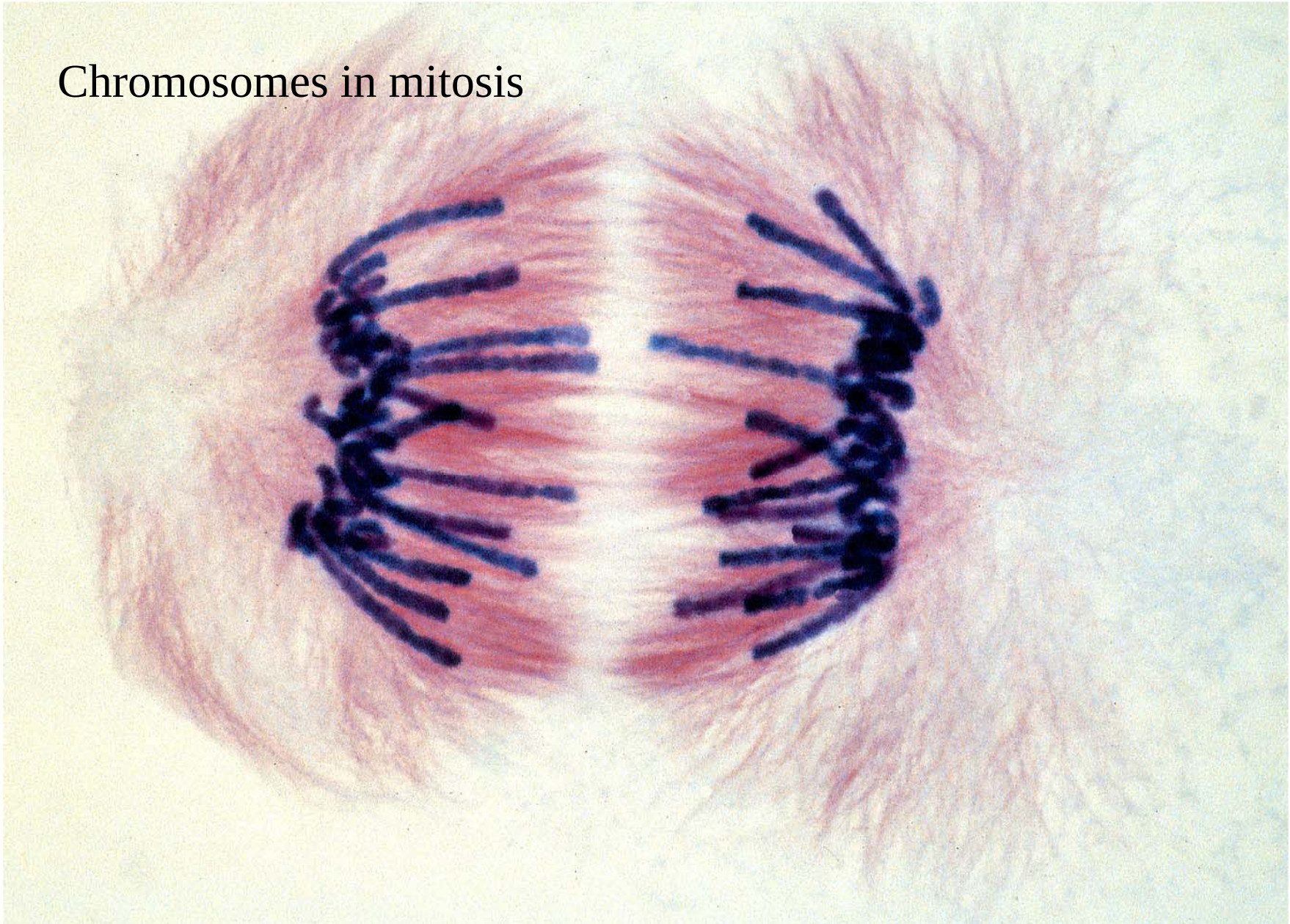
Nucleotide Metabolism

Chromosomes in mitosis



Synthesis of ribonucleotide
Purine
Pyrimidine

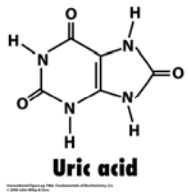
De novo synthesis
Salvage pathway

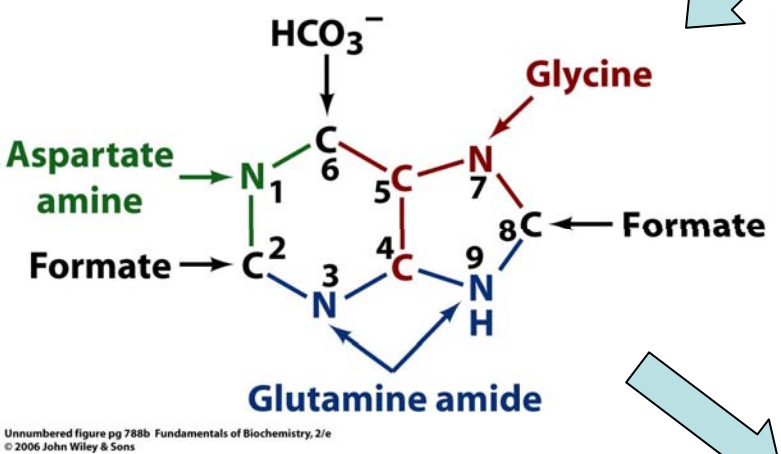
Synthesis of deoxyribonucleotide

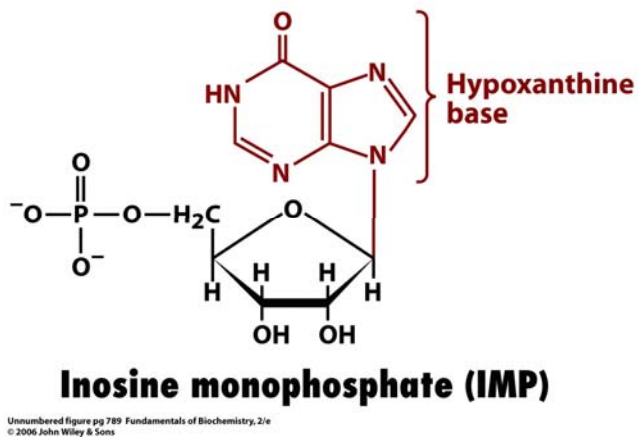
http://web.indstate.edu/thcme/mwking/nucleotide-metabolism.html

