



# 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

# Foye's 2019



CHAPTER **33**

## *Drugs Used to Treat Neoplastic Diseases*

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

# Pharmacologic Classification 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

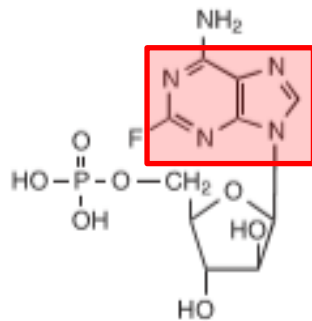




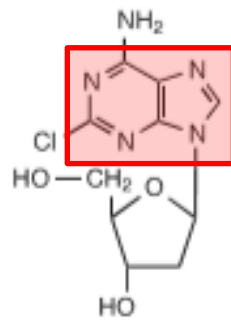
# Antimetabolites-Contd.

## DNA polymerase and chain elongation inhibitors:

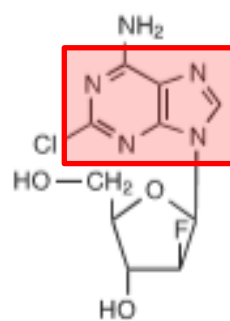
### Purine analogues:



Fludarabine phosphate  
(Fludara)

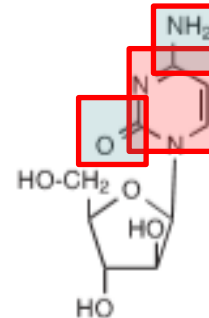


Cladribine  
(Leustatin)

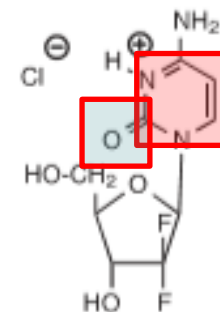


Clofarabine  
(Clolar)

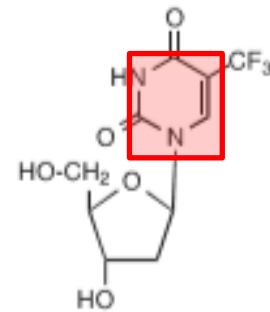
### Pyrimidine analogues:



Cytarabine  
(Tarabine PFS,  
DepoCyt)

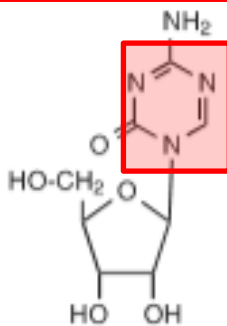


Gemcitabine  
hydrochloride  
(Gemzar)

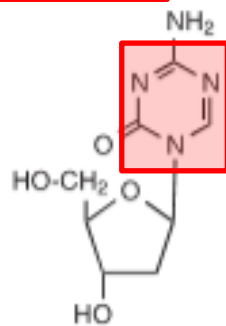


Trifluridine  
(active drug  
in Lonsurf)

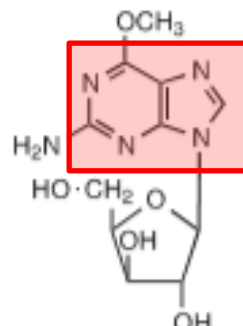
### DNA Methyltransferase Inhibitors



Azacitidine  
(Vidaza)

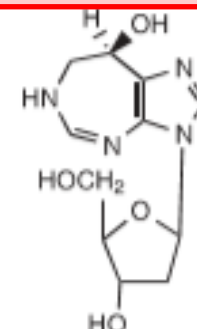


Decitabine  
(Dacogen)

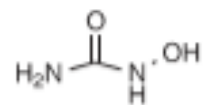


Nelarabine  
(Arranon)

### 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: 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

# Folate Derivatives: FA, DHF, THF: as Substrates & Products of DHFR

- FA & DHF as substrates for DHFR to produce DHF & THF as products, respectively.

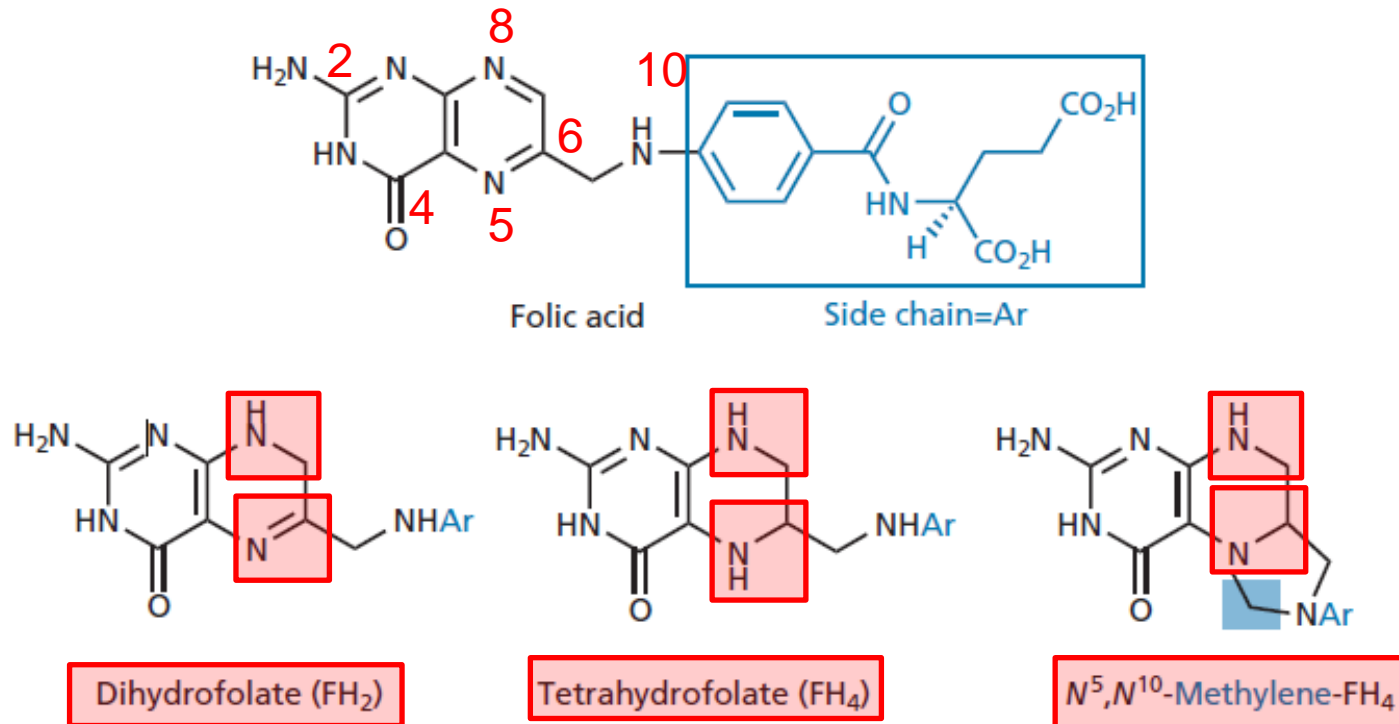
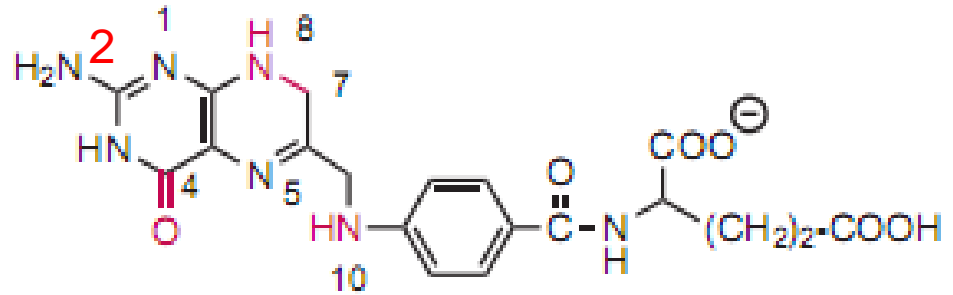


