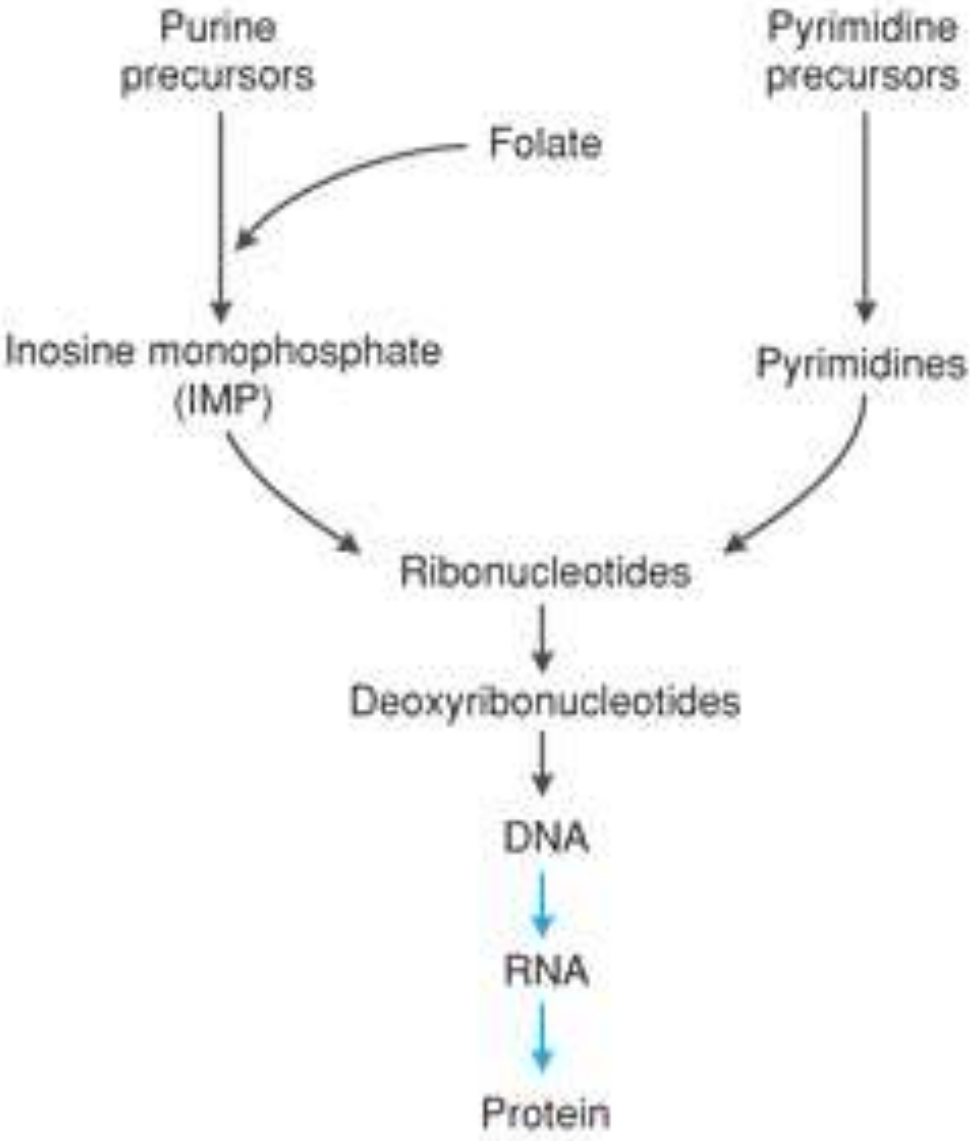
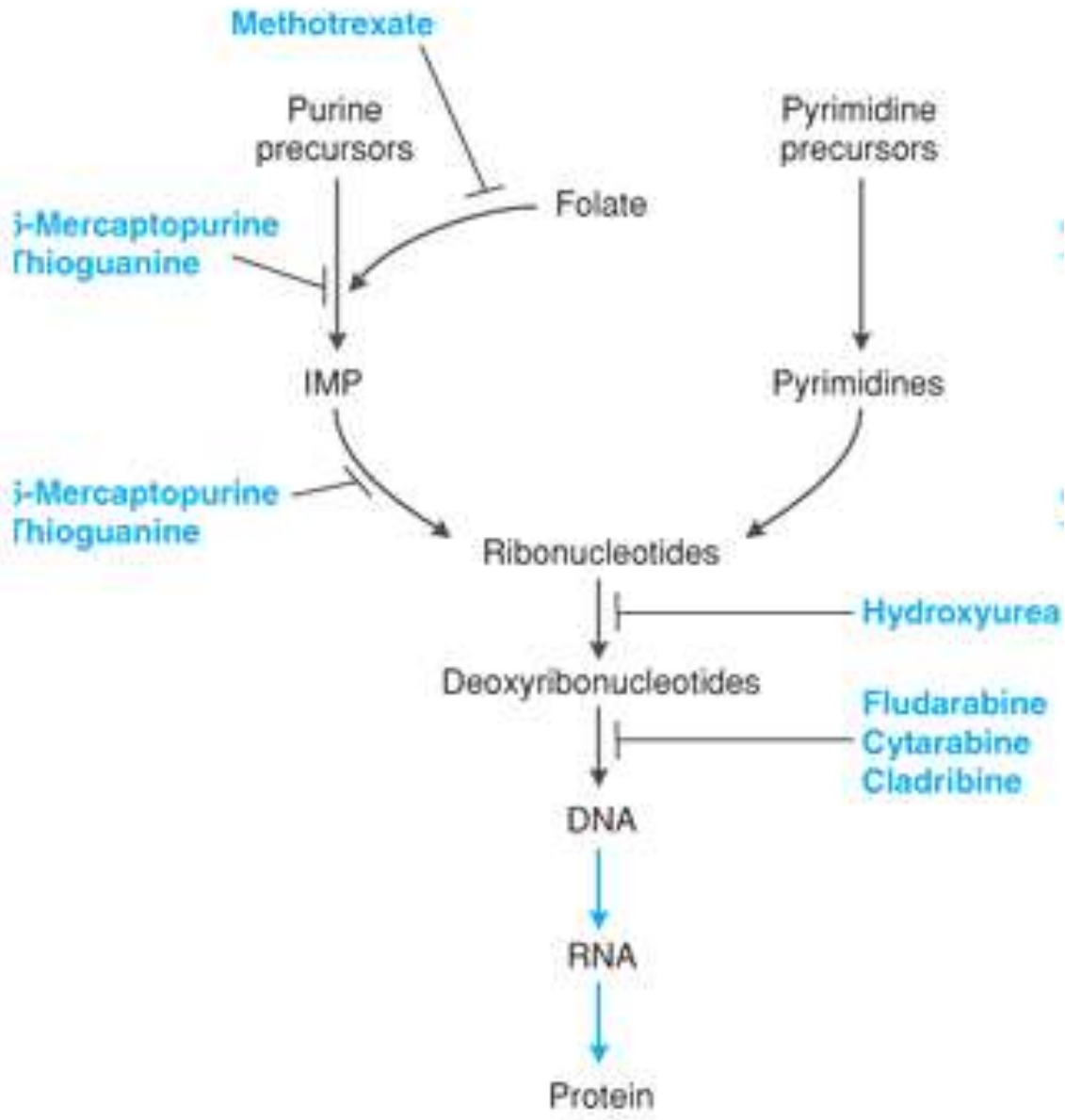
Part II; Drugs acting on enzyme (Antimetabolites)

Antimetabolits: sites of drug action



Antimetabolits: sites of drug action



Antimetabolites

General Characteristics:

- Antimetabolites are S phase-specific drugs that are structural analogues of essential metabolites and that interfere with DNA synthesis.
- Myelosuppression is the dose-limiting toxicity for all drugs in this class.