De novo synthesis of purine ribonucleotides

Isotopically labeled compounds







The precursor of AMP & GMP

de novo synthesis of IMP

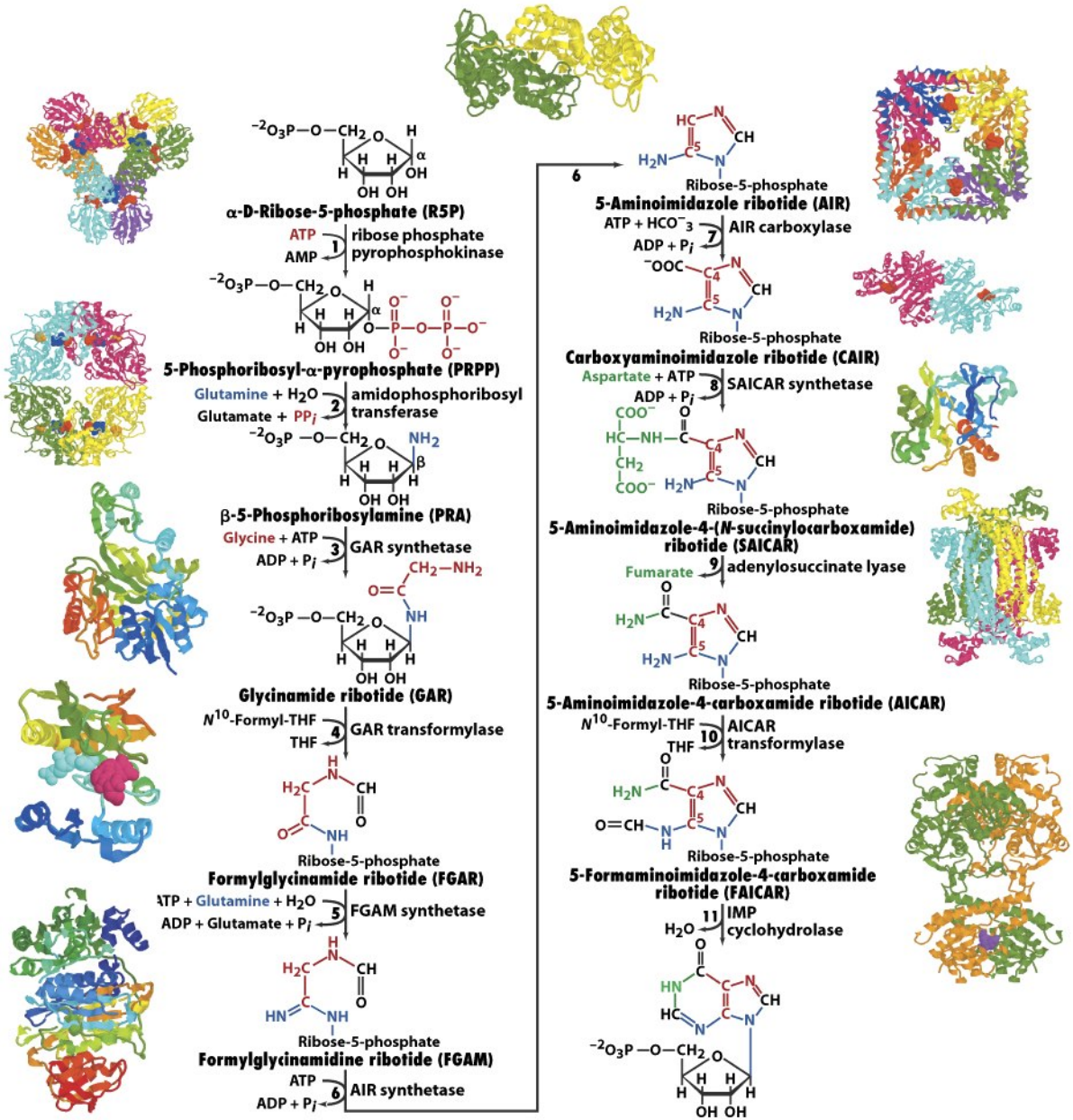


Figure 22-1 Fundamentals of Biochemistry, 2/e

Synthesis of adenine and guanine ribonucleotides

Rapid conversion of IMP to AMP & GMP in two-step reactions

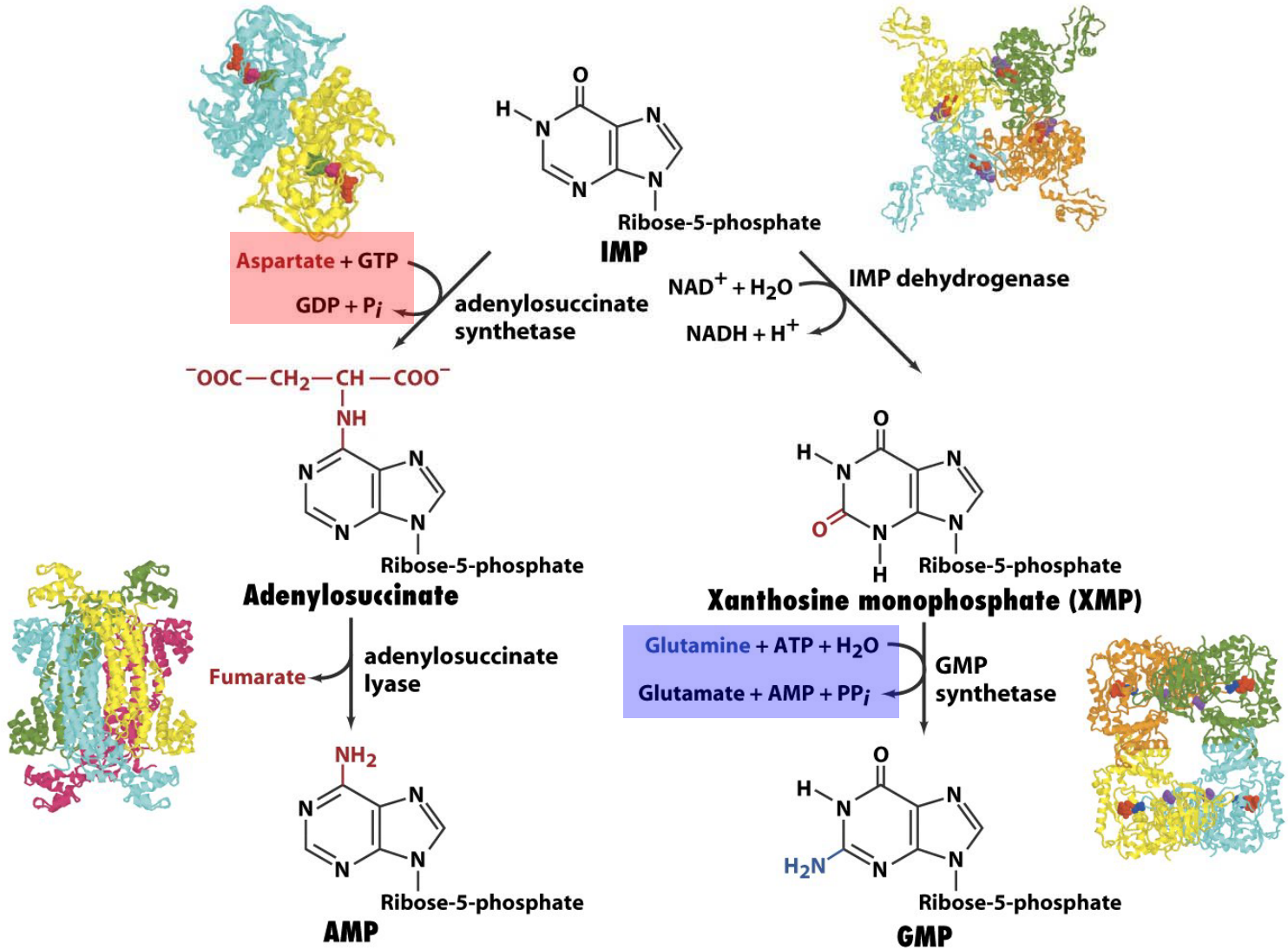


Figure 22-3 Fundamentals of Biochemistry, 2/e

Synthesis of di- and triphosphates

Nucleoside monophosphate kinases (don't discriminate between ribose and deoxyribose)

Adenylate kinase: AMP + ATP ↔ 2 ADP

Guanylate kinase: GMP + ATP ↔ GDP + ADP

Nucleoside diphosphate kinase (no preference for bases or for ribose over deoxyribose)

GDP + ATP ↔ GTP + ADP

Salvage pathway of purines

Adenine phosphoribosyltransferase (APRT)

Adenine + PRPP ↔ AMP + PPi

Hypoxanthine-guanine phosphoribosyltransferase (HGPRT): higher in brain

hypoxanthine + PRPP ↔ IMP + PPi

guanine + PRPP ↔ GMP + PPi

Lesch-Nyhan syndrome: HGPRT deficiency

X-linked recessive

Self-mutilation

Excess uric acid production:

