Chemotherapeutic Agents:
Drugs to Treat Neoblastic Diseases-
Anticancer Agents
Section 2- Antimetabolites- Part 2

SRAmini Nov2024

Foye's

PRINCIPLES OF MEDICINAL CHEMISTRY

8TH EDITION

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SECTION 7 **DRUGS IMPACTING INFECTIOUS AND NEOPLASTIC DISEASE PROCESSES**

Foye's 2019

Principles of Medicinal Chemistry
by William Foye, 2019

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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

Pharmacologic lassification of Chemotherapeutic Agents- Contd.

V. Mitosis inhibitors: natural compounds

VI. Tyrosine Kinase & related inhibitors

VII. Histone deacetylase inhibitors

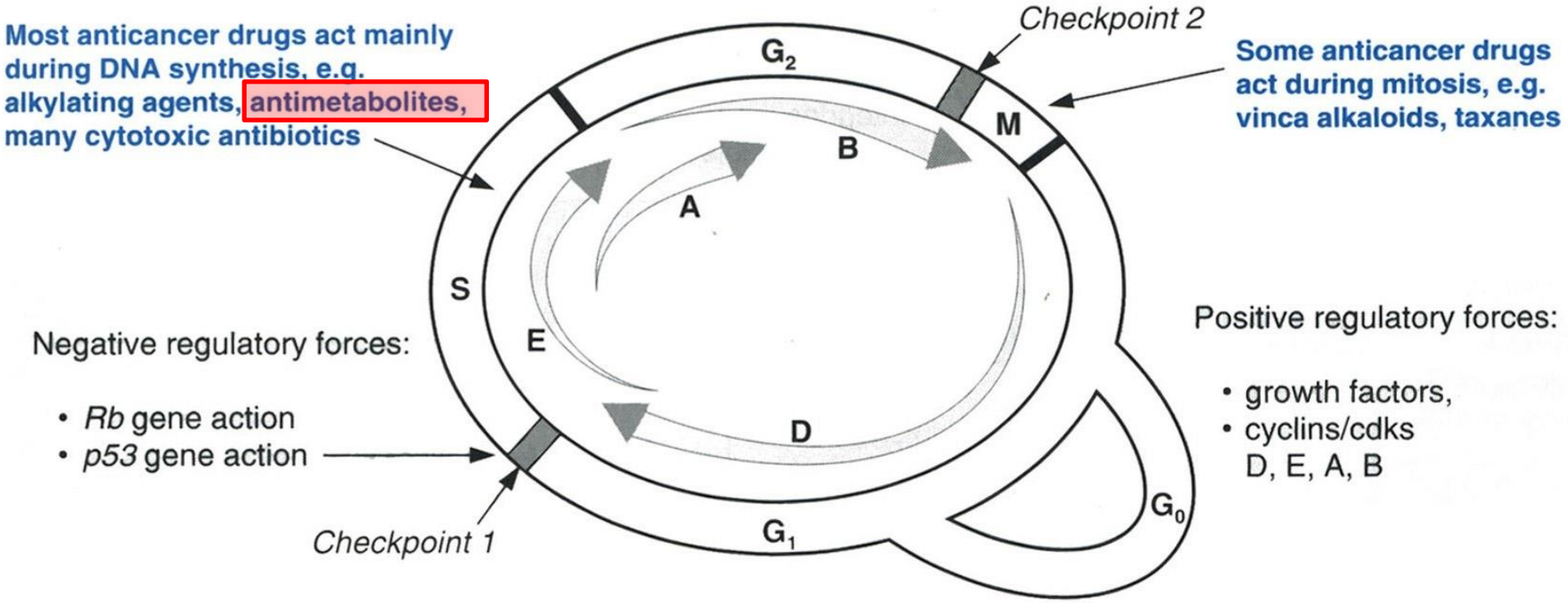
VIII. Angiogenesis Inhibitor & Immunomodulators

IX. Miscellaneous: hormonal, and specific agents

II. Anti-metabolites

7

Established Possible Targets for Anticancer Agents in Cell Cycle



[1] Rang , Dale, Ritter *Pharmacology*. 4th ed.; 1999.p.664-6.

II. Antimetabolites: Chemical Classification

II.1. Folate antimetabolites

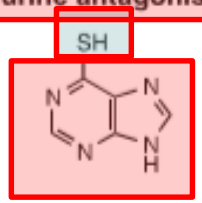
II.2. Pyrimidine antimetabolites

II.3. Purine antimetabolites

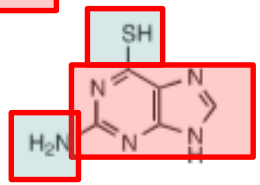
II.4. Miscellaneous / unclassified antimetabolites

Antimetabolites

Purine antagonists:

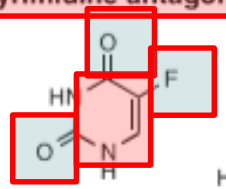


Mercaptopurine (Purinethol)

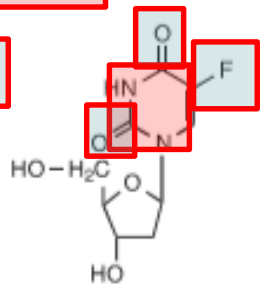


Thioguanine (Tabloid)

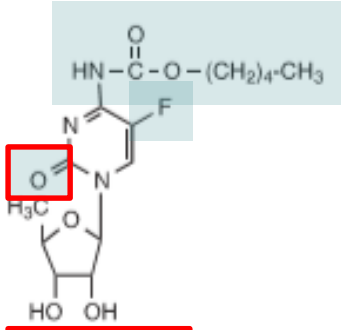
Pyrimidine antagonists:



Fluorouracil (Adrucil)

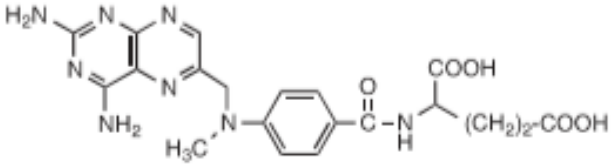


Floxuridine (FUDR)

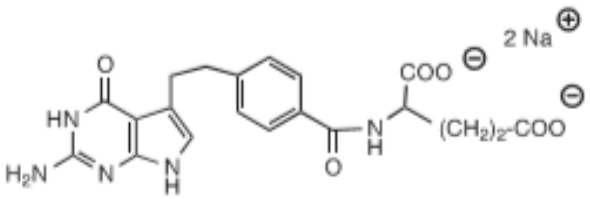


Capecitabine (Xeloda)

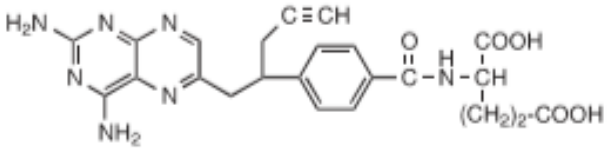
Folate antagonists:



Methotrexate (Trexall)



Pemetrexed disodium (Alimta)



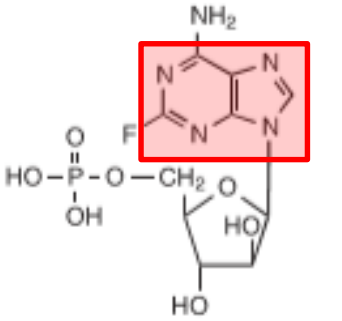
Pralatrexate (Folotyn)

Figure 33.41 Antimetabolites.

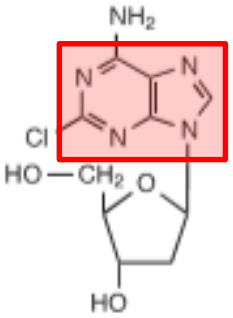
Antimetabolites-Contd.

DNA polymerase and chain elongation inhibitors:

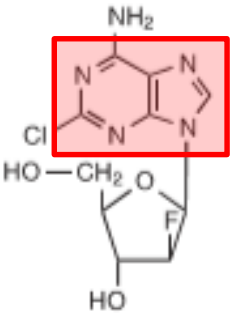
Purine analogues:



Fludarabine phosphate
(Fludara)

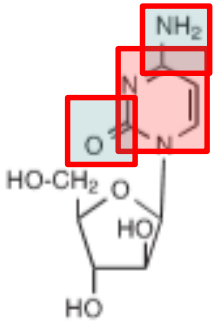


Cladribine
(Leustatin)

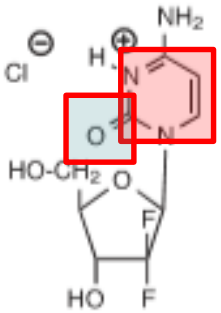


Clofarabine
(Clolar)

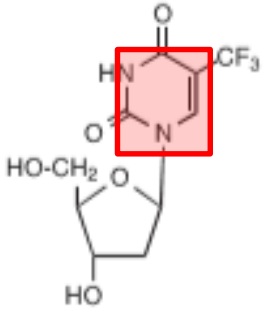
Pyrimidine analogues:



Cytarabine
(Tarabine PFS, DepoCyt)

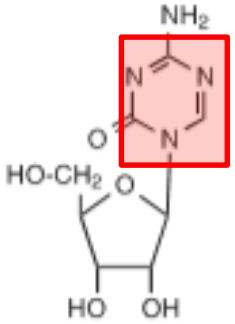


Gemcitabine hydrochloride
(Gemzar)

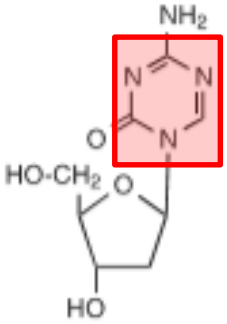


Trifluridine
(active drug in Lonsurf)

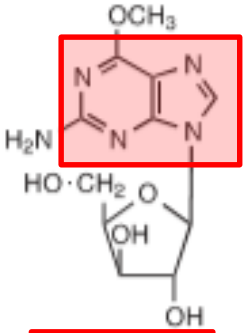
DNA Methyltransferase Inhibitors



Azacitidine
(Vidaza)

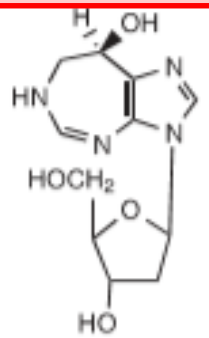


Decitabine
(Dacogen)

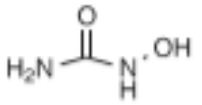


Nelarabine
(Arranon)

Miscellaneous antimetabolites:



Pentostatin
(Nipent)



Hydroxyurea
(Hydrea)

Figure 33.41 Antimetabolites.

II. Antimetabolites: Chemical Sub-Classification

II.1. Folate antimetabolites

- ✓ pteridine / PABA mimicking / Glu mimicking analogue

II.2. Pyrimidine antimetabolites

- ✓ uracil analogue
- ✓ cytosine
- ✓ deamino(6-oxo)cytosine
- ✓ cytidine/uridine analogue

II.3. Purine antimetabolites

- ✓ purinethiol analogue
- ✓ guanine analogue
- ✓ adenine analogue

II.4. Miscellaneous / unclassified antimetabolites

II. Antimetabolites: Mechanistic Classification

II.1. Folates antagonists / false substrate / antimetabolites:

II.1.a. Di-Hydro-Folate-Reductase (DHFR) inhibitors

II.1.b. Thymidylate Synthase (TS) inhibitors

II.1.c. Glycine-Amido-Phospho-Ribosyl-formylTransferase (GART) inhibitors

II. 2. Pyrimidine antagonists / false substrate / antimetabolites:

- ✓ II. 2.a. Thymidylate synthase inhibitors; dTMP synthesis inhibitor
- ✓ II.2.b. DNA polymerase inhibitors; chain elongation inhibitors
- ✓ II.2.c. DNA Methyl Transferase (DNMT) inhibitors

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

- ✓ II.3.a. Amido-phospho-ribosyl transferase inhibitor

(Glutamine 5-phospho-ribosyl-pyrophosphate amidotransferase); HGPRT involved

- ✓ II.3.b. DNA polymerase inhibitors; chain elongation inhibitors
- ✓ II.3.c. DNA Methyl Transferase (DNMT) inhibitors

IV.4. Miscellaneous antimetabolites

IV.4.a. Adenosine deaminase inhibitor

IV.4.b. Ribonucleotide reductase inhibitor

Three Targets as MOAs for II. 2,3.Pyrimidine/ Purine Antimetabolites

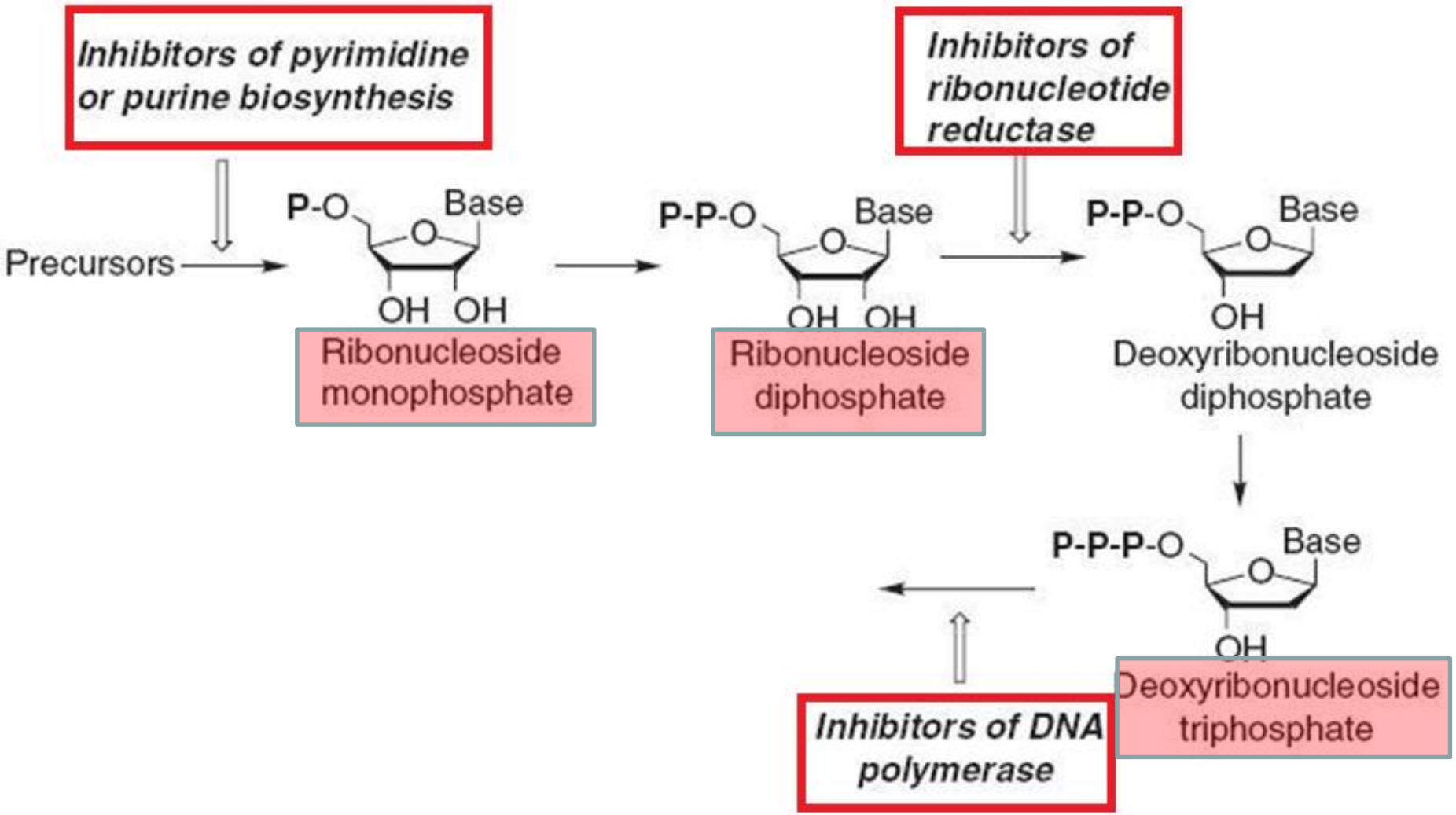


FIGURE 2.1 Types of anticancer drugs that interfere with DNA biosynthesis.

