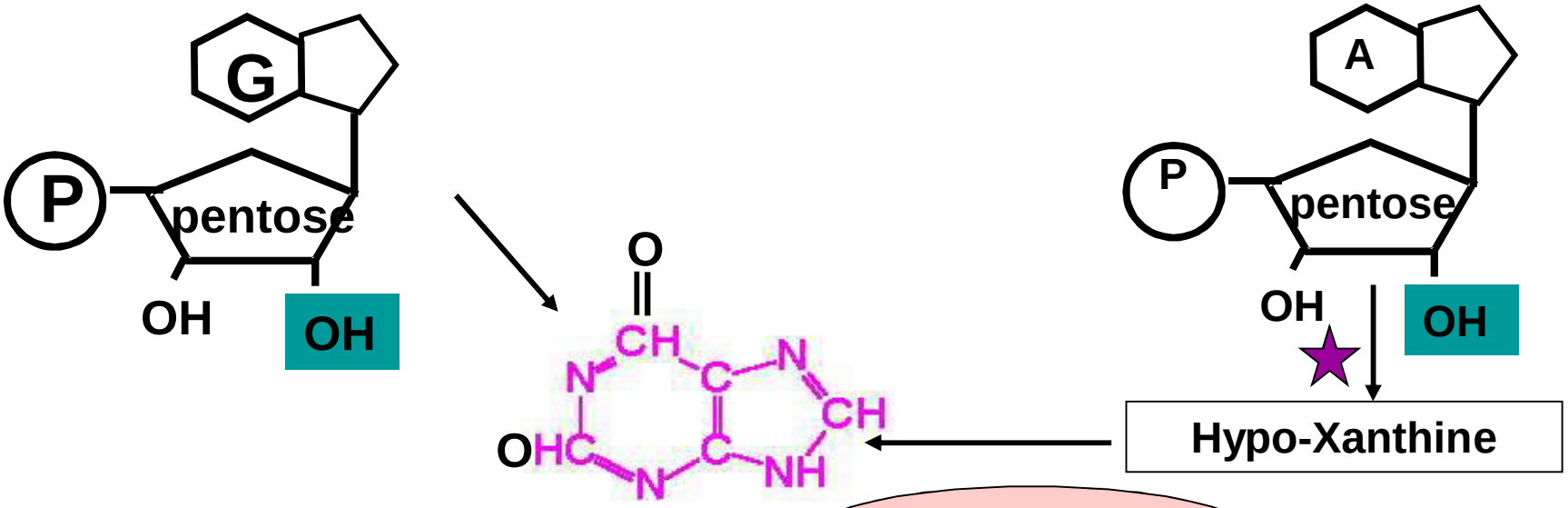
Hypoxanthine-guanine phosphoribosyltransferase

A genetic disorder, lacking of Hypoxanthine-guanine phosphoribosyltransferase, results in Lesch-Nyhan syndrome

Hypoxanthine and guanine arise constantly from the breakdown of nucleic acids. PRPP levels rise and purines are overproduced by the de novo pathway → high uric acid production → goutlike damage to tissue. Brain is especially dependent on the salvage pathways.

Seen almost in male children by the age of 2 years, poorly coordinated and mentally retarded. They are extremely aggressive and show compulsive self-destructive tendencies: they hurt themselves by biting off their fingers, toes, and lips.

Catabolism



Adenosine deaminase

Deficiency of this enzyme leads to severe immuno-deficiency disease ⟶ do not survive unless isolated in a sterile "bubble" environment.