Antimetabolite

- Pyrimidine Antagonists
  - Methotrexate, Fluorouracil, Floxuridine, Capecitabine
- Purine Antagonists
  - Mercaptopurine, Thioguanine
- DNA Polymerase/ DNA Chain Elongation Inhibitors
  - Cytarabine, Gemcitabine, Fludarabine, Cladribine, Clofarabine
- Miscellaneous Antimetabolite
  - Hydroxyurea

Pyrimidine Antagonist

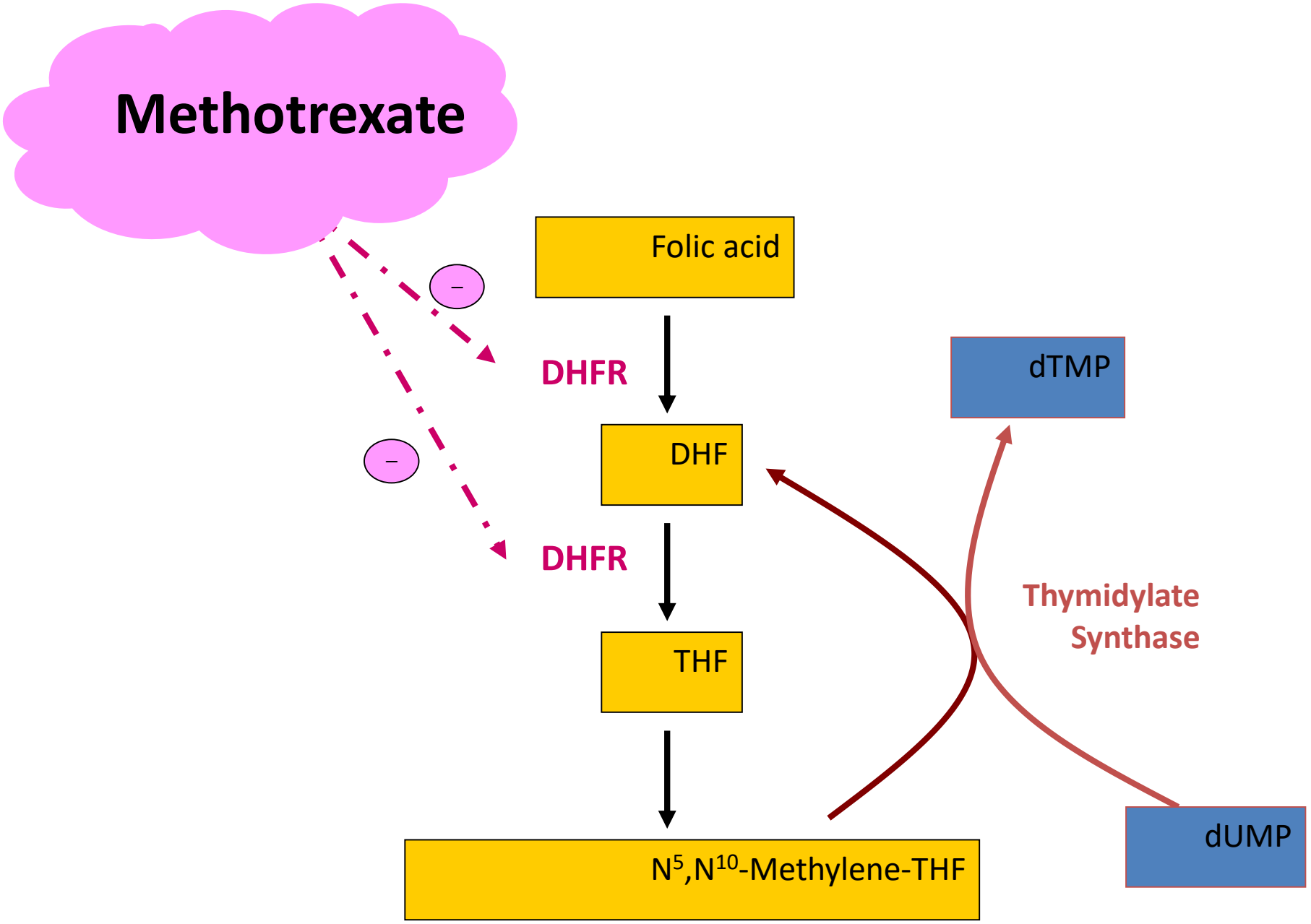
- dTMP Synthesis Inhibitors
  - Direct inhibitor: Fluorouracil, Floxuridine, Tegafur.
  - Indirect inhibitors: Methotrexate

Antimetabolites—Folic Acid Antagonist

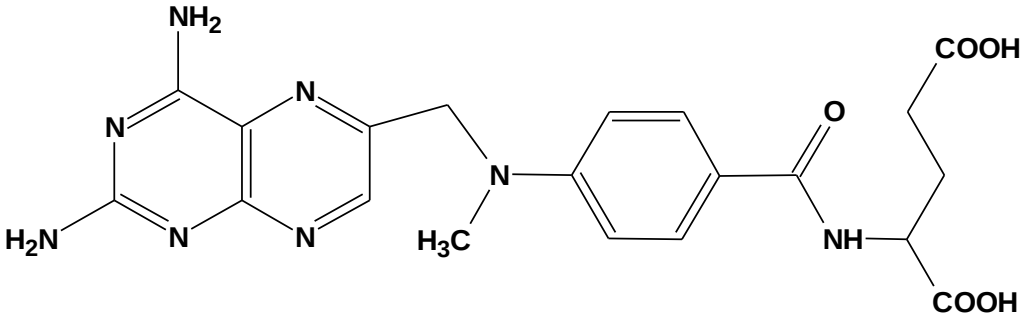
Methotrexate （MTX）

Mechanism of Action:

- The structures of MTX and folic acid are similar. MTX is actively transported into mammalian cells and inhibits dihydrofolate reductase, the enzyme that normally converts dietary folate to the tetrahydrofolate form required for thymidine and purine synthesis.

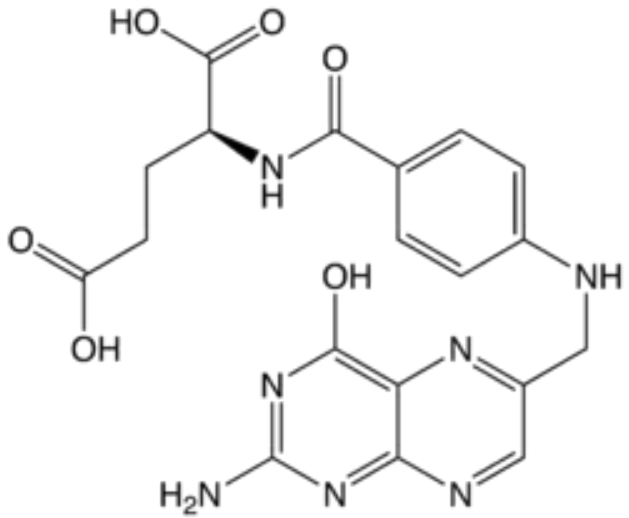

Methotrexate
Folic acid
DHFR
DHF
DHFR
THF
N5,N10-Methylene-THF
dTMP
Thymidylate Synthase
dUMP

