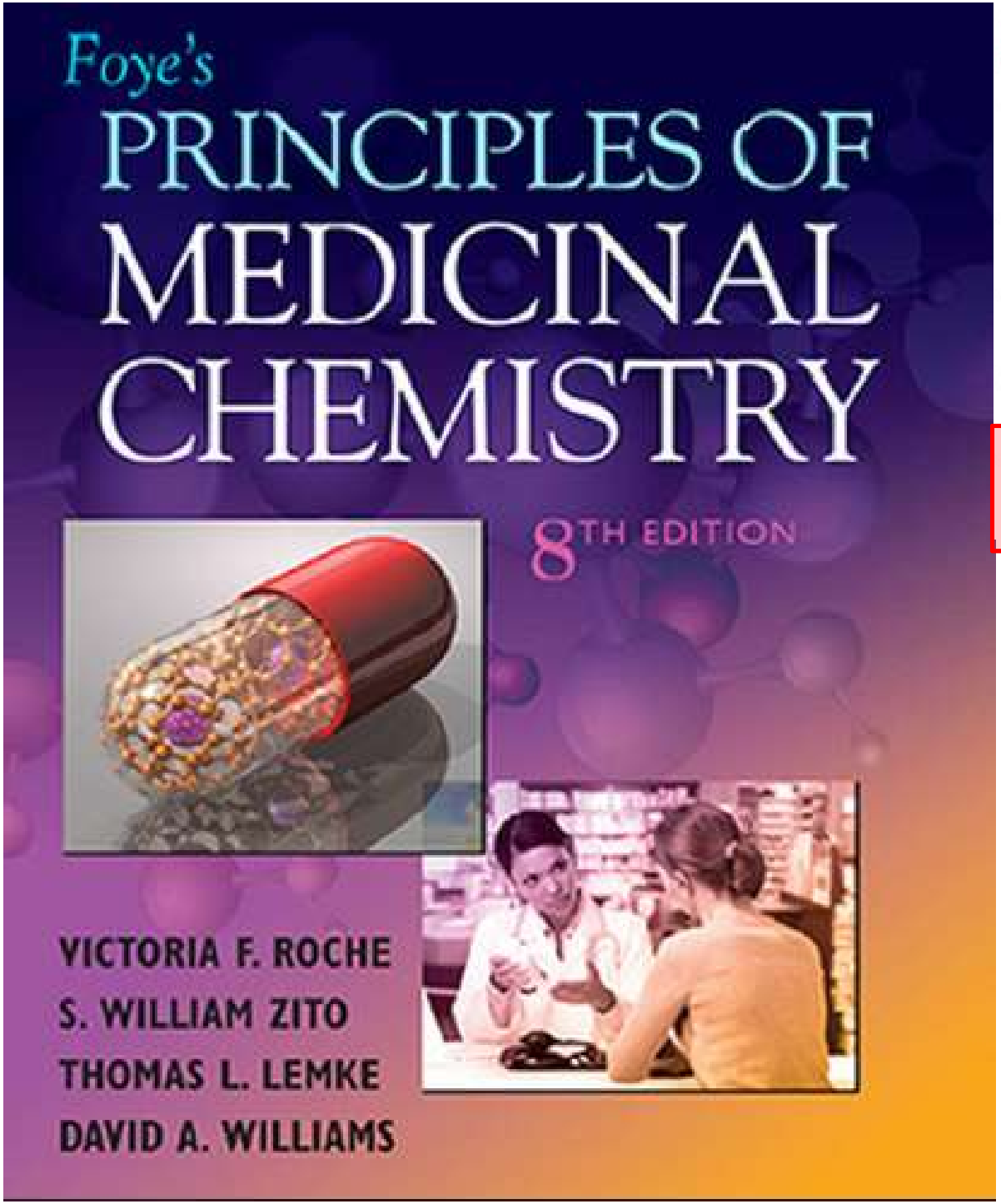
# Chemotherapeutic Agents:
# Drugs to Treat Neoblastic Diseases-
# Anticancer Agents
# Section 2- Antimetabolites