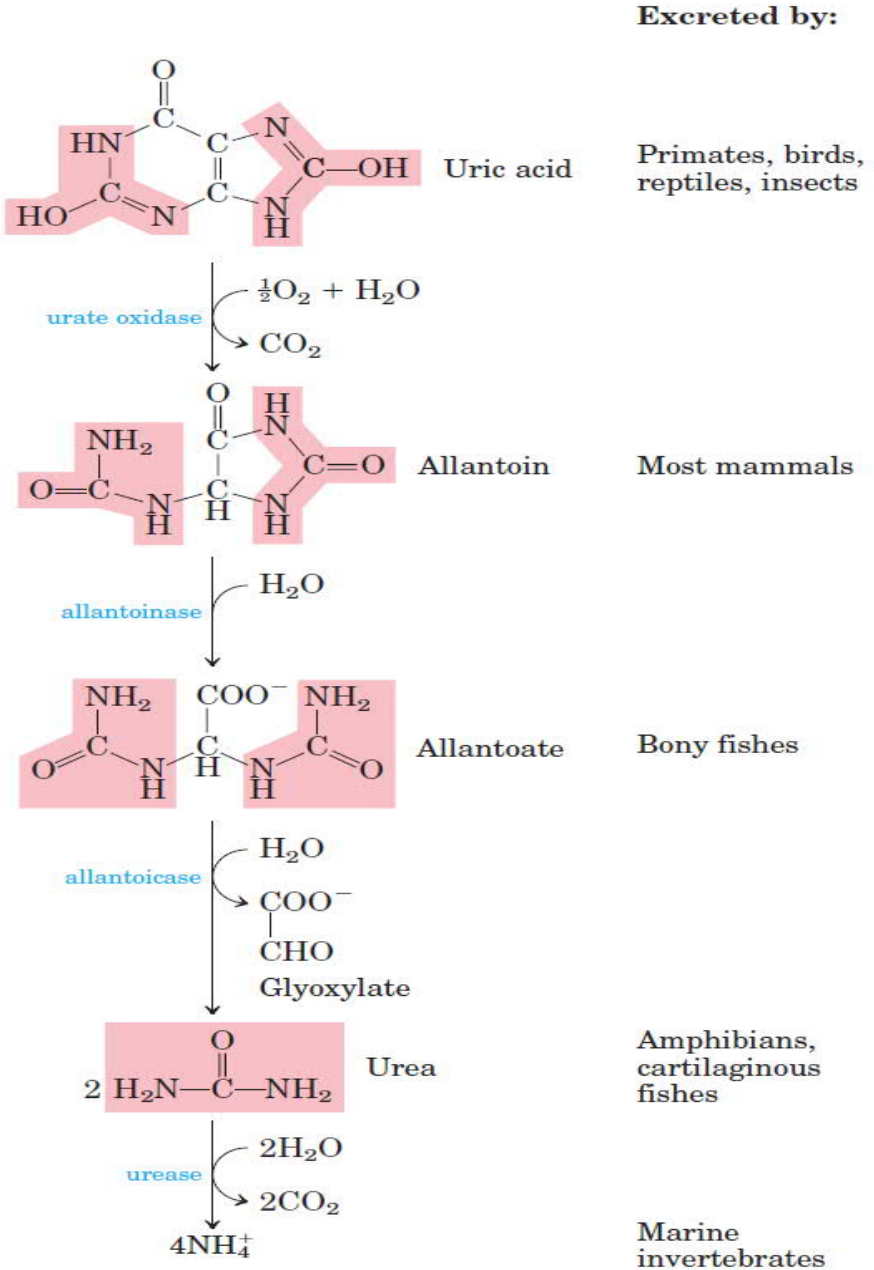
High level of dATP inhibits ribonucleotide reductase→ dNTP deficiency

Human

Excrete Uric acid 0.6 g/24h

. . . . . .

End products of purine catabolism



Uric acids	**Primate, birds, reptiles, insects**
Allantoin	**Most mammals**
Allantoate	**Bony fishes**
Urea	**Amphibians, cartilaginous fishes**
Ammonia	**Marine invertebrate**

Low nucleotide ……

High ……in blood and tissues

Excess uric acid deposited in joints, kidney

Drug

Sodium urate crystal

Inflamed, painful, arthritic

……

Gertrude Elion (1918–1999) and
George Hitchings (1905–1998)