FIGURE 21.17 Structures of folic acid and related cofactors.

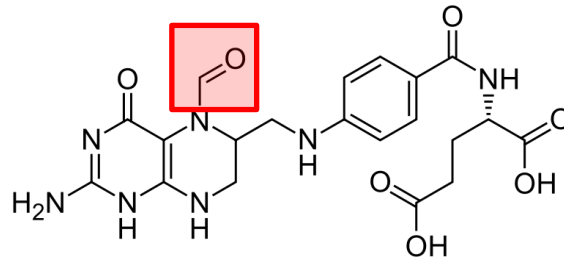
# Folate Derivatives & Analogues

- FA & DHF & THF

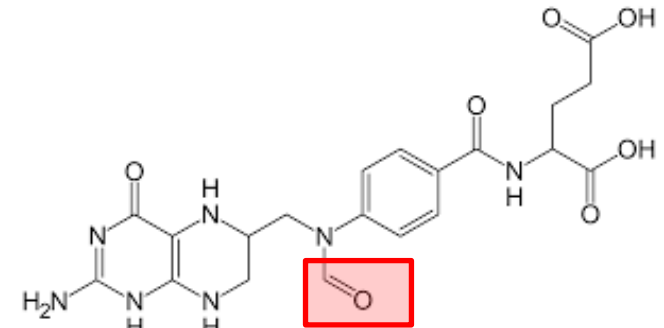


7,8-Dihydrofolate

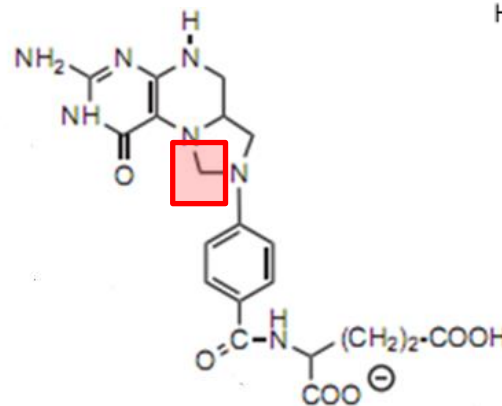