SRAmini Nov2024




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

# Foye's 2019


Principles of Medicinal Chemistry
by William Foye, 2019

Foye's2019

## 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

# II. Antimetabolites: Chemical Classification

II.1. Folate antimetabolites

II.2. Pyrimidine antimetabolites

II.3. Purine antimetabolites

II.4. Miscellaneous / unclassified antimetabolites

# Antimetabolites

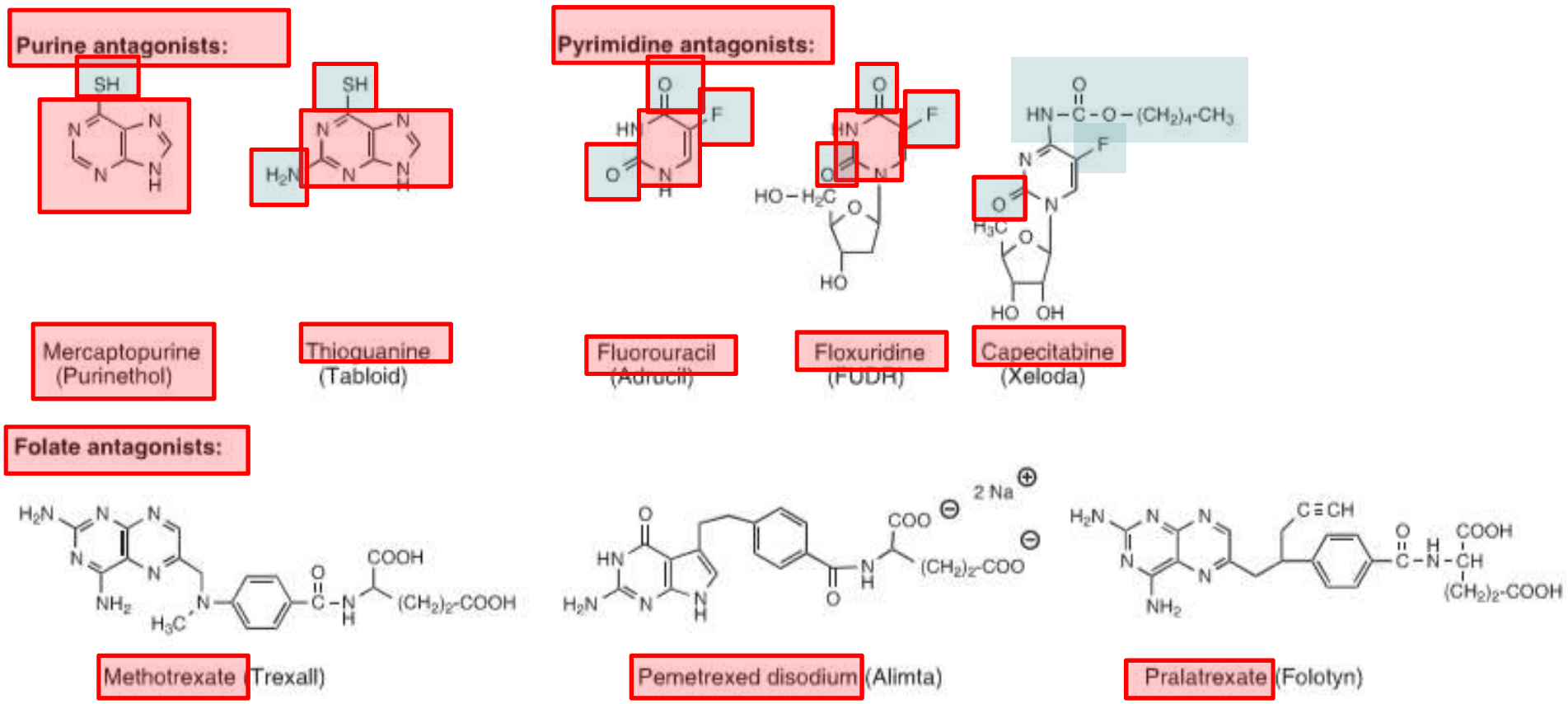
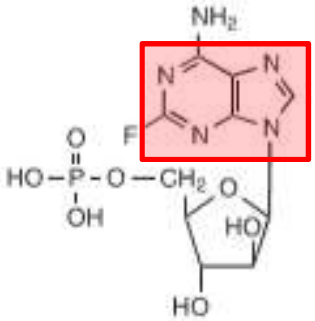



Figure 33.41 Antimetabolites.

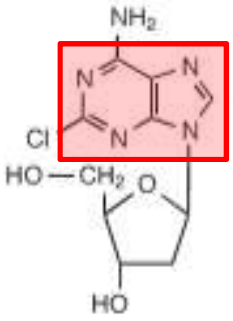
# Antimetabolites-Contd.

**DNA polymerase and chain elongation inhibitors:**

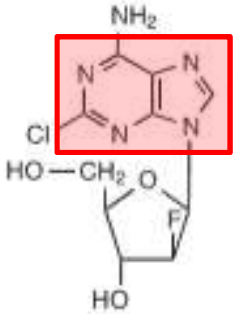
**Purine analogues:**



Fludarabine phosphate
(Fludara)

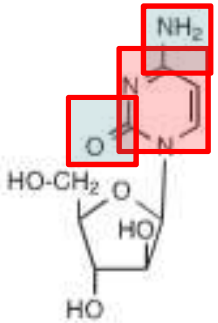


Cladribine
(Leustatin)

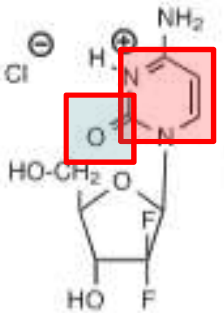


Clofarabine
(Clolar)

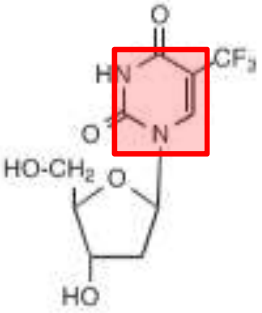
**Pyrimidine analogues:**



Cytarabine
(Tarabine PFS, DepoCyt)

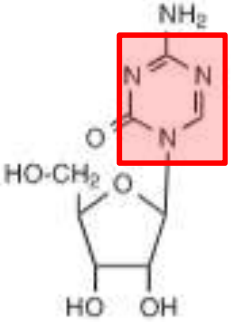


Gemcitabine
hydrochloride
(Gemzar)

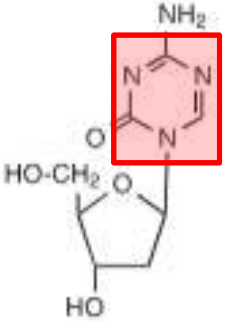


Trifluridine
(active drug in Lonsurf)

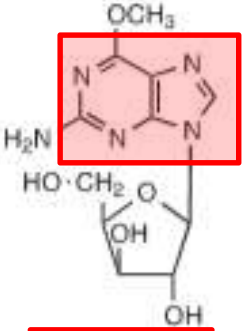
**DNA Methyltransferase Inhibitors**



Azacitidine
(Vidaza)

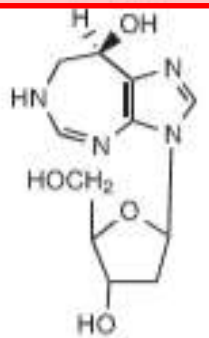


Decitabine
(Dacogen)

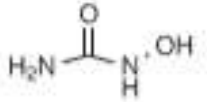


Nelarabine
(Arranon)

**Miscellaneous antimetabolites:**



Pentostatin
(Nipent)



Hydroxyurea
(Hydrea)

**Figure 33.41** Antimetabolites.

# II. Antimetabolites: Mechanism of Action(MOA)

- Stop de novo synthesis of DNA
- Stop synthesis of nucleotide
- irreversible or pseudo-irreversible inhibition of related enzymes