Antimetabolites——
Folic Acid Antagonist



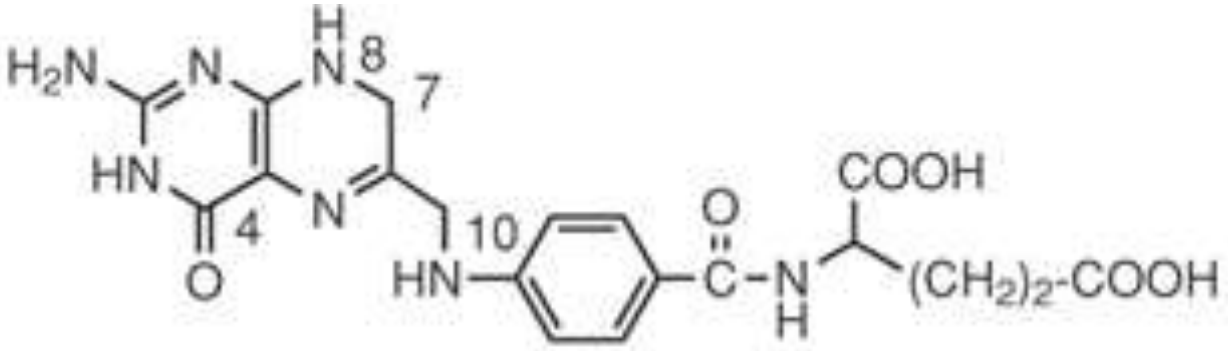
Methotrxate

L-(+)-*N*-[*p*[[2,4-diamino-6-pteridinyl)methyl]methylamino]-benzoyl]-glutamic acid



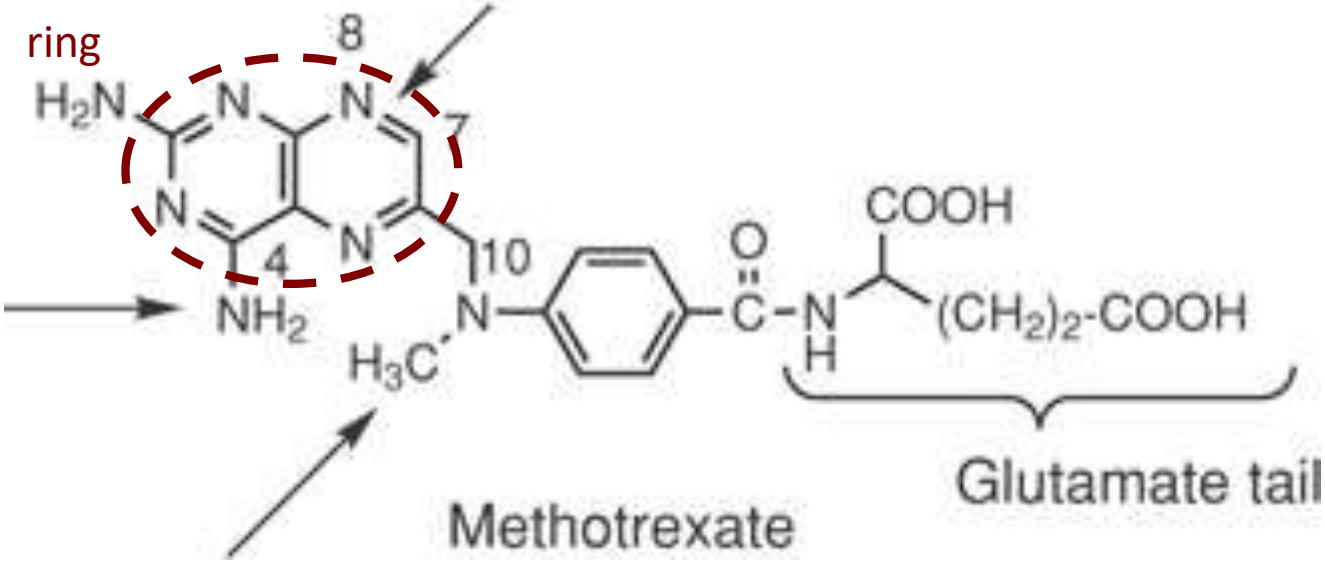
Folic acid

Methotrexate

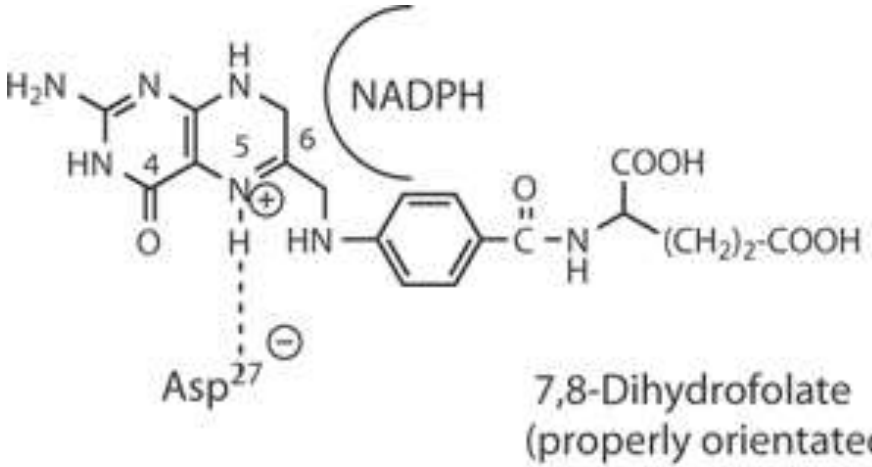


7,8-Dihydrofolate (DHF)

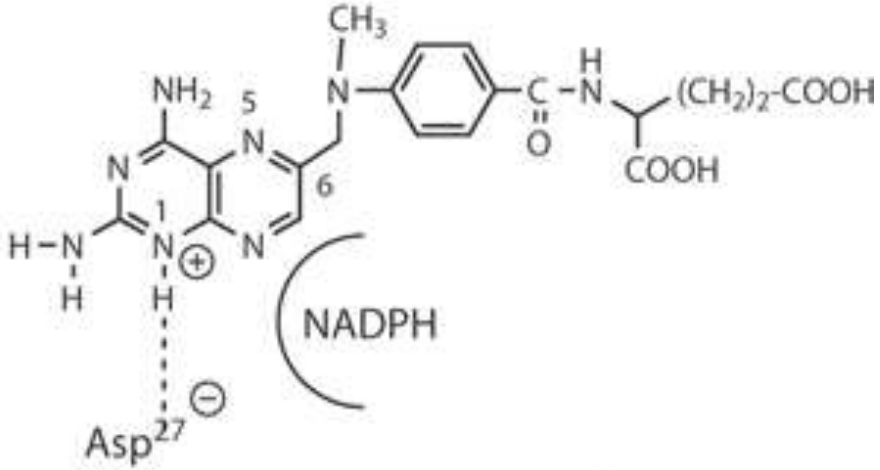
pteridine ring



DHFR ---- MTX -----DHF



7,8-Dihydrofolate
(properly orientated)



Methotrexate
(misorientated)

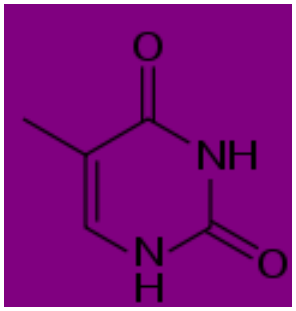
Antimetabolites——
Folic Acid Antagonist

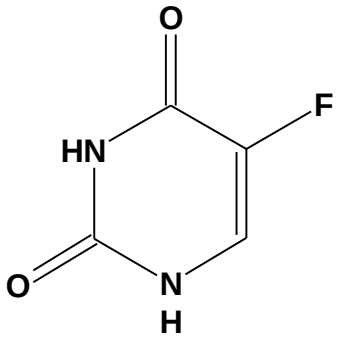
Methotrexate （MTX）

Adverse Effects：

- MTX is myelosuppressive, producing severe leukopenia, bone marrow aplasia, and thrombocytopenia.
- This agent may produce severe gastrointestinal disturbances.
- Renal toxicity may occur because of precipitation (crystalluria) of the 7-OH metabolite of MTX.