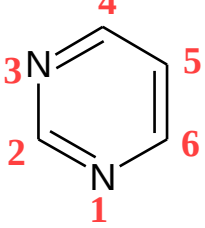
II. Antimetabolites: 2. Pyrimidine Antagonists: Chemical Classification

II.2. Pyrimidine antimetabolites

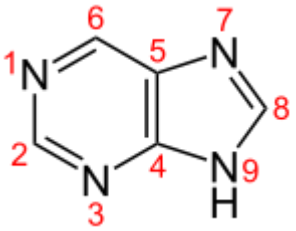
- ✓ uracil analogue
- ✓ uridine analogue

&

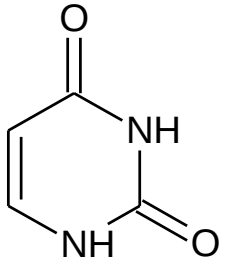
- ✓ cytosine analogue
- ✓ cytidine analogue
- ✓ De-amino(6-oxo)cytosine



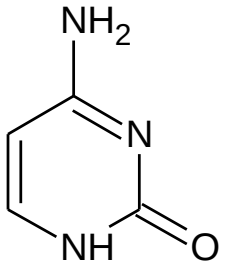
Nucleic Acid Components



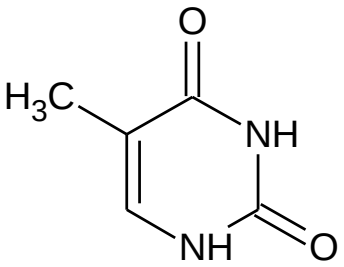
- Pyrimidines: U, C, T



Uracil

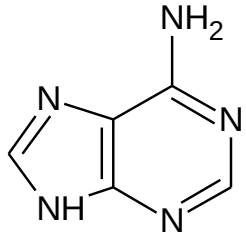


Cytosine

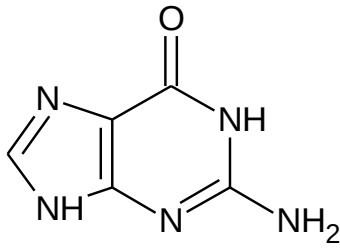


Thymine

- Purines: A, G

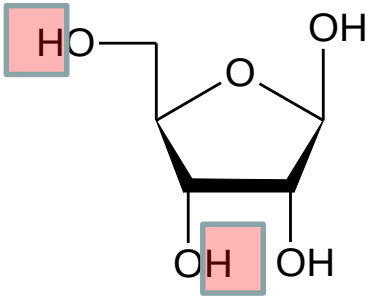


Adenine

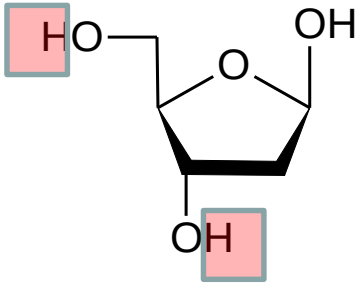


Guanine

- Ribose



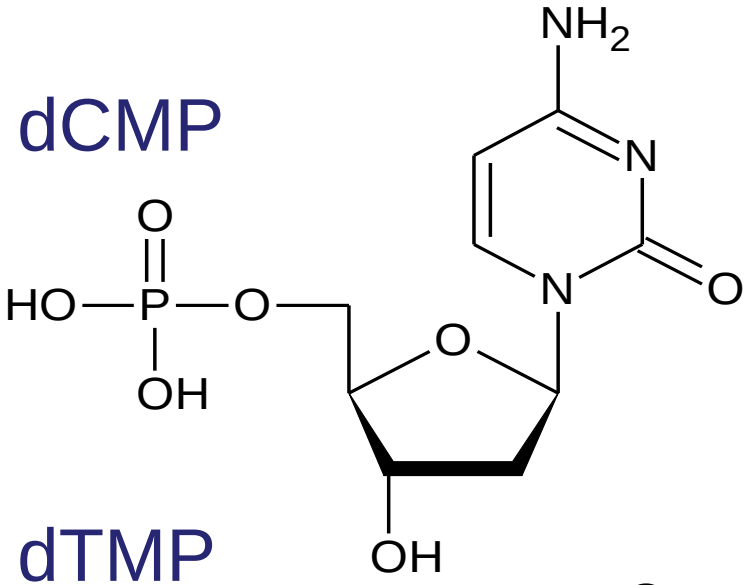
- 2-Deoxyribose



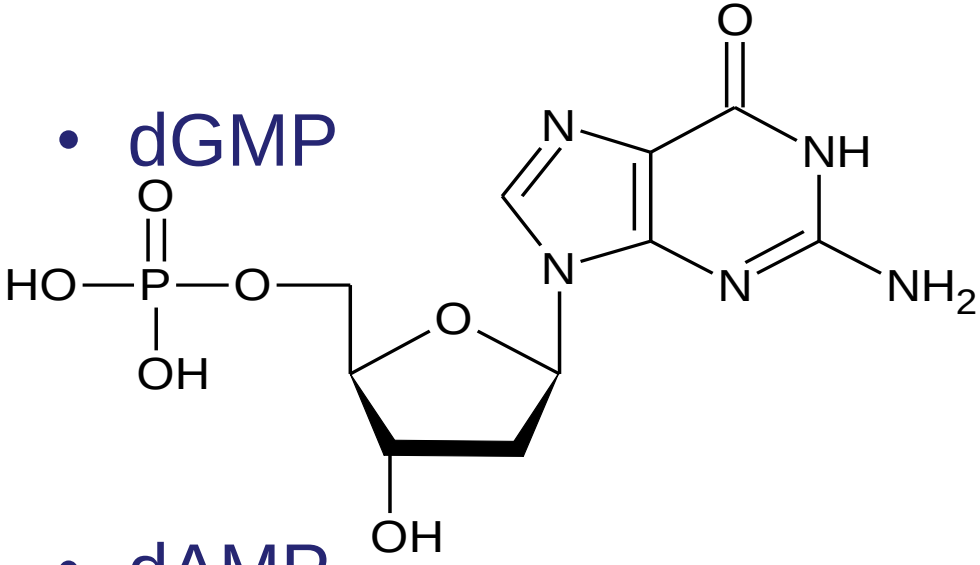
- Phosphate Group: PO_4^{3-}: HO-P(O)(OH)-O-

dCMP; dTMP; dAMP; dGMP

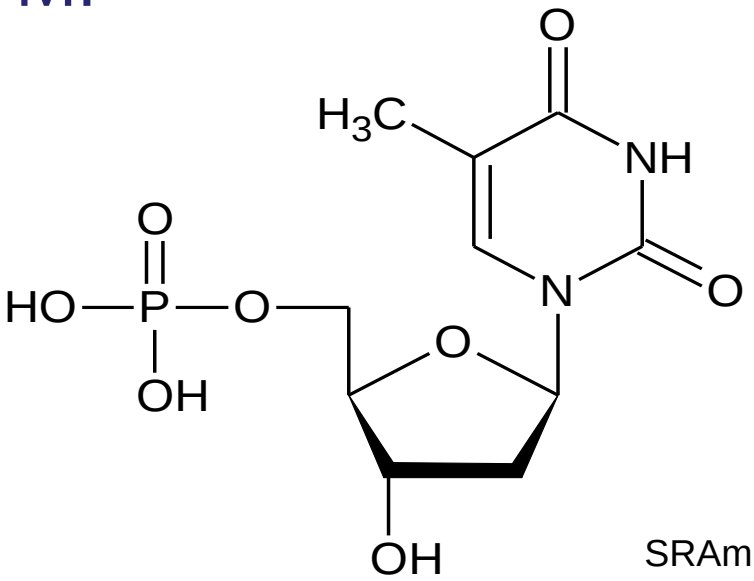
- dCMP



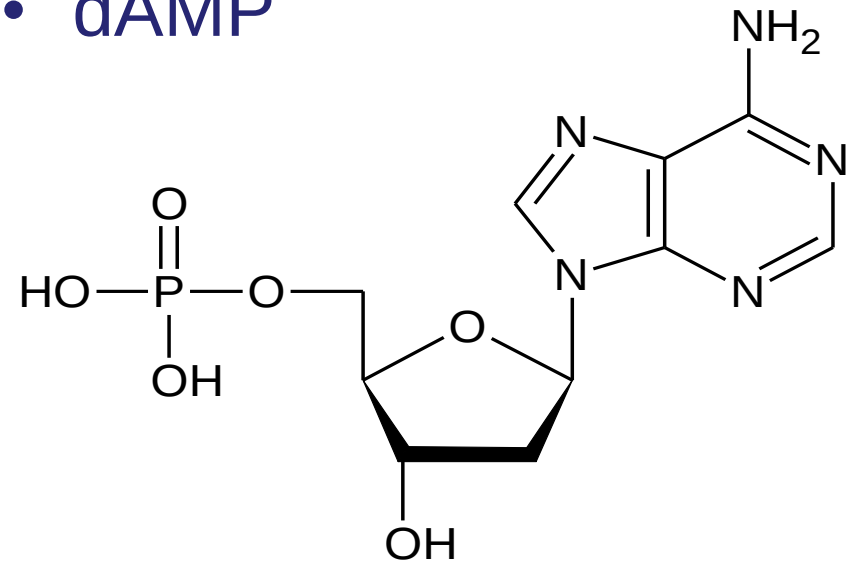
- dGMP



- dTMP



- dAMP



II. Antimetabolites: 2. Pyrimidine Antagonists: Pharmacologic Mechanistic Classification

II. 2. Pyrimidine antagonists / false substrate / antimetabolites:

- ✓ II. 2.a. Thymidylate synthase inhibitors & dTMP synthesis inhibitors
- ✓ II.2.b. DNA polymerase inhibitors; chain elongation inhibitors
- ✓ II.2.c. DNA Methyl Transferase (DNMT) inhibitors

II. Antimetabolites: 2. Pyrimidine Antagonists: Chemical Classifications of Pharmacologic Classifications

II. 2.a. Thymidylate synthase inhibitors & dTMP synthesis inhibitors

- ✓ uracil analogue
- ✓ uridine analogue
- ✓ cytosine / cytidine analogue: carbamylated cytidine analogue

- II.2.b. DNA polymerase inhibitors & chain elongation inhibitors

- ✓ cytidine / uridine analogue:
- ✓ possessing 2'-epimerized ribose; 2'-halogenated ribose

- II.2.c. DNA methyl transferase inhibitors

- ✓ cytosine analogue: C5 is replaced by N: triazine

II.2. Pyrimidine Antimetabolite: Possible MOAs

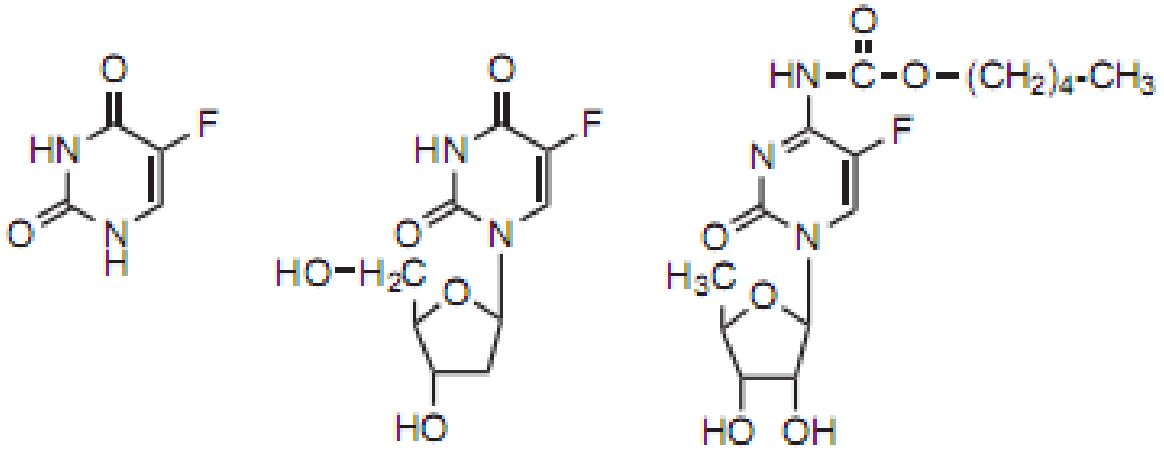
- Pyrimidine biosynthesis enzyme inhibitor
- Kinase inhibitor
- dTMP synthesis inhibitor: thymidylate synthase inhibitor
- False substrate: Incorporation into DNA or RNA: misreading
- DNA polymerase inhibition
- DNA elongation inhibition

