



Chemotherapeutic Agents: Drugs to Treat Neoplastic Diseases- Section 2- Antimetabolites

SRAmimi Mar2024

PART III ● Pharmacodynamic Agents

SECTION 7 DRUGS IMPACTING INFECTIOUS AND NEOPLASTIC DISEASE PROCESSES

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Victoria F. Roche

Drugs covered or mentioned in this chapter—Continued

PYRIMIDINE ANTAGONISTS

- Capecitabine
- Floxuridine
- Fluorouracil

ANTIFOLATES

- Methotrexate
- Pemetrexed
- Pralatrexate

DNA POLYMERASE INHIBITORS

- Cladribine
- Clofarabine
- Cytarabine
- Fludarabine
- Gemcitabine
- Trifluridine/tipiracil

DNA METHYLTRANSFERASE INHIBITORS

- Azacitidine
- Decitabine
- Nelarabine

MISCELLANEOUS ANTIMETABOLITES

- Hydroxyurea
- Pentostatin

DNA CROSS-LINKING AGENTS

NITROGEN MUSTARDS

- Bendamustine
- Chlorambucil
- Cyclophosphamide
- Ifosfamide
- Mechlorethamine
- Melphalan
- Thiotepa

TRIAZENES AND PROCARBAZINE

- Dacarbazine
- Procarbazine
- Temozolomide

NITROSOUREAS

- Carmustine

- Lomustine
- Streptozocin

ORGANOPLATINUM COMPLEXES

- Carboplatin
- Cisplatin
- Oxaliplatin

MISCELLANEOUS ANTICANCER AGENTS

- Arsenic trioxide
- Bexarotene
- Bleomycin
- Dactinomycin
- Gemtuzumab ozogamicin conjugate
- Inotuzumab ozogamicin conjugate
- Mitomycin
- Mitotane
- Trabectedin
- Tretinoin

Pharmacologic Classification of Chemotherapeutic Agents

I. DNA(cross) linking agents; DNA alkylating agents

II. Antimetabolites

III. DNA topoisomerase poisons & DNA intercalating agents:

III.1. Camptothecins; III.2. Epipodophyllotoxins;

III.3. Antibiotics: III.3.a. Anthracyclines; III.3.b. Anthracenediones

IV. DNA interacting miscellaneous antibiotics:

IV.1. Phenoxazine; IV.2. Glycopeptide; IV.3. Mitomycin

II. Anti-metabolites

II. Antimetabolites: Chemical Classification

II.1. Folate antimetabolites

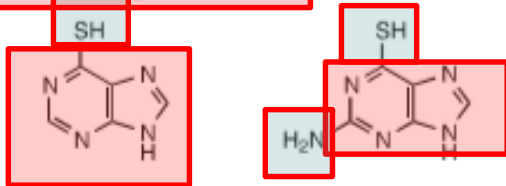
II.2. Pyrimidine antimetabolites

II.3. Purine antimetabolites

II.4. Miscellaneous / unclassified antimetabolites

Antimetabolites

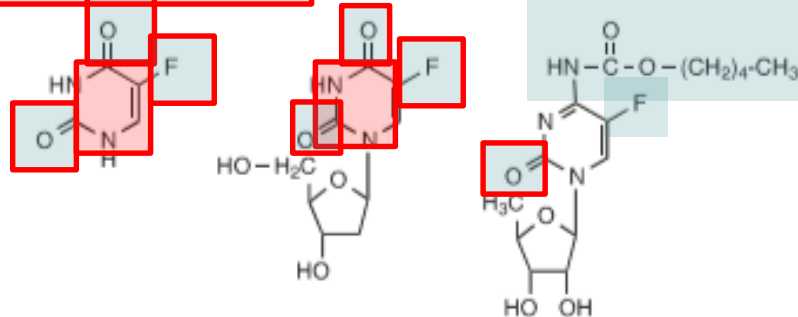
Purine antagonists:



Mercaptopurine
(Purinethol)

Thioguanine
(Tabloid)

Pyrimidine antagonists:

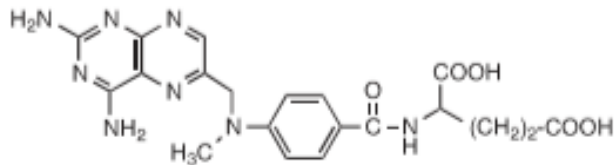


Fluorouracil
(Adrucil)

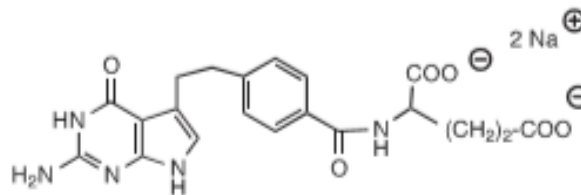
Floxuridine
(FUDR)

Capecitabine
(Xeloda)

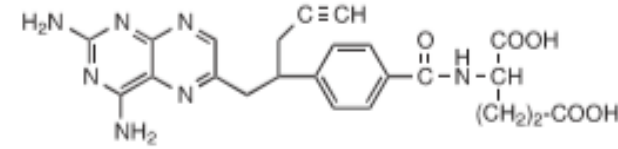
Folate antagonists:



Methotrexate (Trexall)



Pemetrexed disodium (Alimta)

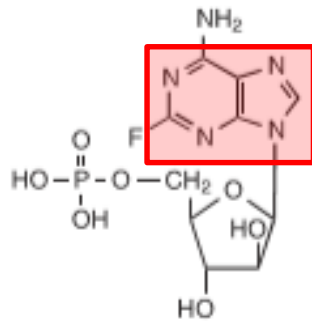


Pralatrexate (Folotylin)

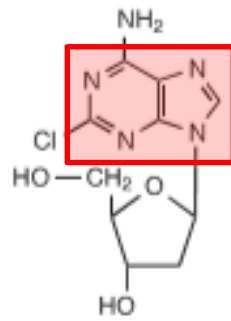
Antimetabolites-Contd.

DNA polymerase and chain elongation inhibitors:

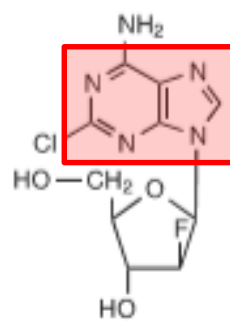
Purine analogues:



Fludarabine phosphate
(Fludara)

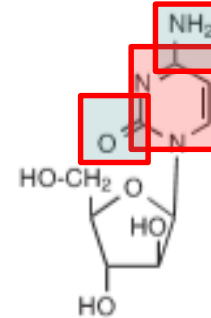


Cladribine
(Leustatin)

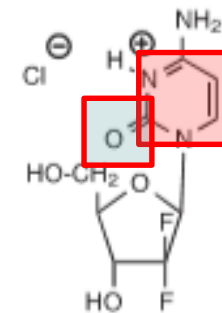


Clofarabine
(Clolar)

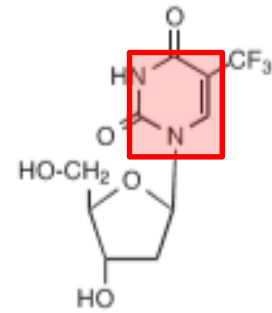
Pyrimidine analogues:



Cytarabine
(Tarabine PFS,
DepoCyt)

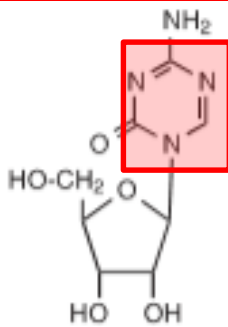


Gemcitabine
hydrochloride
(Gemzar)

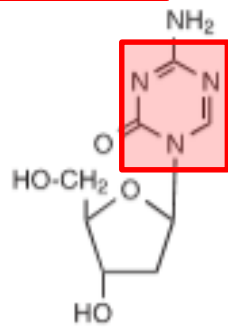


Trifluridine
(active drug
in Lonsurf)

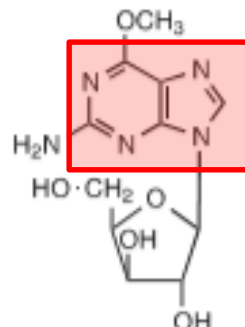
DNA Methyltransferase Inhibitors



Azacitidine
(Vidaza)

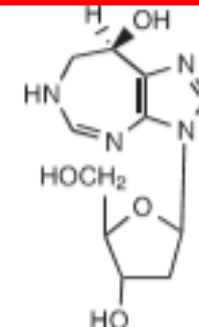


Decitabine
(Dacogen)

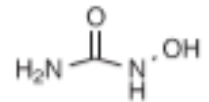


Nelarabine
(Arranon)

Miscellaneous antimetabolites:



Pentostatin
(Nipent)



Hydroxyurea
(Hydrea)

Figure 33.41 Antimetabolites.

dTMP Biosynthesis Pathway in Brief

- Thymidylate Synthase:
 - ✓ Cys-SH in active site: Michael type attack:
enolate type intermediate
 - ✓ substrate: dUMP
 - ✓ cofactor: N5,N10-methylenethylenetetrahydrofolate
 - ✓ Product: dTMP



Interaction Points of Active Site of Thymidylate Synthase to dUMP & 5,10-Methylene-THF

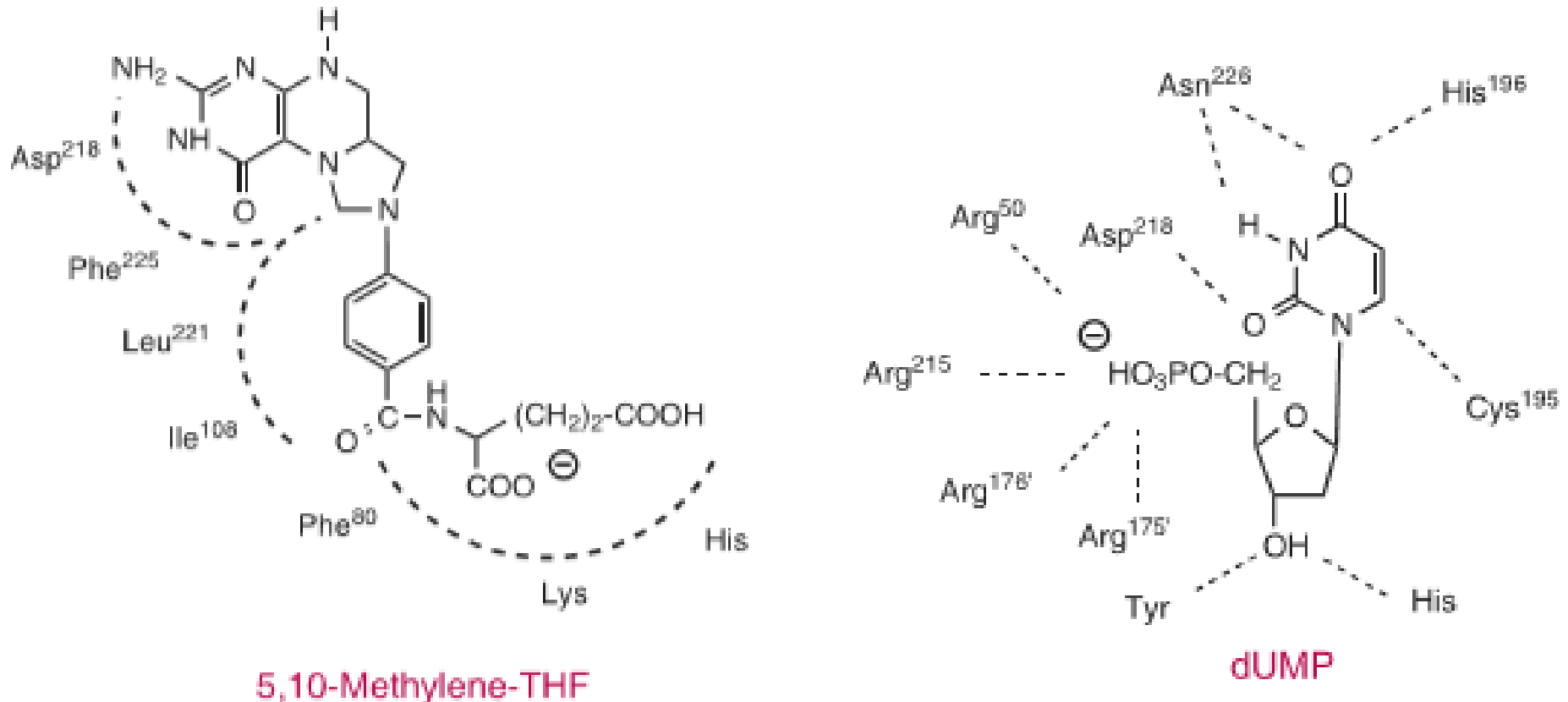


Figure 33.46 dUMP and 5,10-methylene-THF binding to thymidylate synthase.