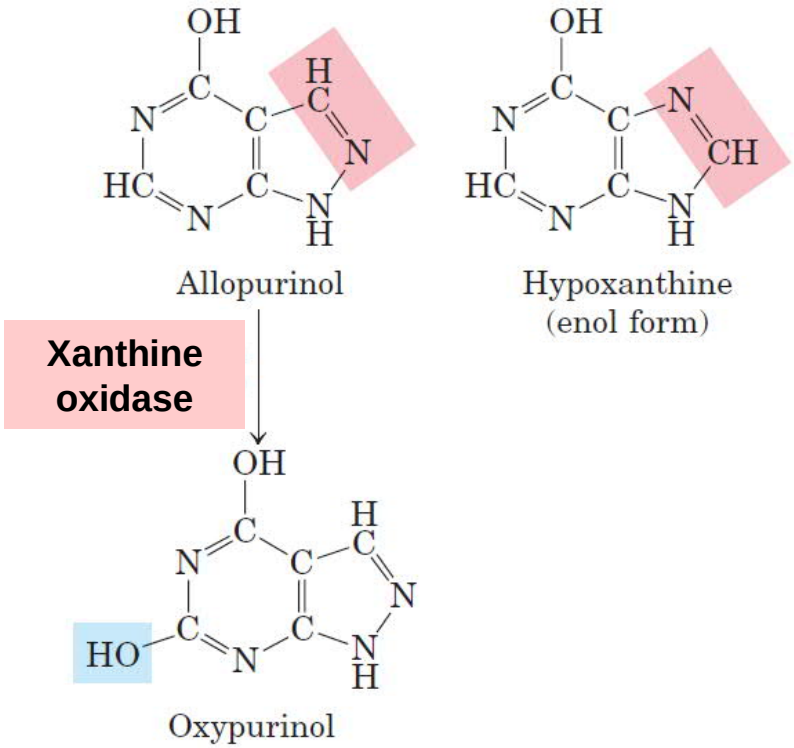
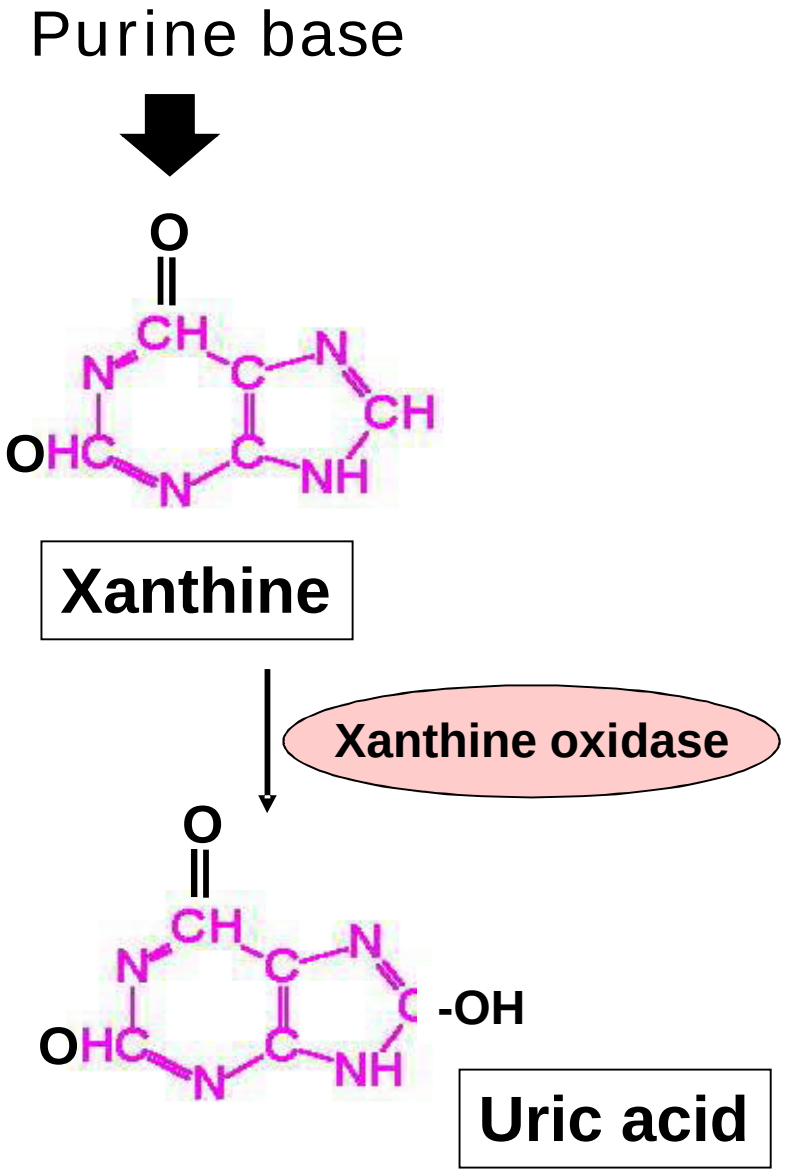
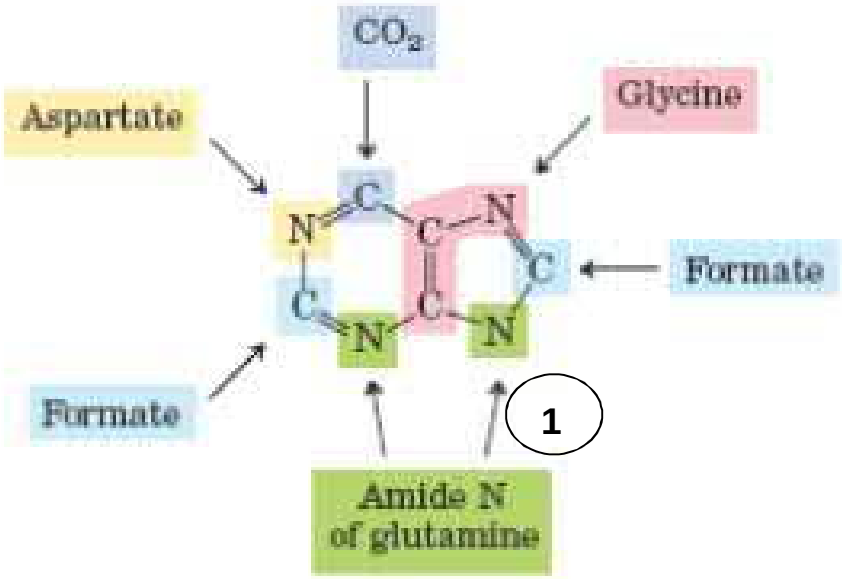
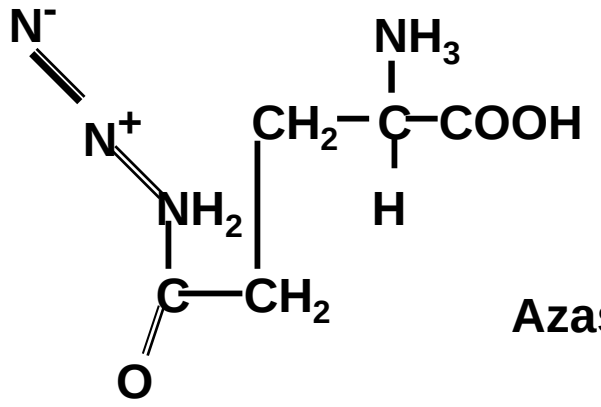