# 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

# II. Antimetabolites: Anti-Folates: 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

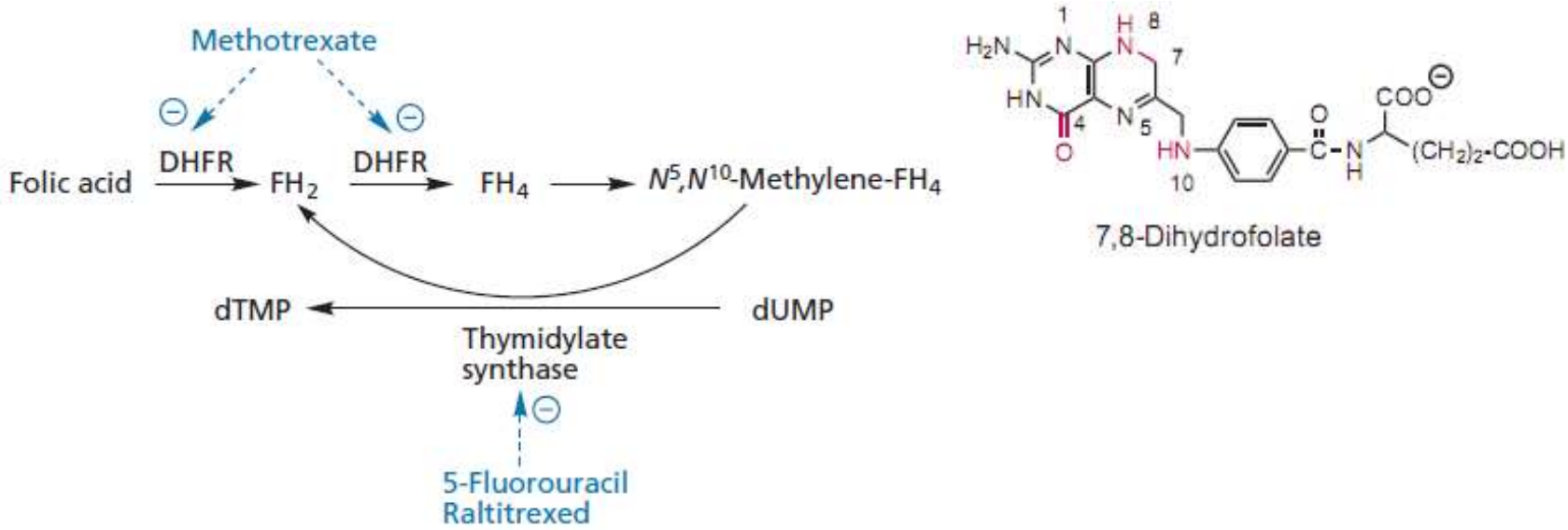
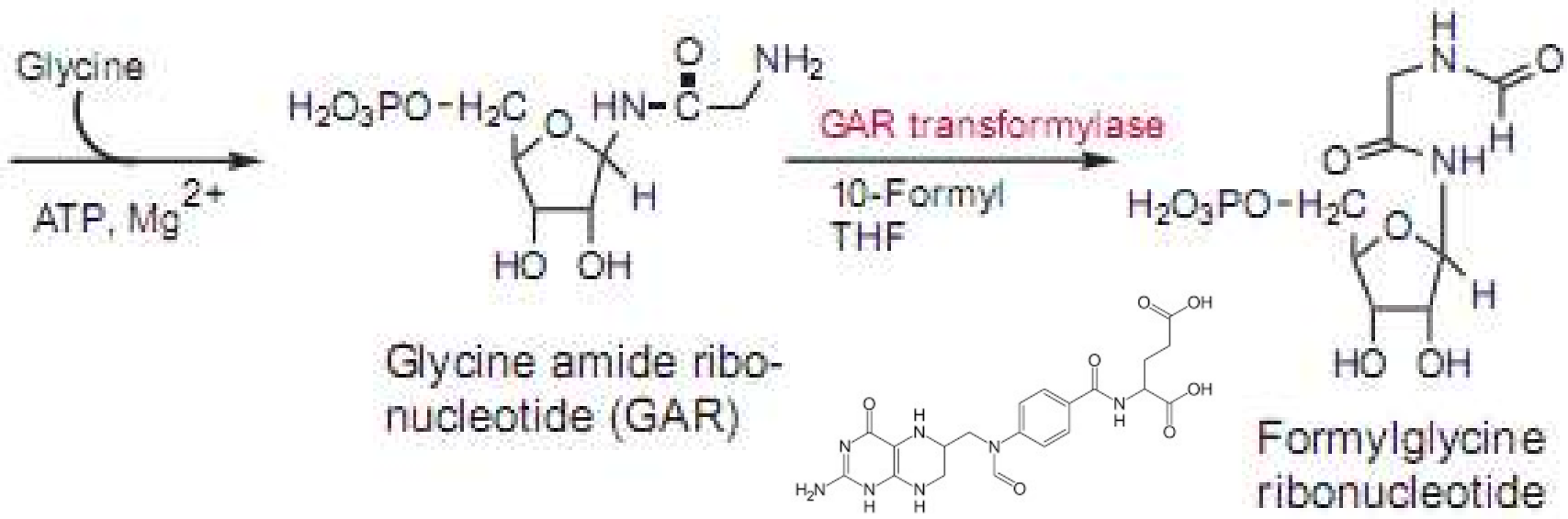
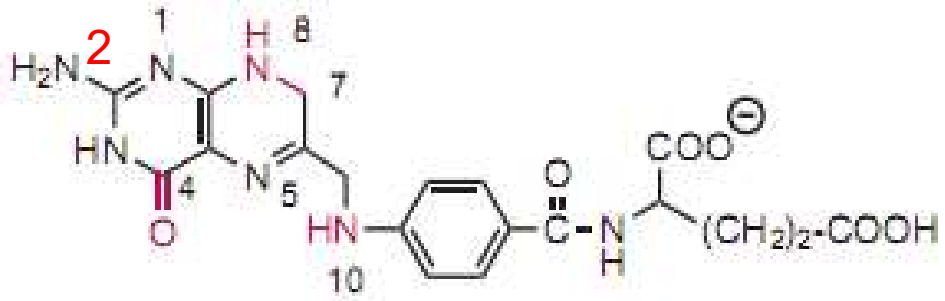