II. 2. Pyrimidine Antagonists:
2.a. TS Inhibitors & dTMP Biosynthesis Inhibitor: SAR

II. 2.a. Thymidylate synthase inhibitors & dTMP synthesis inhibitors

- ✓ uracil analogue
- ✓ uridine analogue
- ✓ cytosine / cytidine analogue: carbamylated cytidine analogue

Pyrimidine antagonists:



Fluorouracil (Adrucil) | Floxuridine (FUDR) | Capecitabine (Xeloda)

Uracil to Thymine by Thymidylate Synthase (TS)

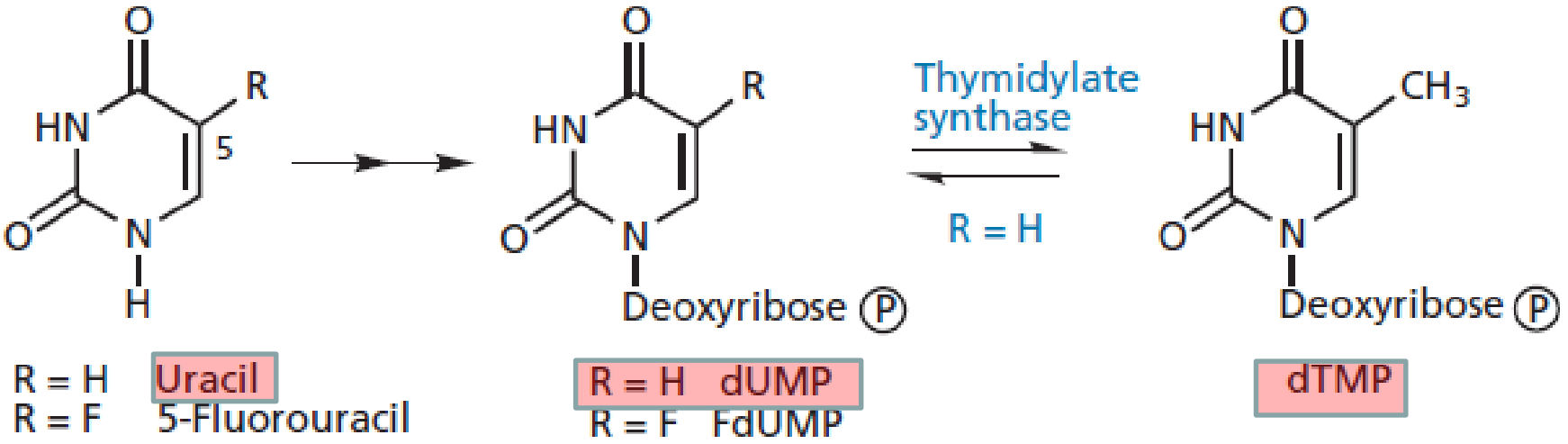
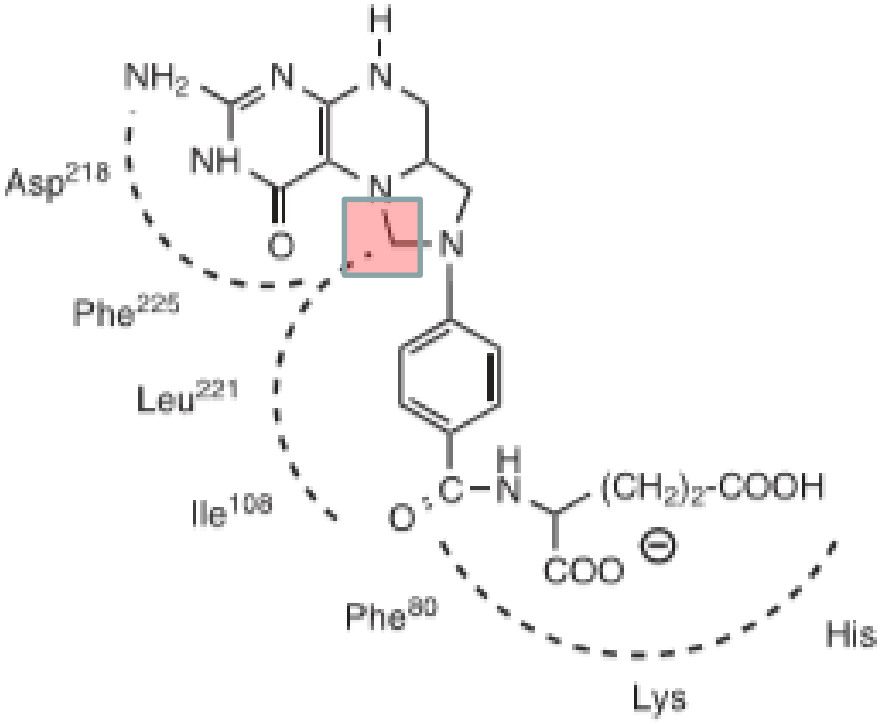
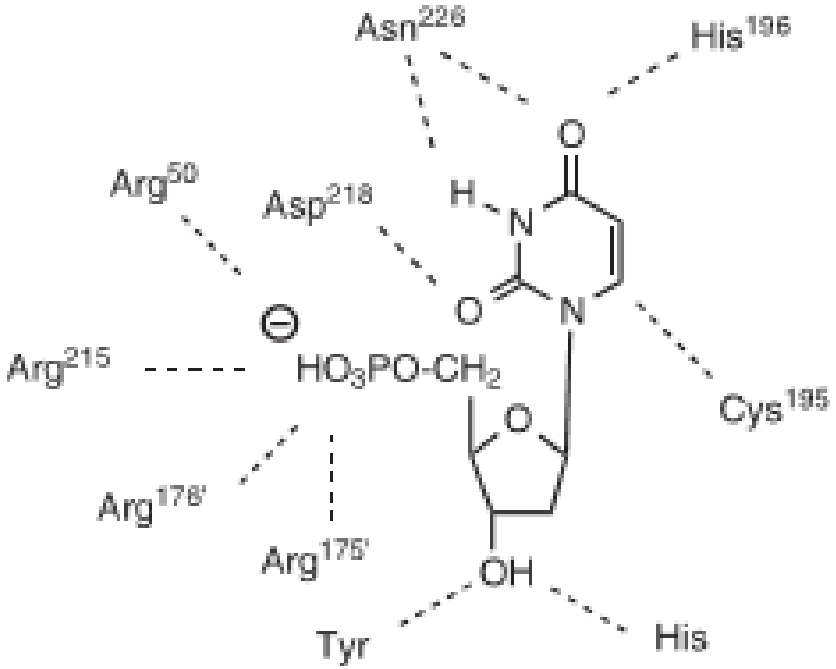


FIGURE 21.19 Biosynthesis of dTMP. Ⓟ = phosphate.

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



5,10-Methylene-THF



dUMP

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

Biosynthesis of dTMP from dUMP byThymidylate Synthase

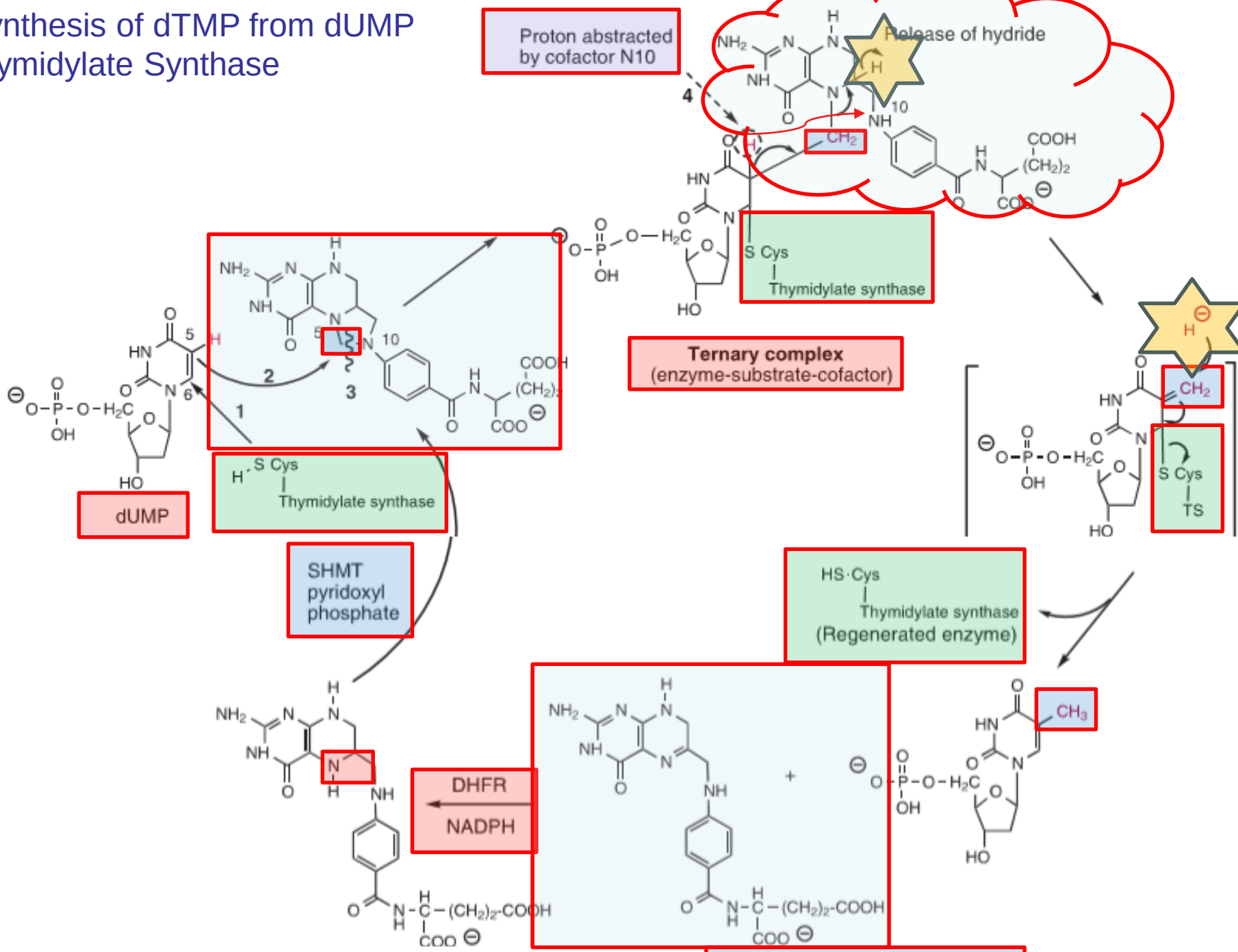
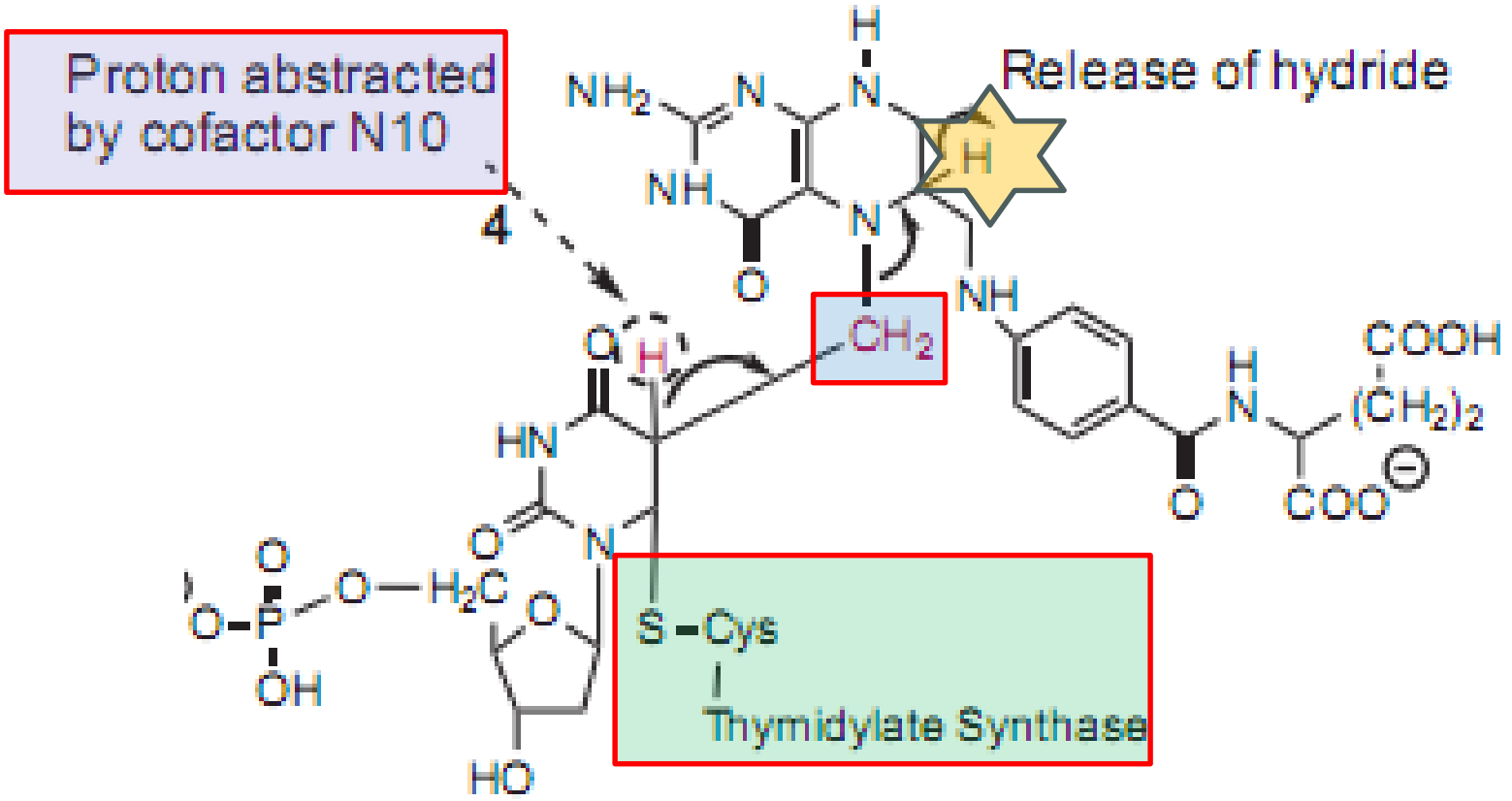