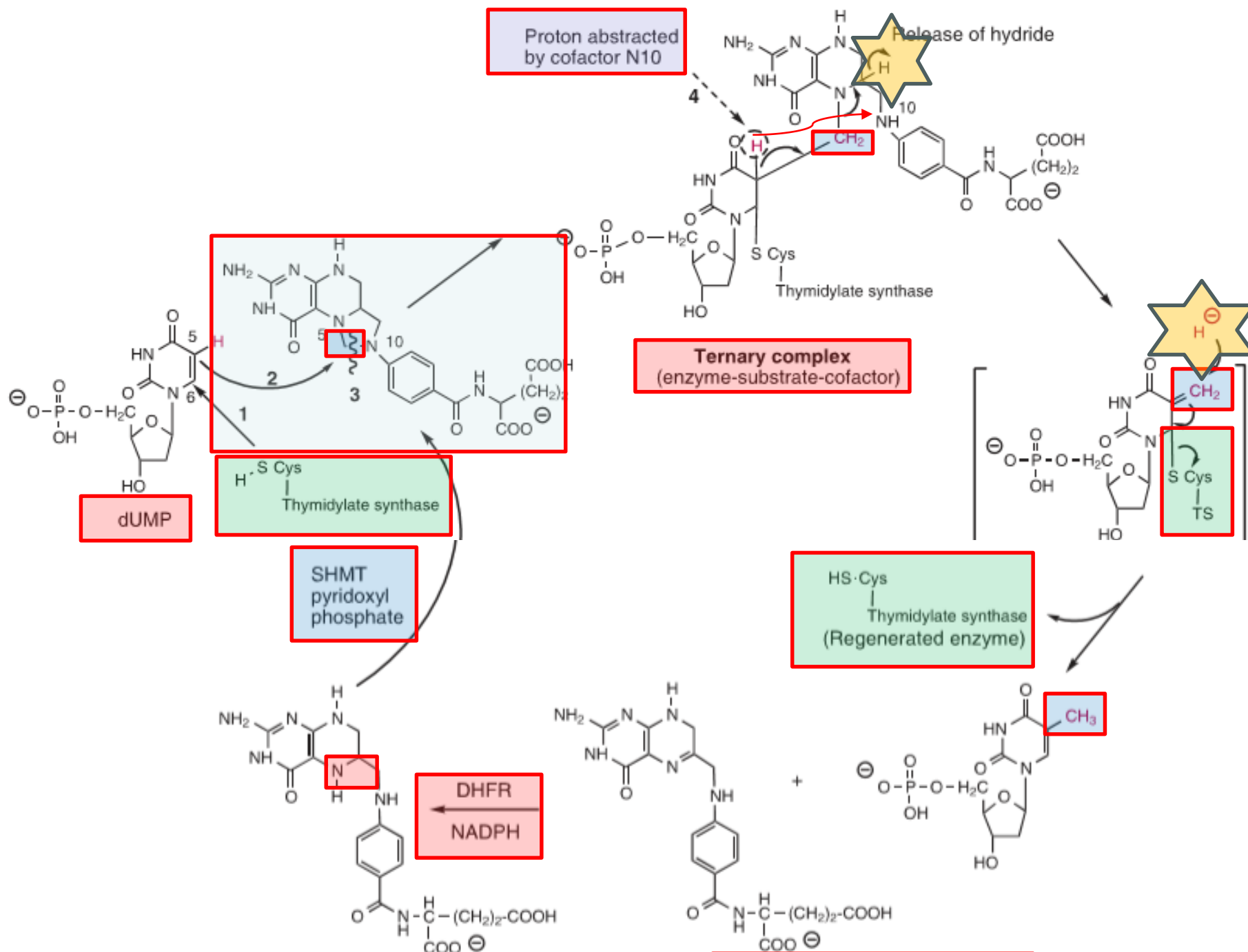
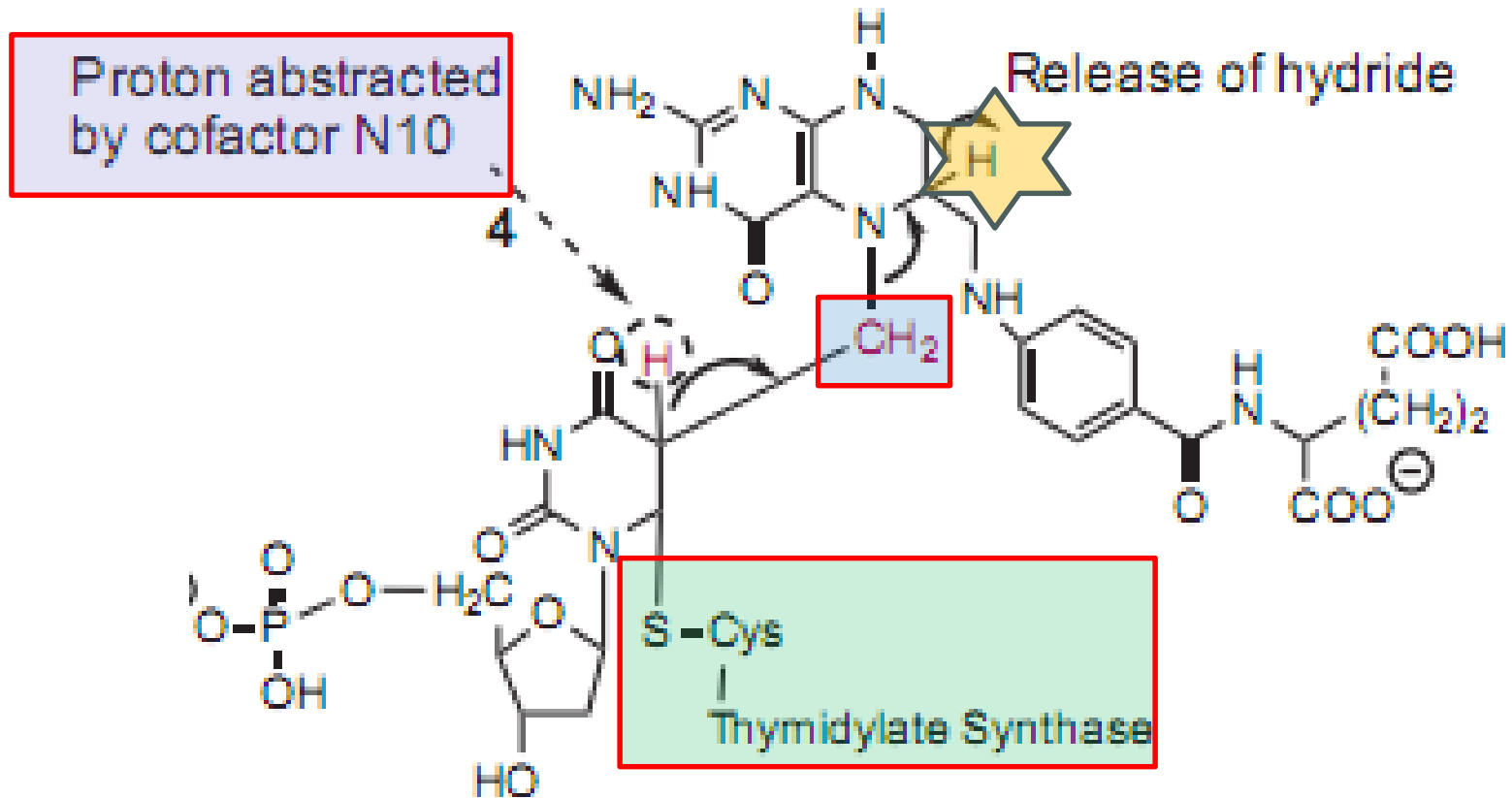


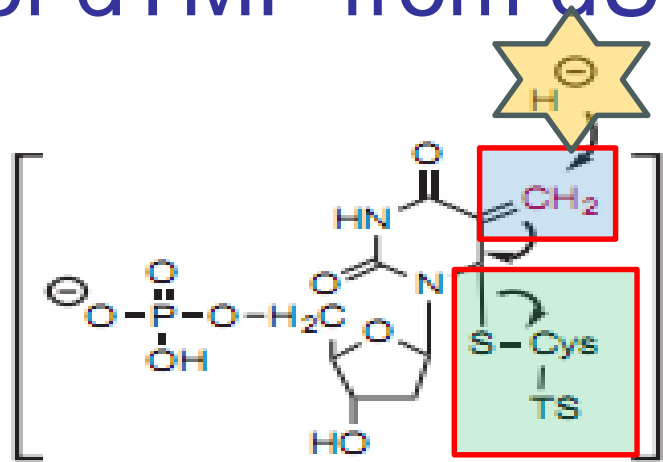
Figure 33.45 Synthesis of deoxythymidine monophosphate (dTMP). DHFR, dihydrofolate reductase; SHMT, serine hydroxymethyltransferase; TS, thymidylate synthase.

Critical Ternary Complex Formation in Biosynthesis of dTMP from dUMP

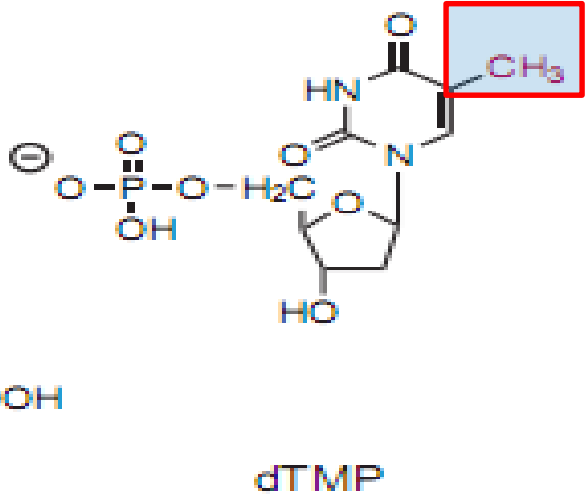
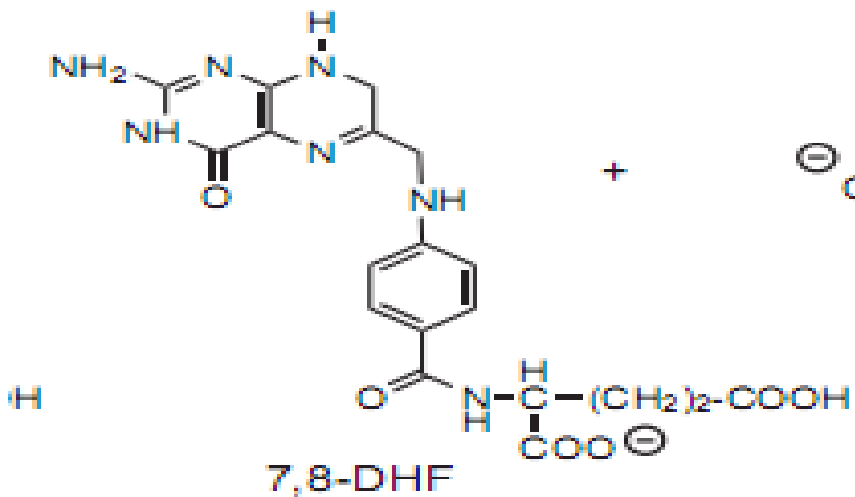