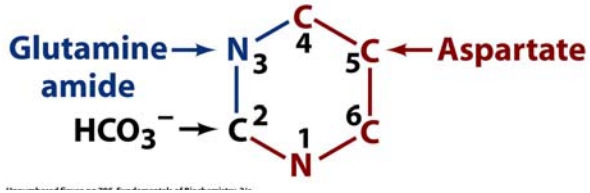
Accumulation of PRPP

Activate amidophosphoribosyl transferase

Accelerated synthesis of purine nucleotides

Synthesis of pyrimidine ribonucleotides

Synthesis of UMP



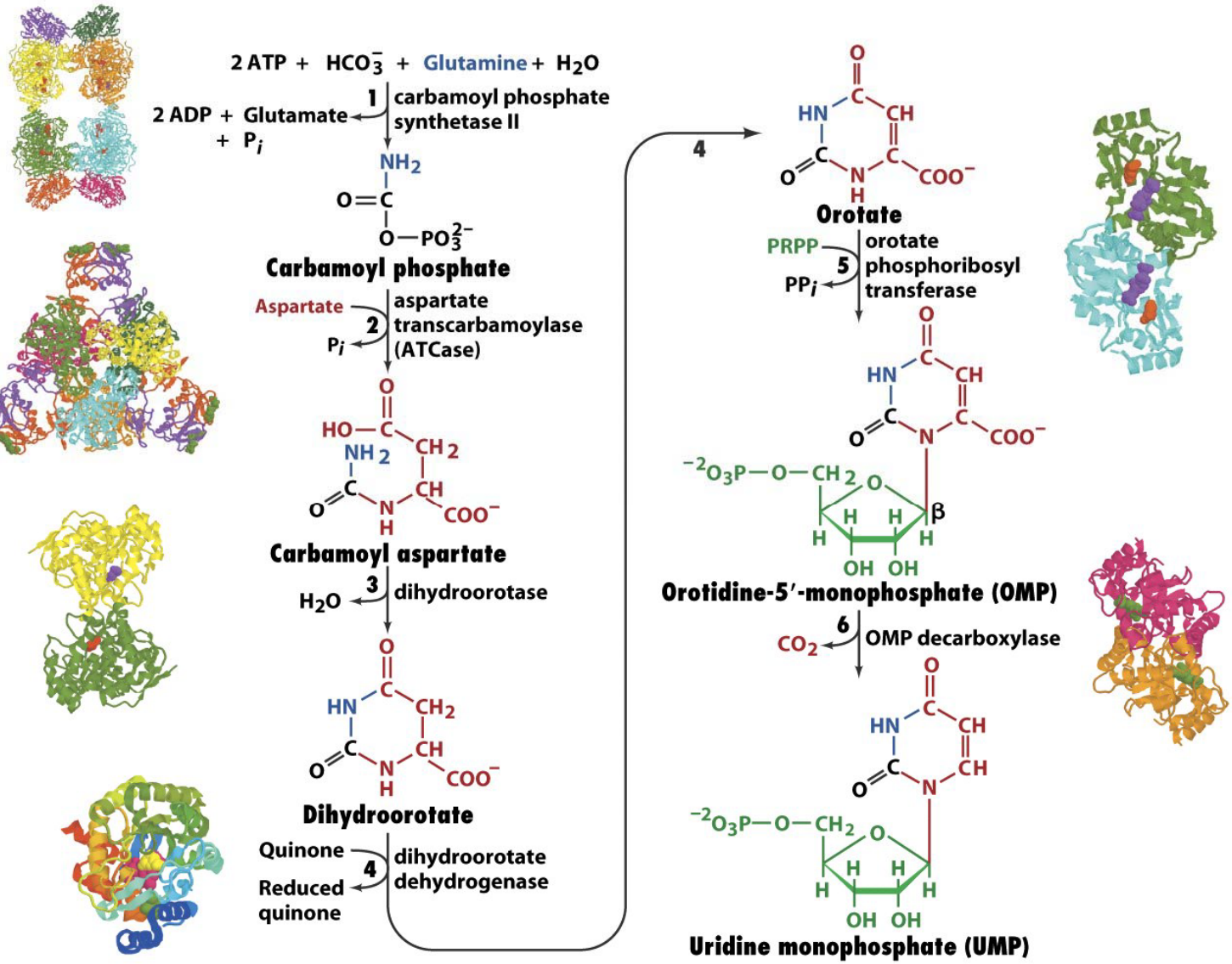


Figure 22-5 Fundamentals of Biochemistry, 2/e

Salvage synthesis

Uracil to UMP — Uridine phosphorylase: uracil + ribose-1-P → uridine + Pi
Uridine kianse: uridine (or cytidine) + ATP → UMP + ADP

Thymine to dTMP — Thymine phosphorylase: thymine + deoxyribose-1-P → thymidine + Pi
Thymidine kinase: thymidine + ATP → dTMP + ADP

Deoxycytidine kinase: deoxycytidine + ATP → dCMP + ADP

Synthesis of UTP and CTP

Same as purine nucleoside triphosphates

UMP + ATP ↔ UDP + ADP (nucleoside monophosphate kinase)

UDP + ATP ↔ UTP + ADP (nucleoside diphosphate kinase)

CTP synthetase: amination of UTP to CTP

The source of amino group (glutamine in animal, ammonia in bacteria)

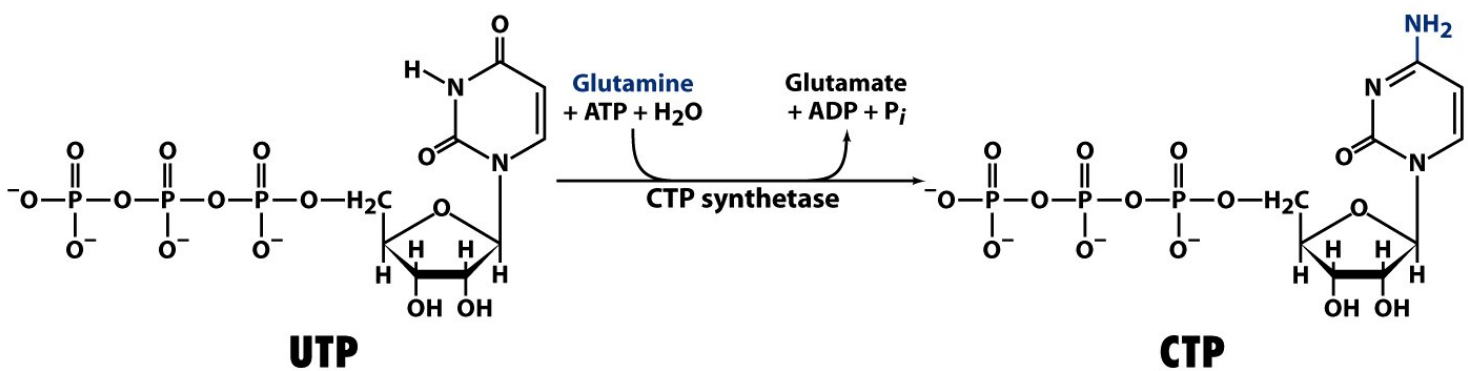


Figure 22-7 Fundamentals of Biochemistry, 2/e

Regulation of Pyrimidine nucleotide biosynthesis

Bacteria: allosteric regulation of ATCase
Animals:
- allosteric regulation of carbamoyl phosphate synthetase II
- OMP decarboxylase: competitive inhibition by UMP & CMP

<u>Orotic aciduria</u>
Deficiency of bifunctional enzyme (step 5 & 6)
Retarded growth and severe anemia
Administration of uridine/cytidine
Converted to UMP by phosphorylation
Inhibits carbamoyl phosphosphate synthetase II