- N<sub>5</sub>-Formyl THF: leucovorin



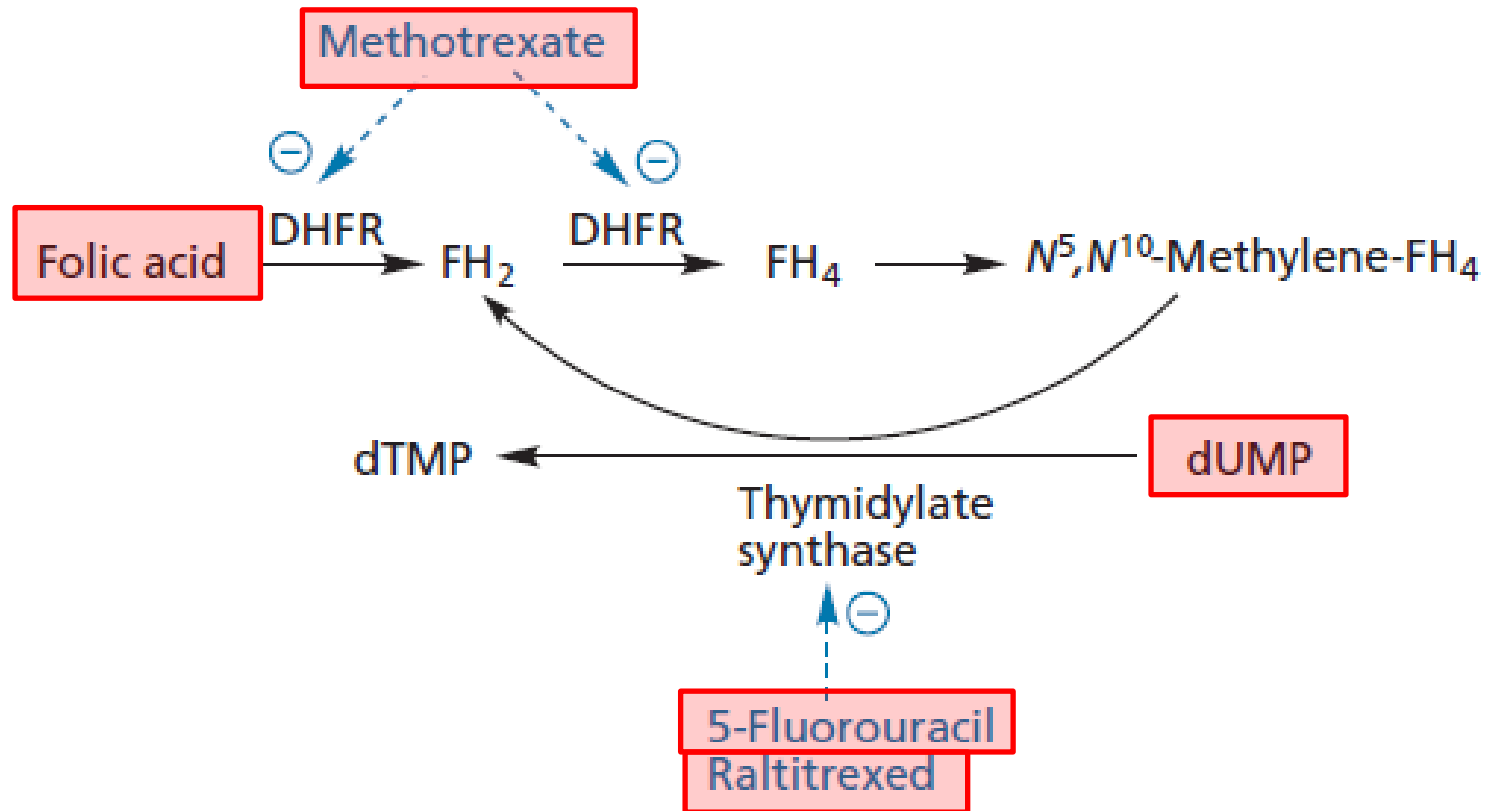
- N10-formyl THF



- 5,10-Methylene THF



# Function of DHFR, TS & DHFR Inhibitor, TS Inhibitor

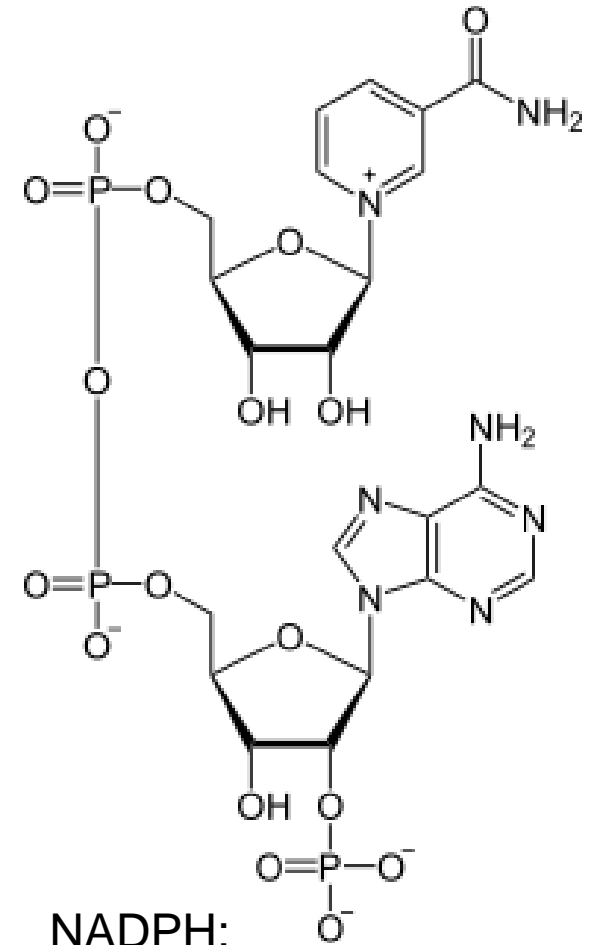
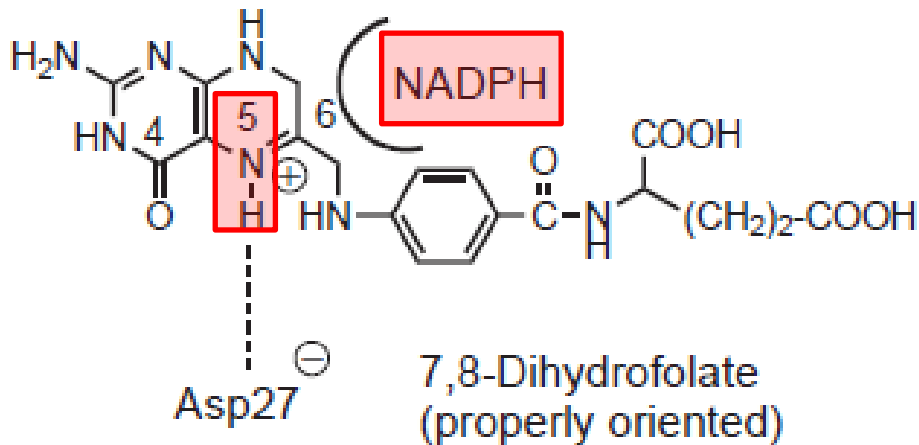