Ternary complex
(enzyme-substrate-cofactor)

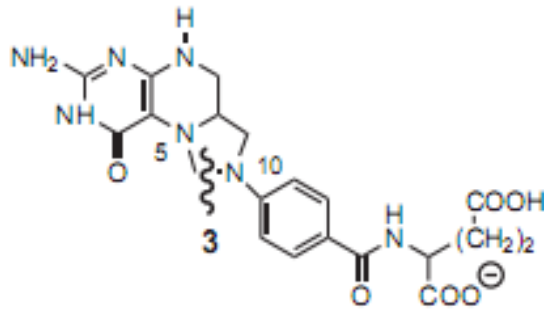
Last Step of Biosynthesis of dTMP from dUMP



HS-Cys
 |
 Thymidylate Synthase
 (Regenerated enzyme)

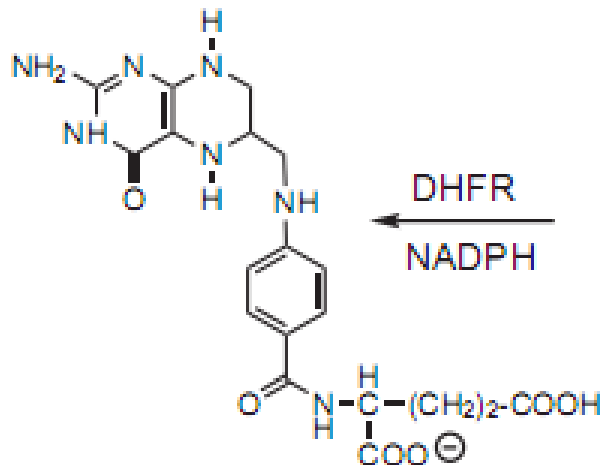


Regeneration of TS & THF in Biosynthesis of dTMP

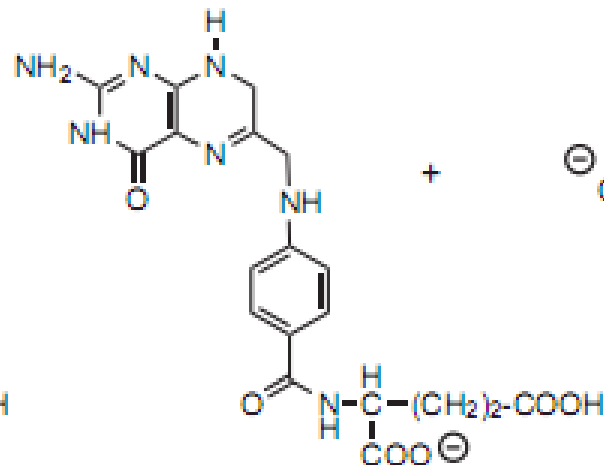


SHMT
pyridoxyl
phosphate

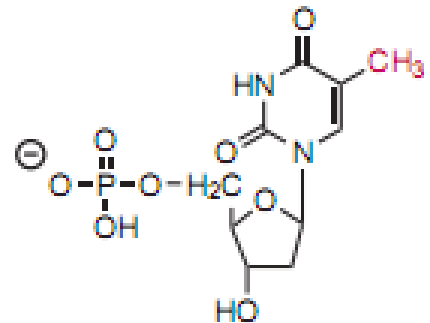
HS-Cys
|
Thymidylate Synthase
(Regenerated enzyme)



THF



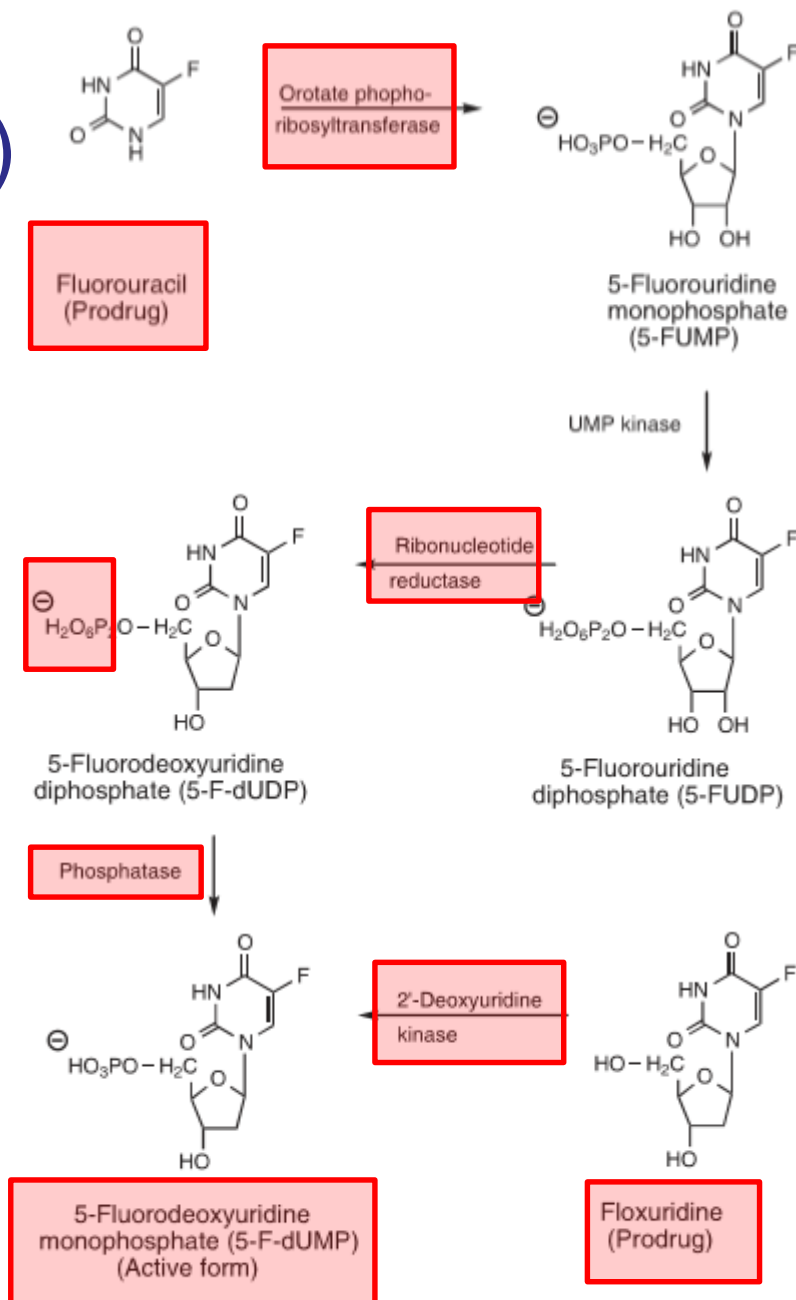
7,8-DHF



dTMP

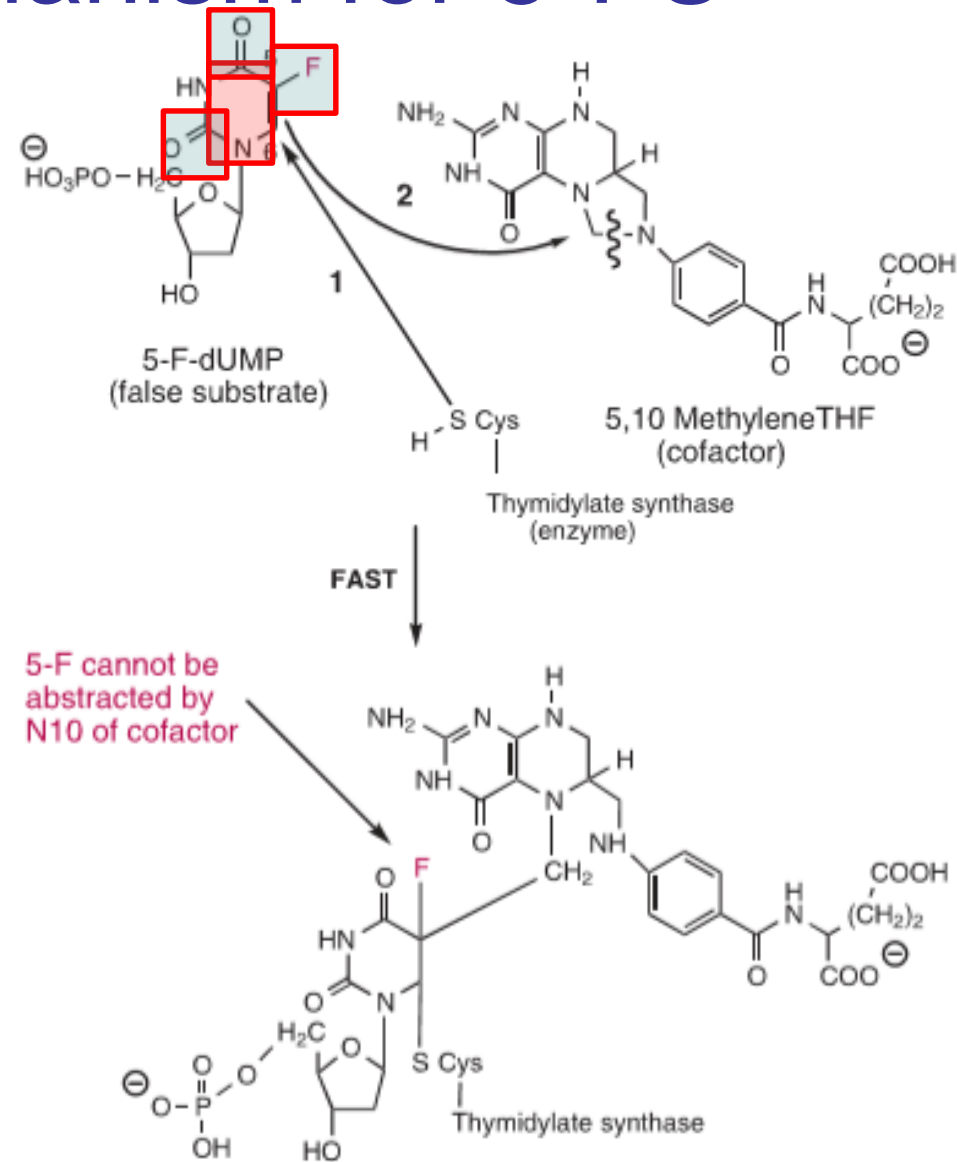
Bio-Activation of 5-FU & 5-FdUR (fluoxuridine)

- Both are prodrugs
- Active metabolite:
✓ 5-FdUMP



Molecular Mechanism for 5-FU

- Thymidylate synthase inh.:
- Direct inh.: thymineless
- Ternary Complex formation
- ✓ 5-FdUMP (active metabolite):
- ✓ in the presence of 5,10-methyleneTHF



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Stable fluorinated ternary complex

Figure 33.48 Mechanism of action of fluorouracil.