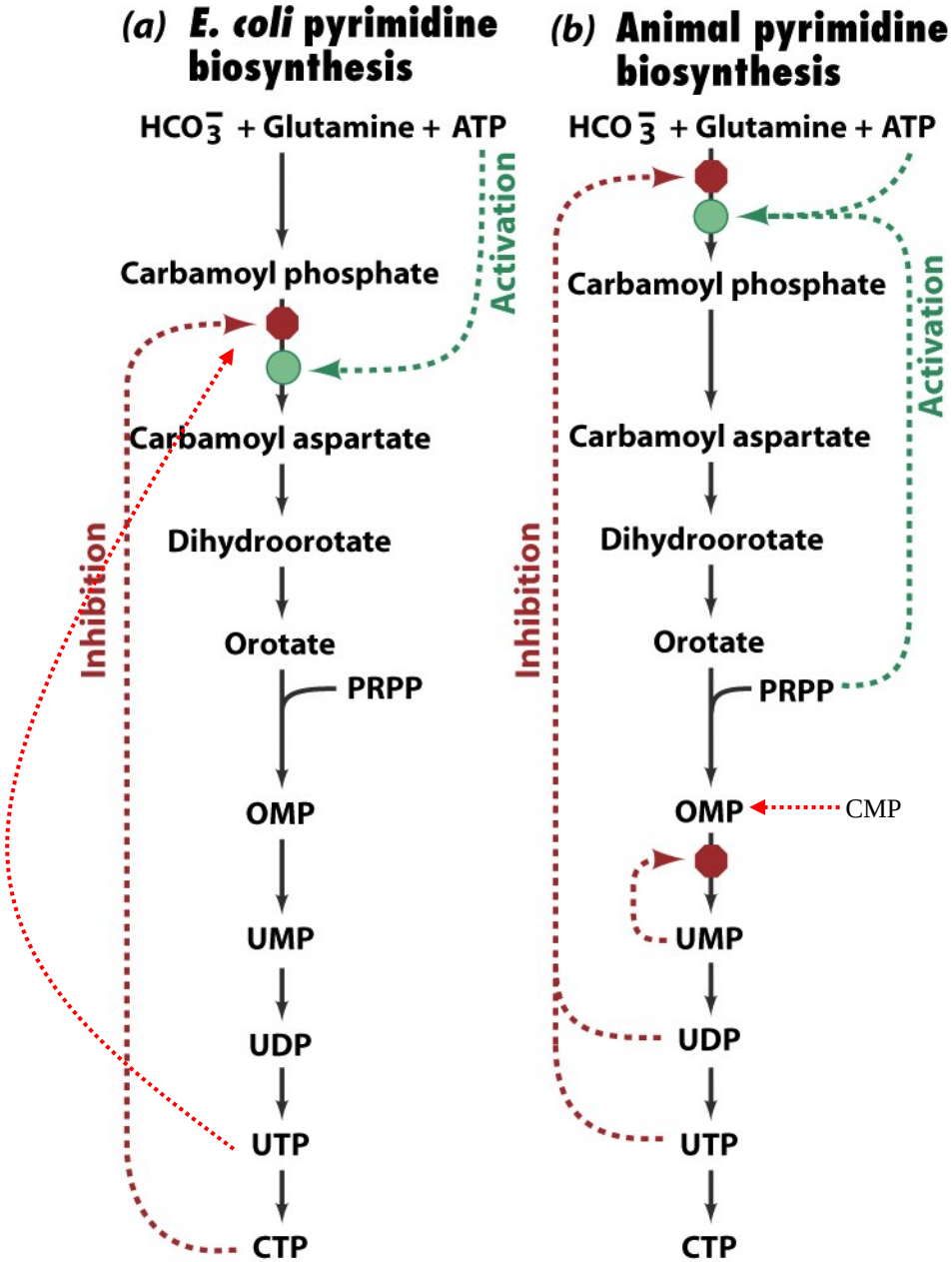


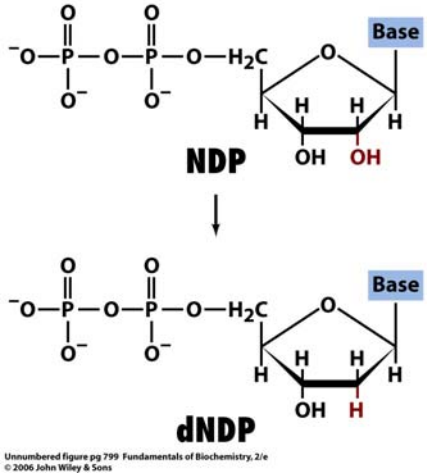
Figure 22-8 Fundamentals of Biochemistry, 2/e

Formation of deoxyribonucleotides

DNA has 2'-deoxyribose & thymine (5-methyluracil)

Production of deoxyribose residues

Ribonucleotide reductases (RNRs)
3 classes: differ in their prosthetic groups
Class I RNRs (most eukaryotes and aerobic prokaryotes)
Heterotetramer: inactive heterodimeric $R1_2$ and $R2_2$



Unnumbered figure pg 799 Fundamentals of Biochemistry, 2/e
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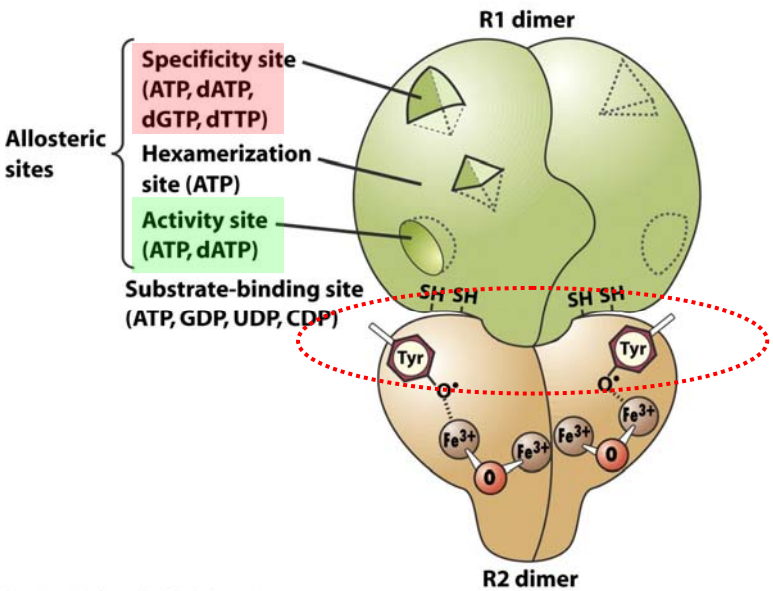

Figure 22-9a Fundamentals of Biochemistry, 2/e
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$R2_2$

