Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology III
Lecture: 5

ANTICANCER DRUGS II

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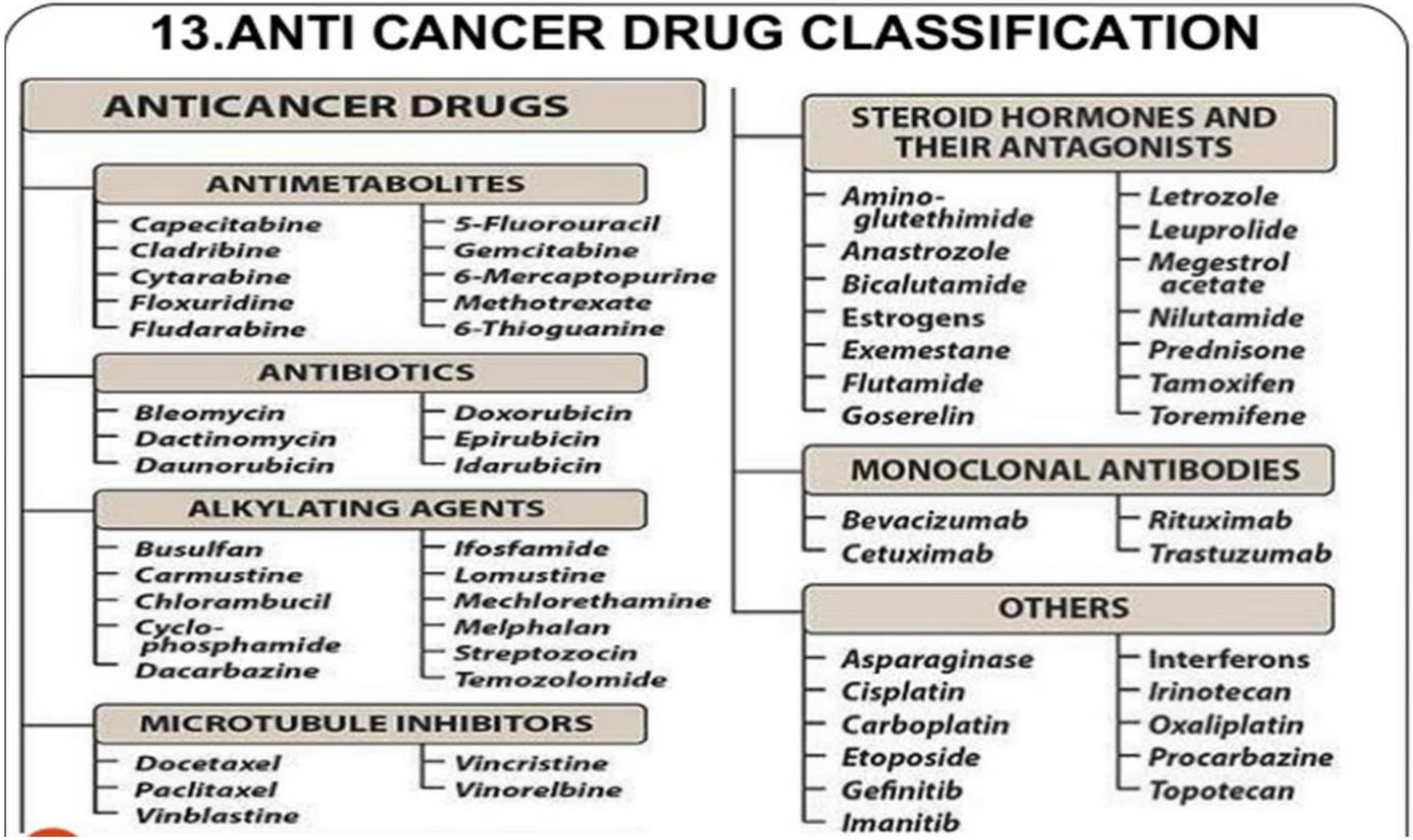