Metabolism of 5-FU

- Metabolism enzyme: **DPD** (Dihydro-Pyrimidine-Dehydrogenase)

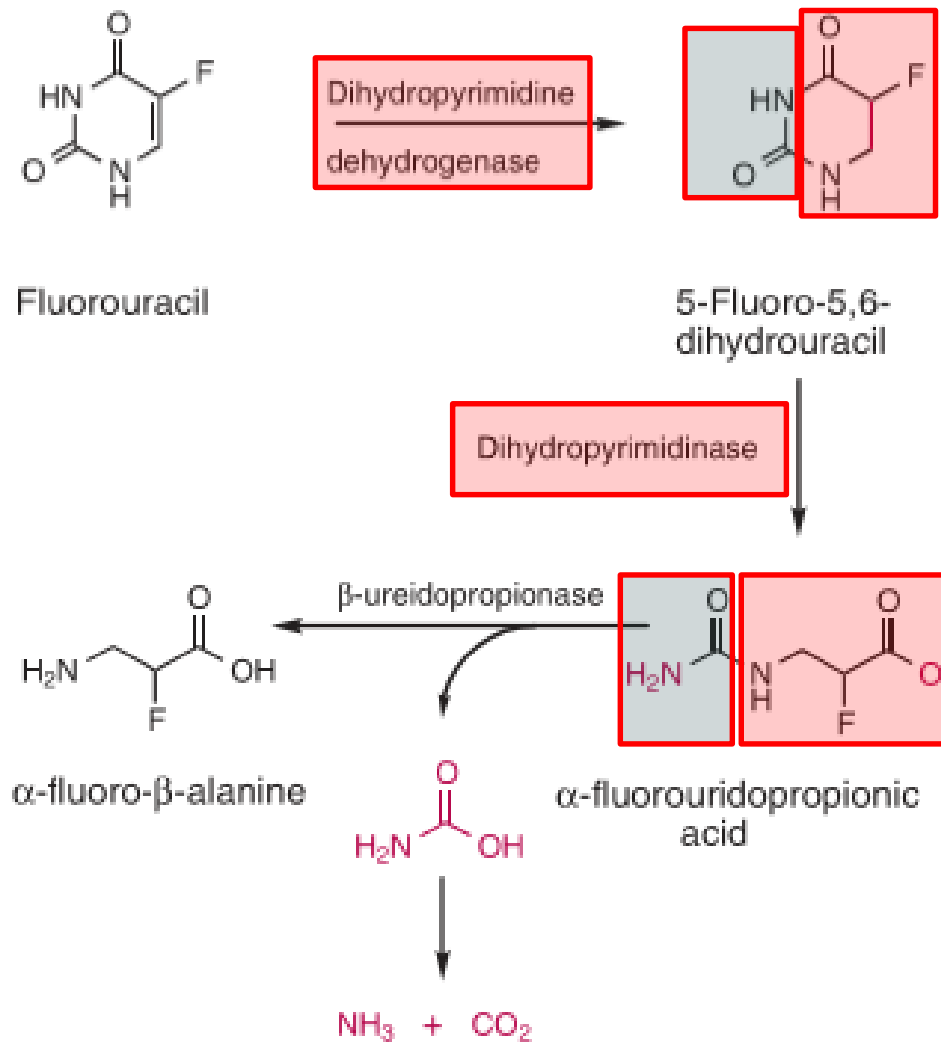
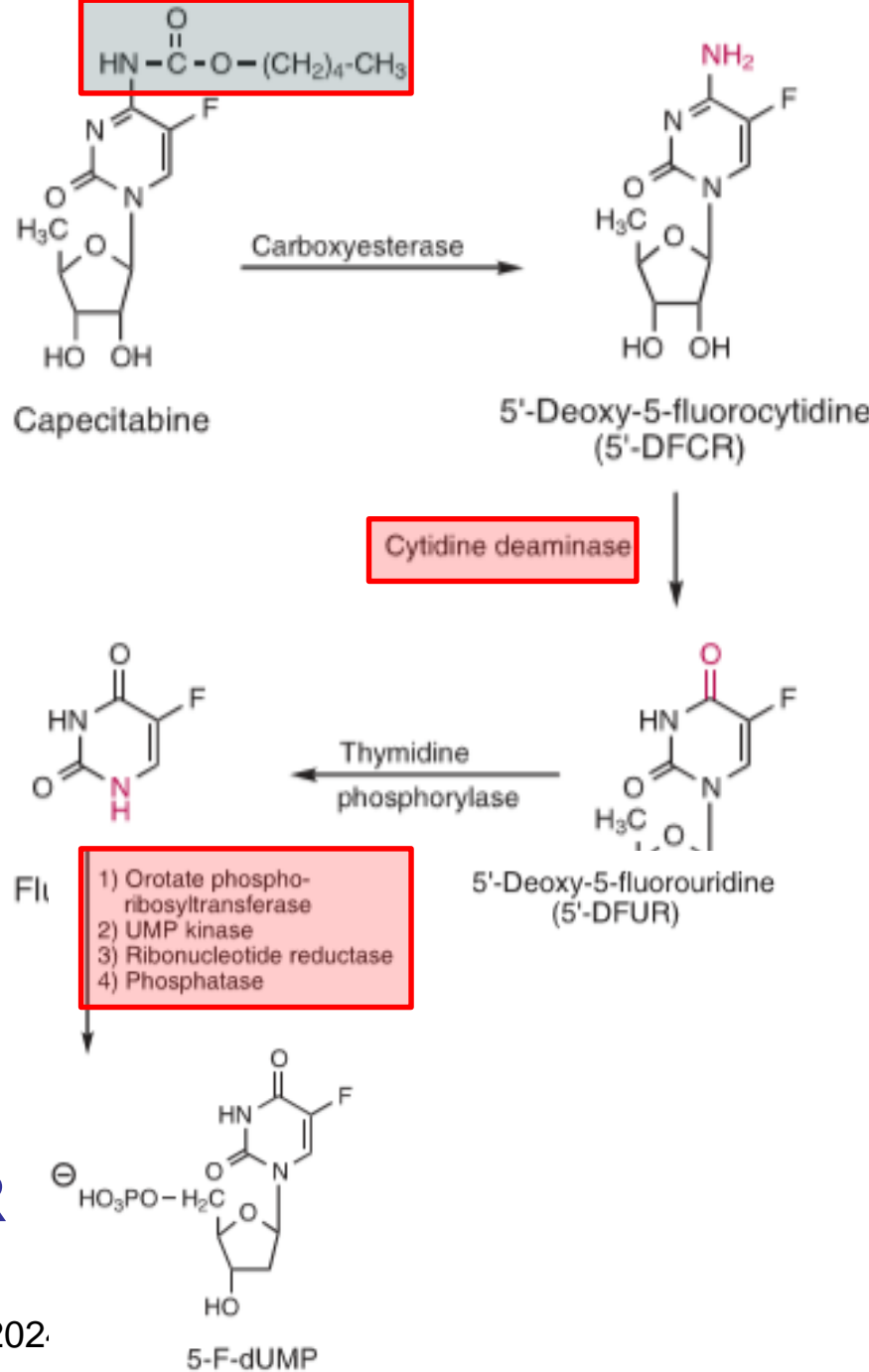


Figure 33.49 Fluorouracil metabolism.

Bio-Activation of Capecitabine

- Prodrug: carbamylated cytidine
- Involving enzymes:
 - ✓ carboxy-esterase
 - ✓ cytidine deaminase
 - ✓ thymidine phosphorylase
 - ✓ ribosyl-transferase
 - ✓ kinase
 - ✓ ribonucleotide reductase
 - ✓ phosphatase
- Metabolites:
 - ✓ intermediate: 5'-dFCR & 5'-dFUR
 - ✓ active: 5-FU; 5-FdUMP



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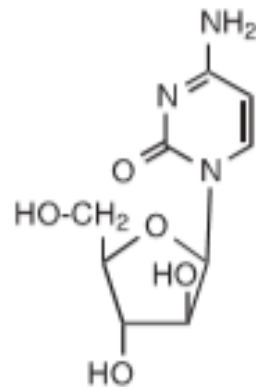
Figure 33.50 Capecitabine activation.

II. 2. Pyrimidine Antimetabolites:

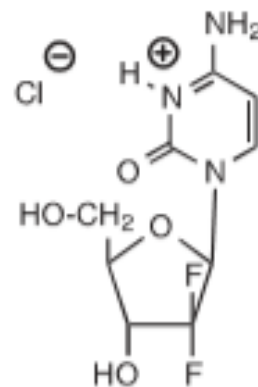
b: DNA Polymerase and/or Chain Elongation Inhibitors: Chemical Classification & SAR

- II.2.b.DNA polymerase inhibitors & DNA chain elongation inhibitors
- Cytidine/uridine analogue: modified via:
 - ✓ 3- CF_3 or 2'- epimerized or 2'&2'-di-halogenated ribose
 - ✓ Cytarabine
 - ✓ Gemcitabine
 - ✓ Trifluridine

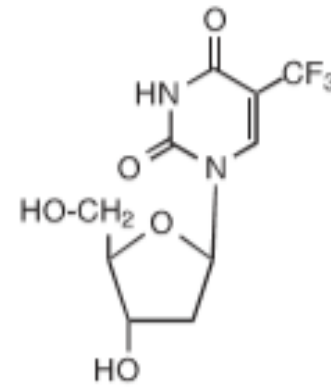
Pyrimidine analogues:



Cytarabine
(Tarabine PFS,
DepoCyt)



Gemcitabine
hydrochloride
(Gemzar)



Trifluridine
(active drug
in Lonsurf)

DNA Polymerase Inhibition by Gemcitabine

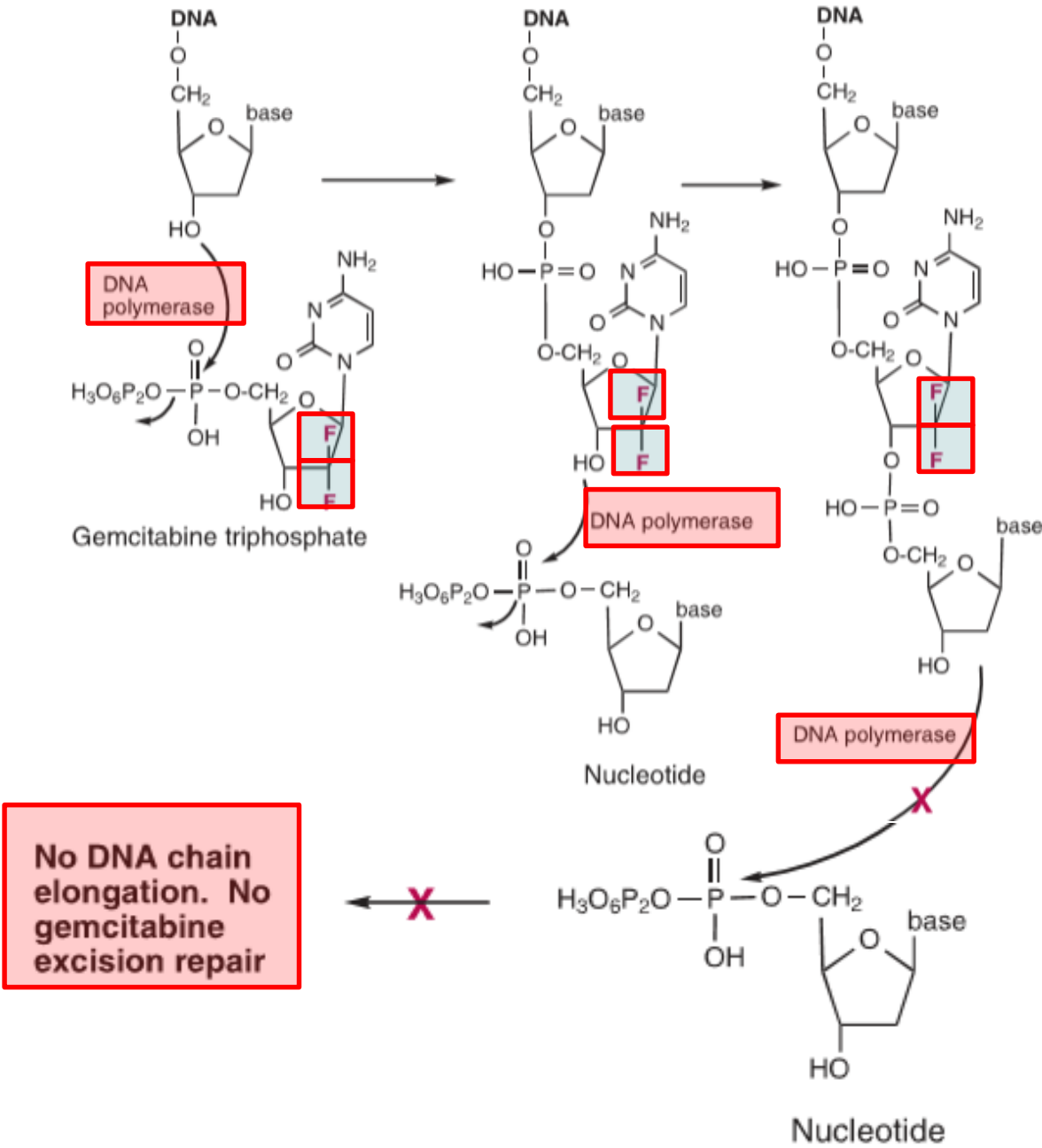


Figure 33.52 Gemcitabine triphosphate inhibition of DNA polymerase.