Antimetabolites——Pyrimidine Antagonists

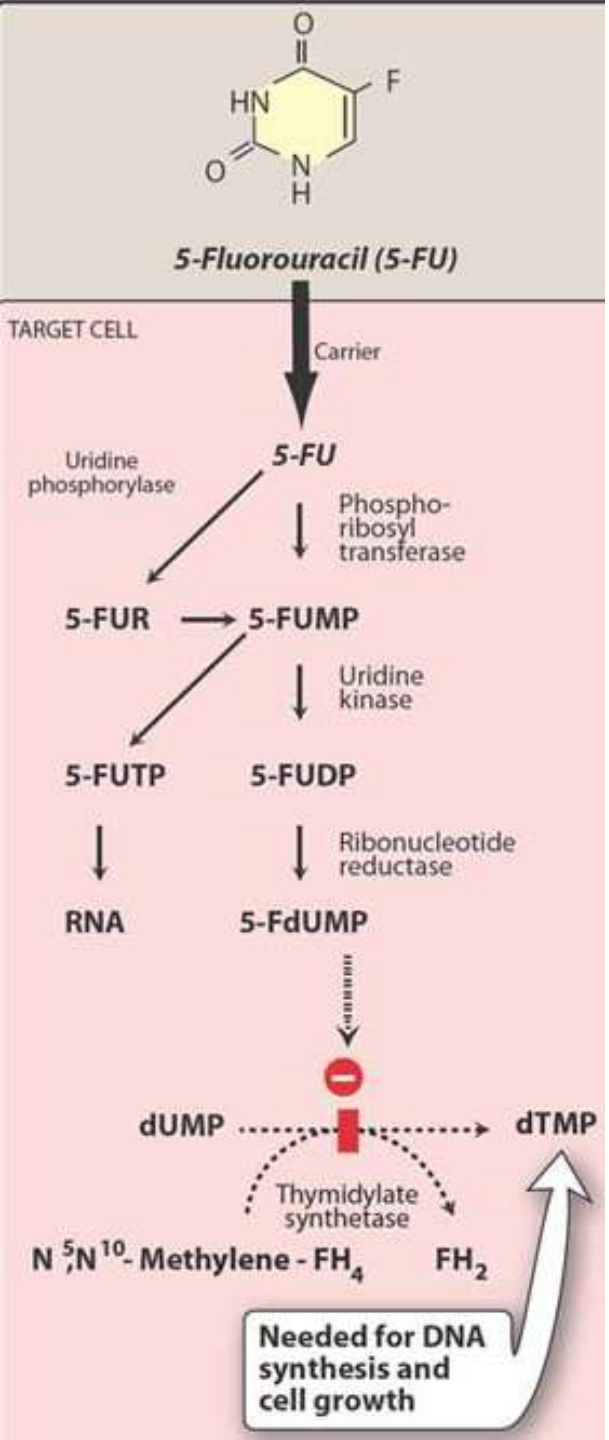




5-Fluorouracil (5-FU)

Mechanism of Action:

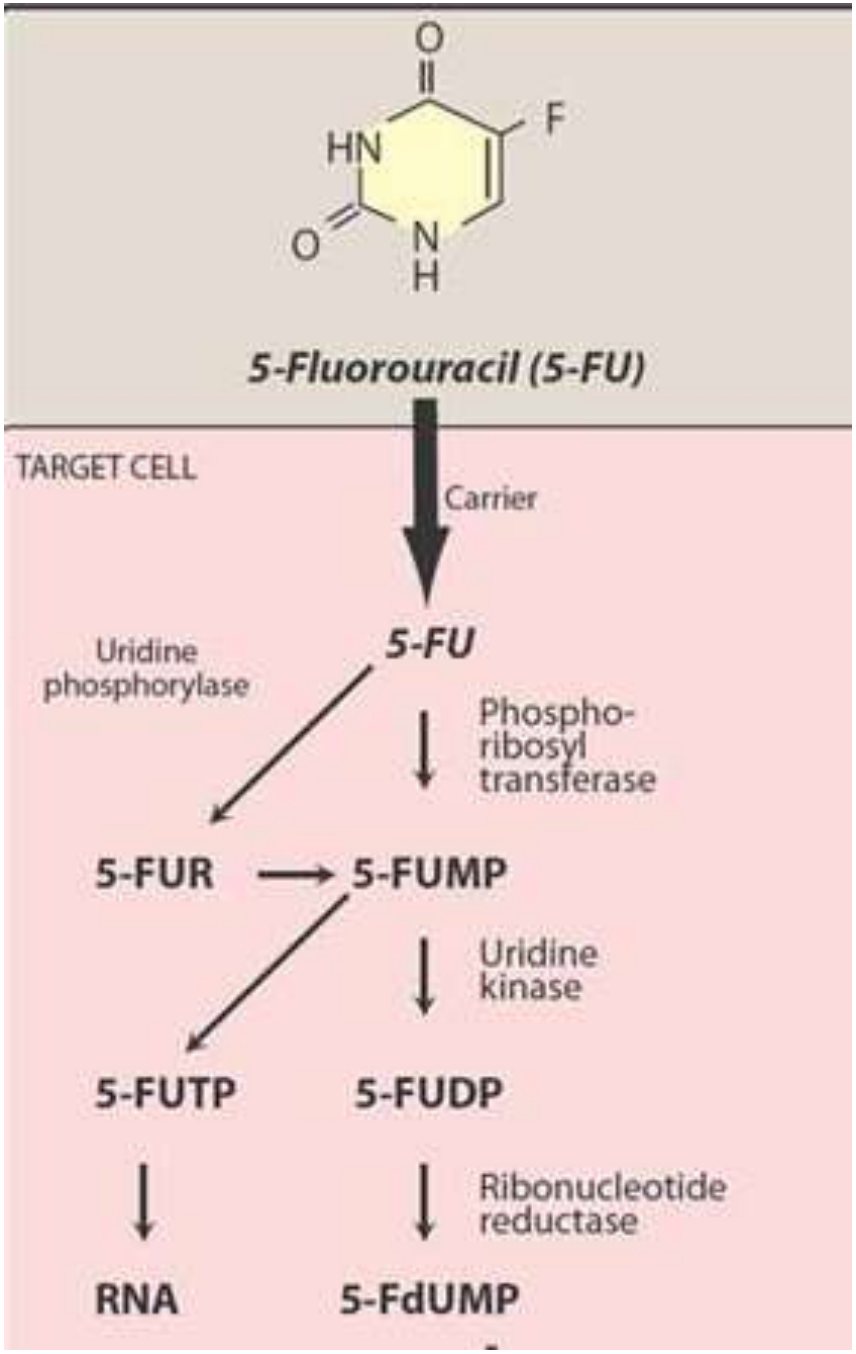
- Fluorouracil is an analogue of thymine in which the methyl group is replaced by a fluorine atom. It has two active metabolites: 5-FdUMP and 5-FdUTP. 5-FdUMP inhibits thymidylate synthetases and prevents the synthesis of thymidine, a major building block of DNA. 5-FdUTP is incorporated into RNA by RNA polymerase and interferes with RNA function.