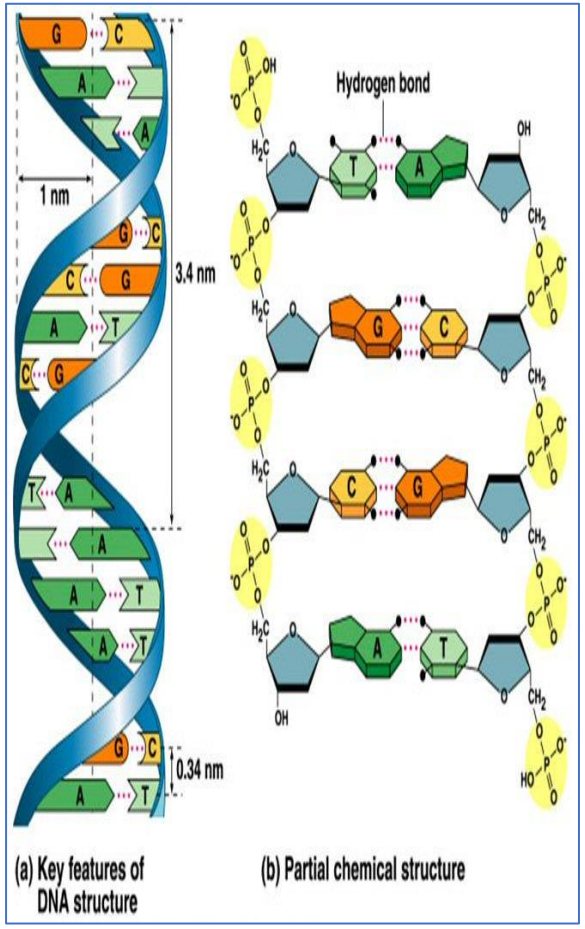
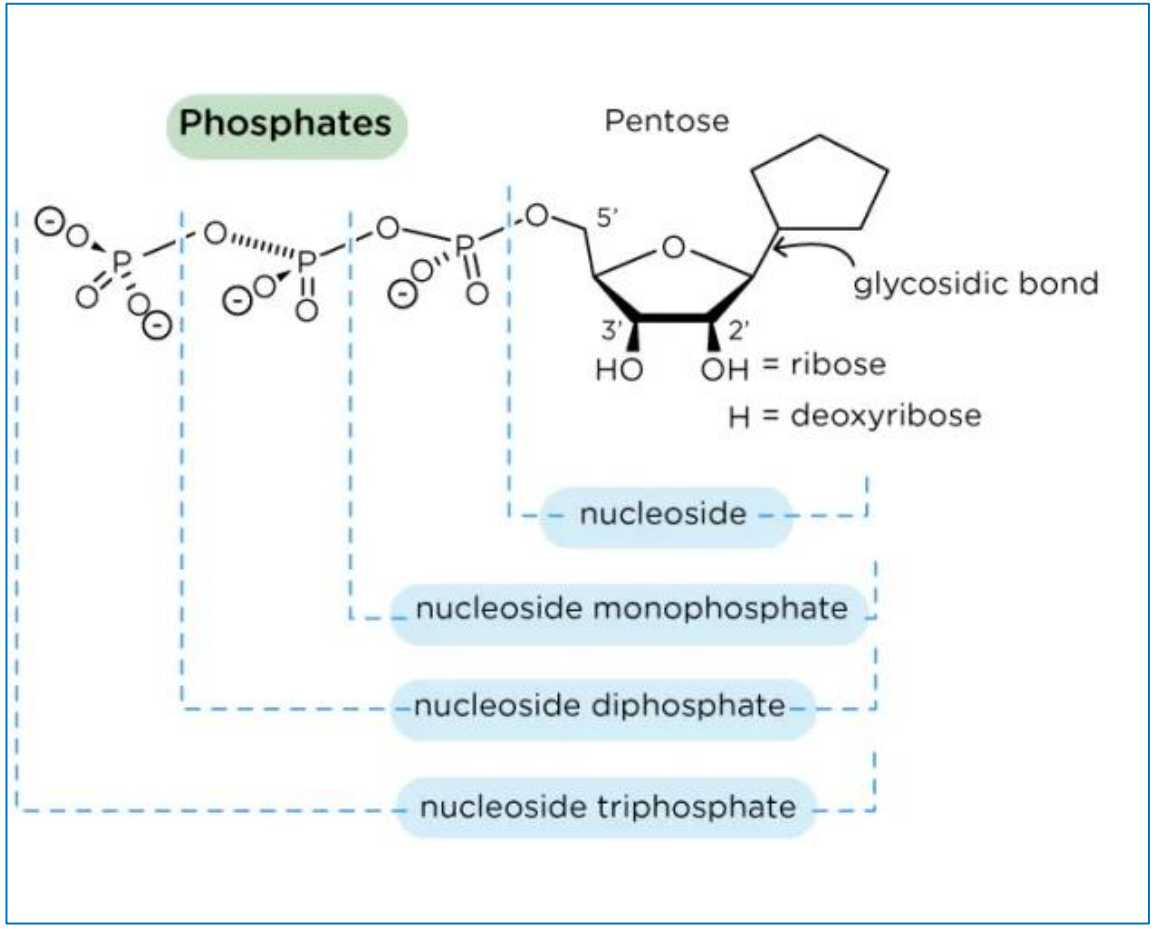
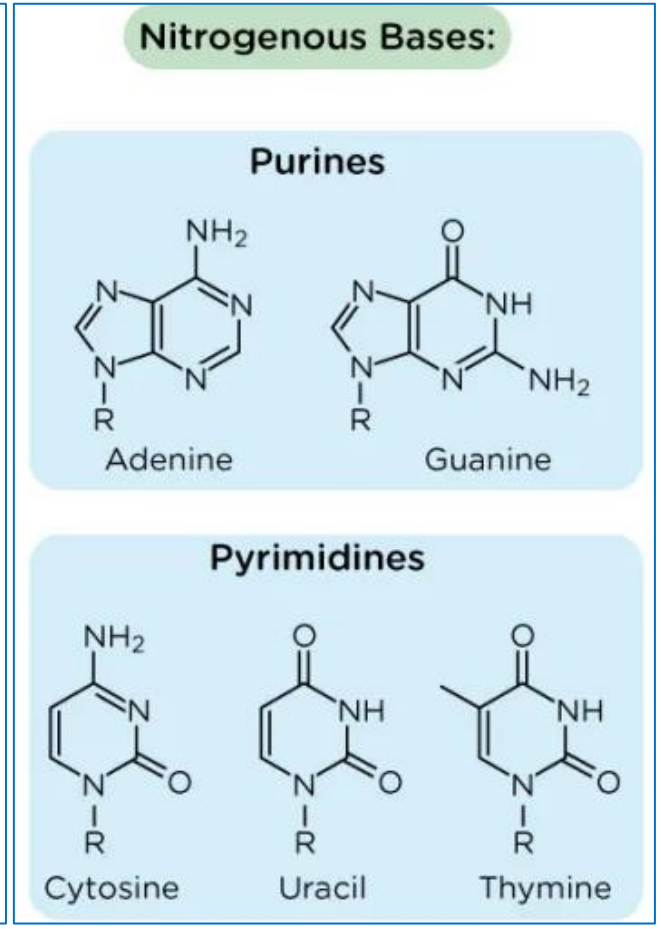
Classification of anticancer drugs