**FIGURE 21.16** Reactions catalysed by dihydrofolate reductase and thymidylate synthase.



# Dihydro-Folate as Substrate of DHFR

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



# N<sup>5</sup>&N<sup>10</sup>-Methylene-THF as Cofactor of TS in Biosynthesis of Thymine from Uracil

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

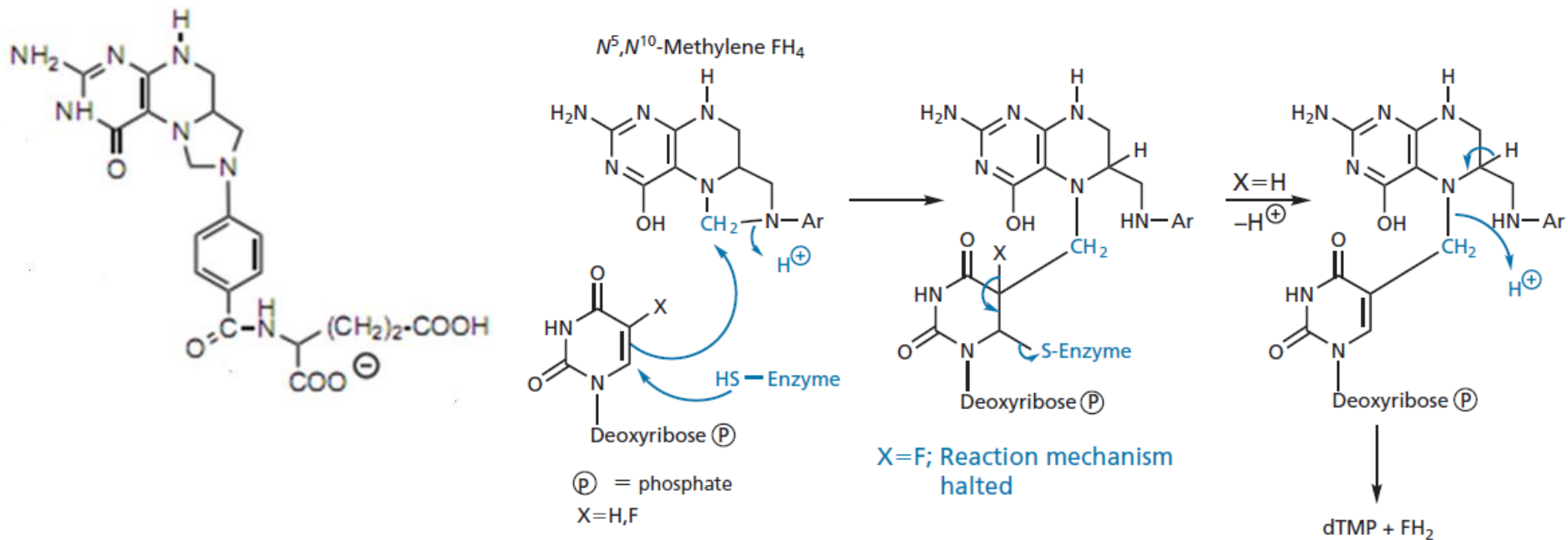
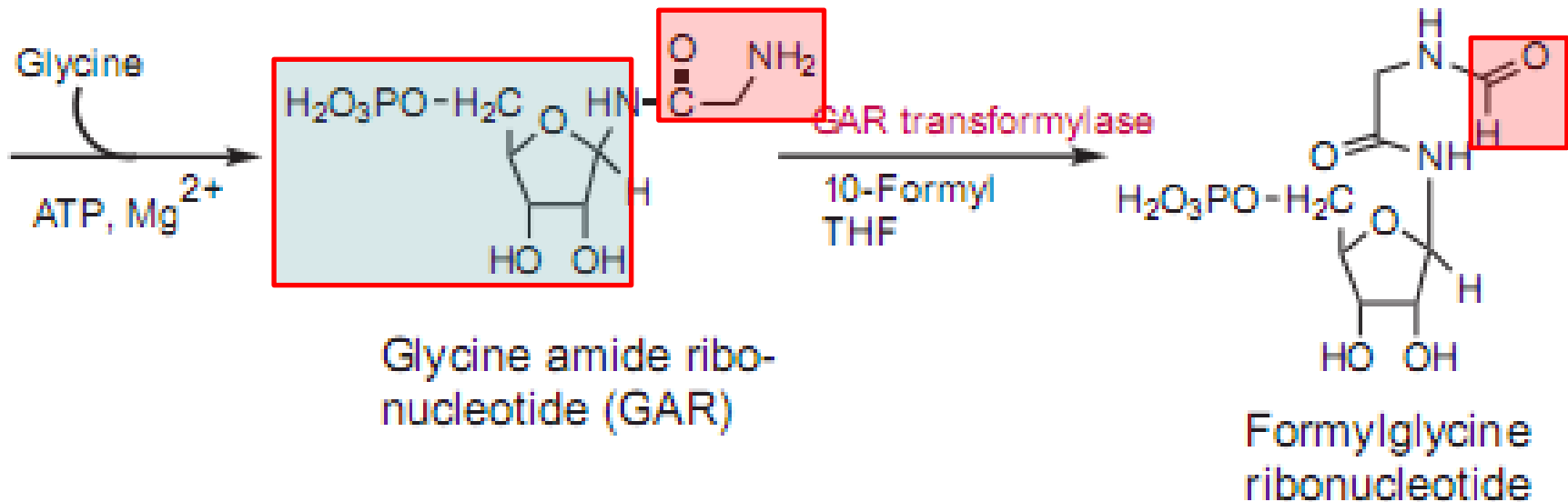


FIGURE 21.20 Use of 5-fluorouracil as a prodrug for a suicide substrate.

# 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**

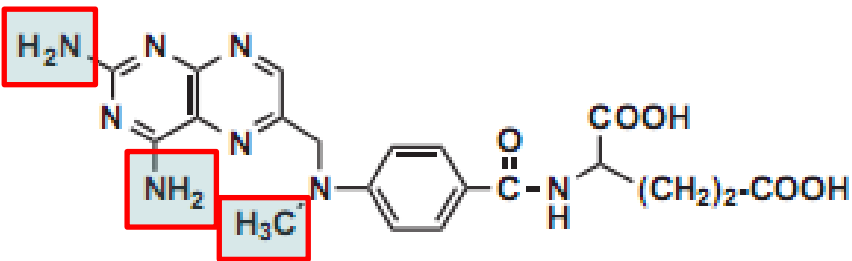


# II. Antimetabolites: 1. Anti-Folates: SAR

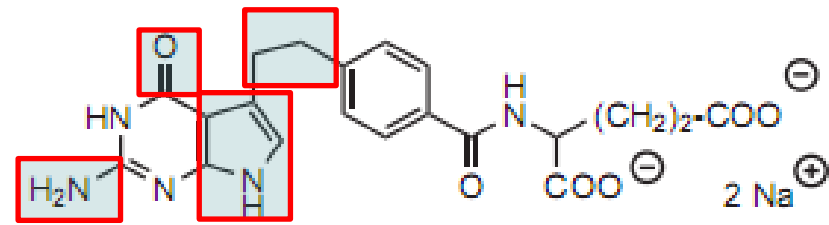
- Chemistry:

✓ Pteridine / mimic + PABA / mimic + Glutamic acid

Folate antagonists:

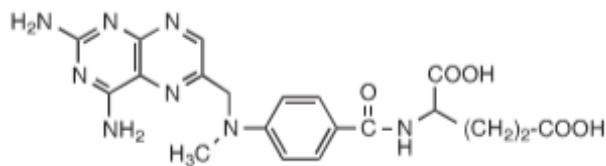


Methotrexate (Trexall)