**FIGURE 21.16** Reactions catalysed by dihydrofolate reductase and thymidylate synthase.



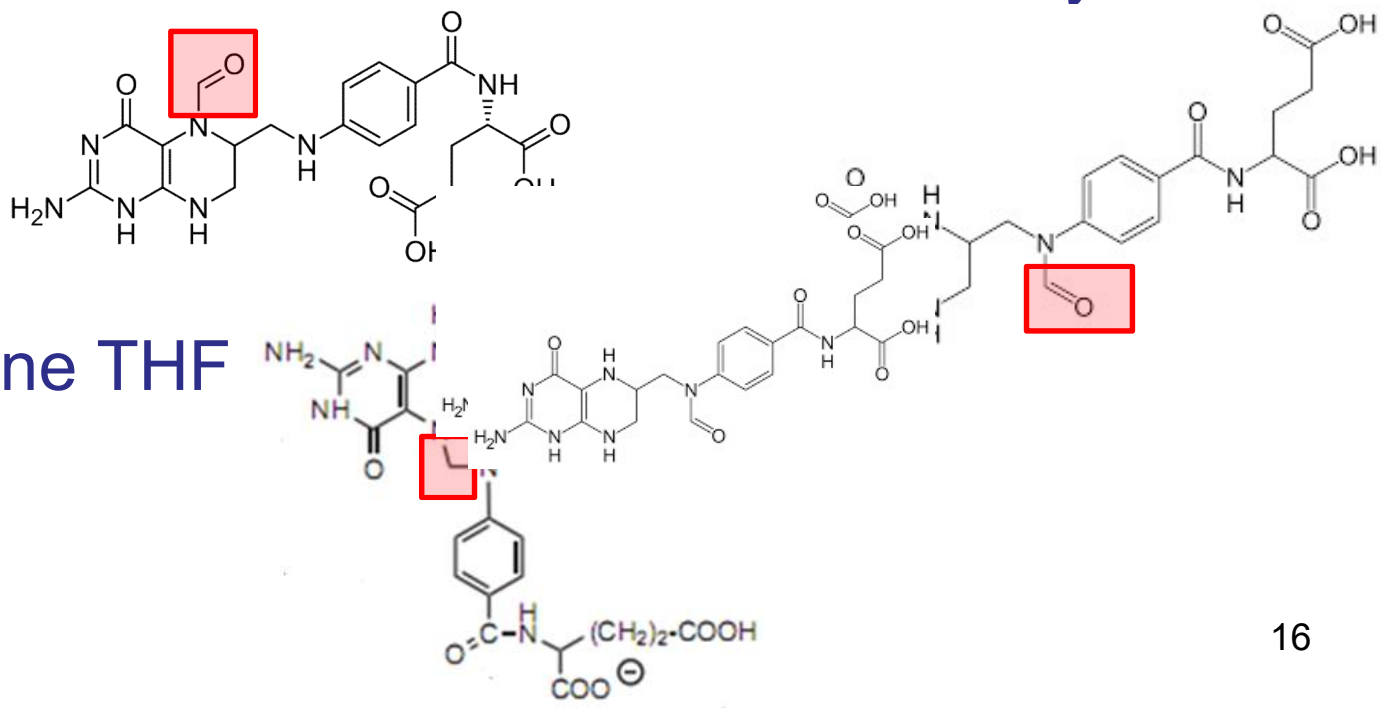
# Folate Derivatives & Analogues

- FA & DHF & THF




- $N_5$-Formyl THF: leucovorin

N10-formyl THF