Cytarabine Metabolism

- Active Ara-cytidine triphosphate analogue

- Inactive uracil metabolite

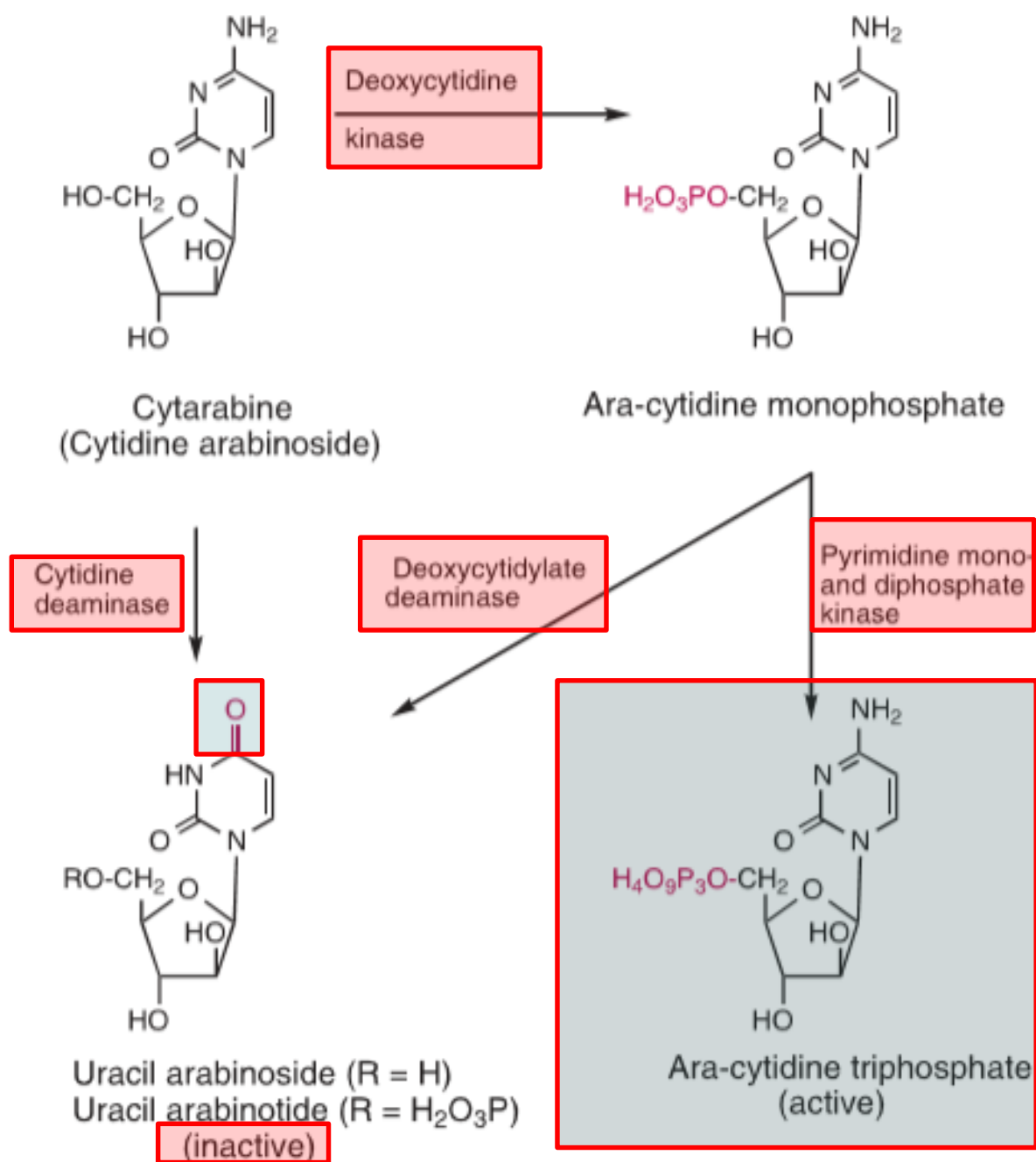
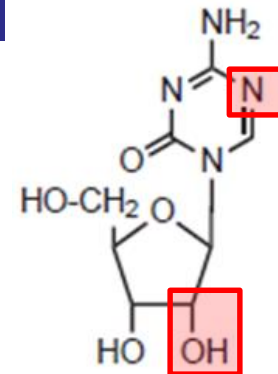


Figure 33.53 Cytarabine metabolism.

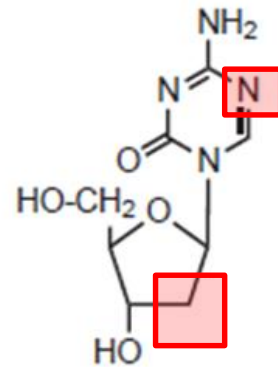
II. 2. Pyrimidine Antimetabolites:

c: DNA MethylTransferase(DNMT) Inhibitor: MOA & SAR

- Inhibit DNA alkylation specifically methylation at:
 - ✓ adenine (C6) & cytosine (C5)
 - ✓ block abnormal cellular proliferation
 - ✓ especially responsible for differentiation & growth
 - ✓ mistakenly incorporated into DNA: false nucleotide
 - ✓ irreversible inhibitor
- Vulnerable to deaminase: short half l
- Activated by kinase: tri-phosphate
- Chemistry: amino-triazine



Azacitidine
(Vidaza)



Decitabine
(Dacogen)

Metabolism & Mechanism of Azacitidine & Decitabine

- Active metabolite: ✓ triphosphate analogue

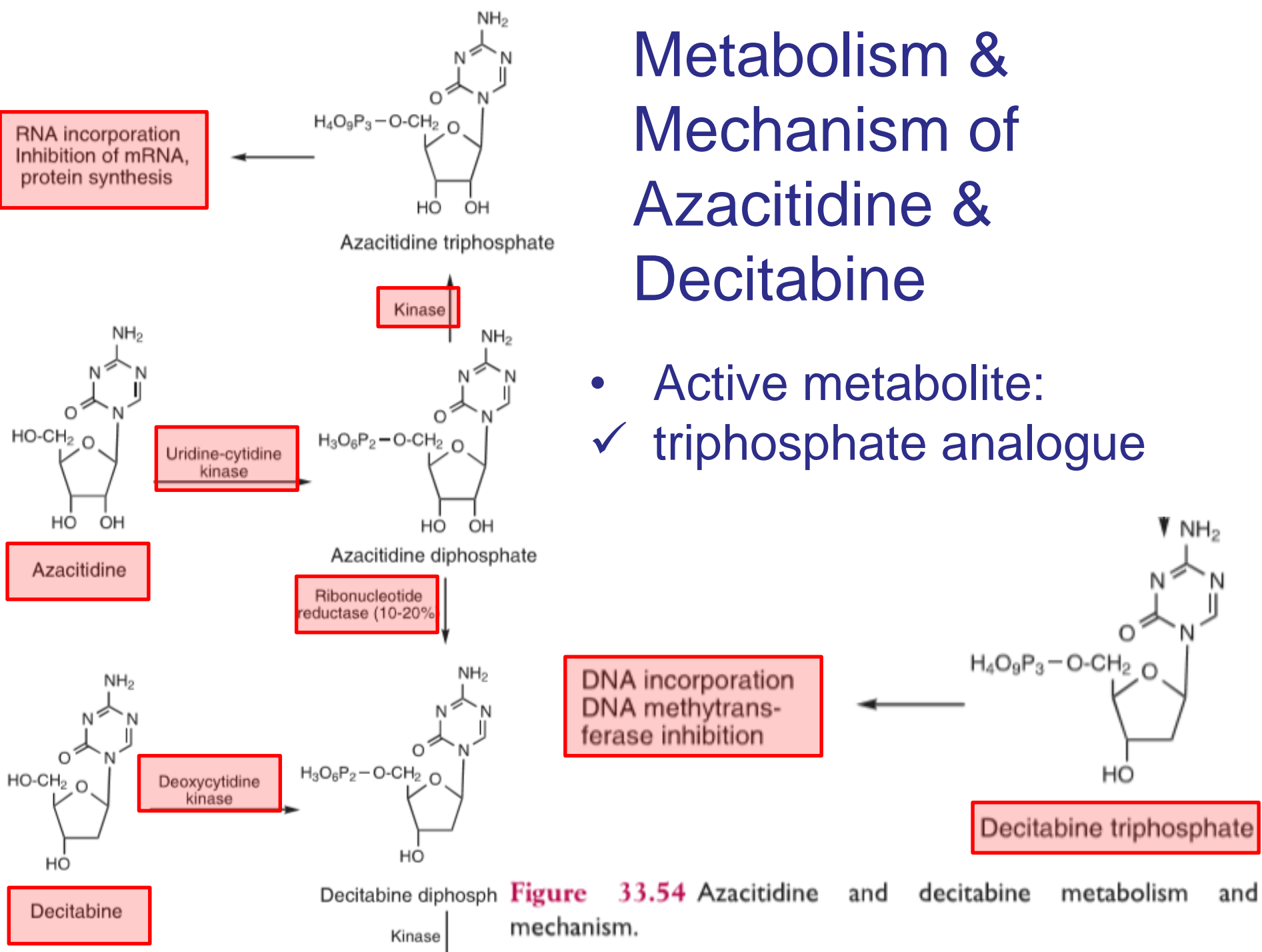


Figure 33.54 Azacitidine and decitabine metabolism and mechanism.

II. Antimetabolites: 3. Purine Antagonists: Mechanistic Classification

II.3. Purine antagonists/false substrate/antimetabolites:

- ✓ II.3.a. Amido-phospho-ribosyl transferase inhibitor;
& also might involve HGPRT
- ✓ II.3.b. DNA polymerase inhibitors; chain elongation inhibitors
- ✓ II.3.c. DNA Methyl Transferase (DNMT) inhibitors

II. Antimetabolites: 3. Purine Antagonists:

Purine antagonists/False substrates/antimetabolites:

Chemical Classification:

II. 3.a. Purine biosynthesis inhibitor:

glutamine 5-phospho-ribosyl-pyrophosphate amido-transferase inhibitor(amido-phospho-ribosyl transferase inhibitor)

&

Hypoxanthine Guanine Phosphoribosyl Transferase(HGPRT) inh.