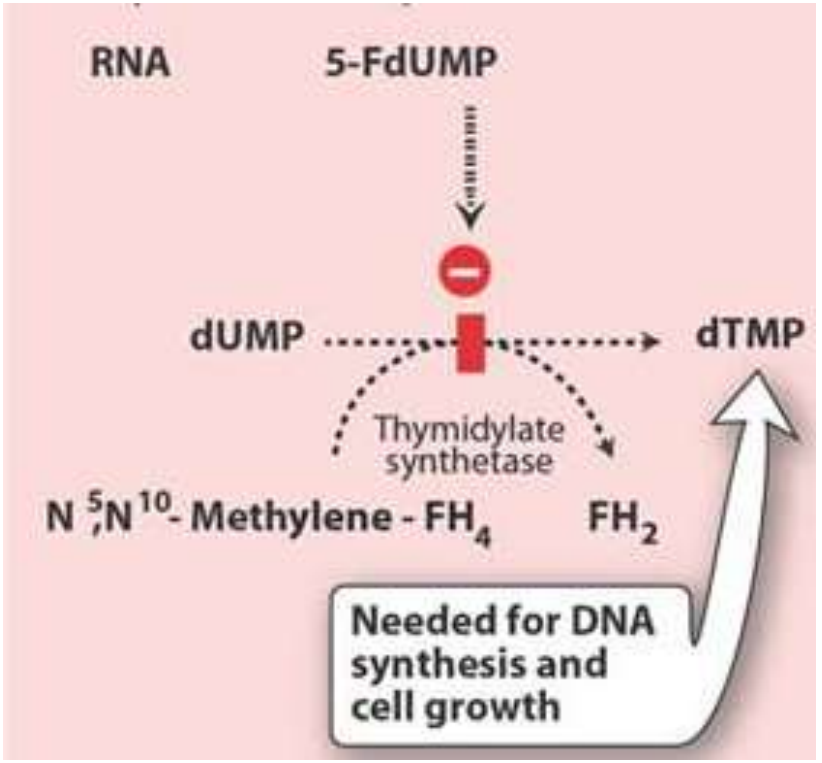


5-FU

Mechanism of the cytotoxic action of 5-FU

- **5-FU is converted to 5-FdUMP, which competes with deoxyuridine monophosphate (dUMP) for the enzyme thymidylate synthetase.**
- **5-FU = 5-fluorouracil**
- **5-FUR = 5-fluorouridine**
- **5-FUMP = 5-fluorouridine monophosphate**
- **5-FUDP = 5-fluorouridine diphosphate**
- **5-FUTP = 5-fluorouridine triphosphate**
- **dUMP = deoxyuridine monophosphate**
- **dTMP = deoxythymidine monophosphate**
- **5-FdUMP = 5-fluorodeoxyuridine monophosphate.**


O
HN
F
O
N
H
5-Fluorouracil (5-FU)
TARGET CELL
Carrier
5-FU
Uridine phosphorylase
Phospho-ribosyl transferase
5-FUR
5-FUMP
Uridine kinase
5-FUTP
5-FUDP
Ribonucleotide reductase
RNA
5-FdUMP

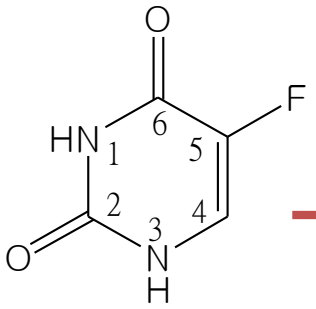

RNA
5-FdUMP
dUMP
dTMP
Thymidylate synthetase
N 5,N 10- Methylene - FH4
FH2
Needed for DNA synthesis and cell growth

Antimetabolites—— Pyrimidine Antagonists

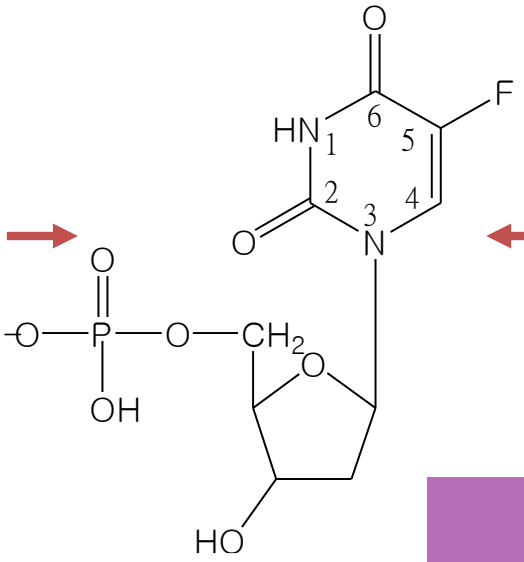
5-Fluorouracil (5-FU)

Adverse Effects:

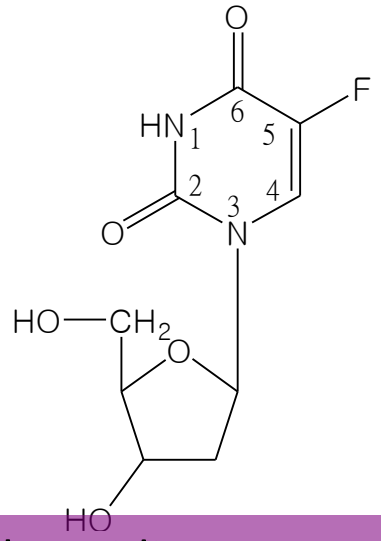
- Fluorouracil may cause nausea and vomiting, myelosuppression, and oral and gastrointestinal ulceration. Nausea and vomitting are usually mild.
- With fluorouracil, myelosuppression is more problematic after bolus injections, whereas mucosal damage is dose-limiting with continuous infusions.



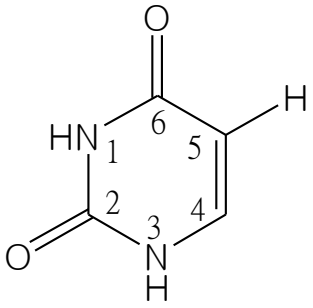
5-Fluorouracil
(fluorinated pyrimidine prodrug)



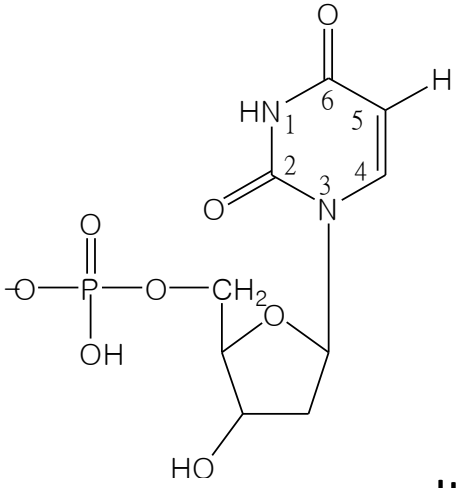
deoxyribonucleotide form;
5-F-dUMP (active form)



2. Floxuridine
(fluoro deoxyuridine nucleoside prodrug)



Uracil
(nucleic pirimidine base)

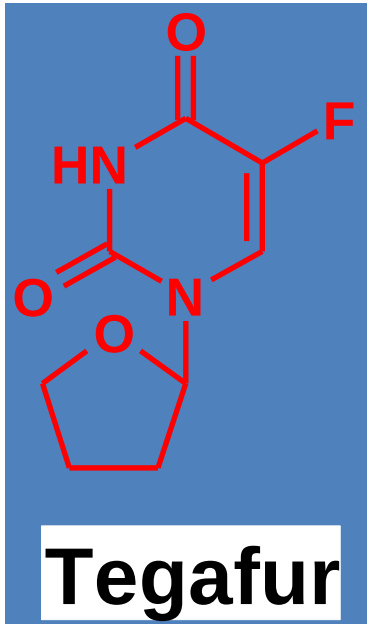


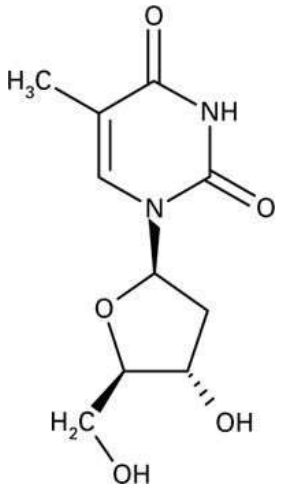
dUMP

Antimetabolites——
Pyrimidine Antagonists

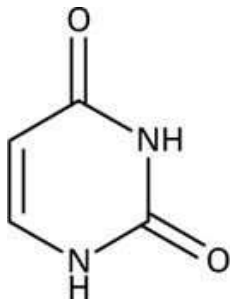
3. Tetrahydrofuranyl derivative of uracil