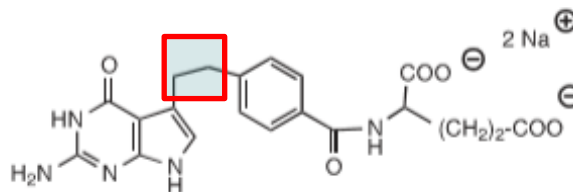


Pemetrexed disodium (Alimta)

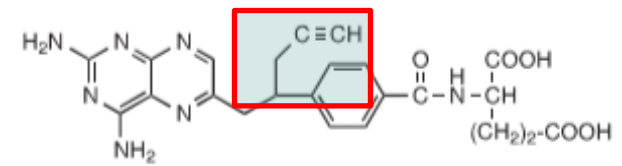
Folate antagonists:



Methotrexate (Trexall)



Pemetrexed disodium (Alimta)



Pralatrexate (Folotyn)

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

- Folate structure modifications to provide antifolates: SAR

## ➤ Pteridine-PABA-Glu analogue:

- Methotrexate:

- ✓ C4-NH<sub>2</sub>; N10-CH<sub>3</sub>

## ➤ Pteridine mimic ring-PABA mimic-Glu analogue:

- ✓ pyrimido pyrrole-PABA mimic-Glu analogue:

- Pemetrexed:

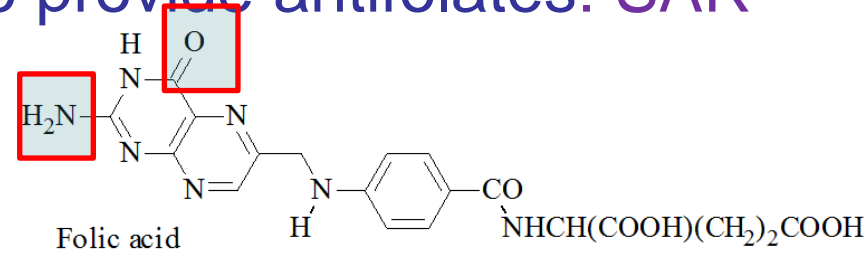
- ✓ diazine in pteridine is substituted by pyrrole;

- ✓ N10 is replaced by CH<sub>2</sub>

## ➤ Pteridine-PABA mimic-Glu analogue:

- Pralatrexate:

- ✓ N10 is replaced by CH(CH<sub>2</sub>-CH≡CH): CH(propargyl)

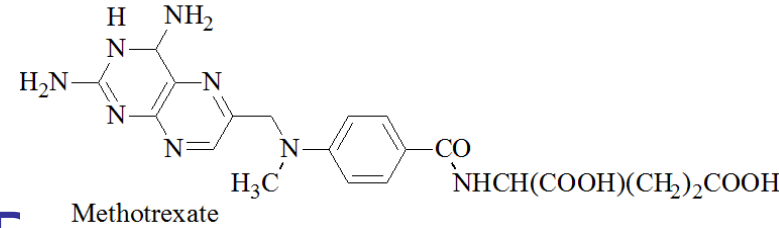


## II. Antimetabolites: 1. Anti-Folates

- Methotrexate(MTX):

- ✓ Distributed centrally

- ✓  $K_i$  MTX(DHFR) <  $K_i$  Pemetrexed(DHFR)



- Pemetrexed(Alimta):

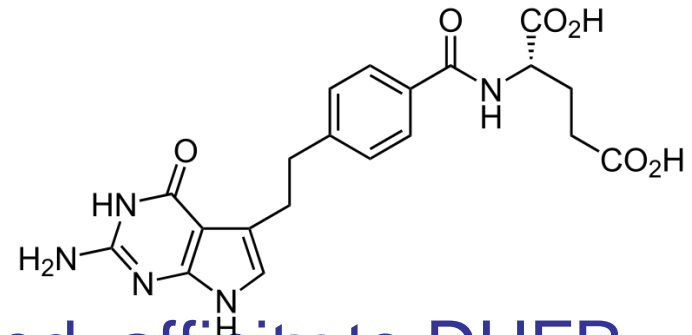
- ✓ not distributed centrally

- ✓ higher affinity to FPGS

- ✓ monoglutamated & polyglutamated: affinity to DHFR

- ✓ polyglutamated(not monoglutamated):

bind tightly to TS & less to GART

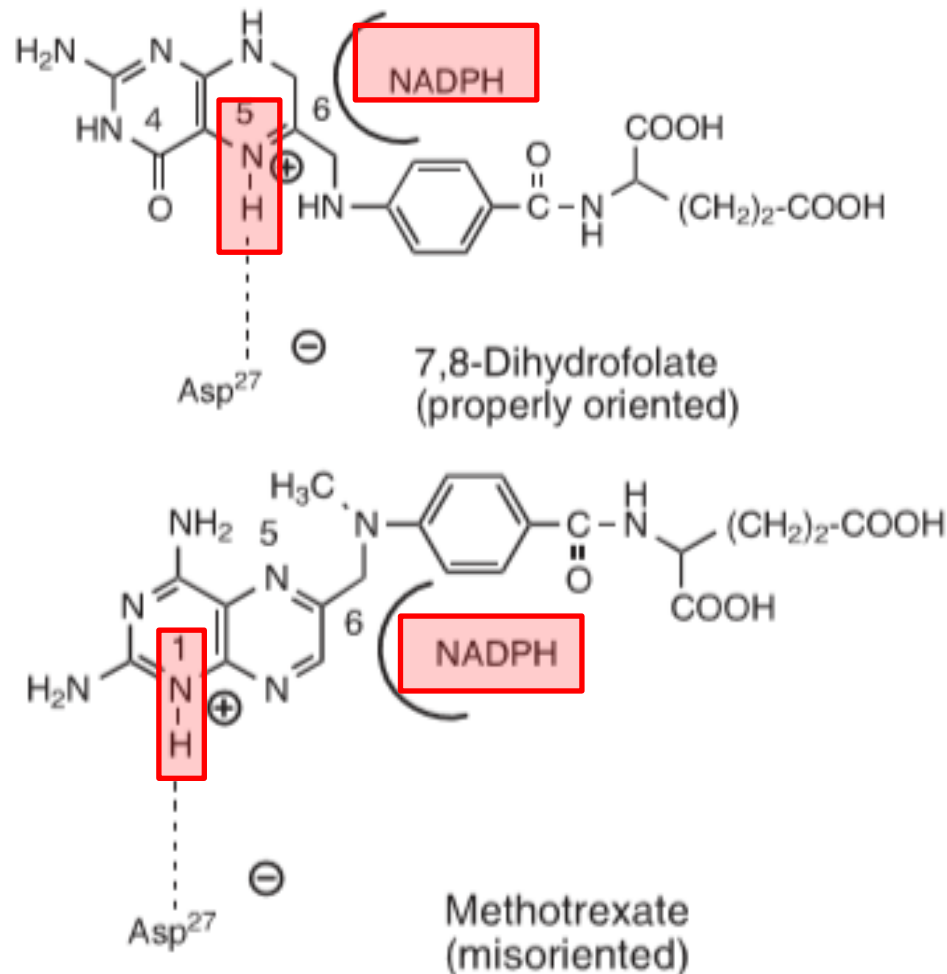
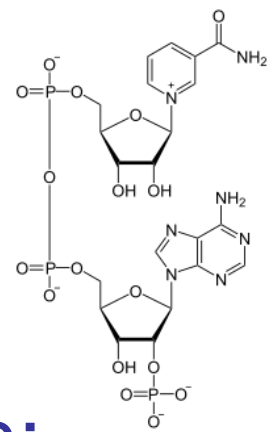