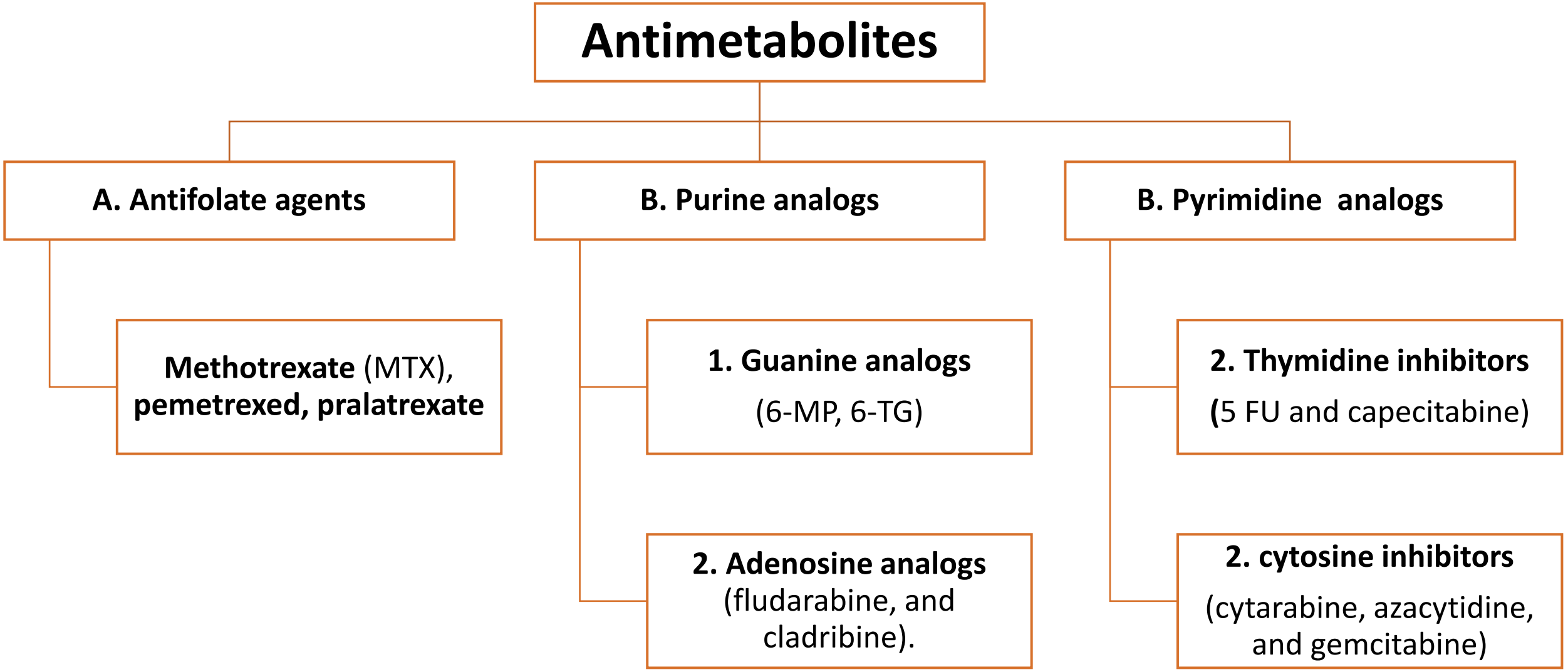
I. ANTIMETABOLITES





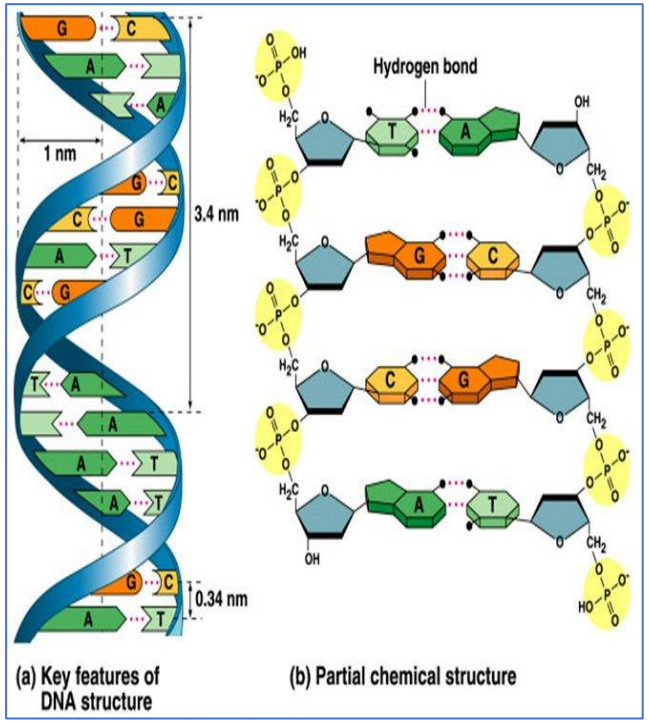


I. Antimetabolites



I. ANTIMETABOLITES

- Antimetabolites are **structurally related** to **normal compounds** that exist within the cell.
- They generally **interfere** with the availability of normal **purine** or **pyrimidine** nucleotide **precursors**, either by **inhibiting** their **synthesis** or by **competing** with them in DNA or RNA synthesis.
- Their maximal cytotoxic effects are **in the S phase** and are, therefore, **cell cycle specific**.