FIGURE 22–47 Allopurinol, an inhibitor of xanthine oxidase. Hypoxanthine is the normal substrate of xanthine oxidase. Only a slight alteration in the structure of hypoxanthine (shaded pink) yields the medically effective enzyme inhibitor allopurinol. At the active site, allopurinol is converted to oxypurinol, a strong competitive inhibitor that remains tightly bound to the reduced form of the enzyme.

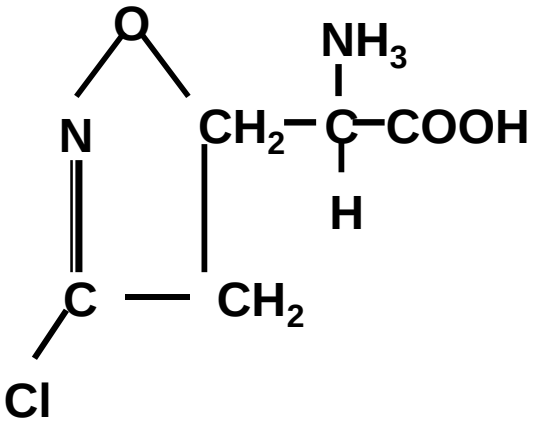


Many chemotherapeutic agents target enzymes in the nucleotide biosynthesis pathways

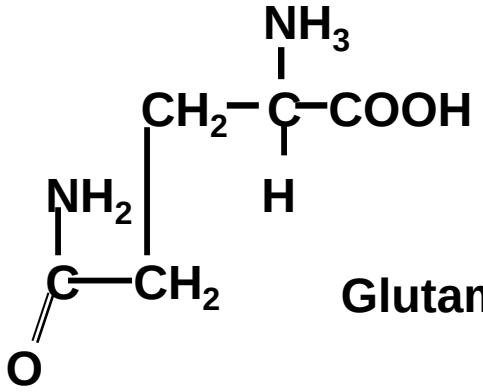




Azaserine



Acivicin



Glutamine

Glutamine analogs inactivate enzyme in de novo synthesis

Anticancer drugs:
Inhibit DNA synthesis