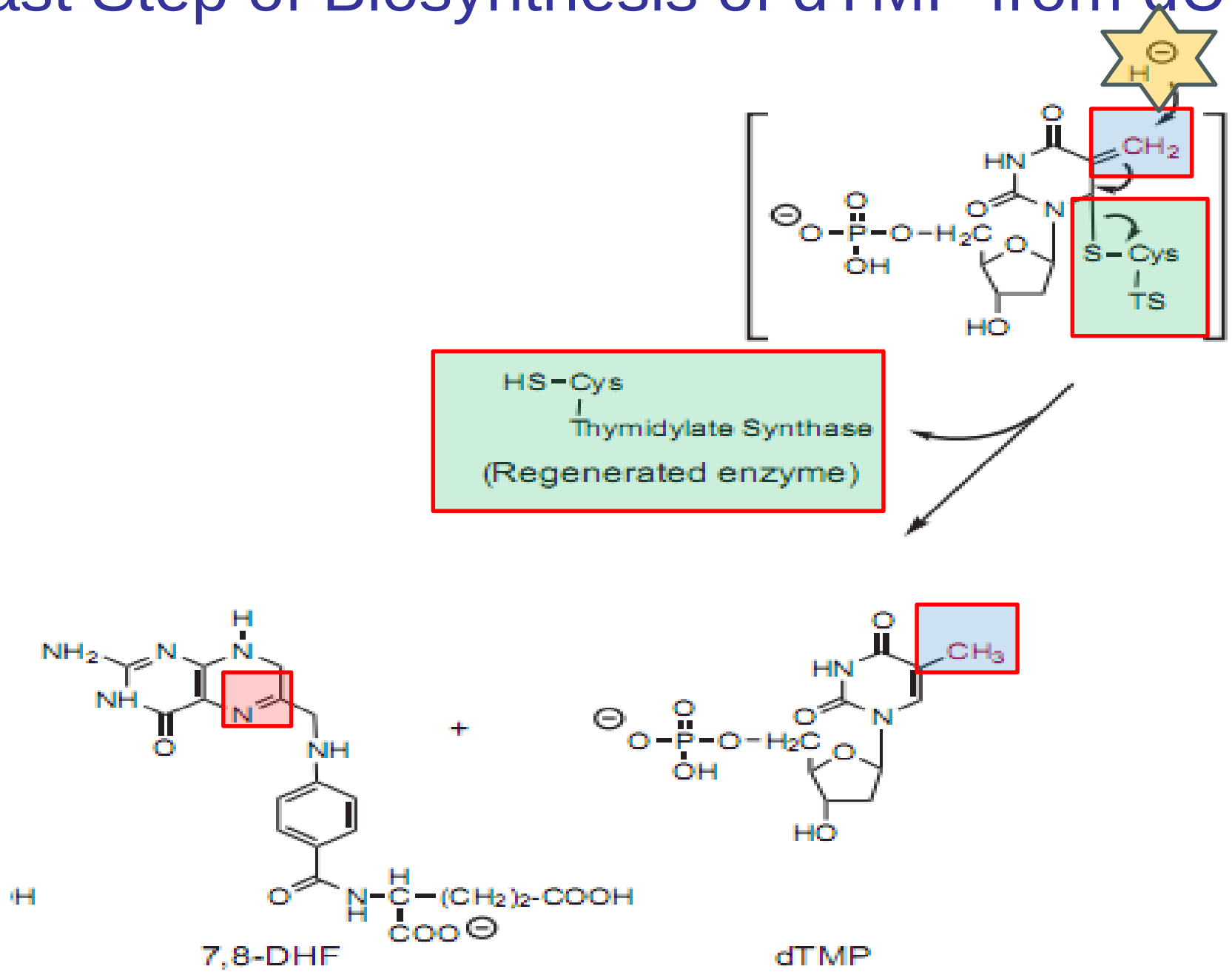
Figure 33.45 Synthesis of deoxythmidine monophosphate (dTMP). DHFR, dihydrofolate reductase; SHMT, serine hydroxymethyltransferase; TS, thymidylate synthase.

Critical Ternary Complex Formation in Biosynthesis of dTMP from dUMP

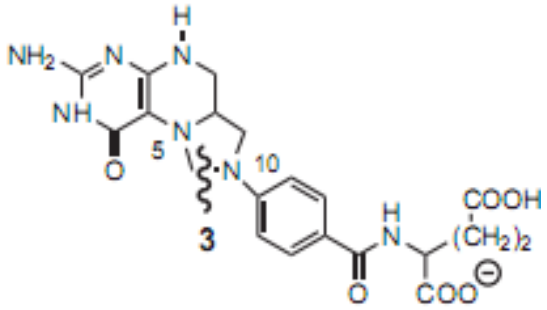


Ternary complex
(enzyme-substrate-cofactor)

Last Step of Biosynthesis of dTMP from dUMP



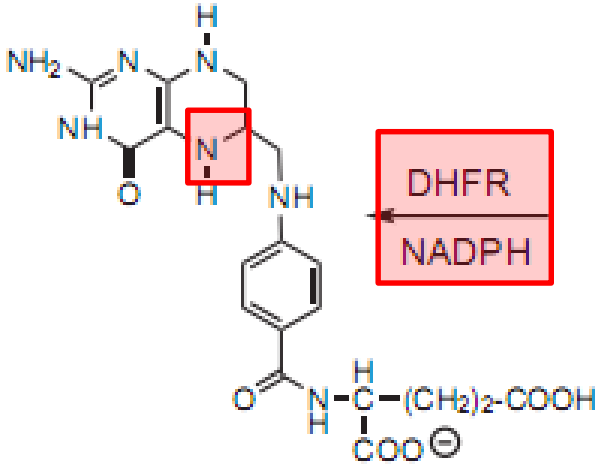
Regeneration of TS & DHF in Biosynthesis of dTMP



SHMT
pyridoxyl
phosphate

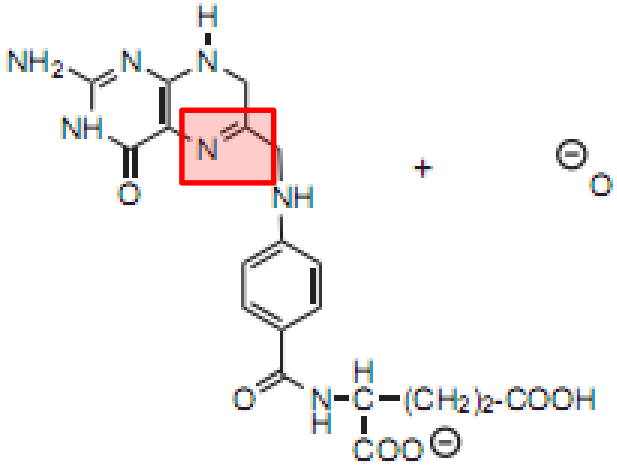
HS–Cys
|
Thymidylate Synthase

(Regenerated enzyme)



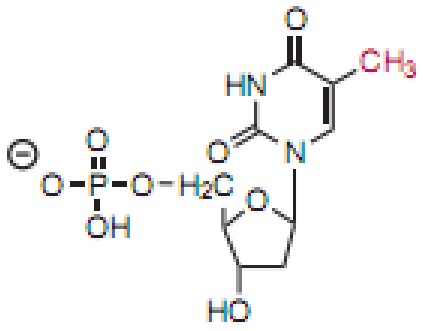
THF

DHFR
NADPH



7,8-DHF

+



dTMP

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

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

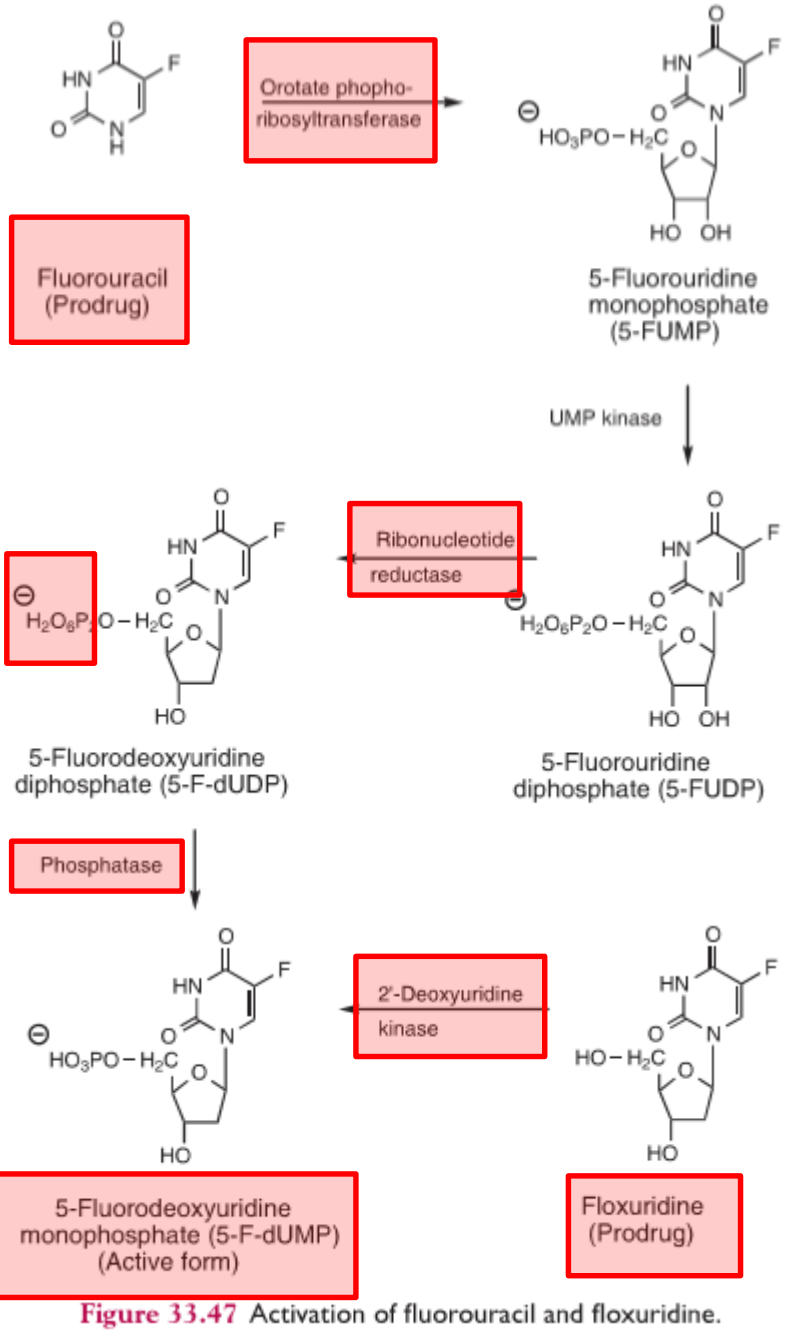


Figure 33.47 Activation of fluorouracil and floxuridine.

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

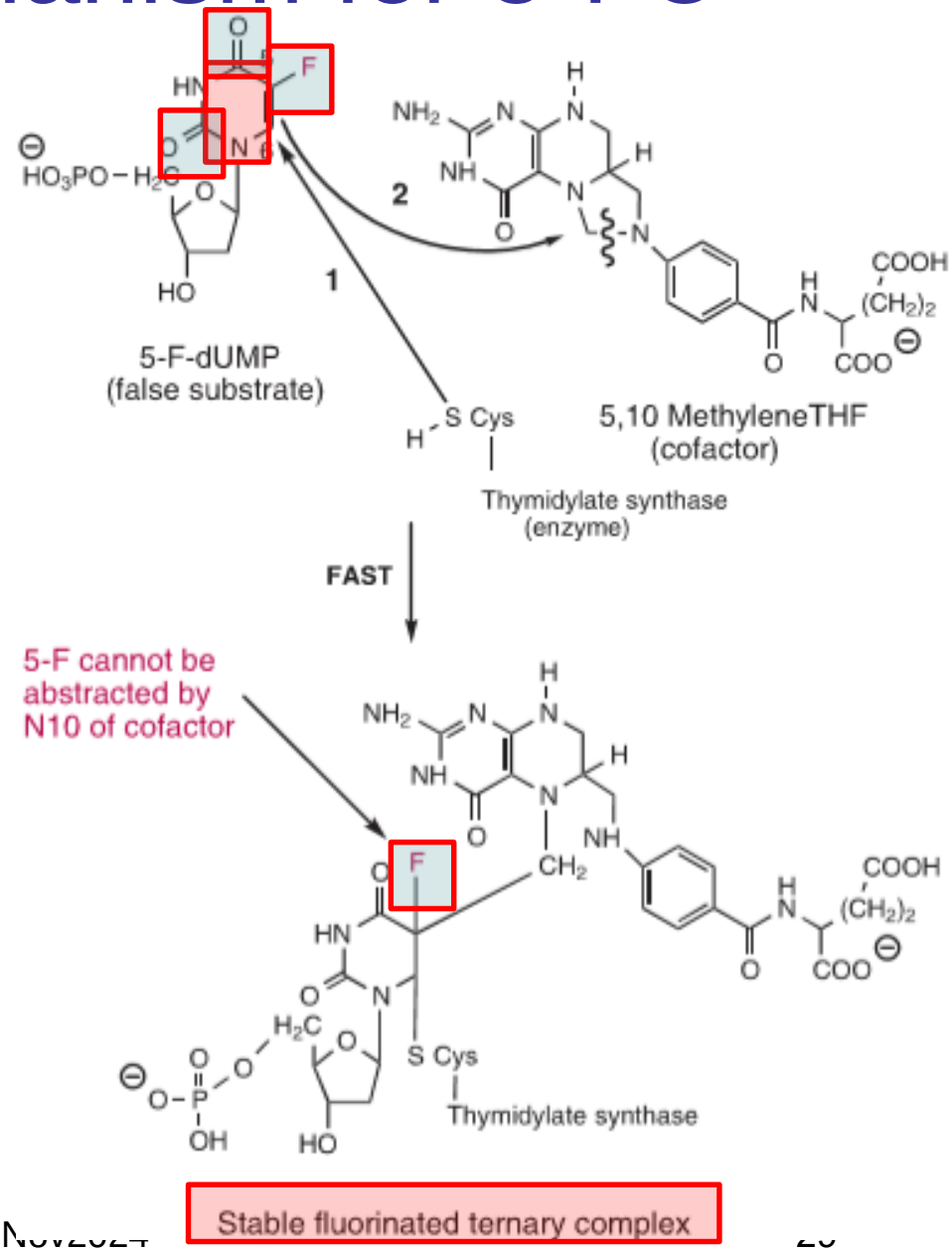


Figure 33.48 Mechanism of action of fluorouracil.