- They **include**: Azacitidine, Capecitabine, Cladribine, Cytarabine Fludarabine, 5-Fluorouracil, Gemcitabine, 6-Mercaptopurine, Methotrexate, Pemetrexed, Pralatrexate.



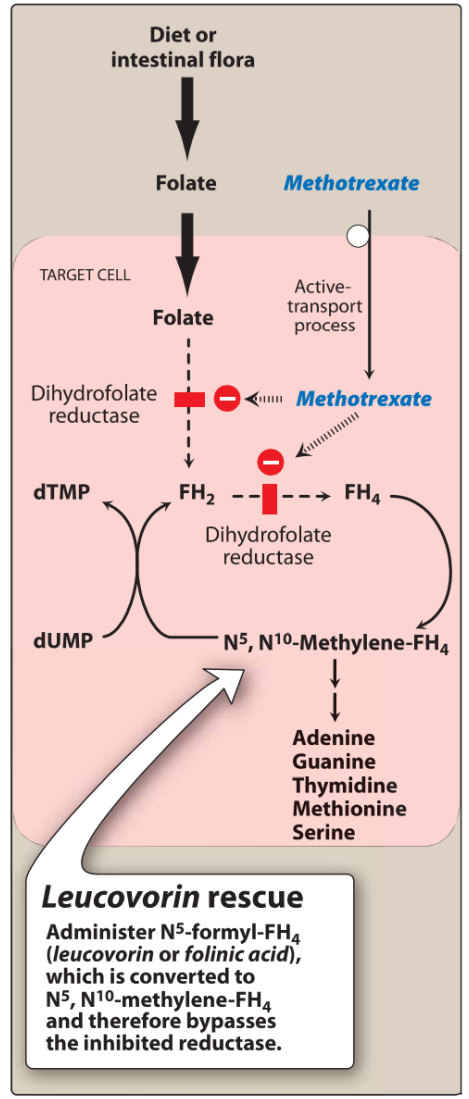
A. Antifolate agents

- The vitamin **folic acid** plays a central role in a variety of **metabolic reactions** involving the transfer of **one-carbon units** and is essential for **cell replication**.
- Folic acid is **obtained** mainly from **dietary sources** and from that produced by **intestinal flora**.
- **Methotrexate** (MTX), **pemetrexed**, and **pralatrexate** are **antifolate agents**.