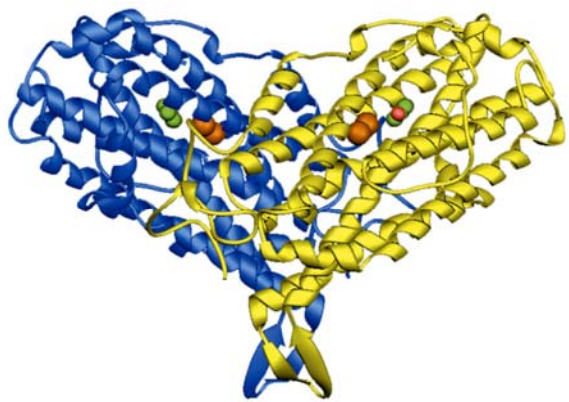
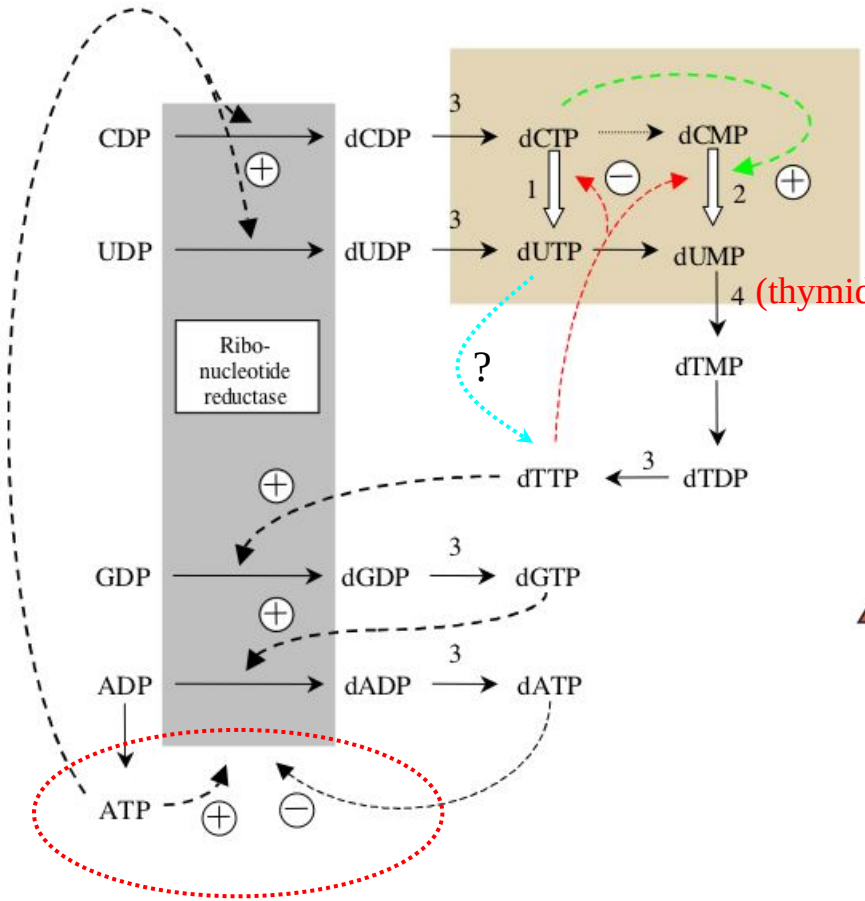


Figure 22-9b Fundamentals of Biochemistry, 2/e

Regulation of RNR

Proper intracellular ratios of the four dNTPs by a complex feedback network

Deficiency of any of dNTPs is lethal, whereas an excess is mutagenic



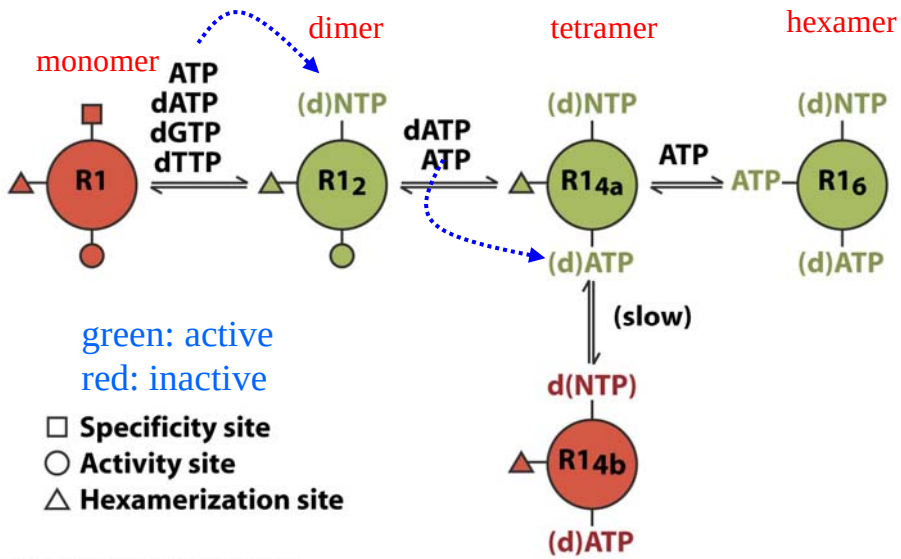


Figure 22-13 Fundamentals of Biochemistry, 2/e
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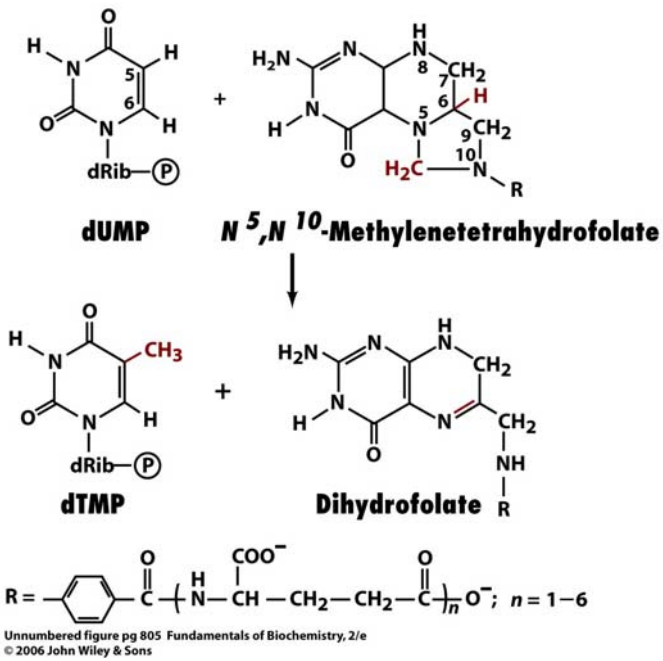
Thymidylate synthase