- Pralatrexate:

- ✓  $K_i$  Pralatrexate(DHFR) <  $K_i$  MTX(DHFR)

- ✓ Polyglutamated similar to pemetrexed & more than MTX

# Compare Interaction Points of DHF & MTX to DHFR



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

**Figure 33.51** Misorientation of methotrexate at DHFR.

# II. Antimetabolites: 2. Pyrimidine Antagonists: Chemical Classification

## II.2. Pyrimidine antimetabolites

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

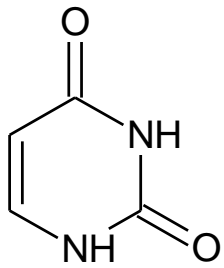


# II.2. Pyrimidine Antimetabolites: Modifications in Designing Process

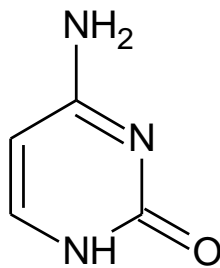
- Modification in pyrimidine substitute
- Modification in sugar moiety
- Modification in pyrimidine ring

# Nucleic Acid Components

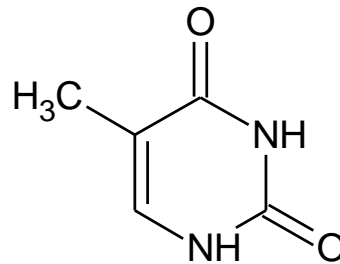
- Pyrimidine



Uracil

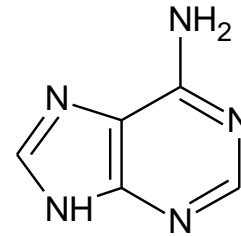


Cytosine

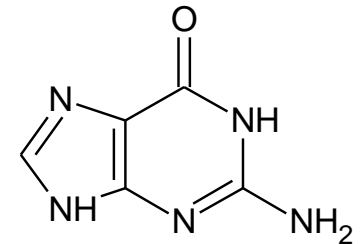


Thymine

- Purine

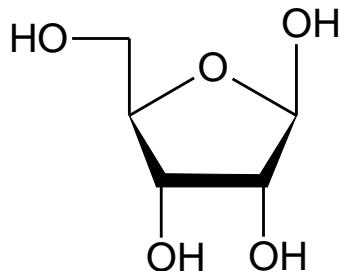