It is a prodrug slowly metabolized to 5-FU

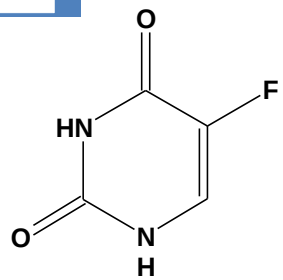




Thymidine



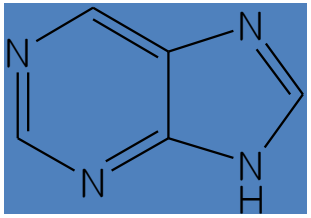
URACIL



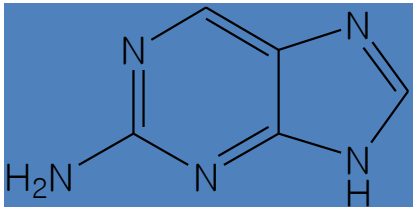
5-FU

Antimetabolites—— *Purine Antagonists*

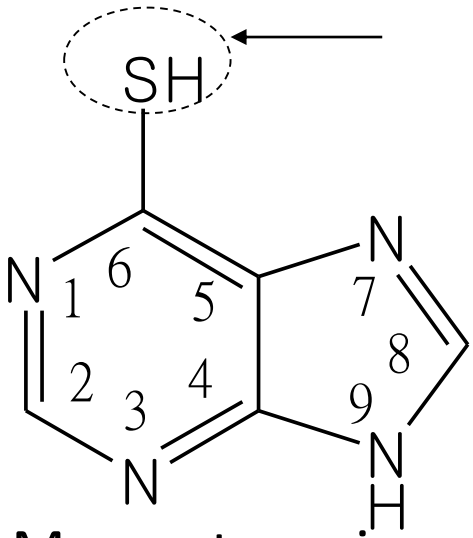
(Mercaptopurine, Thioguanine)



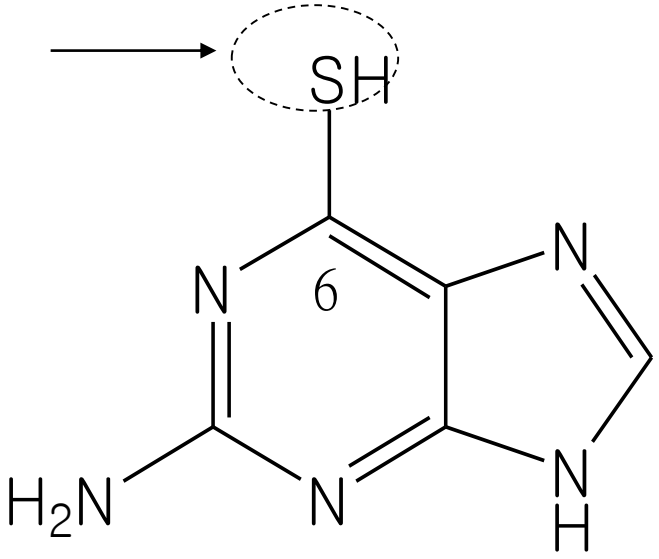
Purine



Guanine

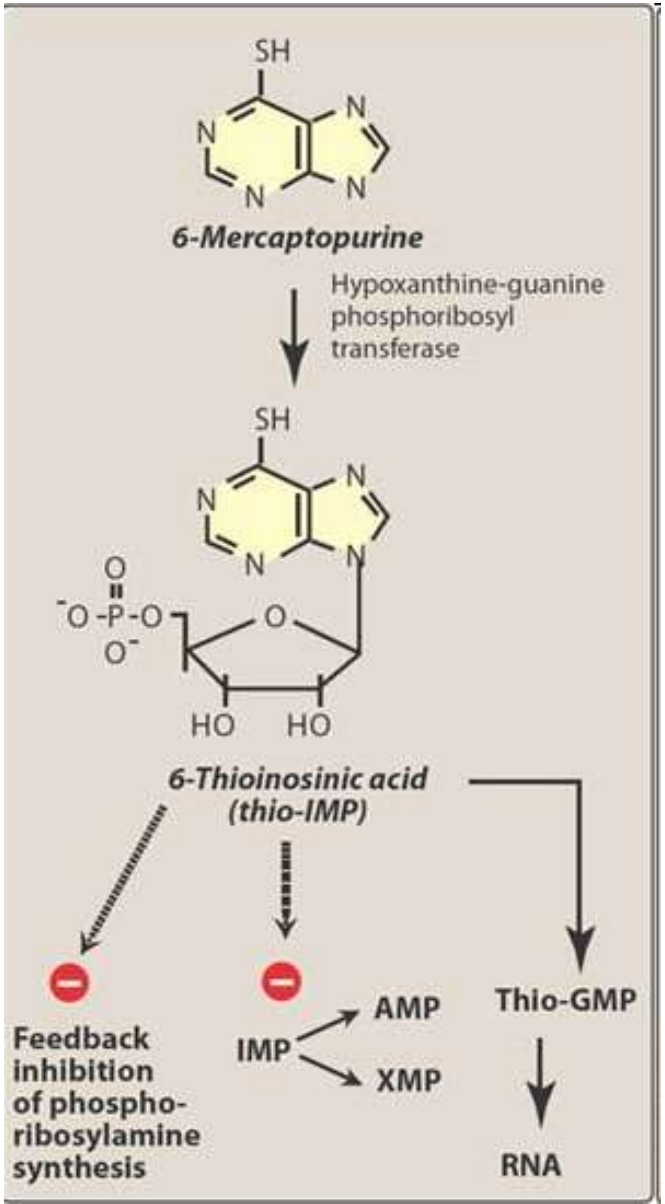


6-Mercaptopurine



6-Thioguanine

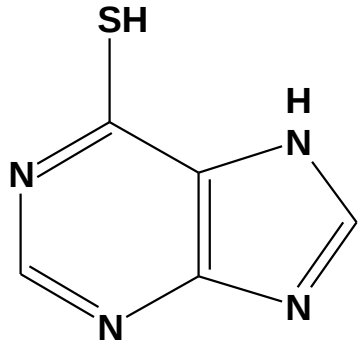
6-Mercaptopurine (6-MP) & Thioguanine



- Both 6-MP and Thioguanine are activated by HGPRT to toxic nucleotides that inhibit several enzymes involved in purine metabolism
- ***Resistance is due to cancer cells having ⇓d activity of HGPRT
- Cancer cells also ⇑es alkaline phosphatase that inactivate toxic nucleotides