- 5,10-Methylene THF

# Function of DHFR, TS & Their Inhibitors: DHFR Inhibitor & TS Inhibitor

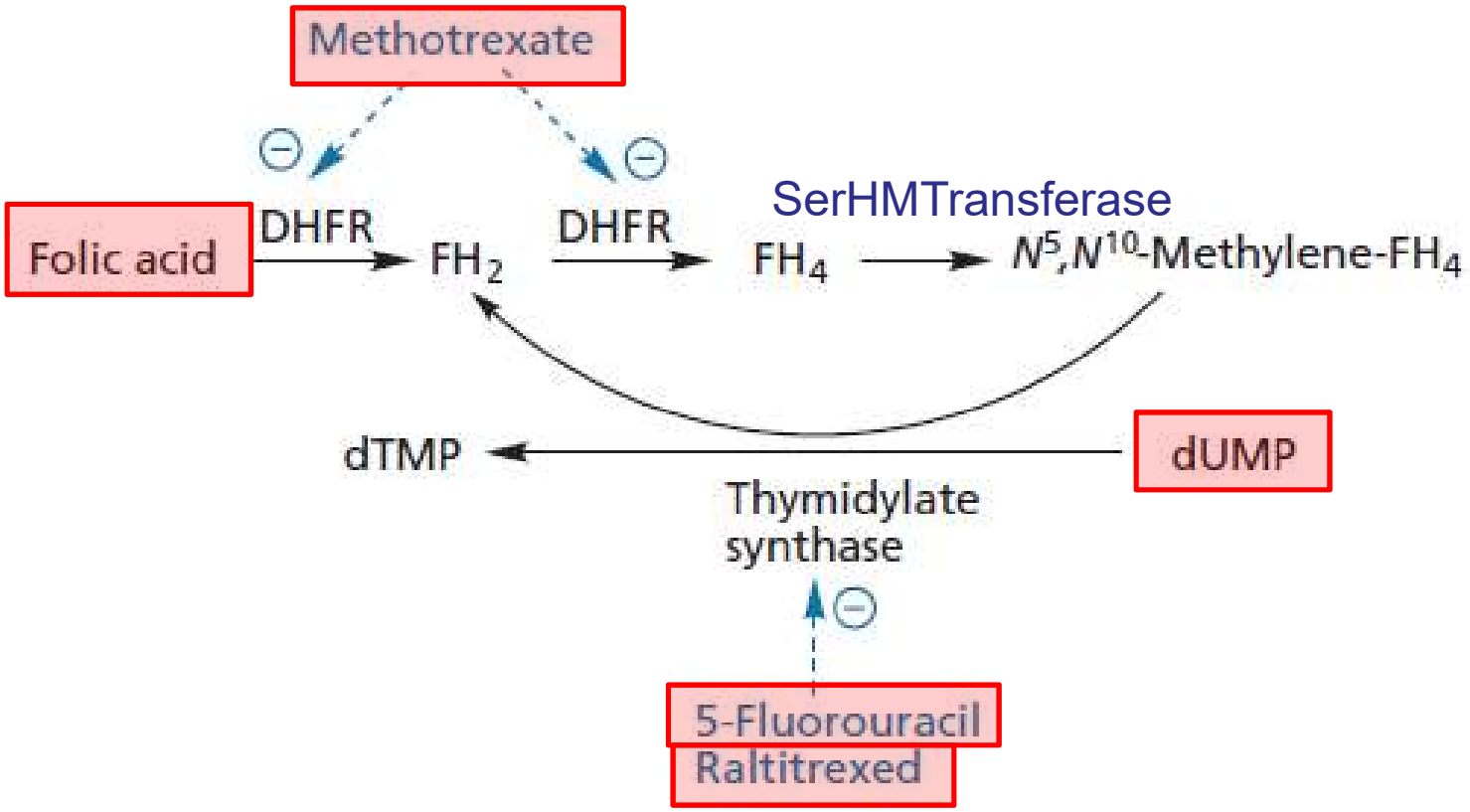
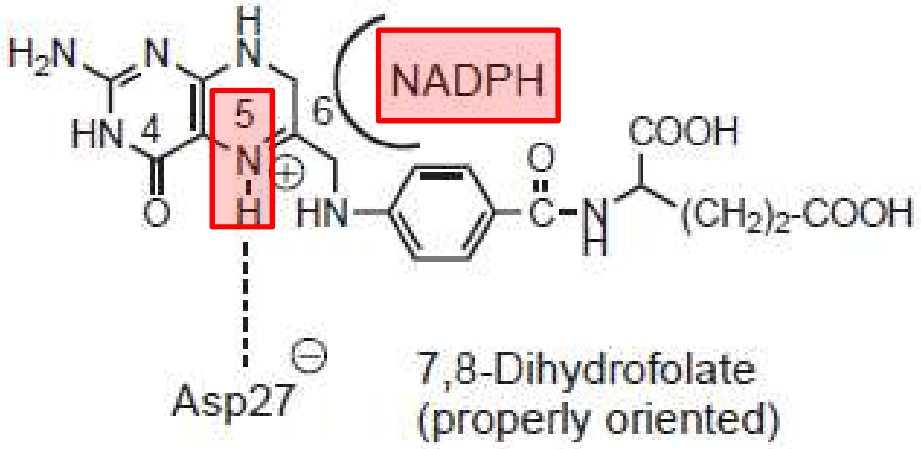
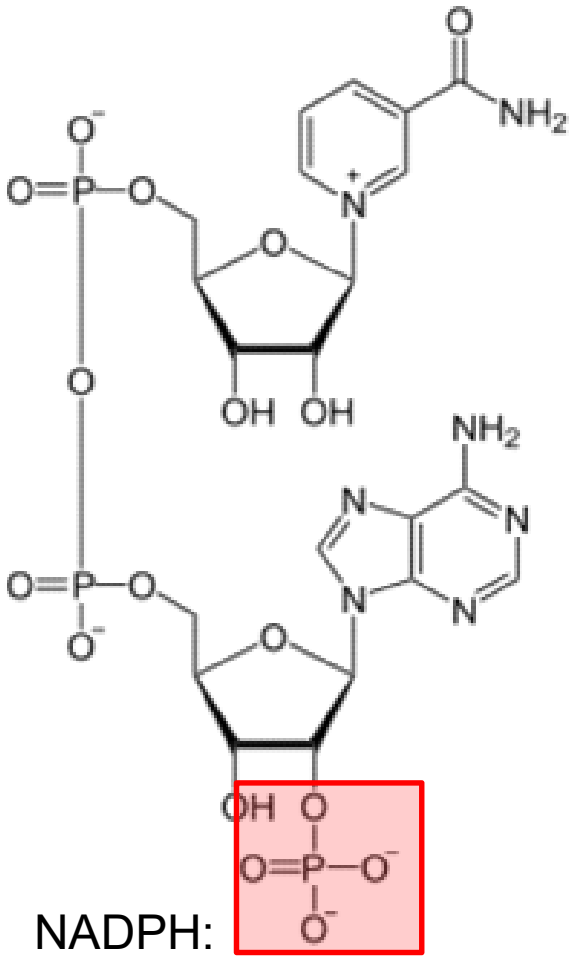