Metabolism of 5-FU

- Metabolism enzyme:

DPD

(Dihydro-

Pyrimidine-

Dehydrogenase)

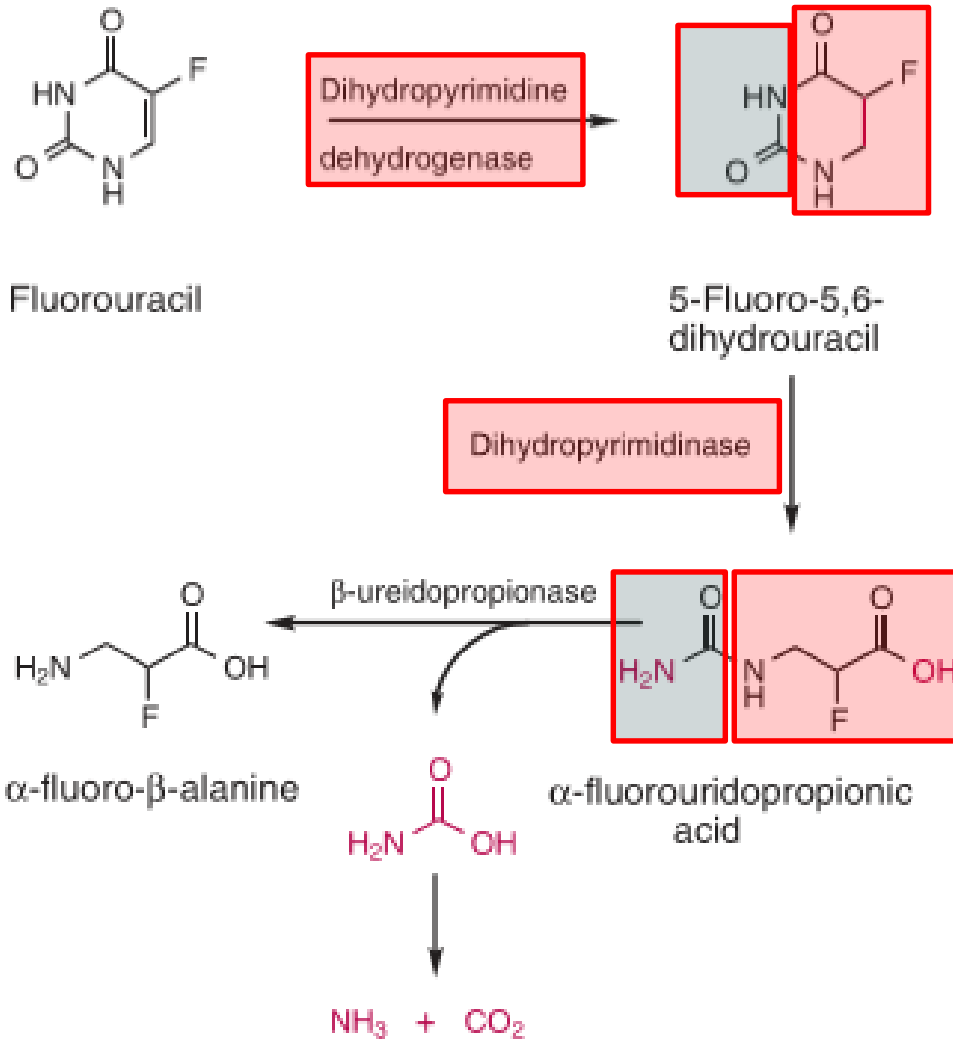


Figure 33.49 Fluorouracil metabolism.

Bio-Activation of Capecitabine

- Prodrug: carbamylated cytidine
- Involving enzymes:

✓ carboxy-esterase

✓ cytidine deaminase

✓ thymidine phosphorylase

✓ ribosyl-transferase

✓ kinase

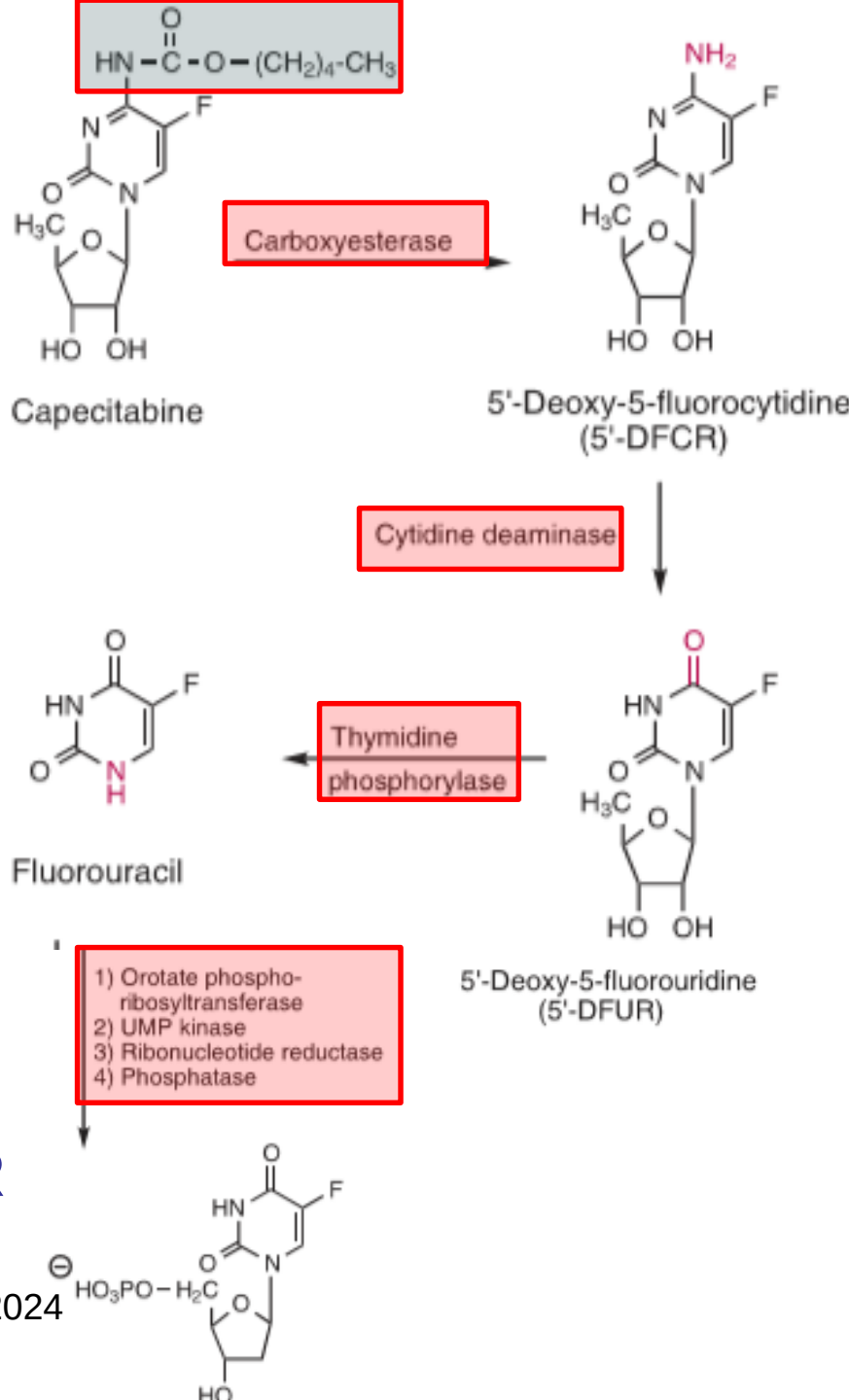
✓ ribonucleotide reductase

✓ phosphatase

- Metabolites:

✓ intermediate:5’-dFCR & 5’-dFUR

✓ active: 5-FdUMP via 5-FU



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

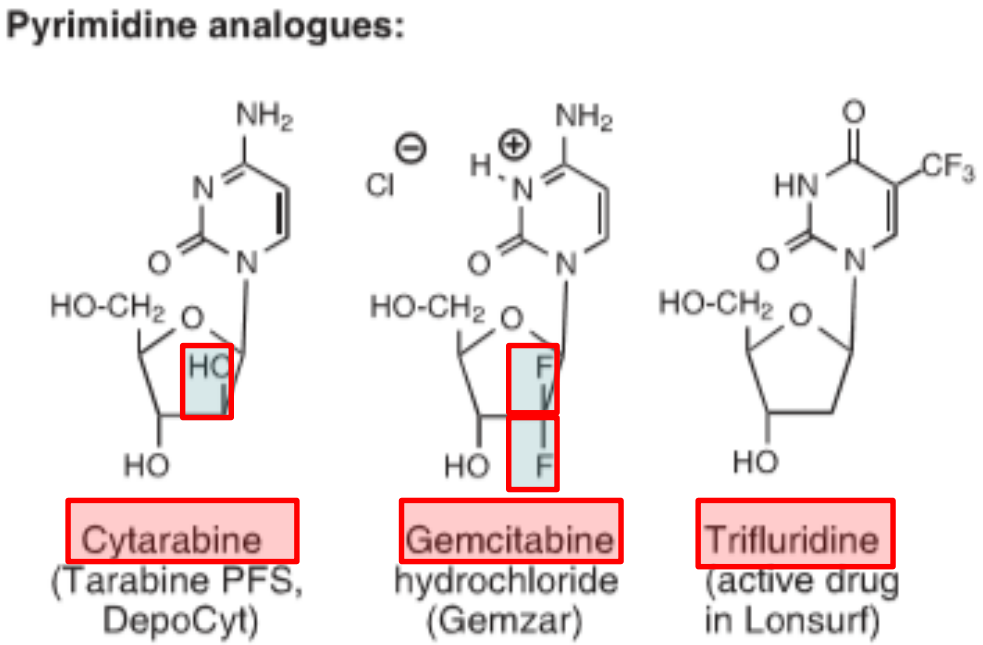
- Cytidine/uridine analogue: modified via:

✓ 3- CF_3 or 2'- epimerized or 2'&2'-di-halogenated ribose

✓ Cytarabine

✓ Gemcitabine

✓ Trifluridine



DNA Polymerase Inhibition by Gemcitabine

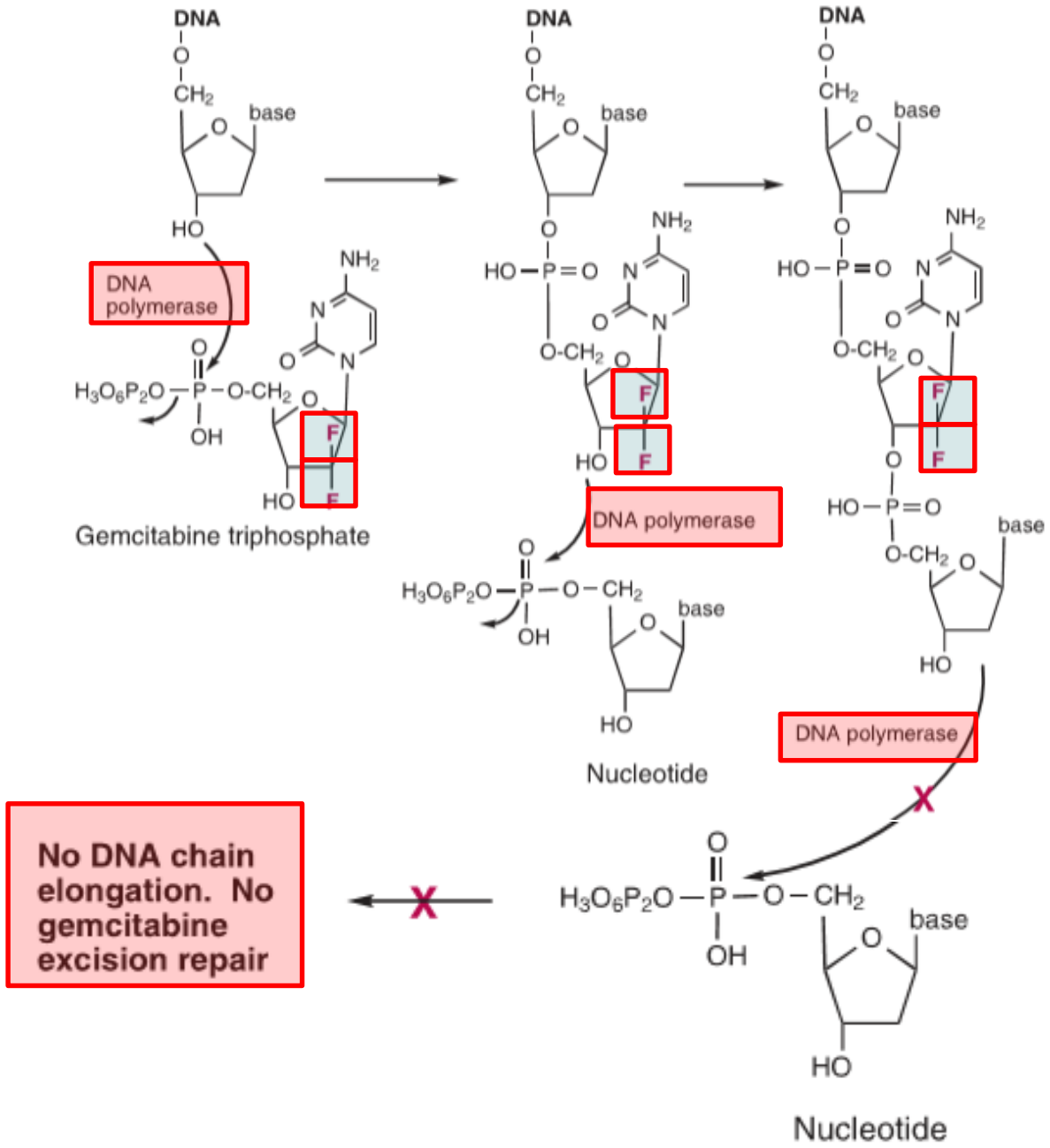


Figure 33.52 Gemcitabine triphosphate inhibition of DNA polymerase.