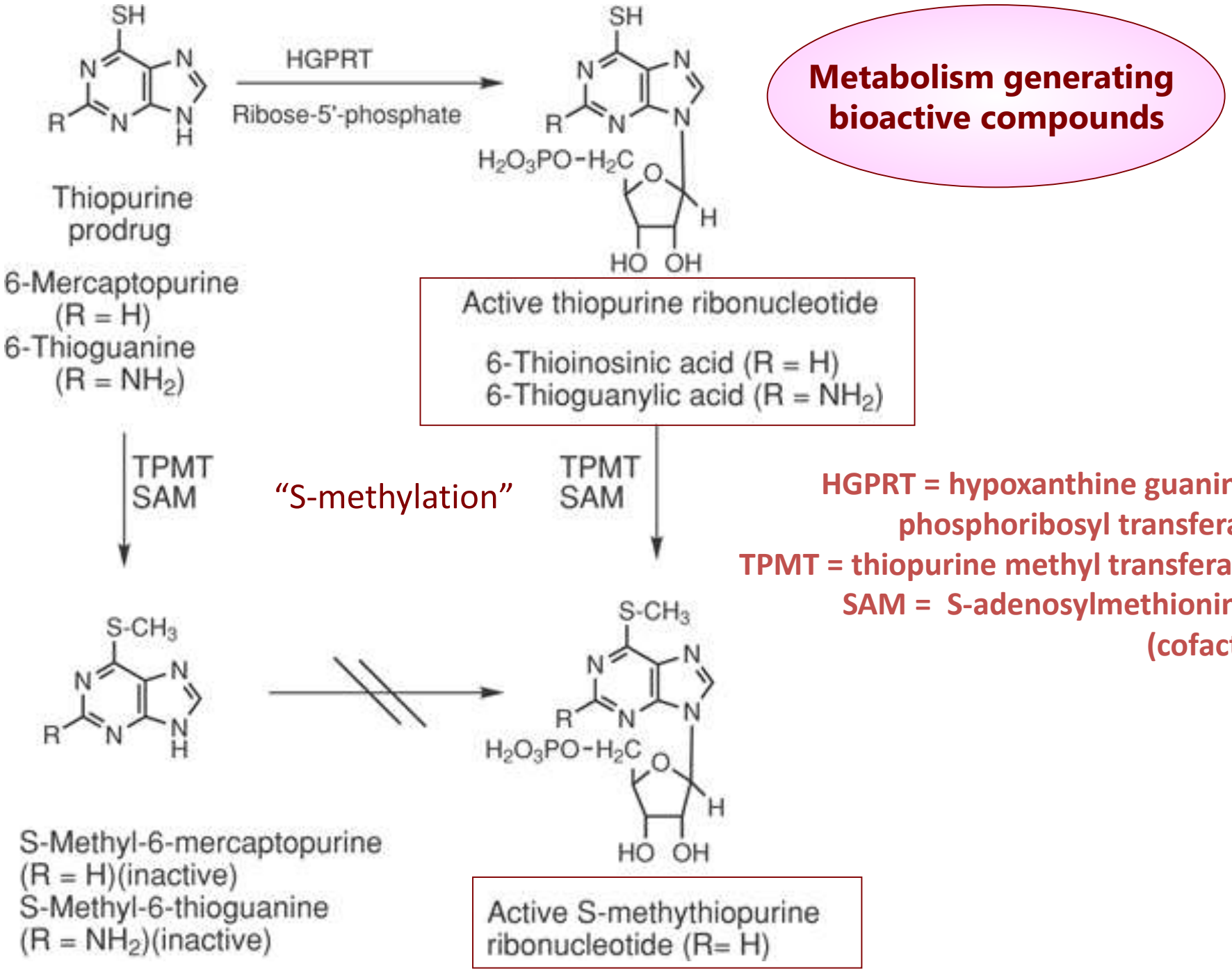
Purines antagonists

6-Mercaptopurine

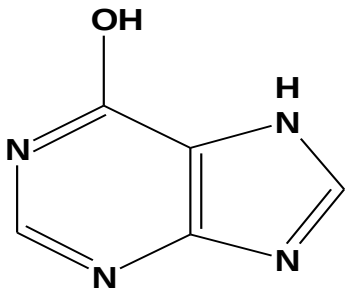


Mode of action:

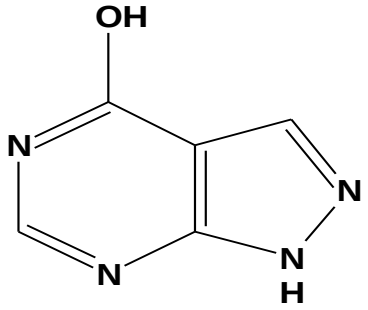
It inhibits purine biosynthesis as it replaces hypoxanthene, which is a natural intermediate in syntheses of nucleic acid purine bases.


Metabolism generating bioactive compounds
HGPRT
Ribose-5'-phosphate
Thiopurine prodrug
6-Mercaptopurine (R = H)
6-Thioguanine (R = NH2)
Active thiopurine ribonucleotide
6-Thioinosinic acid (R = H)
6-Thioguanylic acid (R = NH2)
TPMT SAM
"S-methylation"
TPMT SAM
HGPRT = hypoxanthine guanine • phosphoribosyl transferase
TPMT = thiopurine methyl transferase•
SAM = S-adenosylmethionine • (cofactor)
S-Methyl-6-mercaptopurine (R = H)(inactive)
S-Methyl-6-thioguanine (R = NH2)(inactive)
Active S-methythiopurine ribonucleotide (R= H)

6-mercaptopurine is rapidly metabolized by xanthene oxidase enzyme, which is responsible for oxidation of hypoxanthene and xanthene into uric acid. So when 6-mercaptopurine is co-administered with allopurinol (xanthine oxidase inhibitor) its half-life will be increased.



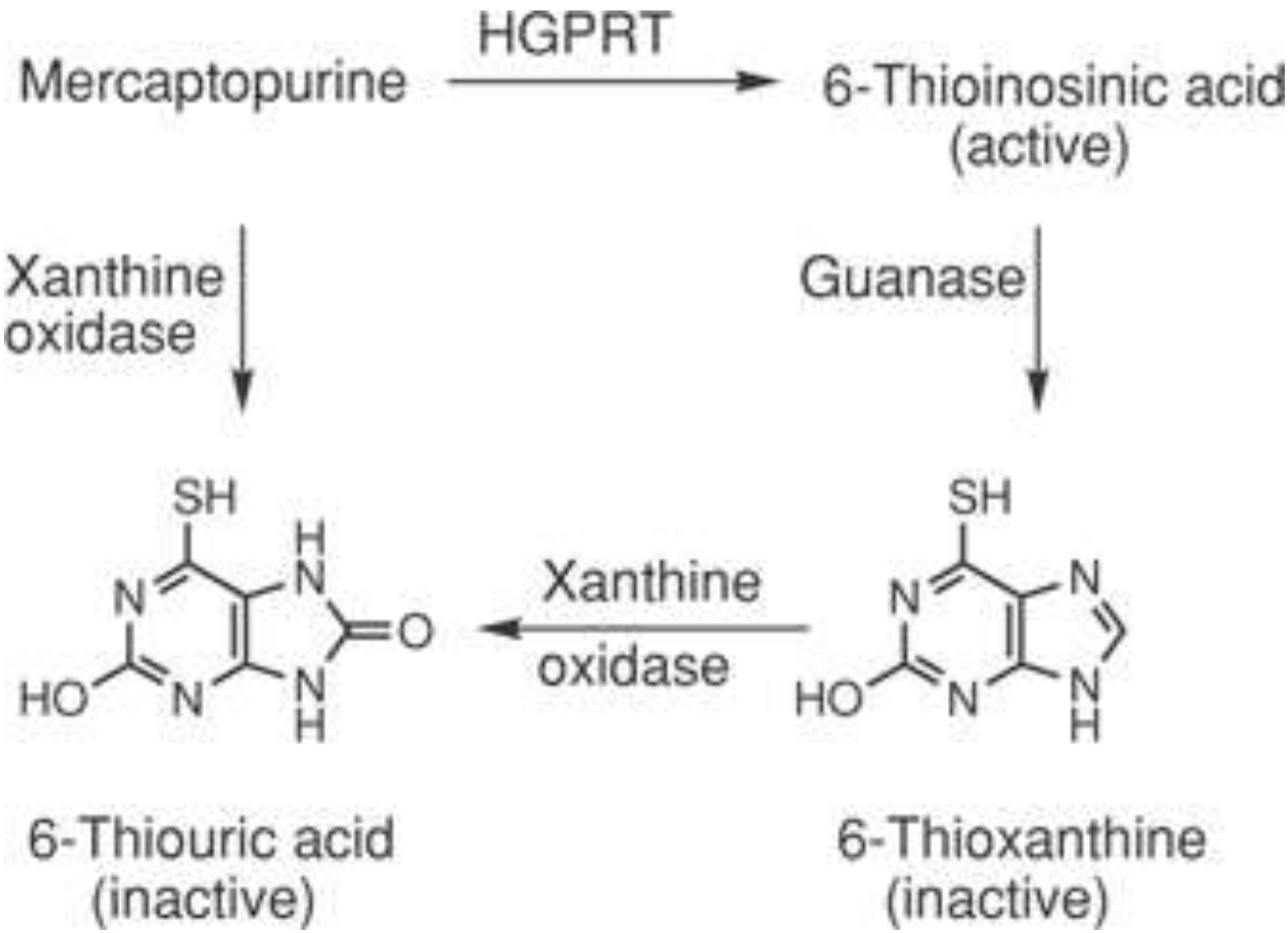
Hypoxanthene



Allopurinol

6-MP & Allopurinol

- 6-MP is metabolized in the liver by xanthine oxidase and the inactive metabolites are excreted in the urine
- ***Allopurinol is used frequently to treat/prevent hyperuricemia caused by many anticancer drugs.
- If Allopurinol is used with 6-MP then the dose of 6-MP is reduced by more than 75%