✓ purine-thiol analogues

• II.3.b. DNA polymerase inhibitor & DNA elongation inhibitor

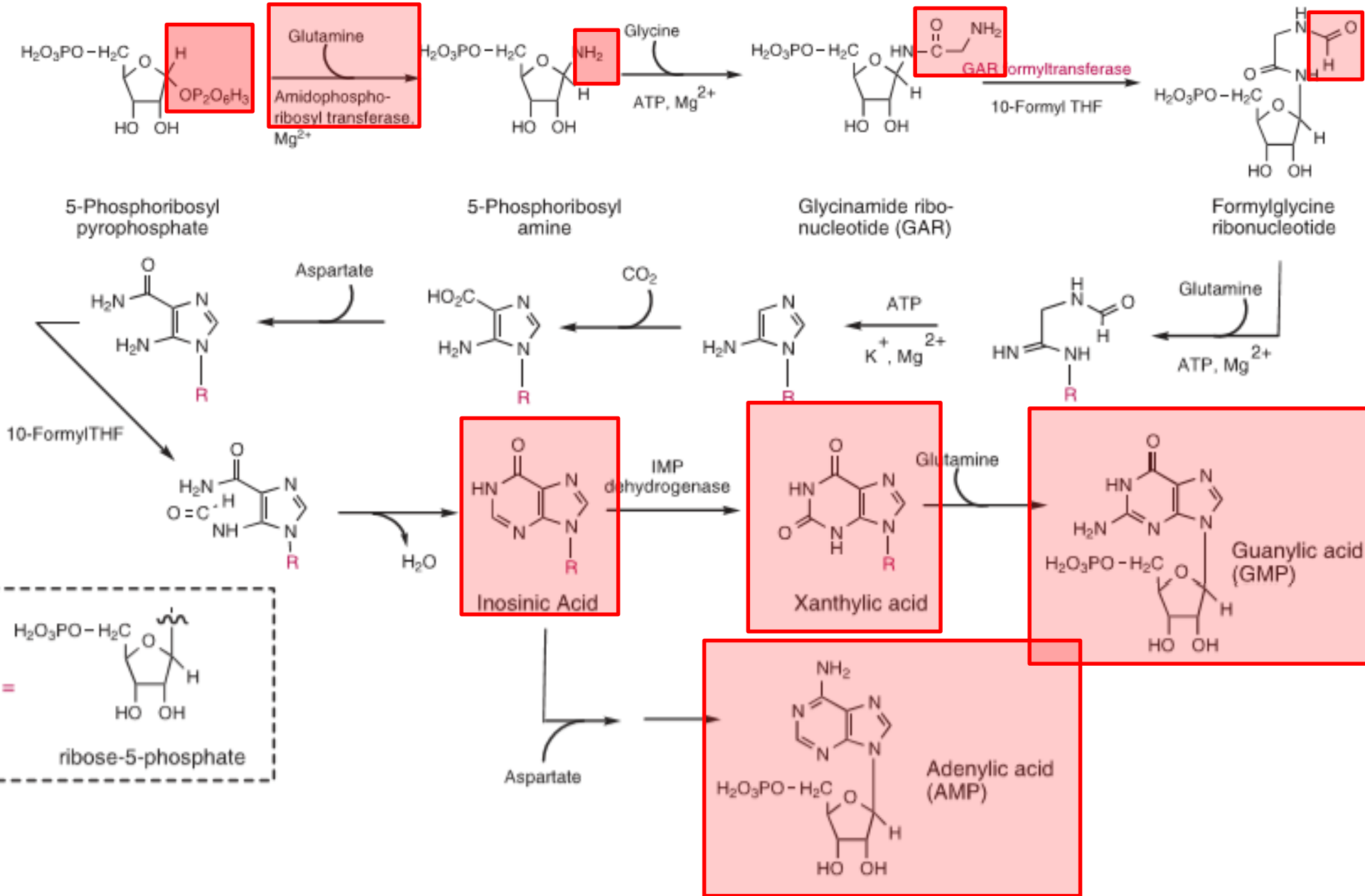
✓ adenine, adenosine analogues:

✓ sugar bioisoster; halogenated purine/sugar

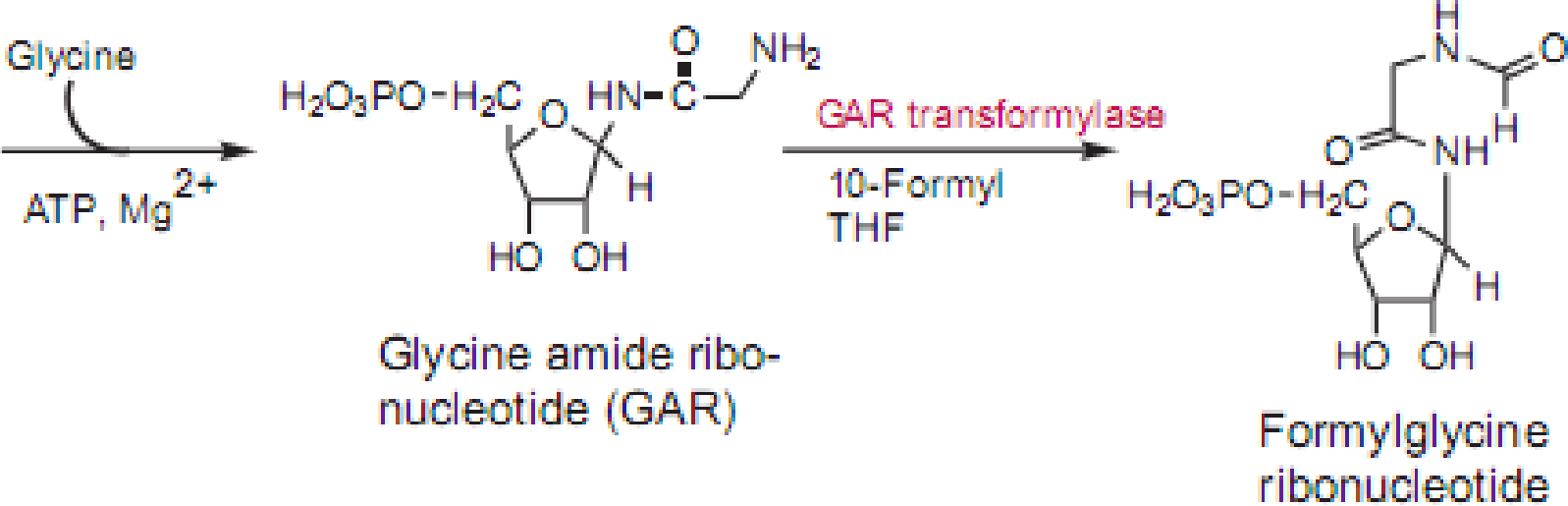
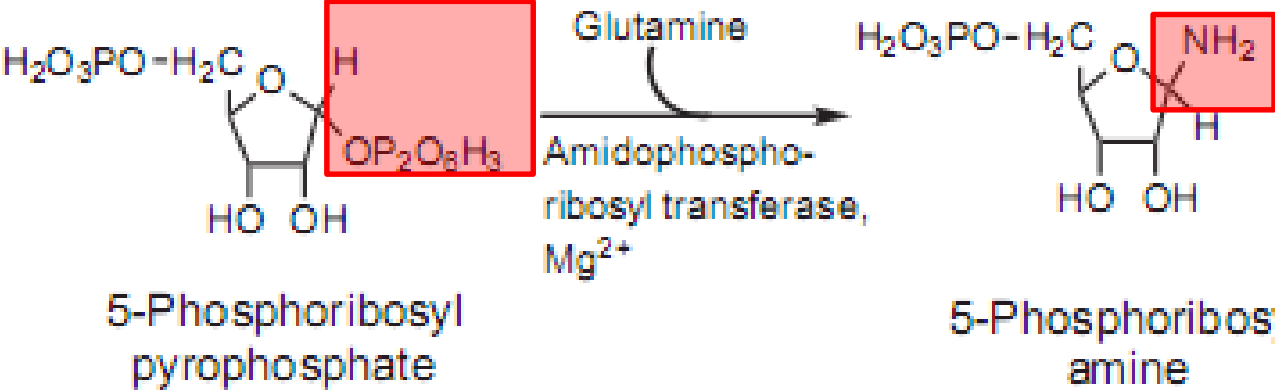
• II.3.c. DNA methyltransferase inhibitor

✓ guanine analogues

Purine Nucleotide Biosynthesis De Novo Pathway



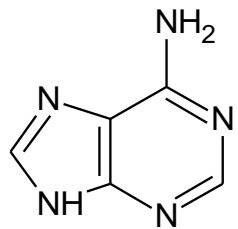
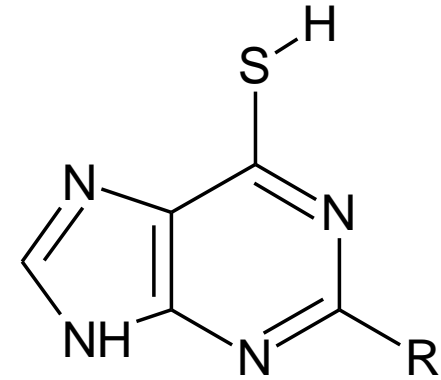
First Steps of Purine Biosynthesis Pathway



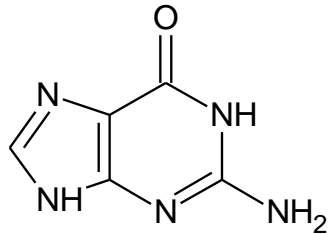
II. 3.a. Purine Antagonists:

Purine Biosynthesis Inhibitor & DNA Polymerase Inhibitor: SAR

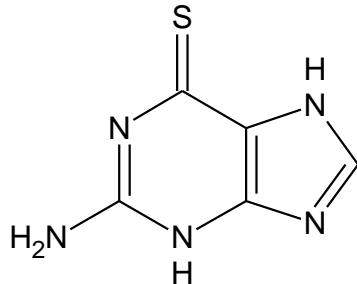
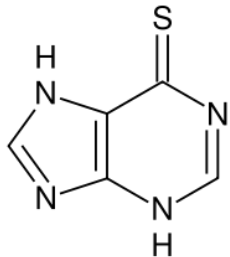
- Purinethiol; 6-thio inosine (G/A)
- ✓ R=: 6-Mercapto-Purine (6-MP)
- ✓ R=NH₂: 6-Thio-Guanine (6-TG)
- Prodrug



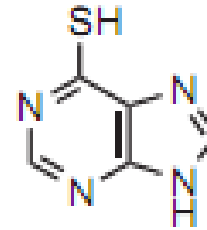
Adenine



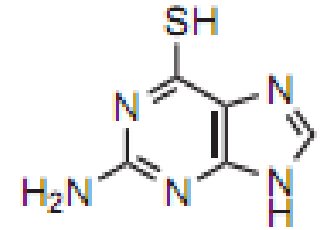
Guanine



Purine antagonists:



Mercaptopurine
(Purinethol)



Thioguanine
(Tabloid)

MP & TG Metabolism & Bio-Activation

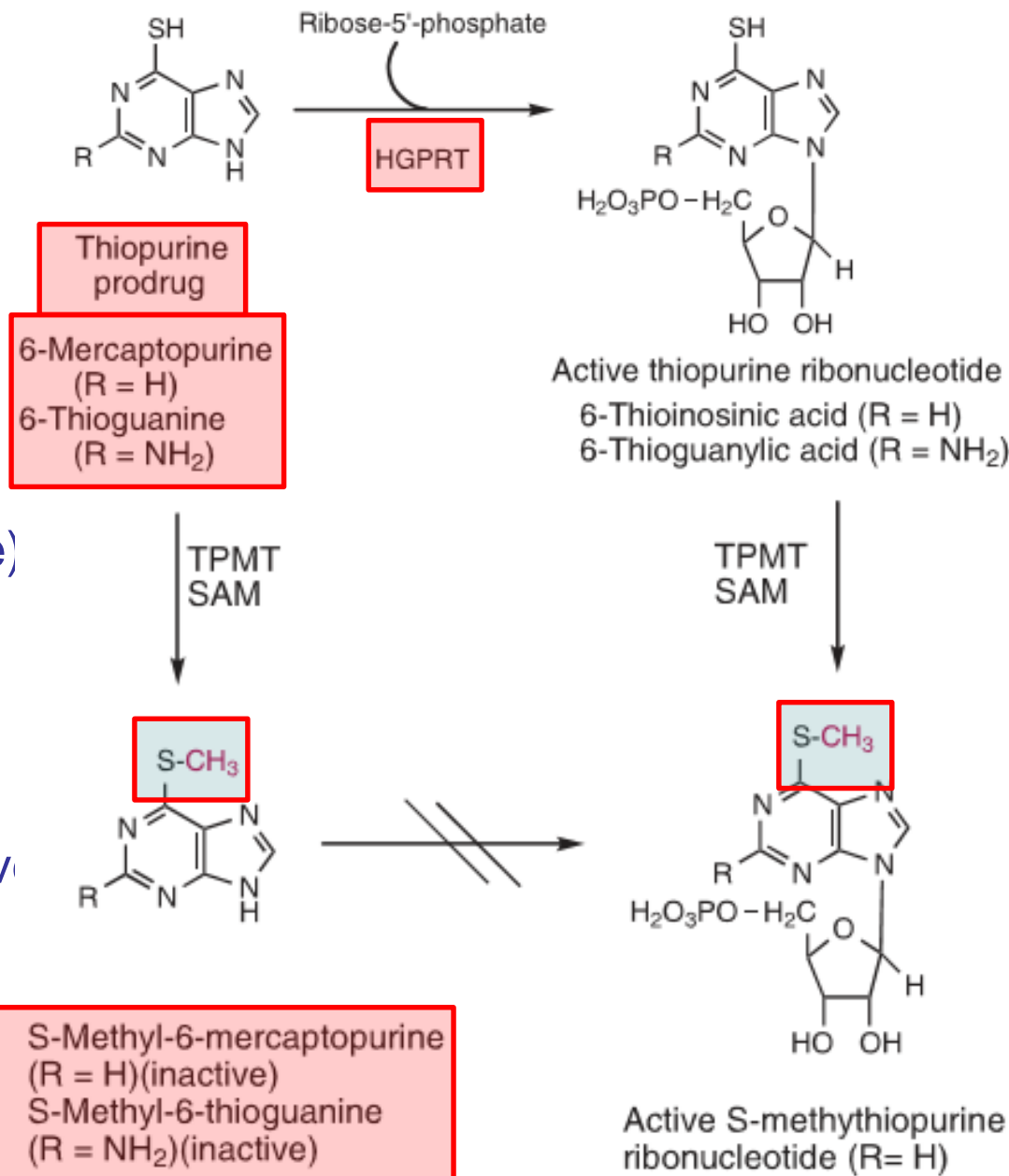
➤ Phospho-ribosylated:

• MP-ribonucleotide

- ✓ 6-MMP (**in**active)
- ✓ 6-thioinosinic acid (active)
- ✓ 6-methylthioinosinic acid (active)

• TG-ribonucleotide

- ✓ 6-MTG (**in**active)
- ✓ 6-thioguanylic acid (active)
- ✓ 6-methyl-thioguanylic acid (active)

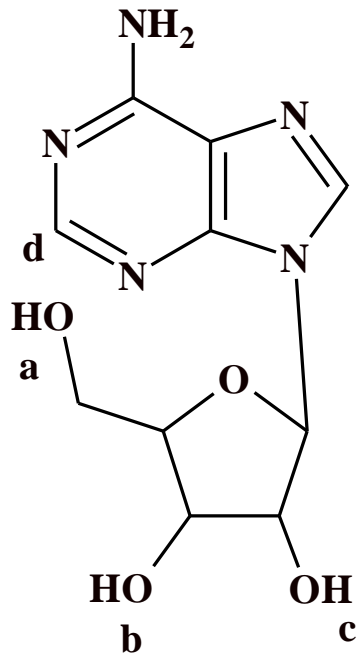


TPMT: Thio-Purine Methyl Transferase
SAM: S-Adenosyl Methionine

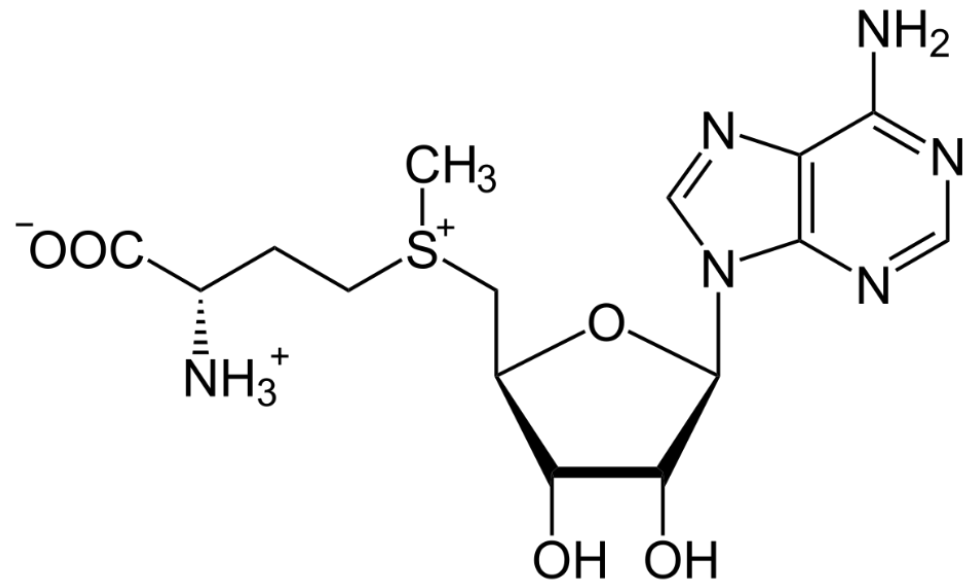
Figure 33.43 Thiopurine metabolism leading to activation and inactivation.

Adenosine & SAM

Adenosine



SAM:S-Adenosyl Methionine



Metabolism & Metabolites of 6-MP

- Activation of 6-MP:
 - ✓ by HGPRT: to produce 6-mercapto(thio)-inosinic acid = 6-thio-inosinic acid

- Inactivation of 6-MP:
 - ✓ by Xanthine Oxidase: to produce 6-thio-uric acid

- Inactivation of 6-thio inosinic acid:
 - ✓ by Guanase: 6-thio-xanthine
 - ✓ by Xanthine Oxidase: 6-thio-uric acid

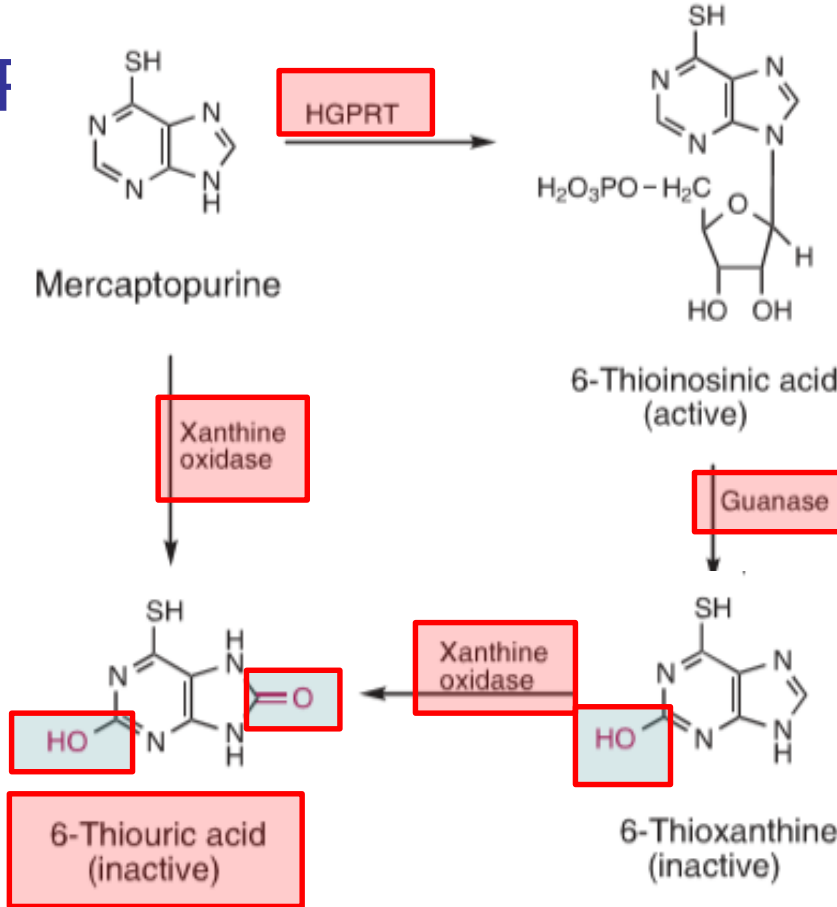
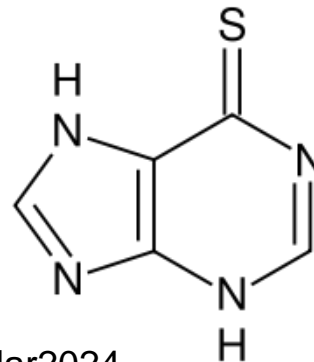


Figure 33.44 Xanthine oxidase inactivation of mercaptopurine and 6-thioinosinic acid.

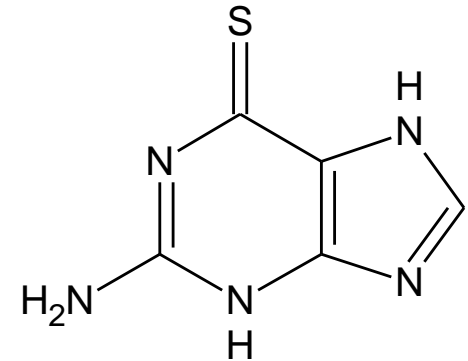
II. 3.a. Purine Antagonists:

Purine Biosynthesis Inhibitor & DNA Polymerase Inhibitor: Molecular Mechanism

- MP/TG: Prodrug: bioactivation: **phosphoribosylated** by HGPRT:
- ✓ MPR/TGR: MP/TG-ribonucleotide:
- ✓ **methyated** by TPMT:MP>TG:MMP/MTG-ribonucleotide
- ✓ Phosphorylated by kinase: MPR-TP & TGR-TP
- MOA:
- ✓ inhibitor of GAPRT: lowers AMP & GMP
- ✓ false incorporation of MPR-TP & TGR-TP within DNA & RNA of tumor cells
- ✓ inhibits further elongation
- ✓ promotes apoptosis
- Little or no 6-thioguaninic acid



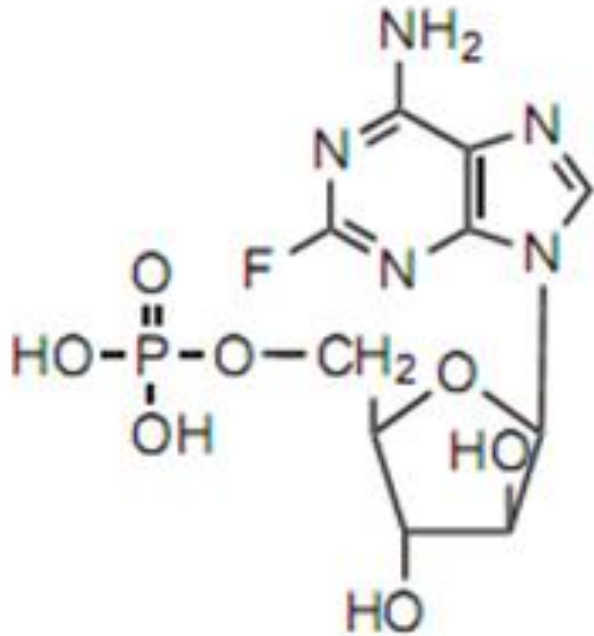
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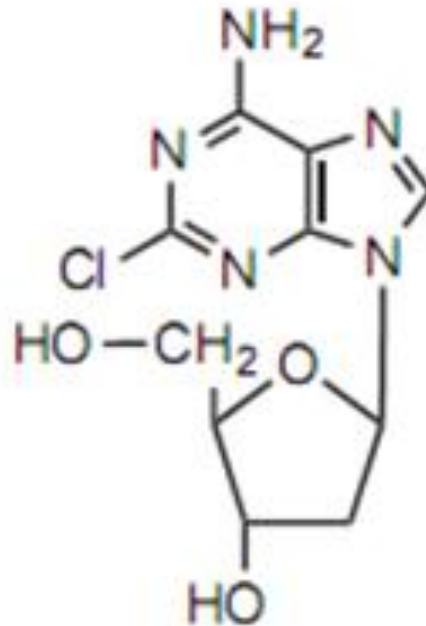
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IV. Antimetabolites: 3. Purine Antimetabolites