A. Antifolate agents

1. Mechanism of action:

- **MTX** is **structurally** related to **folic acid** and acts as an **antagonist** of the vitamin by **inhibiting** mammalian dihydrofolate reductase (**DHFR**), the enzyme that **converts folic acid to its active**, coenzyme form, tetrahydrofolic acid (**FH4**).
- The **inhibition** of DHFR can only be **reversed by a 1000-fold excess** of the natural substrate, dihydrofolate (**FH2**), or by **administration** of **leucovorin**, which **bypasses** the blocked enzyme and replenishes the folate pool.
- **MTX** is specific for the **S phase** of the cell cycle.
- **Pemetrexed** is an antimetabolite **similar** in mechanism to methotrexate. However, in addition to inhibiting **DHFR**, it also **inhibits thymidylate synthase** and **other enzymes** involved in folate metabolism and DNA synthesis.
- **Pralatrexate** is an antimetabolite that also **inhibits DHFR**.



A. Antifolate agents

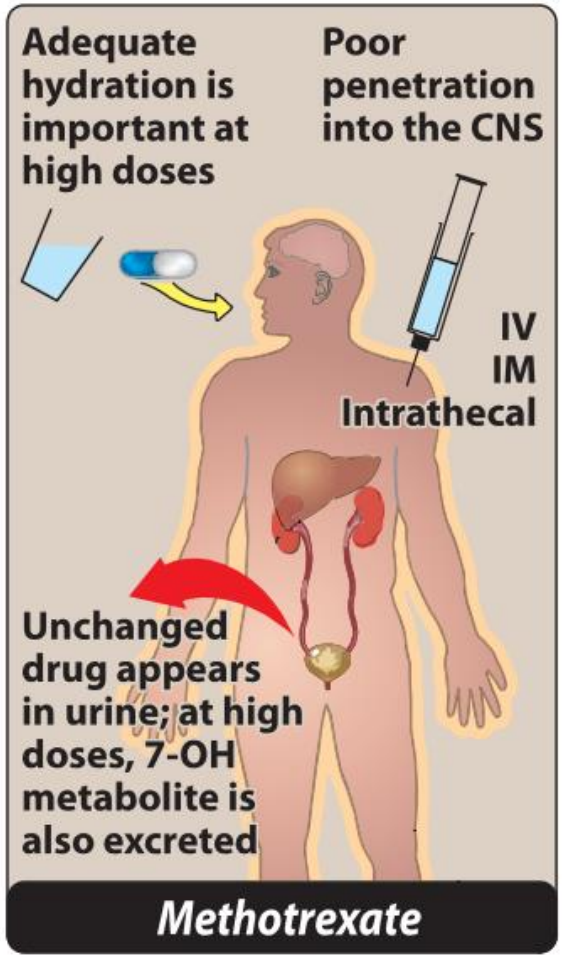
2. Therapeutic uses:

- MTX, usually in **combination** with other drugs, is effective against **acute lymphocytic leukemia, Burkitt lymphoma** in children, **breast cancer, bladder cancer, and head and neck carcinomas**.
- In addition, **low-dose MTX** is effective as a **single** agent against certain **inflammatory diseases**, such as **severe psoriasis** and **rheumatoid arthritis**, as well as **Crohn's disease**.
- **All patien**ts receiving MTX require close **monitoring** for possible toxic effects.
- **Pemetrexed** is primarily used in **non-small cell lung cancer**.
- **Pralatrexate** is used in **relapsed or refractory T-cell lymphoma**.

A. Antifolate agents

3. Pharmacokinetics:

- MTX is variably **absorbed** at low doses from the **GI tract**, but it can also be administered by **IM, IV, and IT** route.
- **Small** amounts of MTX undergo **hydroxylation** at the 7th position to form **7-hydroxymethotrexate**.
- This derivative is **less water soluble** than MTX and may lead to **crystalluria**.
- Therefore, it is important to **keep the urine alkaline** and the patient well **hydrated** to avoid renal toxicity.
- **Excretion** of the parent drug and the 7 -OH metabolite occurs primarily via **urine**.