Mercaptopurine
HGPRT
6-Thioinosinic acid
(active)
Xanthine
oxidase
Guanase
SH
N
H
N
O
HO
N
N
H
Xanthine
oxidase
SH
N
N
HO
N
N
H
6-Thiouric acid
(inactive)
6-Thioxanthine
(inactive)

Antimetabolites——
Purine Antagonists

6-Mercapapurine（6-MP）

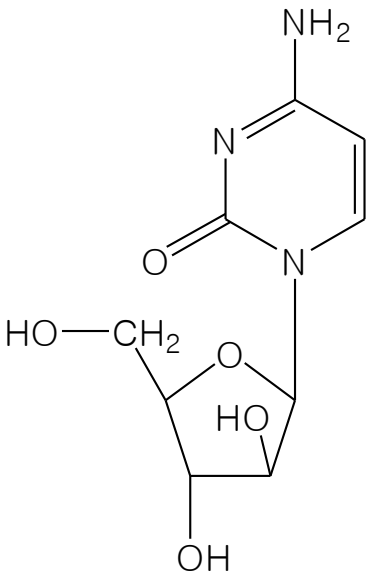
Indications:

- Mercaptopurine is used primarily for the maintenance of remission in patients with acute lymphocytic leukemia and is given in combination with MTX for this purpose.

Adverse Effects:

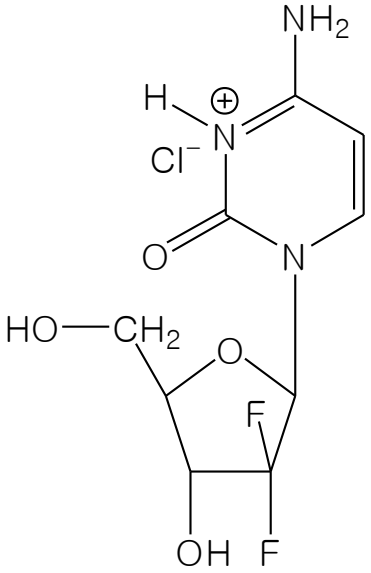
- Well tolerate.
- Myelosuppression is generally mild with thioguanine.Long-term mercaptopurine use may cause hepatotoxicity.

Cytarabine and Gemcitabine



Cytarabine

$T_{1/2}$ = 3.6 hrs



Gemcitabine

$T_{1/2}$ = 19 hrs

Cytidine-base nucleosides

Cytarabine

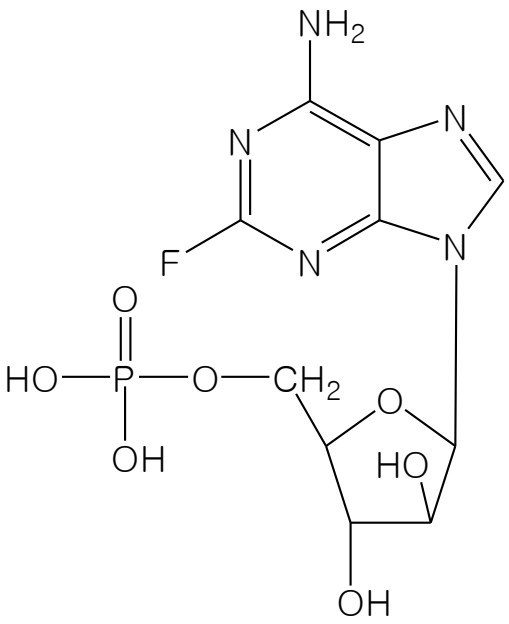
Indications:

- Cytarabine has a narrow clinical spectrum and is primarily used in combination with daunorubicin or thioguanine for the treatment of acute nonlymphocytic leukemia.

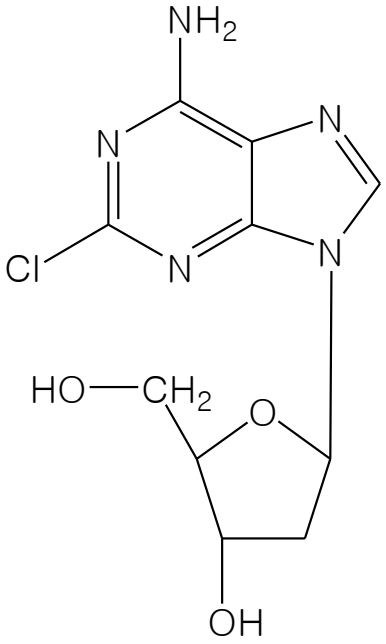
Adverse Effects:

- High doses of cytarabine can damage the liver, heart, and other organs.

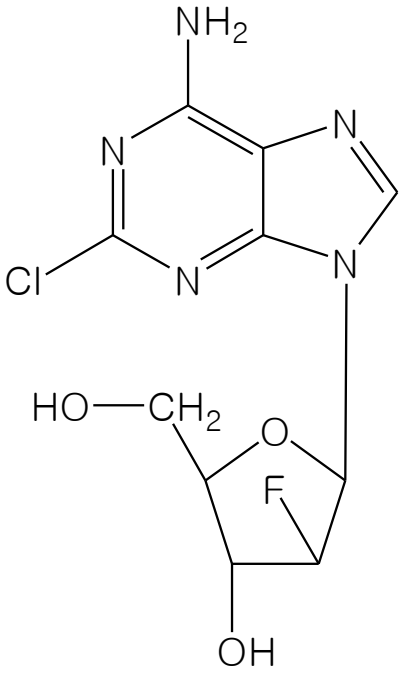
Fludarabine, Clabribine, and Clofarabine



Fludarabine phosphate



Cladribine

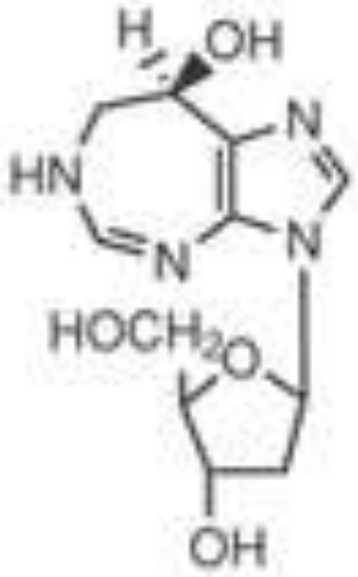


Clofarabine

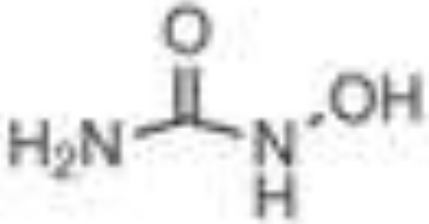
2-Halogenated adenosine base nucleosides

Miscellaneous Antimetabolites

- **Pentostatin and Hydroxyurea (self study)**



Pentostatin



Hydroxyurea

Miscellaneous Antimetabolites

Hydroxyurea

- **Inhibits ribonucleotide reductase**
  - **Important in *de novo* DNA synthesis and DNA repair**
- **Orally bioavailable**