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Reduction of methylene to methyl at the expense of the oxidation of THF to DHF

Anticancer targets

DHFR

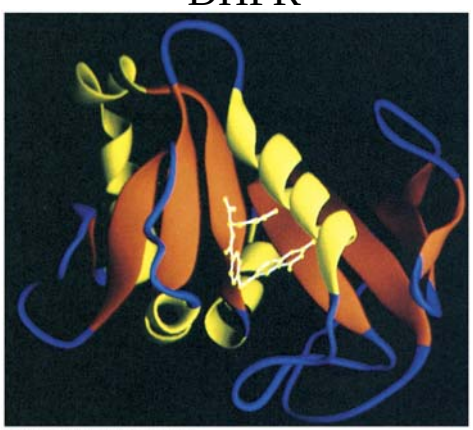


Figure 22-17 Fundamentals of Biochemistry, 2/e

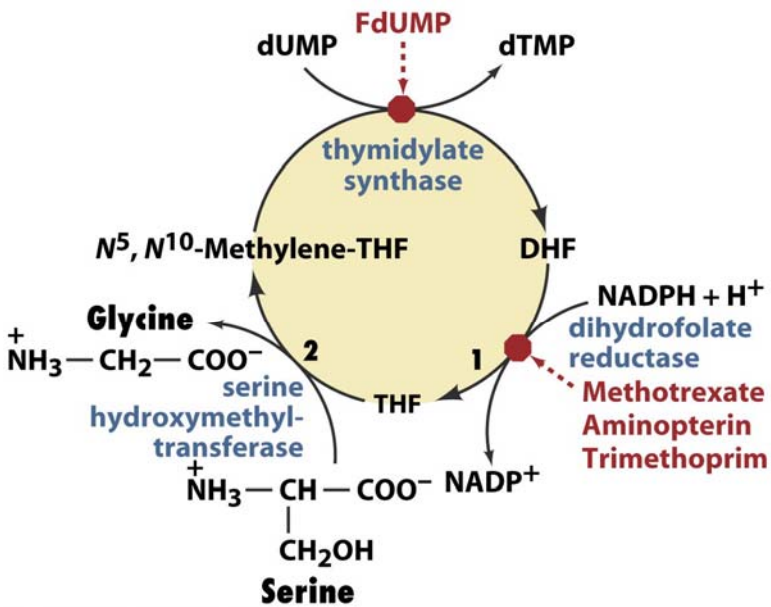


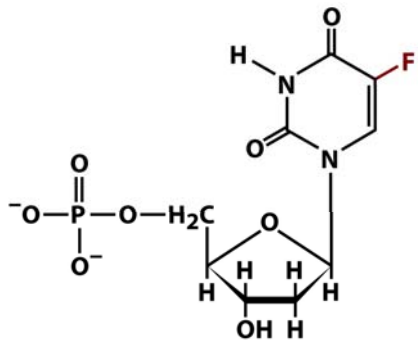
Figure 22-16 Fundamentals of Biochemistry, 2/e

Thymidylate synthase inhibitor: anticancer

FdUMP: suicide substrate (mechanism-based inhibitor)

DHFR inhibitors: anticancer & antibacterial

antifolates



5-Fluorodeoxyuridylate (FdUMP)

Box 22-1 figure 1 Fundamentals of Biochemistry, 2/e
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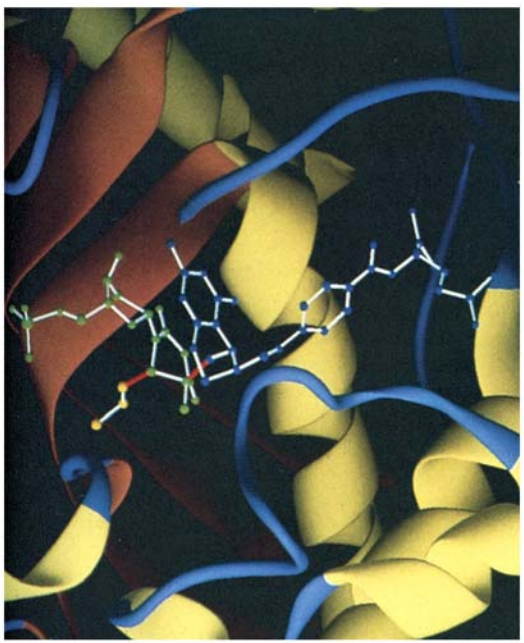
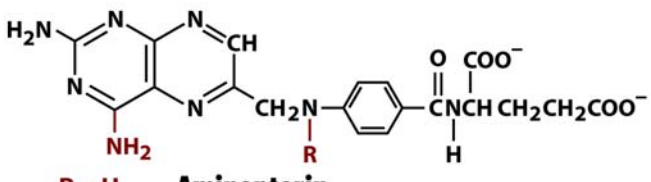
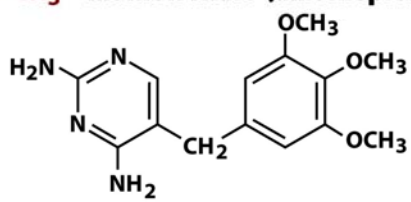


Box 22-1 figure 2 Fundamentals of Biochemistry, 2/e



R = H Aminopterin

R = CH_3 Methotrexate (amethopterin)