A. Antifolate agents

4. Adverse effects:

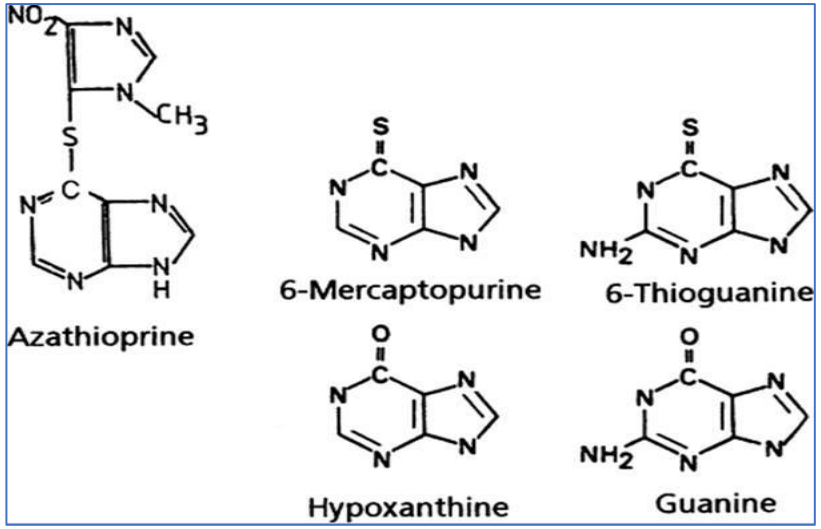
- **MTX, Pemetrexed, and pralatrexate** should be given with **folic acid and vitamin B-12** supplements to **reduce hematologic and GI toxicities**.
- Pretreatment with **corticosteroids** to **prevent cutaneous reactions** is recommended with **pemetrexed**.
- However, it may cause **ocular toxicity**, including **irreversible retinal damage and corneal deposits**, **CNS disturbances**, **GI upset, and skin discoloration and eruptions**.

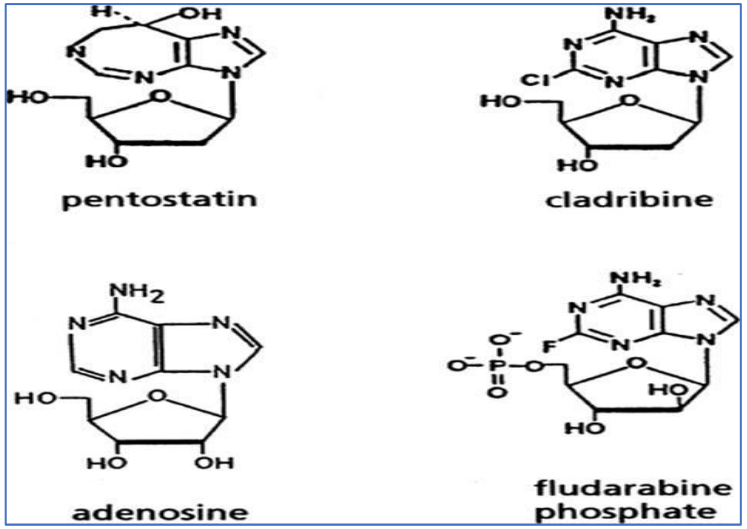
B. Purine analogs

- Drugs that belong to this category are:

1. **Guanine analogs** (6-mercaptopurine, 6-thioguanine)
2. **Adenosine analogs** (fludarabine, and cladribine).

- Some drugs in this category are **not used in cancer chemotherapy** but as **immunosuppressants** (e.g. azathioprine), **antivirals** (e.g. acyclovir, zidovudine), and **hypouricemic agents** (allopurinol).