Cytarabine Metabolism

- Active Ara-cytidine triphosphate analogue

- Inactive uracil metabolite

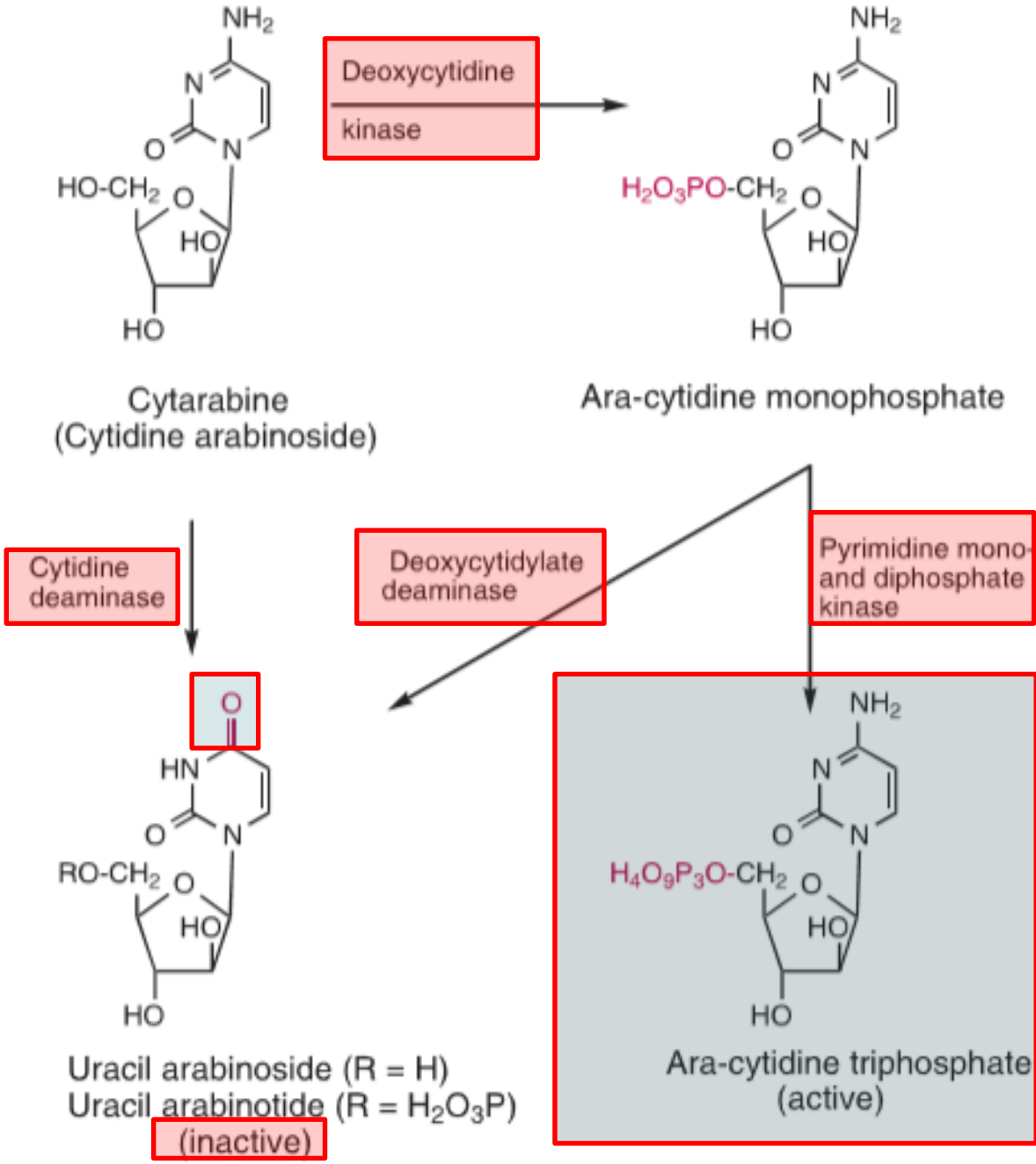


Figure 33.53 Cytarabine metabolism.

II. 2. Pyrimdine Antimetabolites:
c: DNA MethylTransferase(DNMT) Inhibitor: MOA & SAR

- Inhibit DNA alkylation specifically methylation at:

✓ adenine (C6) & cytosine (C5)

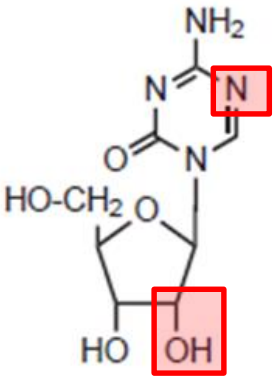
✓ block abnormal cellular proliferation

✓ especially responsible for differentiation & growth

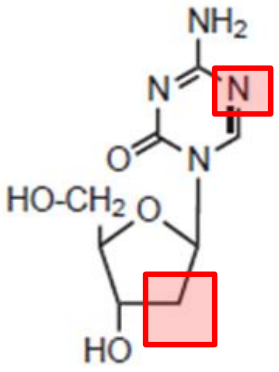
✓ mistakenly incorporated into DNA: false nucleotide

✓ irreversible inhibitor

- Vulnerable to deaminase: short half l
- Activated by kinase: tri-phosphate
- Chemistry: amino-triazine



Azacitidine
(Vidaza)



Decitabine
(Dacogen)

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 Classifications of Pharmacologic Classifications

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

II. Antimetabolites: 3. Purine Antagonists:
3.a. Purine Biosynthesis Inhibitor

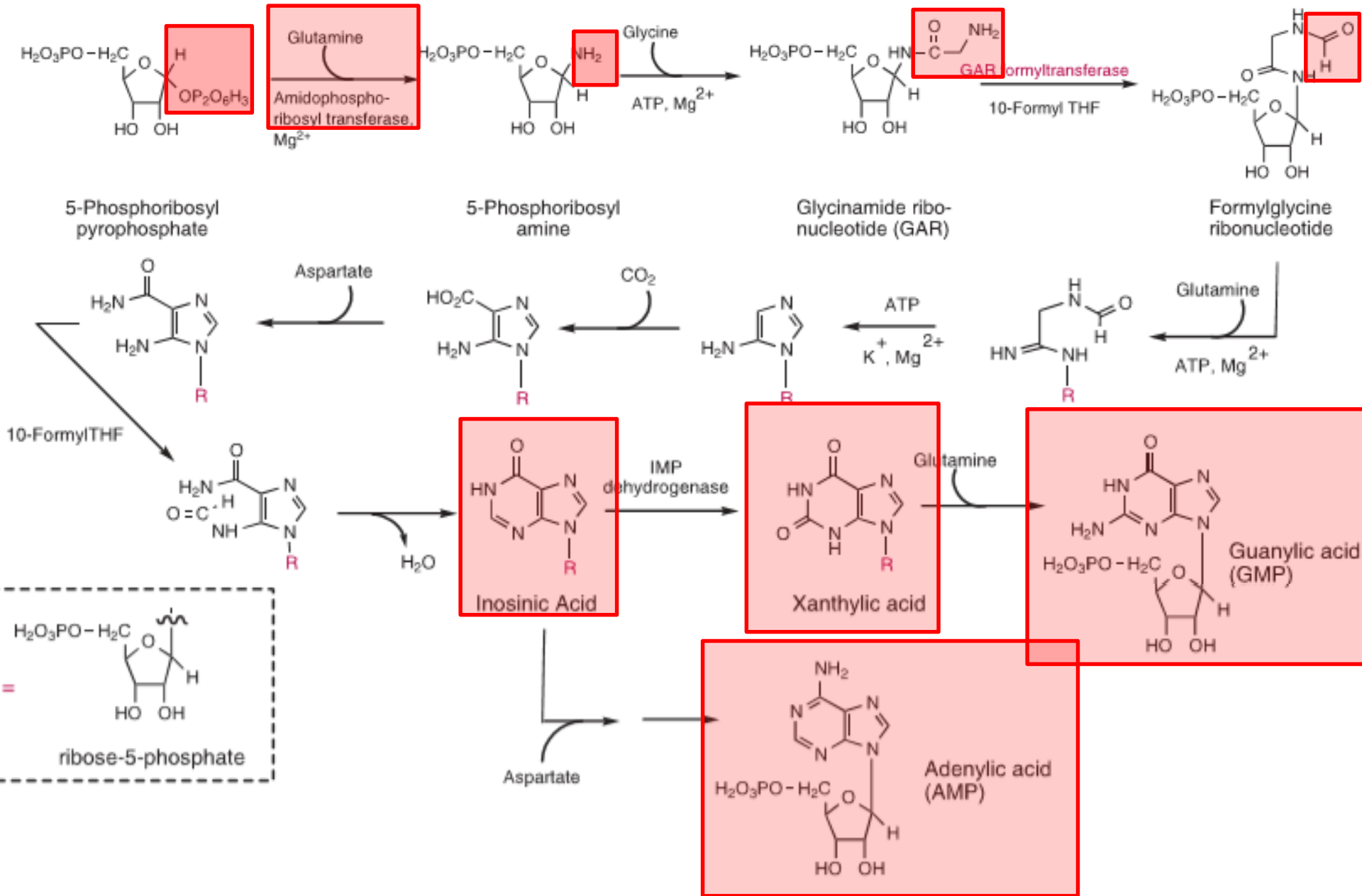
Glutamine 5-phospho-ribosyl-pyrophosphate amidotransferase inhibitor (amido-phospho-ribosyl transferase inhibitor)

&

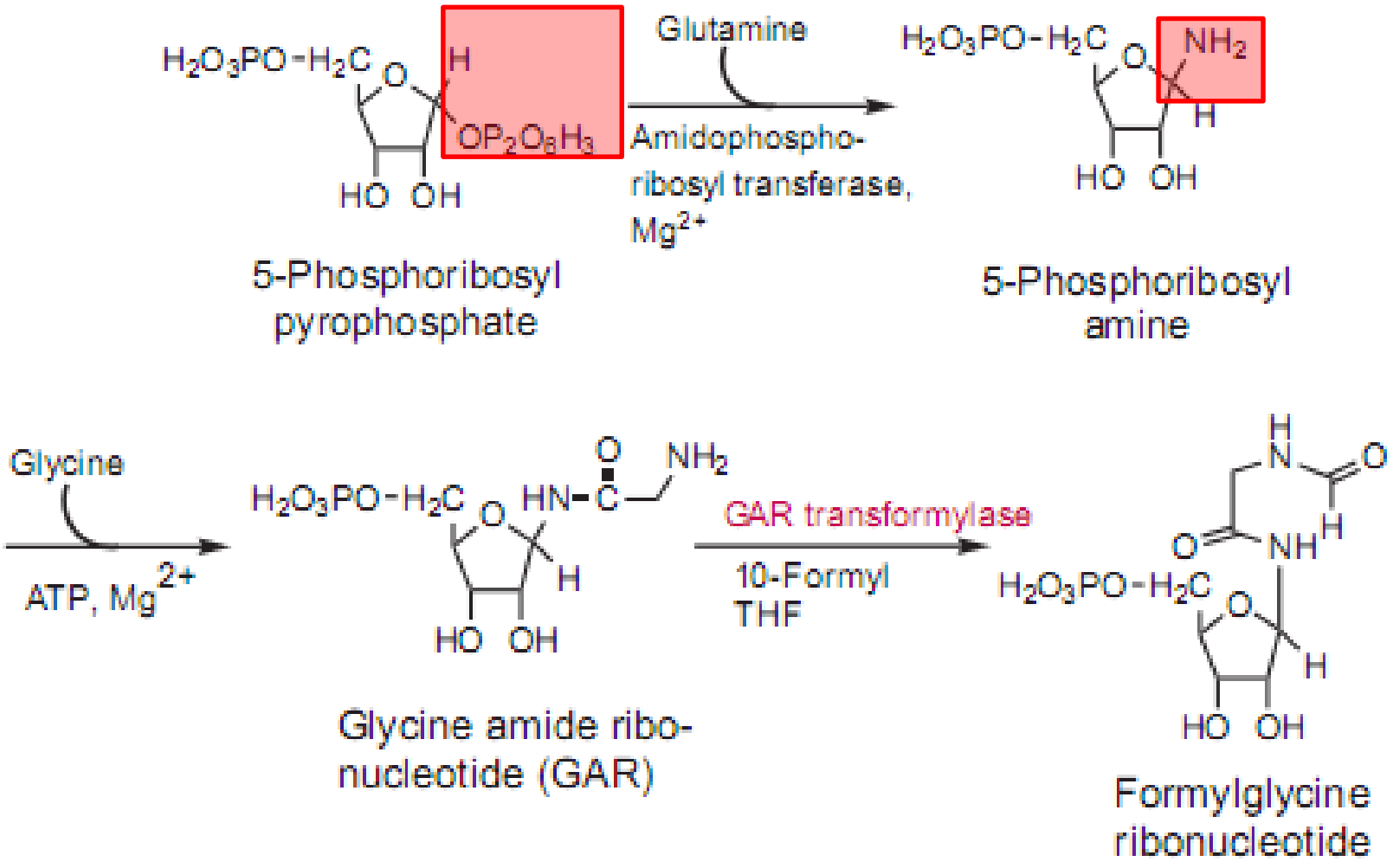
Hypoxanthine Guanine Phosphoribosyl Transferase (HGPRT) inh.