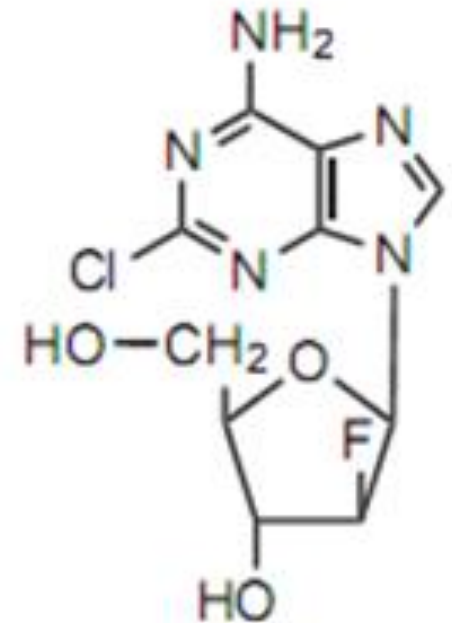
b: DNA Polymerase and/or Chain Elongation Inhibitors



Fludarabine phosphate
(Fludara)



Cladribine
(Leustatin)



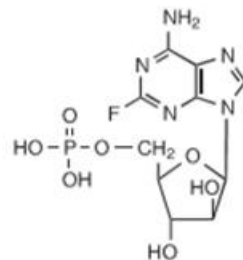
Clofarabine
(Clolar)

II. 3. Purine Antimetabolites:

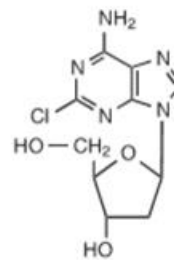
b: DNA Polymerase and/or Chain Elongation Inhibitors: Chemical Classification & SAR

- II.3.b.DNA polymerase inhibitors & DNA chain elongation inhibitors
- Adenosine based analogue: 2- halogenated adenosine
- ✓ possessing 2'-epimerized/halogenated ribose
- ✓ Fludarabine: 2-F&2'-epimer ribose
- ✓ Cladribine: 2-Cl&2'-deoxy
- ✓ Clofarabine: 2-Cl&2'-F
- Phosphorylation by specific kinase: mono & di-phosphate
- Further phosphorylation by specific kinase: triphosphate

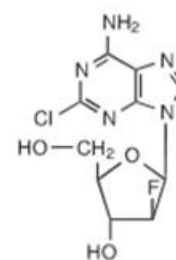
Purine analogues:



Fludarabine phosphate



Cladribine

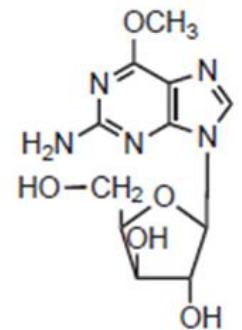


Clofarabine

II. 3. Purine Antimetabolites:

c: DNA MethylTransferase(DNMT) Inhibitor: MOA & SAR

- Inhibit DNA alkylation specifically methylation at:
 - ✓ adenine (C6); cytosine (C5)
 - ✓ especially responsible for differentiation & growth
 - ✓ **block** abnormal cellular proliferation
 - ✓ mistakenly incorporated into DNA: **false** nucleotide
 - ✓ severe & **irreversible** inhibitor
- **Vulnerable** to deaminase: short half life
- Activated by kinase: **tri-phosphate**
- Chemistry:
 - ✓ guanosine O-methylated analogue: 2'-epimerized ribose



Nelarabine
(Arranon)

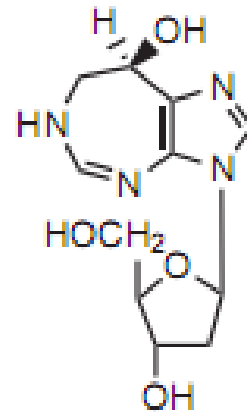
II. Antimetabolites:

4. Miscellaneous / Unclassified Antimetabolites: MOA & SAR

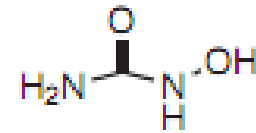
- Ribonucleotide reductase inhibitor:
 - ✓ blocks DNA synthesis through trapping Tyr at catalytic site of ribonucleotide reductase

- Pentostatin
- Hydroxy-urea

Miscellaneous antimetabolites:



Pentostatin
(Nipent)



Hydroxyurea
(Hydrea)

II. 4. Unclassified Antimetabolites: Pentostatin

- SAR: ring expanded purine ribonucleotide
- MOA: halt DNA synthesis **inhibiting**:
 - ✓ adenosine deaminase, directly
 - ✓ ribonucleotide reductase, **in**directly
 - ✓ increment of deoxyadenosine triphosphate (dATP)
- Base of design:
 - ✓ mimic tetrahedral (hydroxylated)intermediate of deaminase

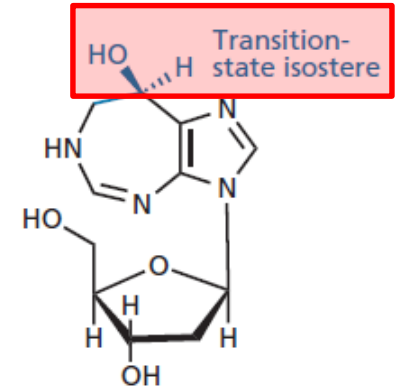
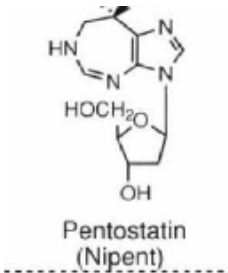


FIGURE 21.24 Pentostatin.



Normal Function of Adenosine Deaminase: to Provide 6-Oxo-Purine from Adenine

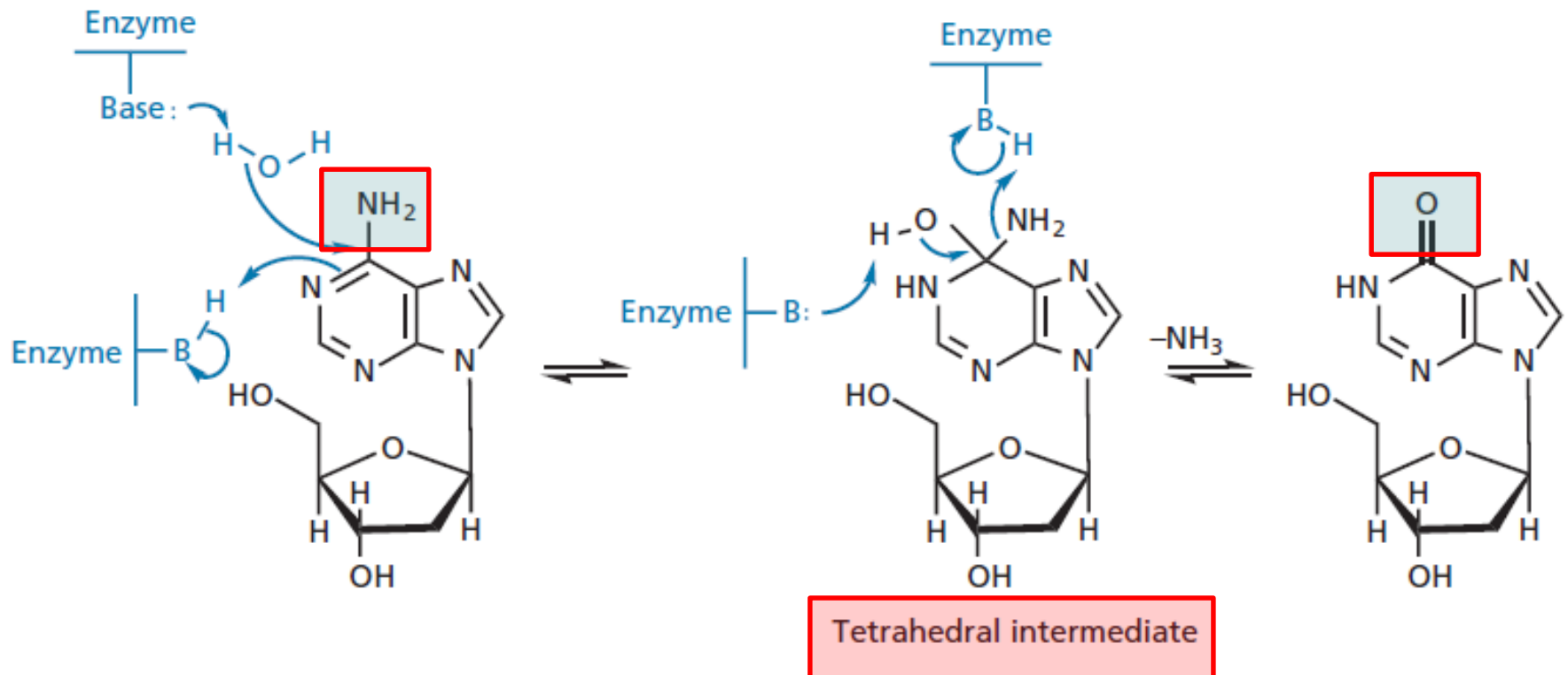
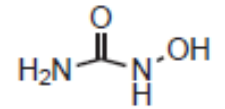


FIGURE 21.23 Mechanism of adenosine deaminase (B = base).

II. 4. Unclassified Antimetabolites: Hydroxyurea

- Hydrea[®]
- SAR:
- MOA: trap Tyr free radical species at ribonucleotide reductase
- ✓ twarts normal damage repair mechanism of surviving cells



Hydroxyurea
(Hydrea)

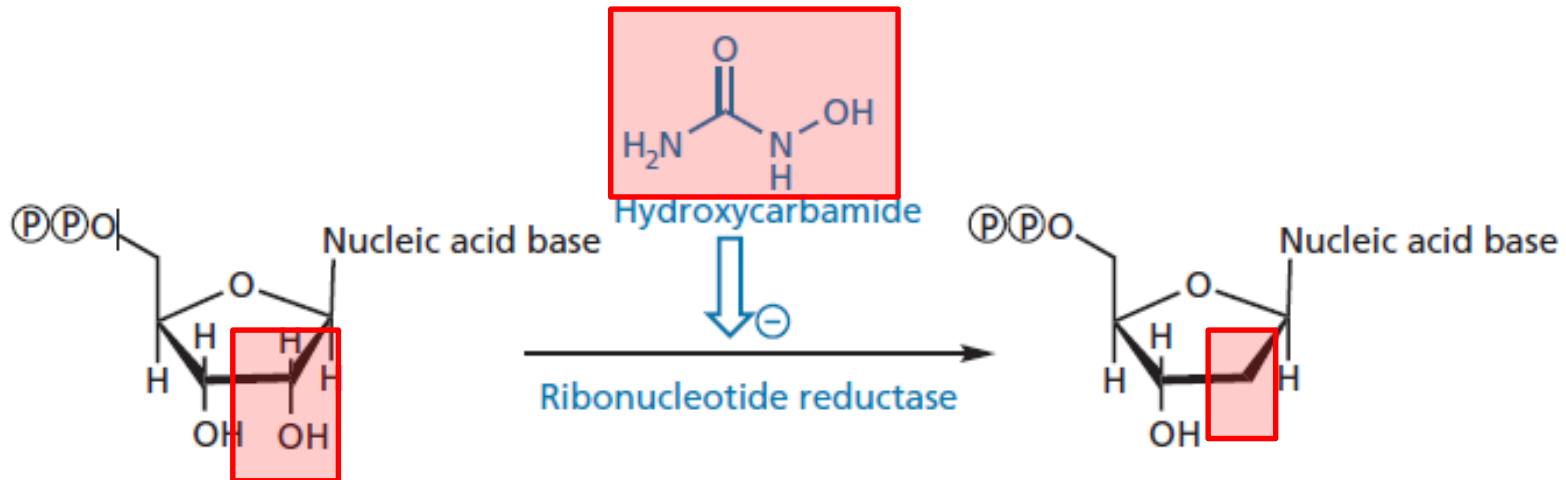


FIGURE 21.22 Reaction catalysed by ribonucleotide reductase (Ⓟ=phosphate).