Adenine

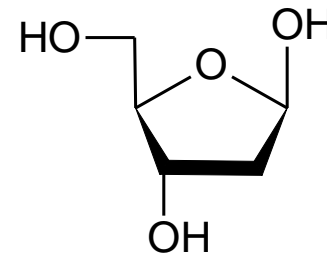


Guanine

- Ribose

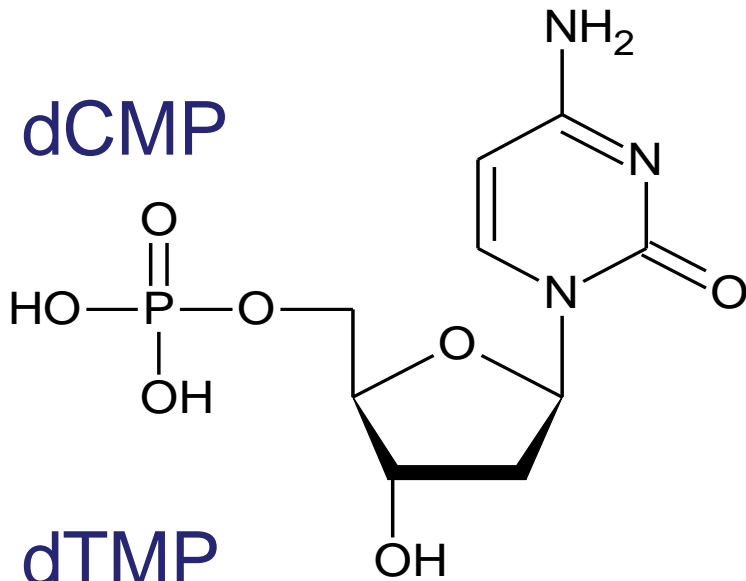


- Deoxyribose

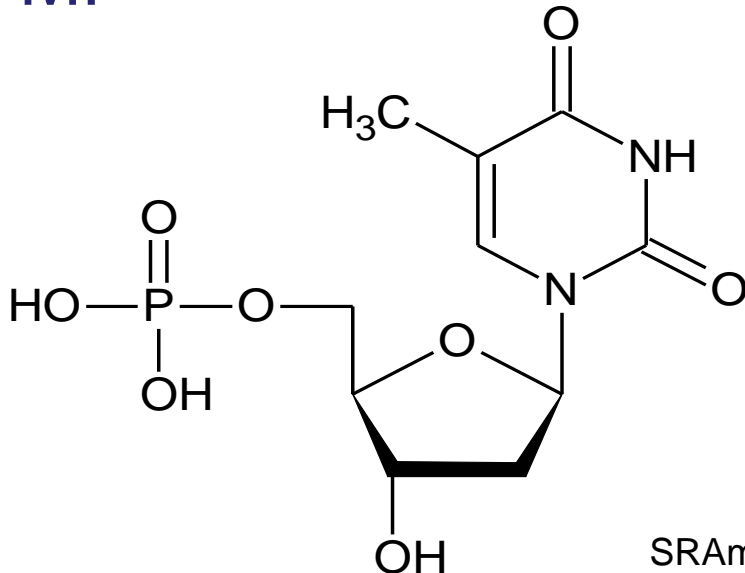


# dCMP; dTMP; dAMP; dGMP

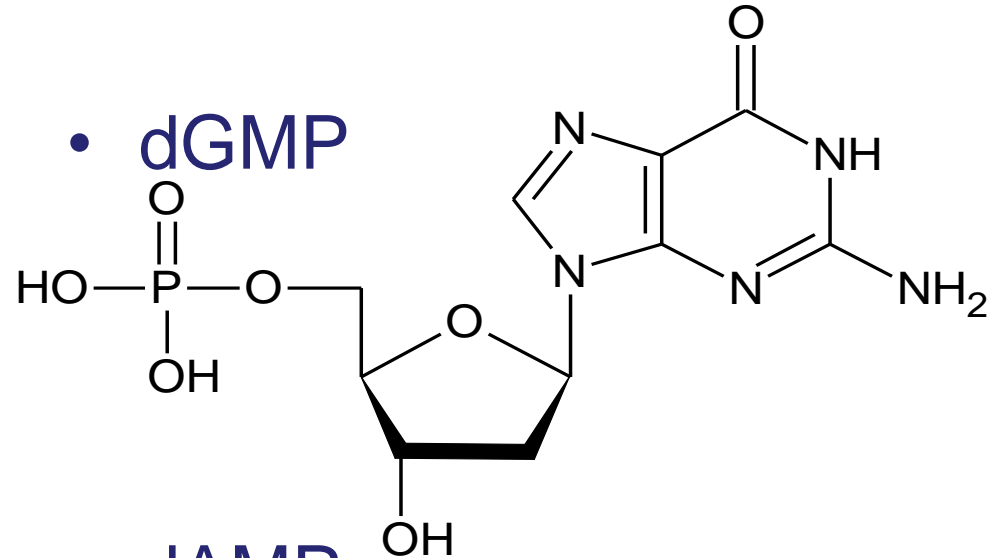
- dCMP



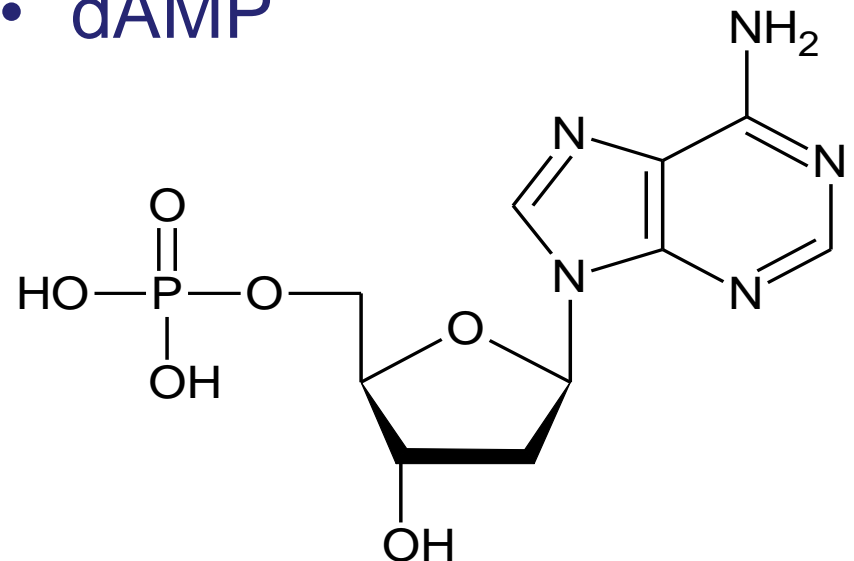
- dTMP



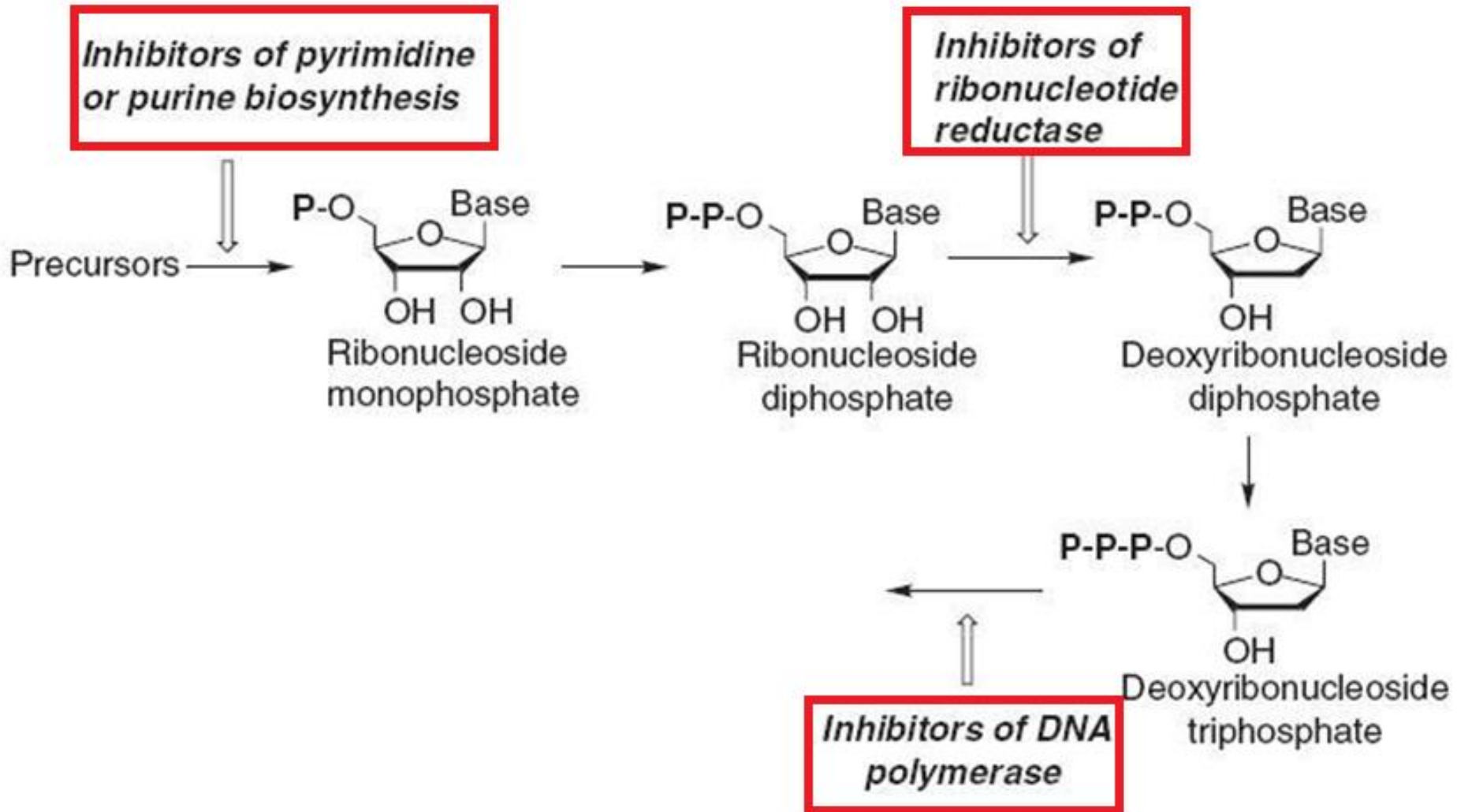
- dGMP



- dAMP



# 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/Purine 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 Classification

### 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

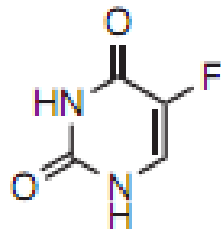
- ✓ cytosine analogue: C5 is replaced by N: triazine

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

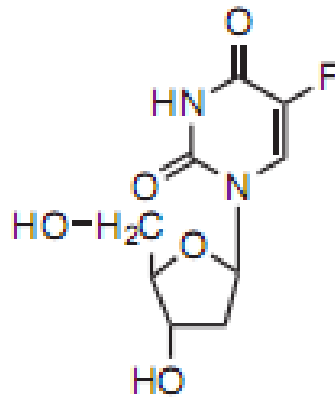
### II. 2.a. Thymidylate synthase inhibitors & dTMP synthesis inhibitors

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

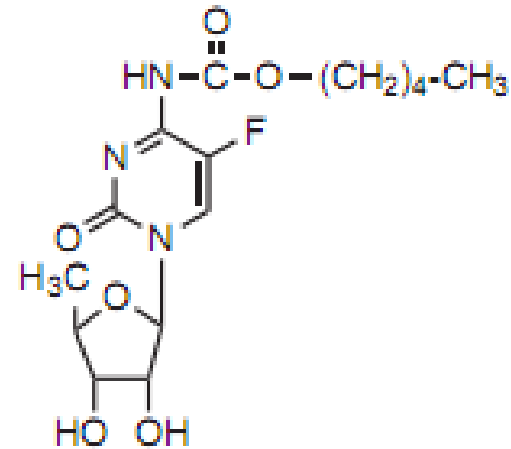
#### Pyrimidine antagonists:



Fluorouracil  
(Aduvicol)