**FIGURE 21.16** Reactions catalysed by dihydrofolate reductase and thymidylate synthase.

# Dihydro-Folate as Substrate of DHFR

- Basicity & protonation
- N5 to Asp27
- NADPH as cofactor of DHFR



NADPH:
Nicotinamide adenine dinucleotide 2'-phosphate

# N5&N10-Methylene-THF as Cofactor of TS in Biosynthesis of Thymine from Uracil

- THF as cofactor of TS
- Thymidylate synthase (TS): is responsible to produce thymine
- Anti-folate as indirect inhibitor of TS: thymineless

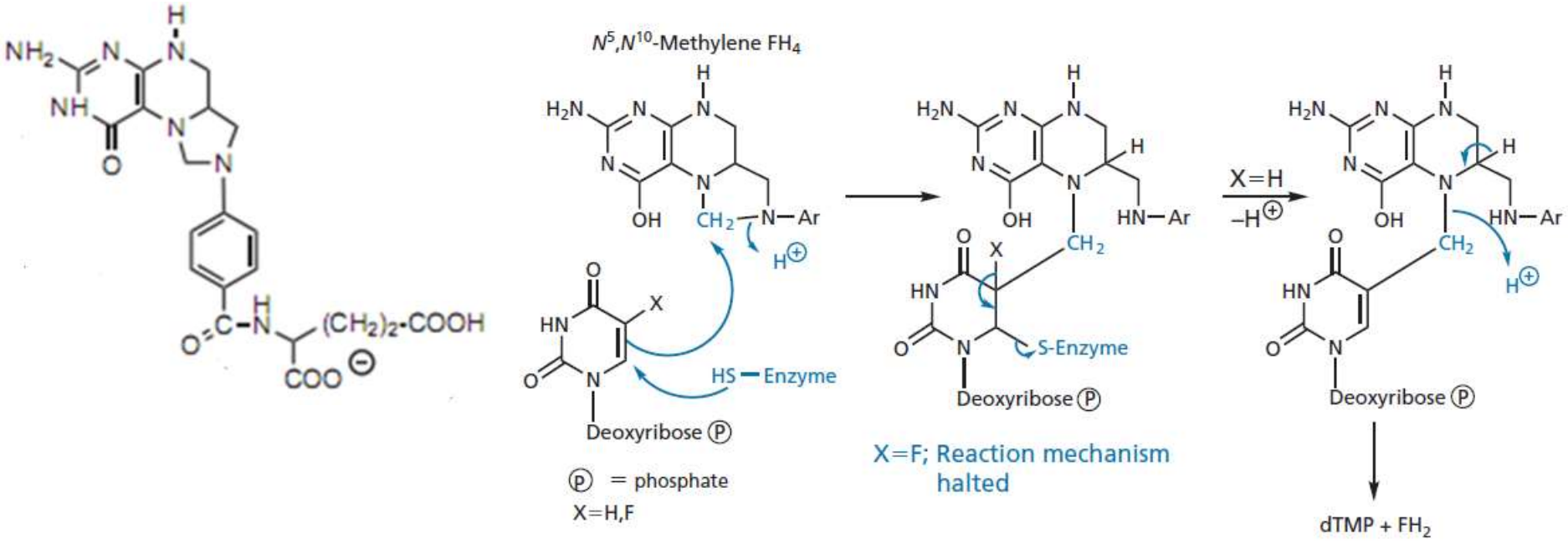
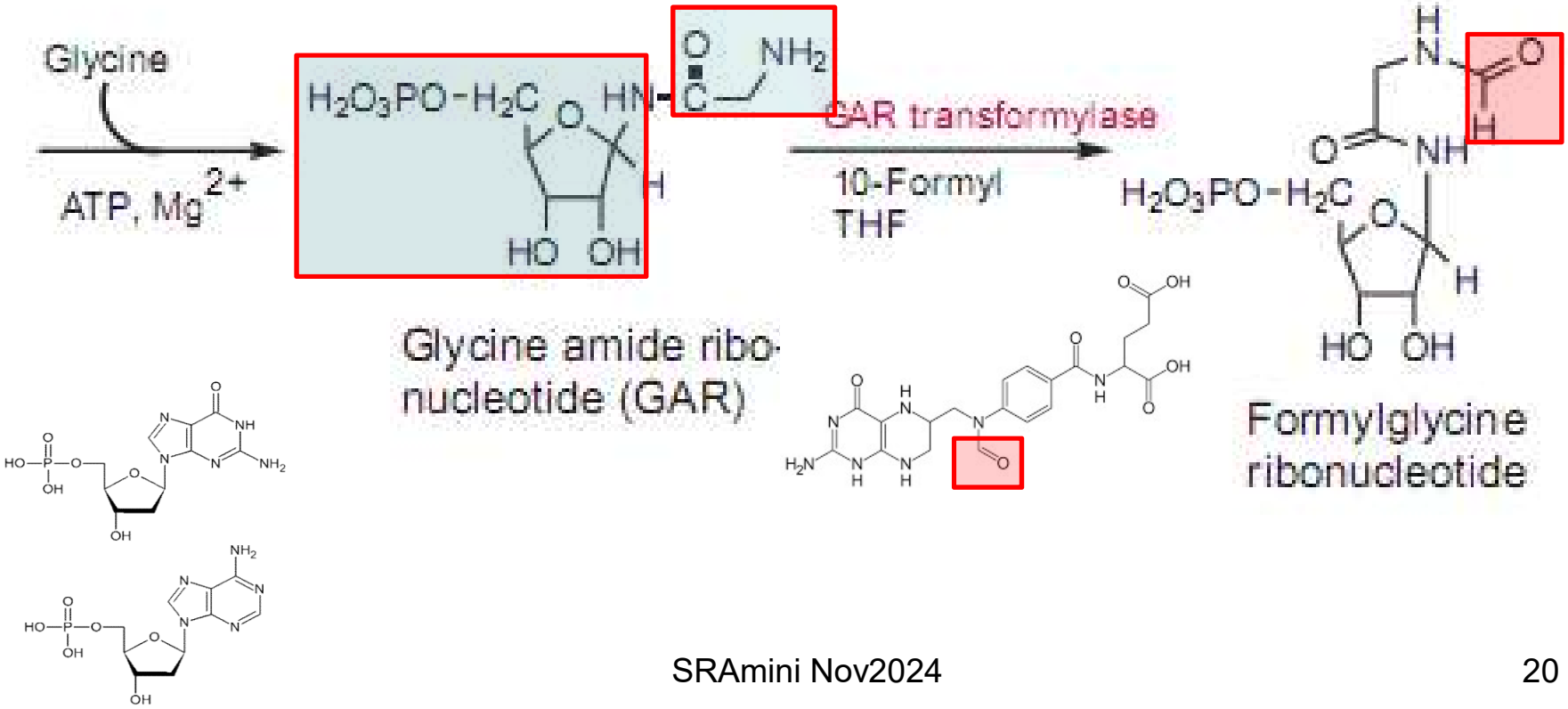



FIGURE 21.20 Use of 5-fluorouracil as a prodrug for a suicide substrate.

# N10-Formyl-THF as Cofactor of GART in De-Novo Biosynthesis of Purine

- Almost first steps of de novo synthesis of purine
- Anti-folate as indirect inhibitor of GART: purineless



# DHFRI

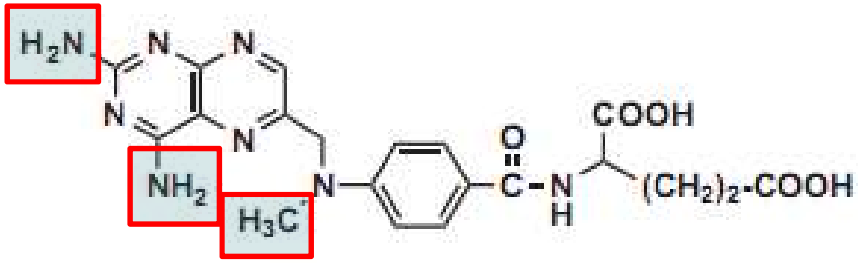
- Pterine like structures
- Biguanide structures
- Aryl pyrimidine structures

# II. Antimetabolites: 1.Anti-Folates: SAR

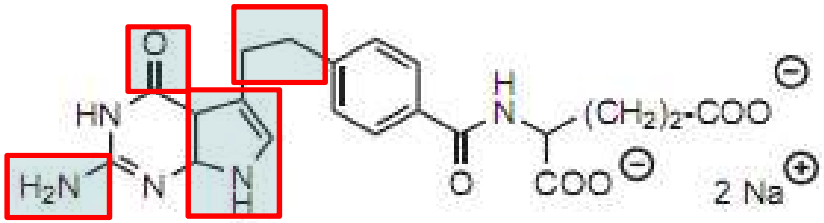
- Chemistry:

✓ Pteridine / mimic + PABA / mimic + Glutamic acid

**Folate antagonists:**

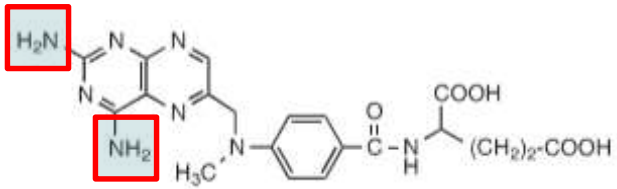


Methotrexate (Trexall)