B. Purine analogs

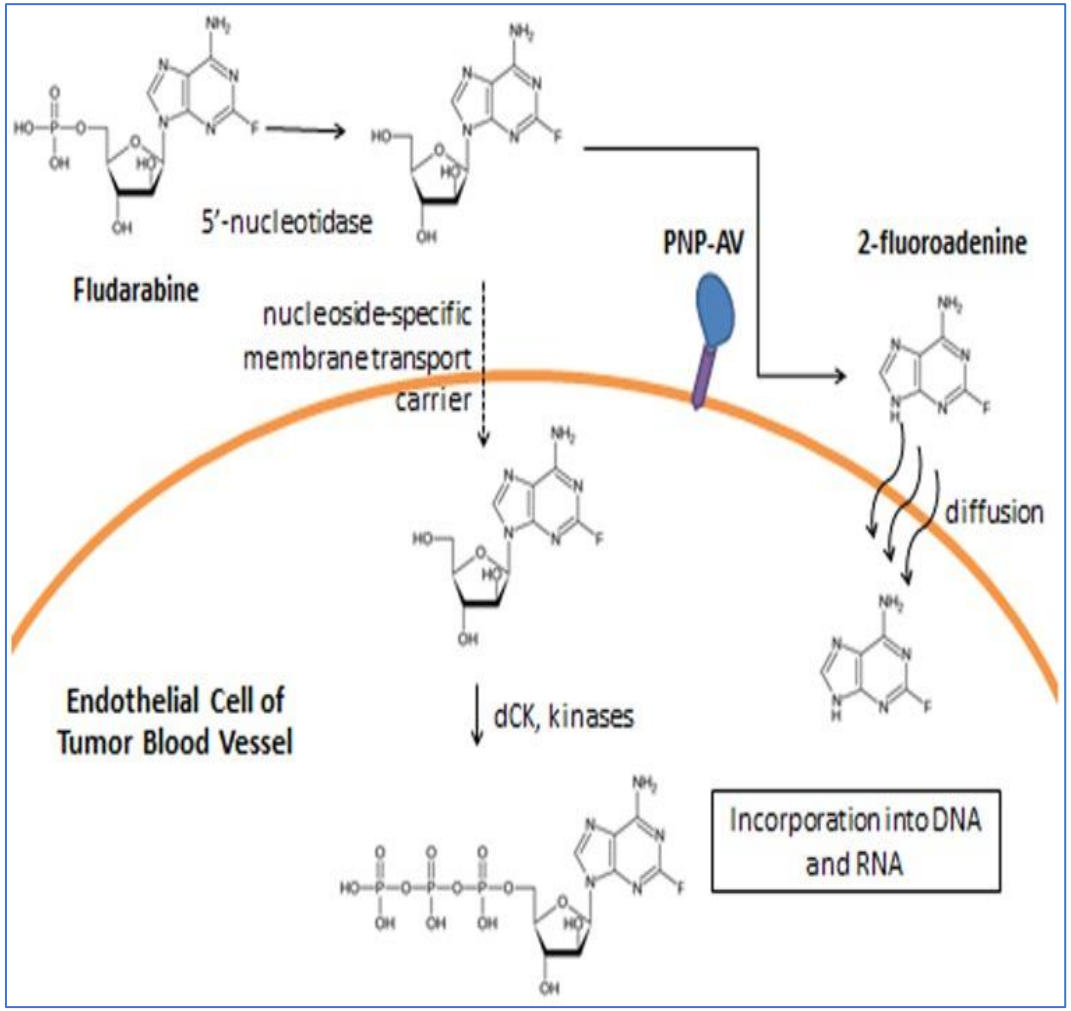
1. Guanine analogs:

- 6-MP a **purine antimetabolite**, is the thiol analog of hypoxanthine.
- **6-MP** and **6-thioguanine** were the **first purine analogs** to prove beneficial for treating **neoplastic disease**.
- **Note: Azathioprine**, an immunosuppressant, exerts its cytotoxic effects after **conversion to 6-MP**.
- **6-MP** is used principally in the **maintenance of remission in acute lymphoblastic leukemia**.
- **6-MP** and its analog, **azathioprine**, are also beneficial in the treatment of **Crohn's disease.**
- **Toxicity** may include N/V/D, myelosuppression, anorexia, and **hepatotoxicity** (Jaundice)

B. Purine analogs

2. Adenosine analogs:

- **Fludarabine and Cladribine** are **adenosine analogs** used in **leukemias and lymphomas**.
- **Fludarabine** is the **5-phosphate** of **2 fluoro-adenine arabinoside**, a purine nucleotide analog.
- It is **useful** in the treatment of **chronic lymphocytic leukemia, hairy cell leukemia, and indolent non-Hodgkin lymphoma**.
- Fludarabine is a **prodrug**, and the **phosphate** is **removed** in the plasma to **form 2 F ara A**, which is **taken up** into cells and **again phosphorylated** (initially by deoxycytidine kinase).



B. Purine analogs

2. Adenosine analogs:

- Although the exact cytotoxic mechanism is uncertain, the **triphosphate** is **incorporated** into both **DNA and RNA**.
- This **decreases** their **synthesis in the S phase** and **affects their function**.
- **Resistance** is associated with **reduced uptake** into cells, **lack of deoxycytidine kinase**, and **decreased affinity** for DNA polymerase, as well as **other** mechanisms.
- Fludarabine is administered **IV rather than orally** because **intestinal bacteria split off** the sugar to yield **the very toxic** metabolite, **fluoroadenine**.

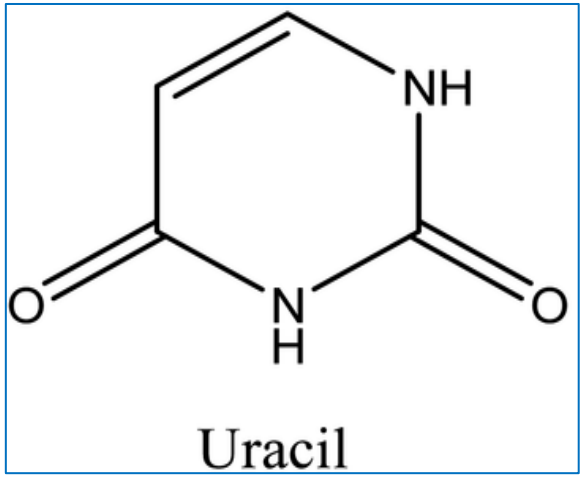
C. Pyrimidine analogs

- This category of chemotherapeutic agents is designed as a **false metabolite** to **inhibit pyrimidine nucleotide synthesis**.
- Thus **inhibit DNA synthesis**, and to a lesser extent **inhibit RNA synthesis**.
- Pyrimidine analogs could be **divided into two groups** according to the **nucleotide target** into **thymidine and cytosine inhibitors**.