Floxuridine  
(FUDR)



Capecitabine  
(Xeloda)

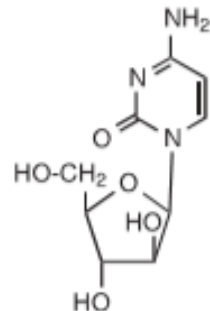
## II. 2. Pyrimidine Antimetabolites:

### b: DNA Polymerase and/or Chain Elongation Inhibitors:

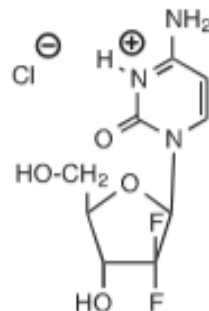
#### Cytidine/Uridine Based Analogues/Nucleotides

- Cytidine based:
  - ✓ Cytarabine: 2'-epimerized ribose (arabinose)
  - ✓ Gemcitabine: 2',2'-di-halogenated deoxyribose: dFdC
- Uridine based:
  - ✓ Trifluridine: tri-fluoromethyl derivative
- Phosphorylation by deoxycytidine kinase: mono& di-phosphate
- Further phosphorylation by pyrimidine kinase: triphosphate

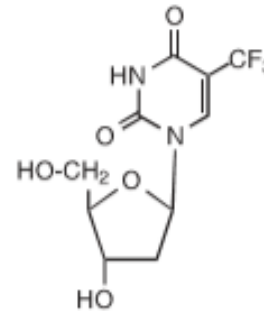
#### Pyrimidine analogues:



Cytarabine  
(Tarabine PFS,  
DepoCyt)



Gemcitabine  
hydrochloride  
(Gemzar)



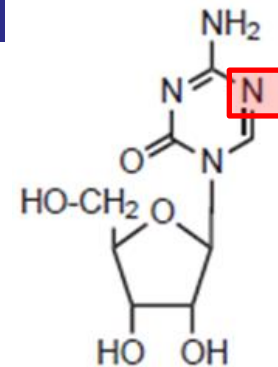
Trifluridine  
(active drug  
in Lonsurf)



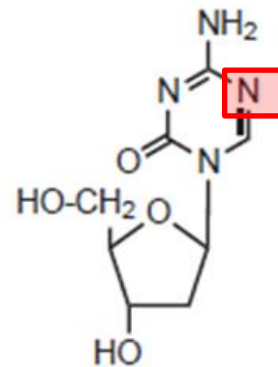
## II. 2. Pyrimidine Antimetabolites:

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)