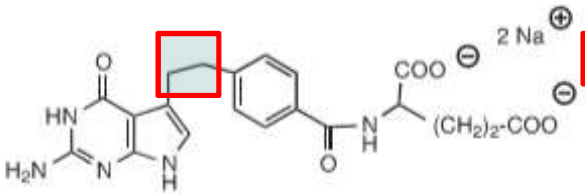


Pemetrexed disodium (Alimta)

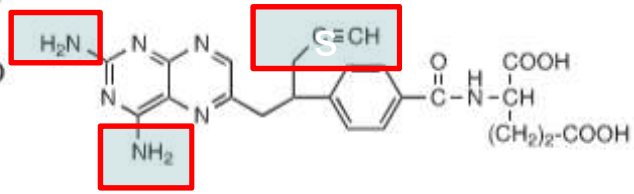
**Folate antagonists:**



Methotrexate (Trexall)

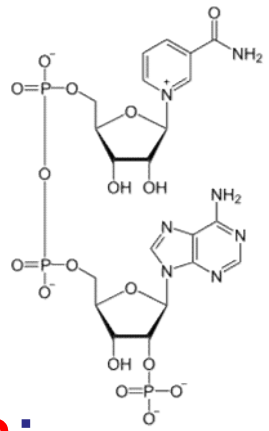


Pemetrexed disodium (Alimta)



Pralatrexate (Folotyn)

# Compare Interaction Points of DHF & MTX to DHFR



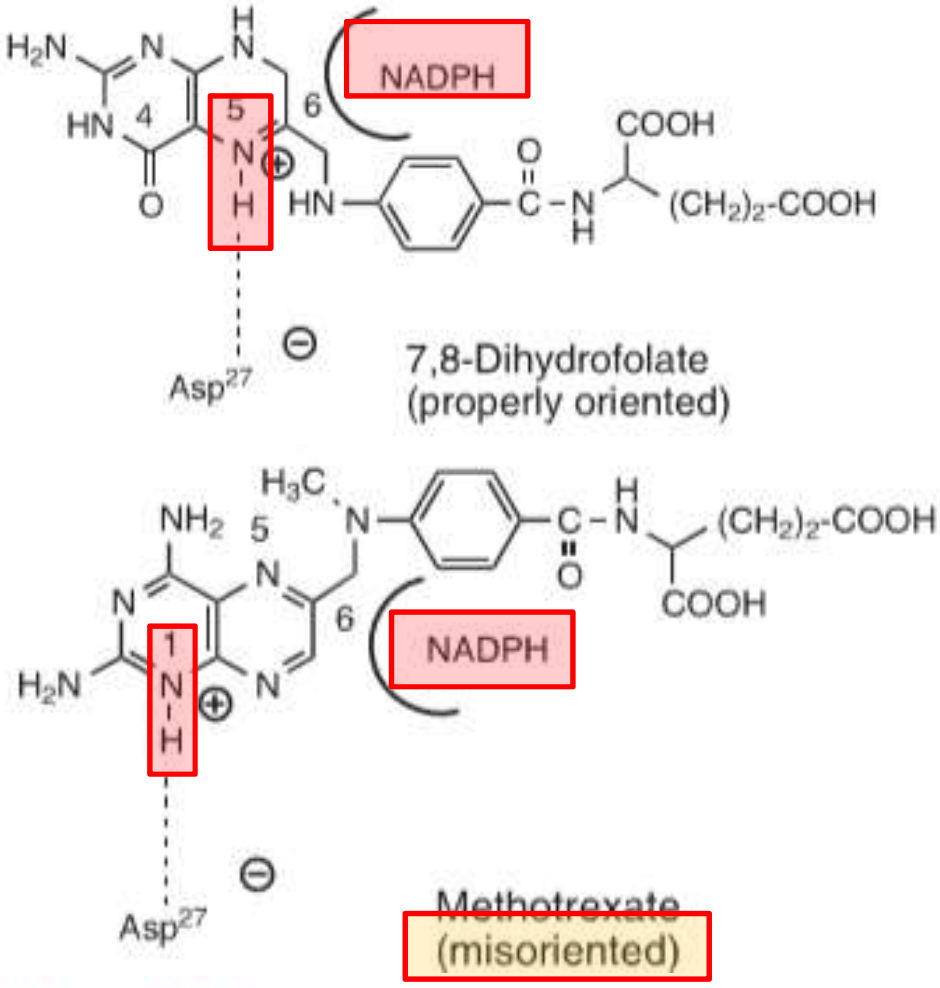



Figure 33.51 Misorientation of methotrexate at DHFR.

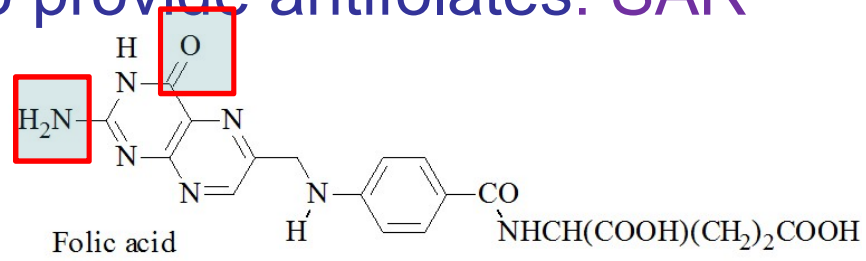
- DHF:
  - ✓N5: electron rich:
  - ✓basic; protonation
- MTX:
  - ✓N1: electron rich:
  - ✓Basic; protonation



NADP/H: Nicotinamide Adenine Dinucleotide 2'-Phosphate/H

# II. Antimetabolites: 1. Anti-Folates: Chemical classification

- Folate structure modifications to provide antifolates: SAR



Folic acid

➢ Pteridine-PABA-Glu analogue:

- Methotrexate:

✓ C4-$NH_2$; N10-$CH_3$

➢ Pteridine mimic ring-PABA mimic-Glu analogue:

✓ pyrimido pyrrole-PABA mimic-Glu analogue:

- Pemetrexed:

✓ diazine in pteridine is substituted by pyrrole;