Trimethoprim

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Nucleotide degradation

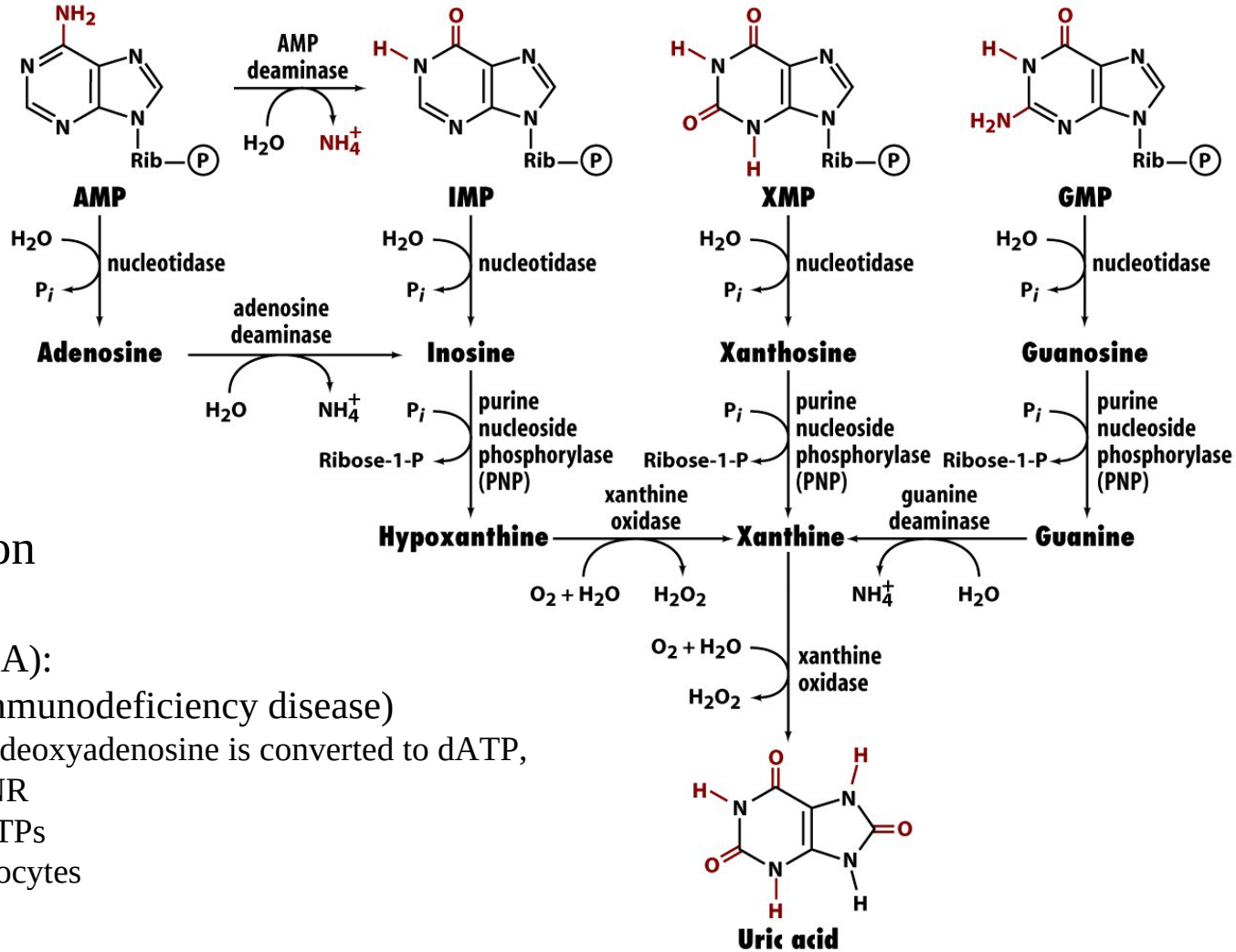


Figure 22-18 Fundamentals of Biochemistry, 2/e

Adenosine deaminase (ADA):

SCID (severe combined immunodeficiency disease)

- In the absence of ADA, deoxyadenosine is converted to dATP, which inhibits RNR
- Prevent synthesis of dNTPs
- Selective killing of leukocytes

Gout is caused by an excess of uric acid

Affects ~3 per 1000 persons

Impaired uric acid excretion: deposition of sodiumurate crystal

HGPRT deficiency

Treatment with allopurinol (xanthine oxidase inhibitor)

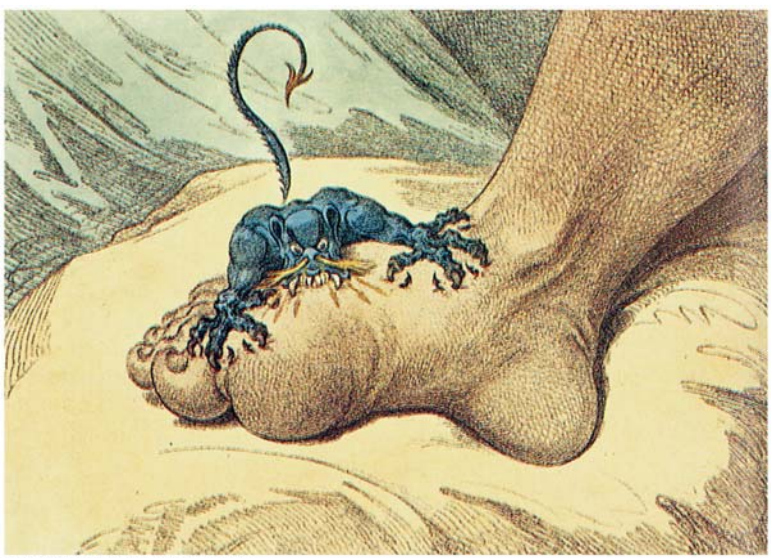
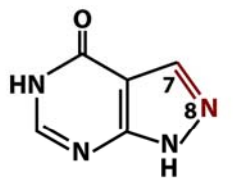
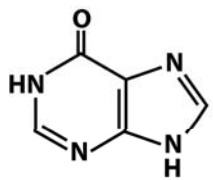


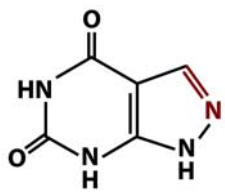
Figure 22-22 Fundamentals of Biochemistry, 2/e



Allopurinol



Hypoxanthine



Alloxanthine

Bound to XO,
thereby inactivating it