- ✓ purine-thiol analogues

Purine Nucleotide Biosynthesis De Novo Pathway

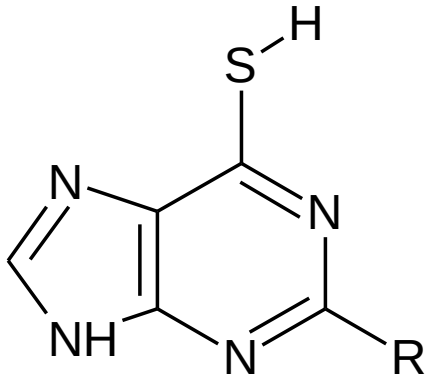


First Steps of Purine Biosynthesis Pathway

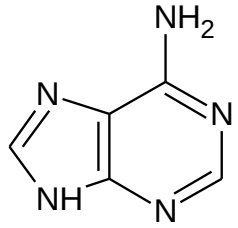


II. 3. Purine Antagonists:

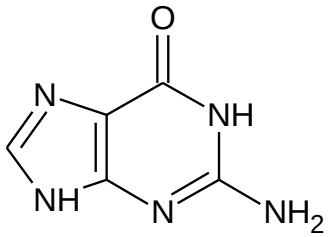
a. Purine Biosynthesis Inhibitor & DNA Polymerase Inhibitor: SAR



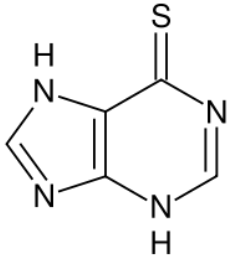
- Purinethiol; 6-thio inosine (G/A)
- ✓ R=: 6-Mercapto-Purine (6-MP)
- ✓ R=NH_2: 6-Thio-Guanine (6-TG)
- Prodrug

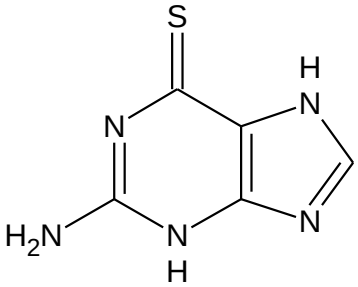


Adenine

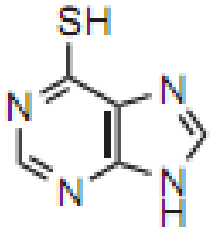


Guanine

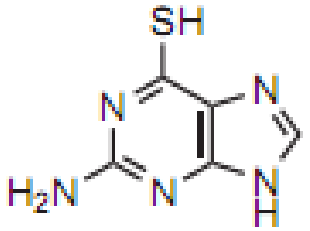




Purine antagonists:



Mercaptopurine
(Purinethol)

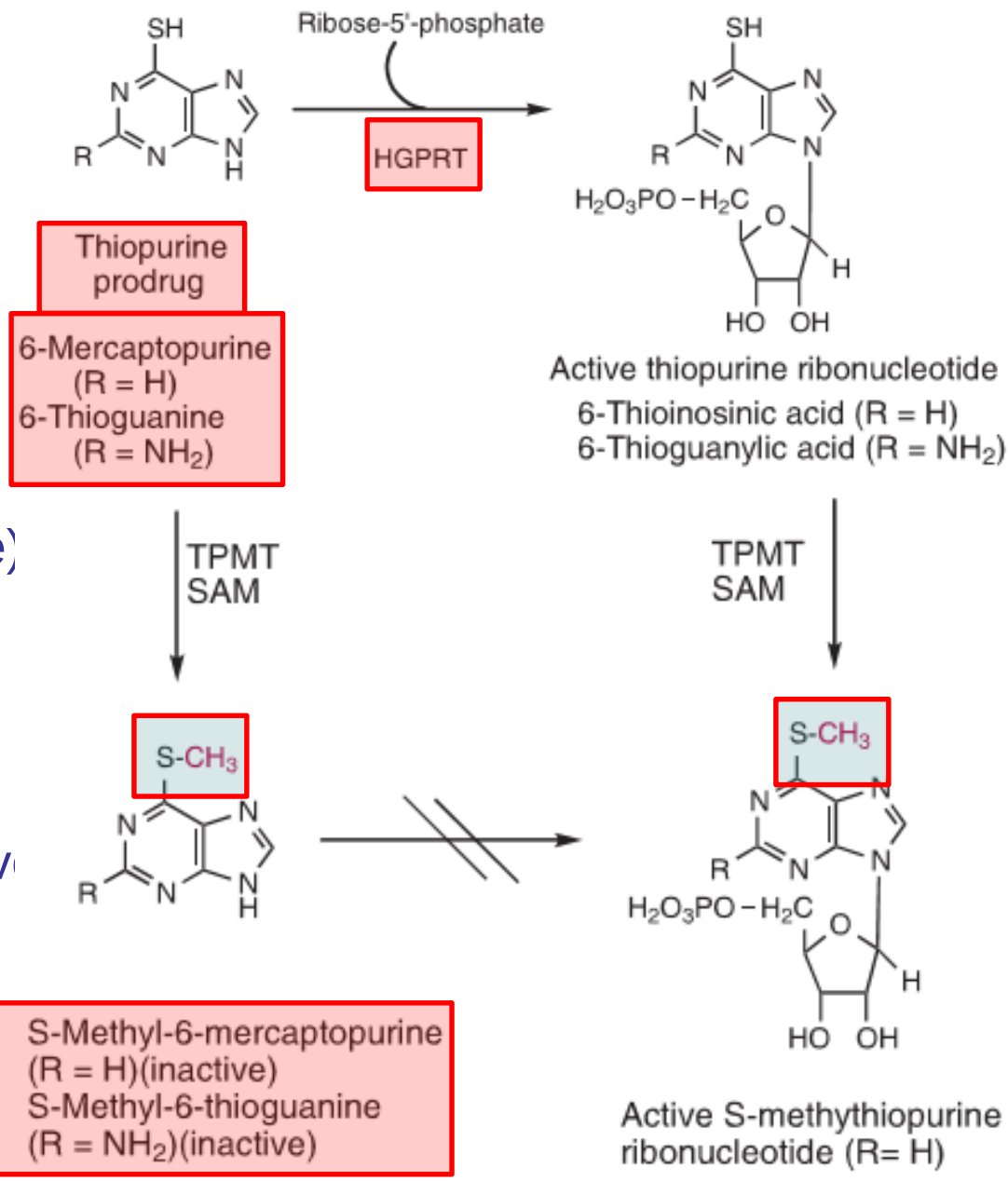


Thioguanine
(Tabloid)

MP & TG Metabolism & Bio-Activation

➢ Phospho-ribosylated:

- MP-ribonucleotide
  - ✓ 6-MMP (inactive)
  - ✓ 6-thioinosinic acid (active)
  - ✓ 6-methylthioinosinic acid (active)
- TG-ribonucleotide
  - ✓ 6-MTG (inactive)
  - ✓ 6-thioguanylic acid (active)
  - ✓ 6-methyl-thioguanylic acid (activ



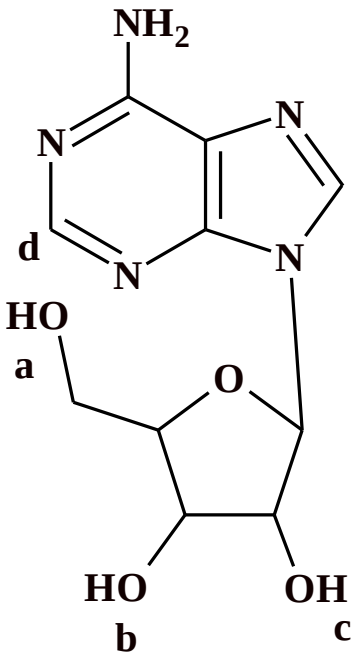
TPMT: Thio-Purine Methyl Transferase

SAM:S-Adenosyl Methionine

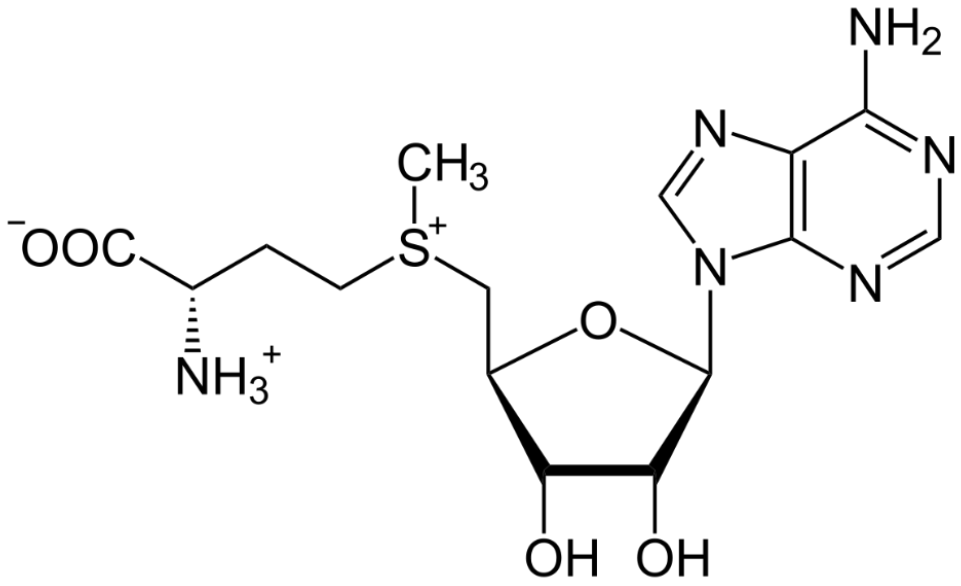
Figure 33.43 Thiopurine metabolism leading to activation and inactivation.

Consider Structures of Adenosine & SAM

Adenosine



SAM:S-Adenosyl Methionine



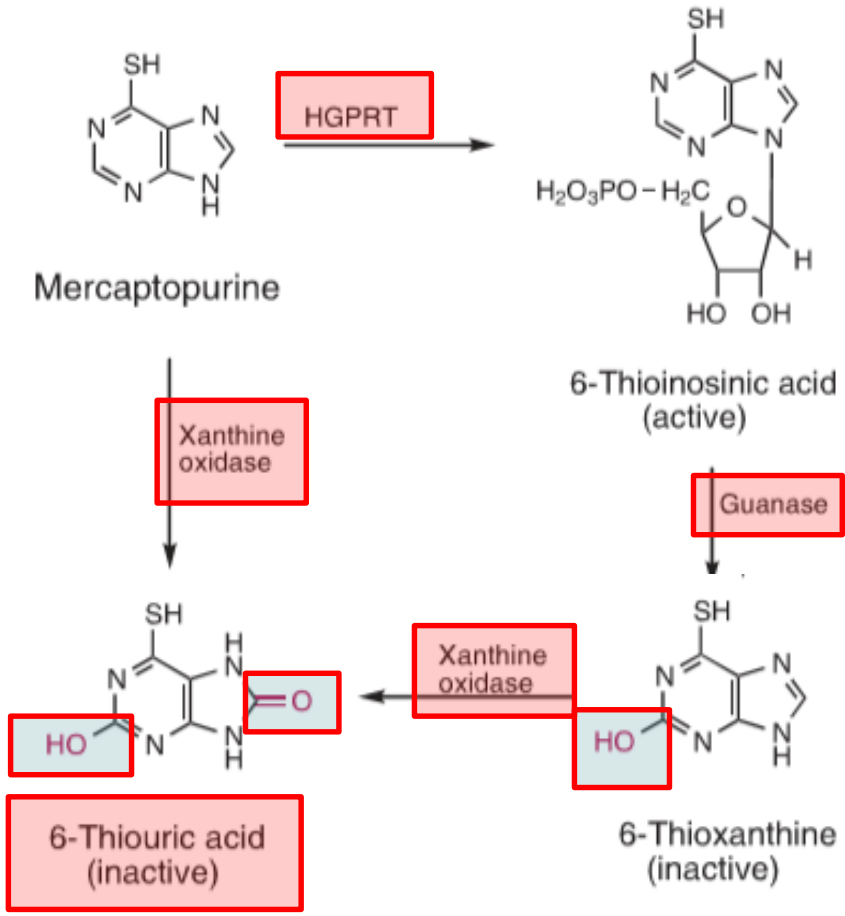
Metabolism & Metabolites of 6-MP

- 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.

Metabolism for 6-MP:

- Activation

by HGPRT

- Inactivation

by
xanthine oxidase

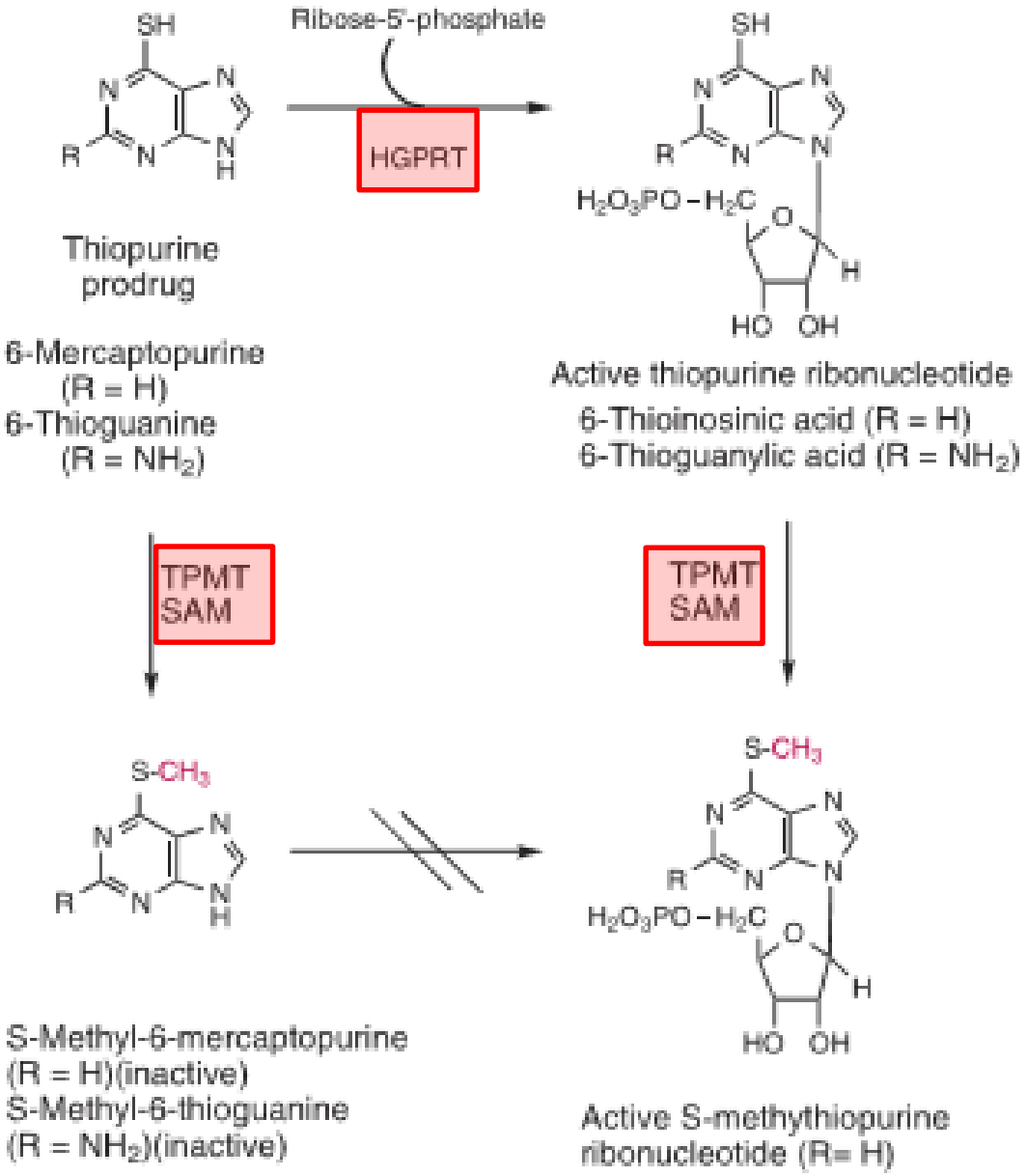
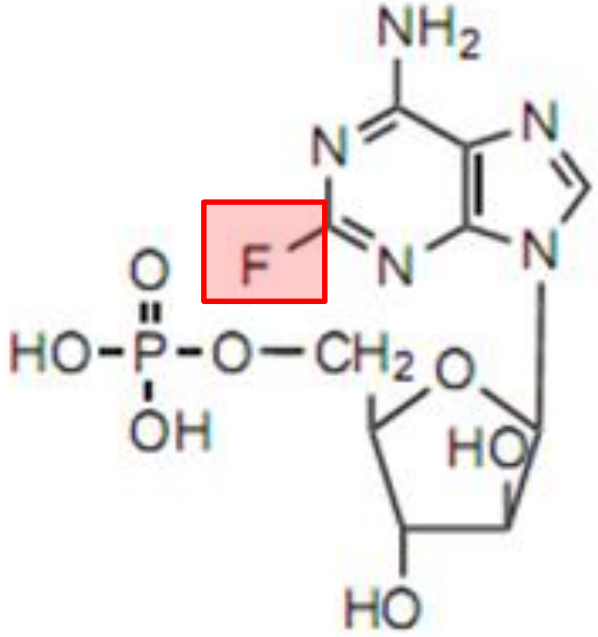
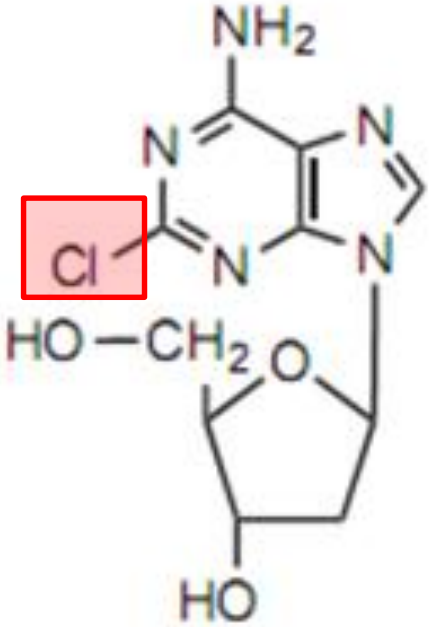


Figure 33.43 Thiopurine metabolism leading to activation and inactivation.

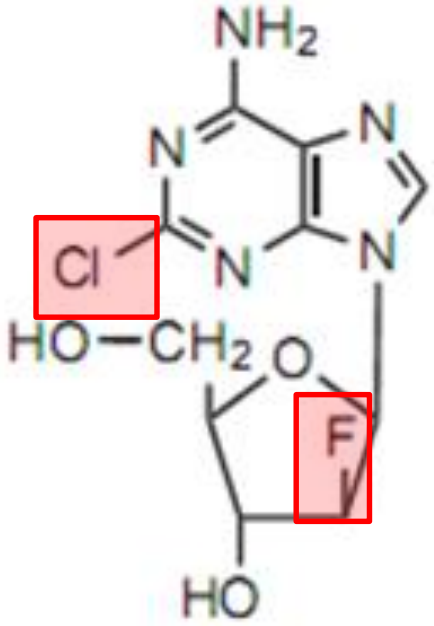
II. Antimetabolites: 3. Purine Antimetabolites:
b: DNA Polymerase and/or Chain Elongation Inhibitors



Fludarabine phosphate
(Fludara)



Cladribine
(Leustatin)



Clofarabine
(Clolar)

II. 3. Purine Antimetabolites:

b: DNA Polymerase and/or Chain Elongation Inhibitors:

Chemical Classification & SAR

- Adenosine based analogue: 2- halogenated adenosine

✓ possessing 2'-epimerized/halogenated ribose

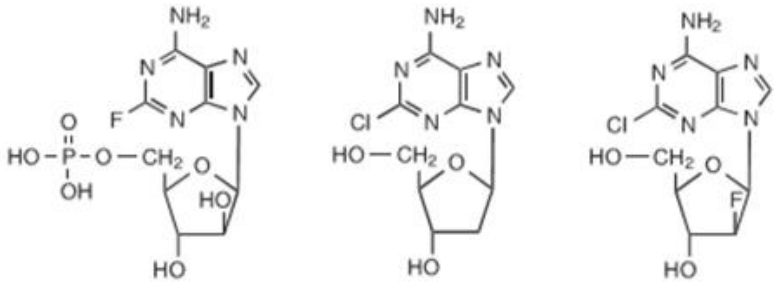
✓ Fludarabine: 2-F&2'-epimer ribose

✓ 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 (Fludara)

Cladribine (Leustatin)

Clofarabine (Clolar)

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

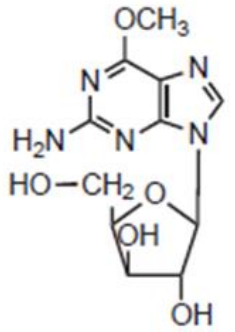
✓ block abnormal cellular proliferation

✓ 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)

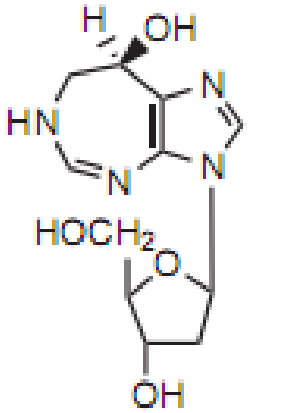
II. Antimetabolites:
4. Miscellaneous / Unclassified Antimetabolites:
MOA & SAR

- Ribonucleotide reductase inhibitor:

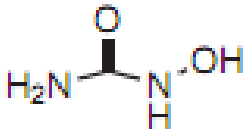
✓ blocks DNA synthesis through trapping Tyr at catalytic site of ribonucleotide reductase

- Pentostain
- Hydroxy-urea

Miscellaneous antimetabolites:



Pentostatin
(Nipent)



Hydroxyurea
(Hydrea)

II. 4. Unclassified Antimetabolites: Pentostatin

- SAR: ring expanded purine ribonucleotide

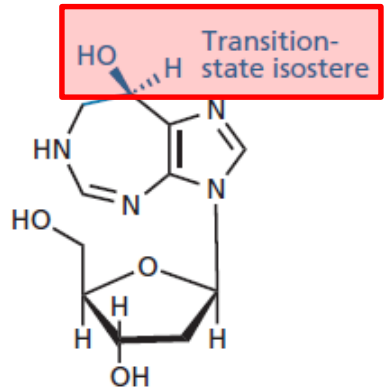


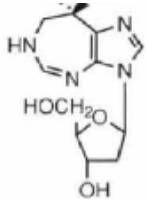
FIGURE 21.24 Pentostatin.

- MOA: halt DNA synthesis inhibiting:

✓ adenosine deaminase, directly

✓ ribonucleotide reductase, indirectly

✓ increment of deoxyadenosine triphosphate (dATP)



Pentostatin
(Nipent)

- Base of design:

✓ mimic tetrahedral (hydroxylated)intermediate of deaminase

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

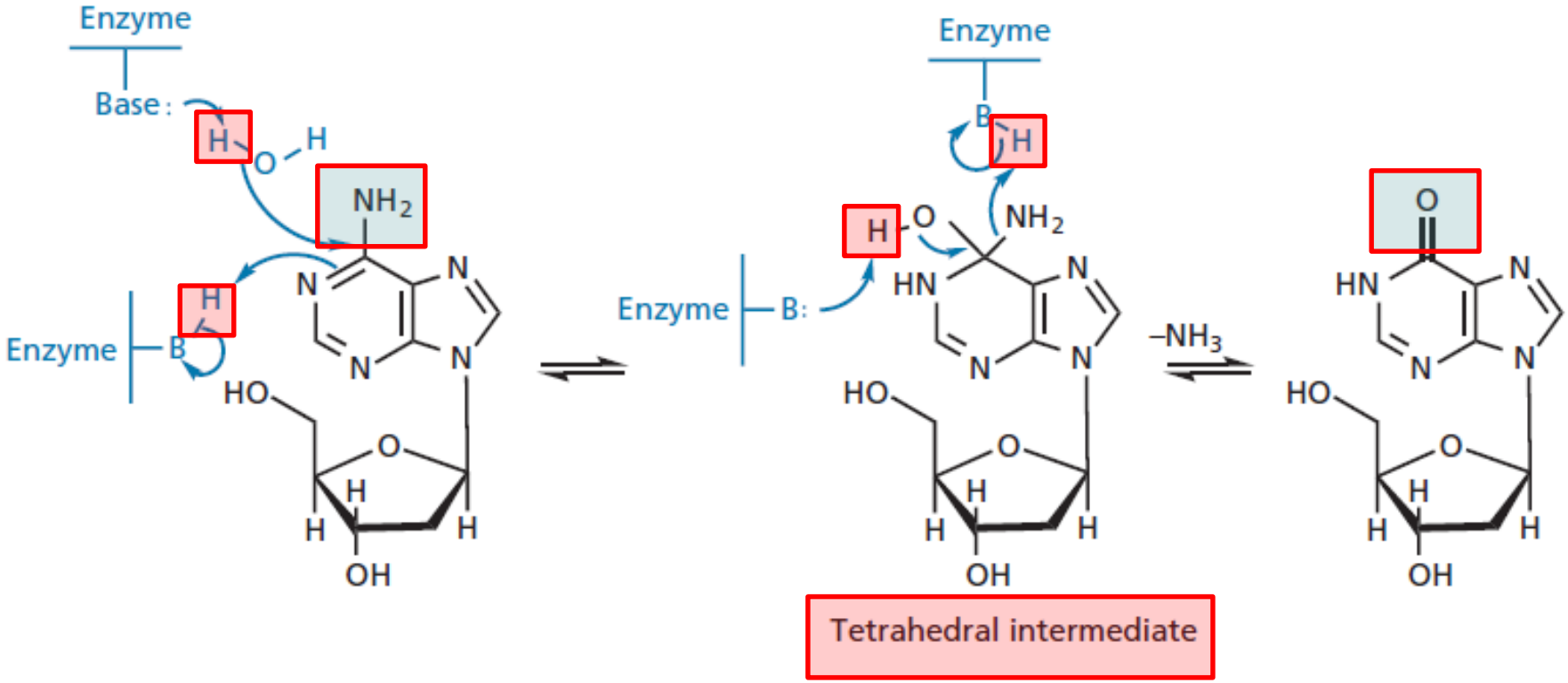
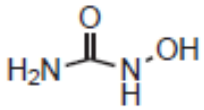


FIGURE 21.23 Mechanism of adenosine deaminase (B = base).

II. 4. Unclassified Antimetabolites: Hydroxyurea

- Hydrea®
- SAR:



Hydroxyurea
(Hydrea)

- MOA: trap Tyr free radical species at ribonucleotide reductase

✓ twarts normal damage repair mechanism of surviving cells

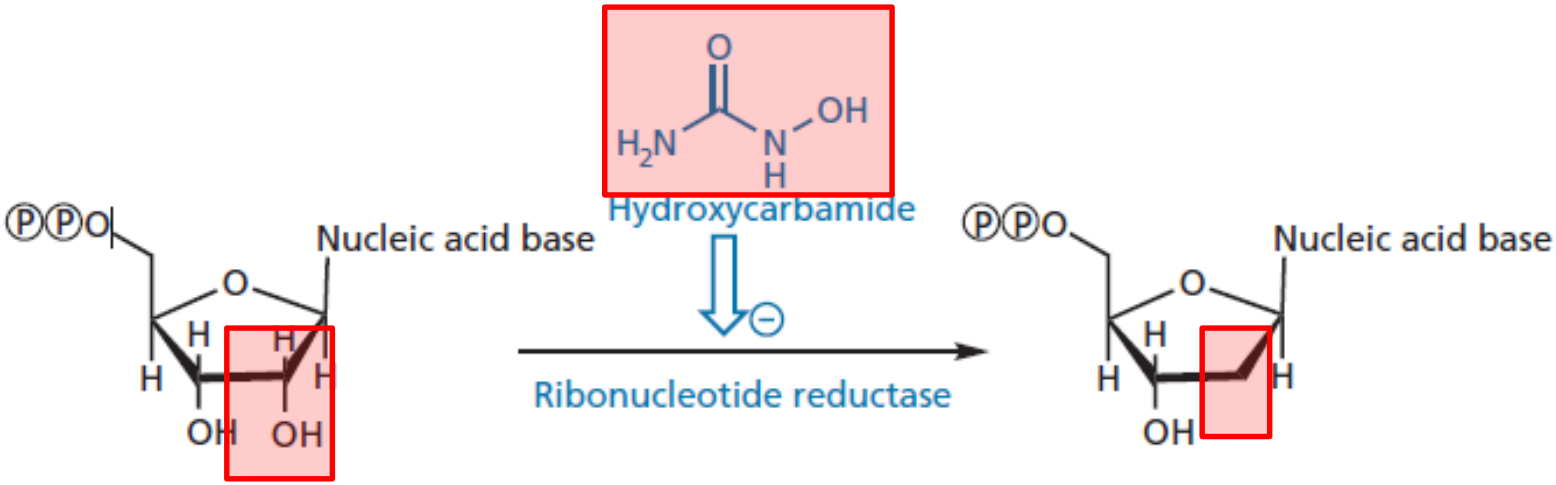


FIGURE 21.22 Reaction catalysed by ribonucleotide reductase (Ⓟ=phosphate).