✓ N10 is replaced by $CH_2$

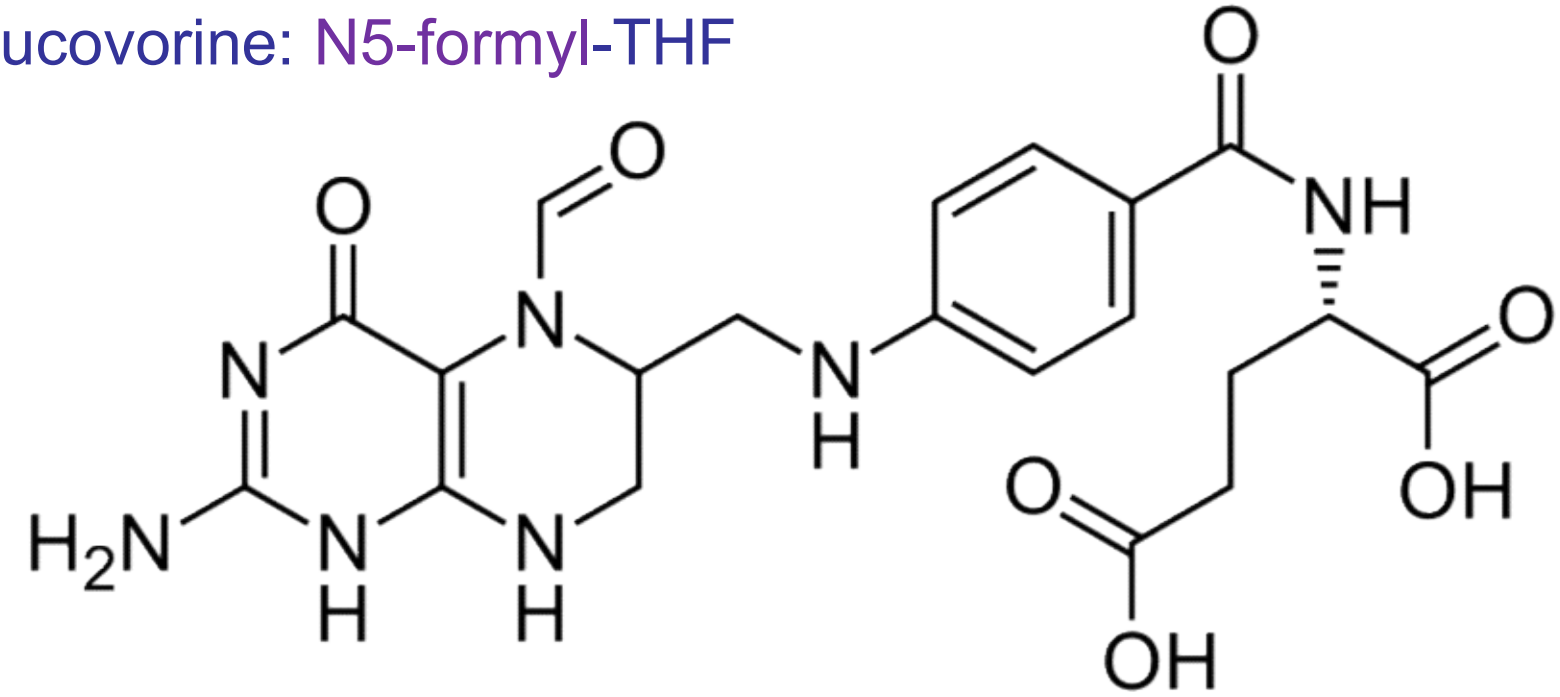
➢ Pteridine-PABA mimic-Glu analogue:

- Pralatrexate:

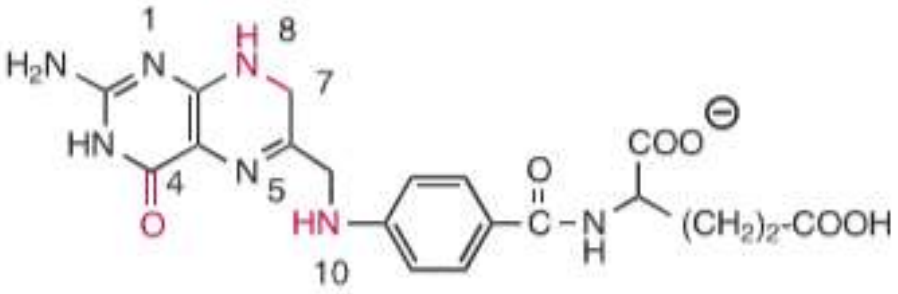
✓ N10 is replaced by CH($CH_2$ -CH≡CH): CH(propargyl)

# Control of Side Effects of MTX as Folate Antagonists Using A Folate Analogue

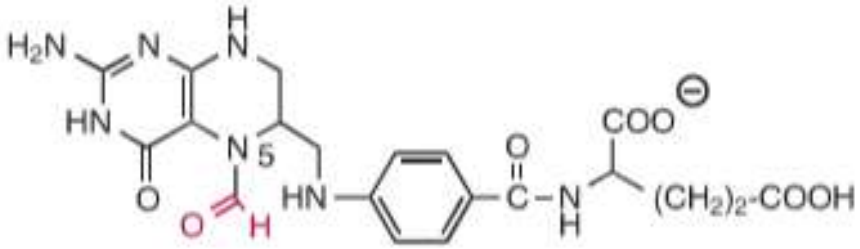
- Co-administration:
- Leucovorine: N5-formyl-THF



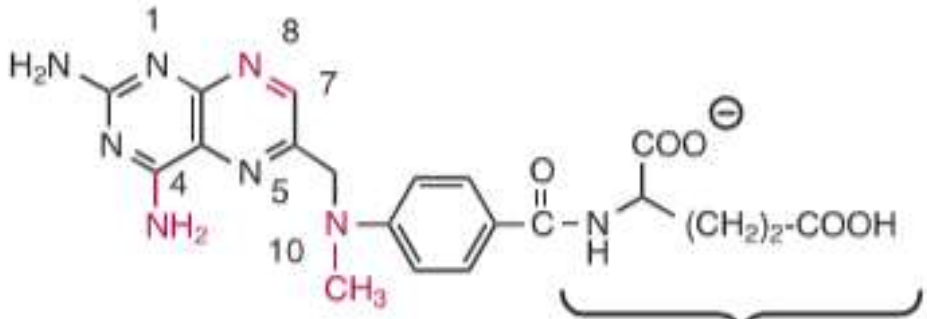
# Compare DHF & MTX & Leucovorin




7,8-Dihydrofolate




5-Formyltetrahydrofolate
(Leucovorin)




Methotrexate

Glutamate tail