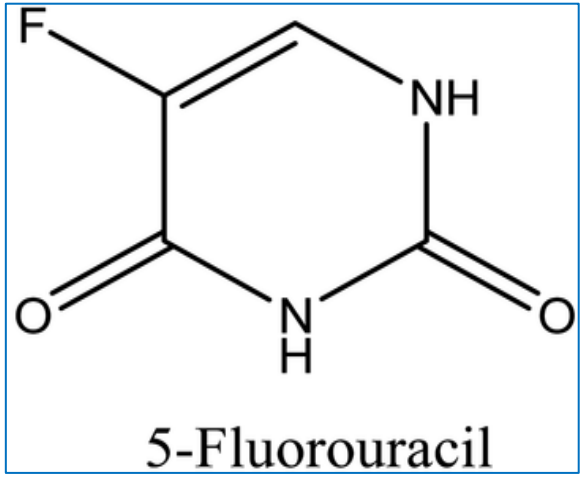
1. **Thymidine inhibitors** include 5 fluorouracil (5 FU) and capecitabine.
2. **cytosine inhibitors** include cytarabine, azacytidine, and gemcitabine.

1. 5-Fluorouracil

- 5-FU, a **pyrimidine analog**, has a stable **fluorine atom** in place of a **hydrogen** atom at position **5** of the uracil ring.
- The fluorine **interferes** with the **conversion of deoxyuridylic acid to thymidylic acid**, thus **depriving** the cell of **thymidine**, one of the essential precursors for **DNA synthesis**.
- 5-FUis employed primarily in the **treatment** of **slow-growing solid tumors** (for example, **colorectal, breast, ovarian, pancreatic, and gastric carcinomas**).
- When applied **topically**, 5-FU is also effective for the treatment of **superficial basal cell carcinomas**.



Uracil

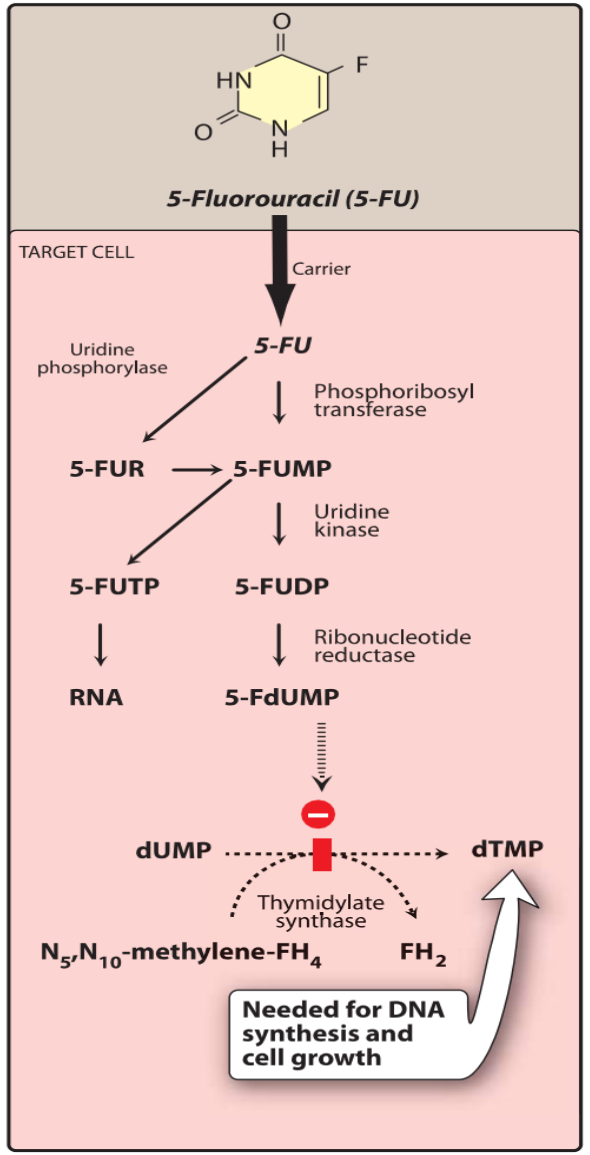


5-Fluorouracil

1. 5-Fluorouracil

1. Mechanism of action:

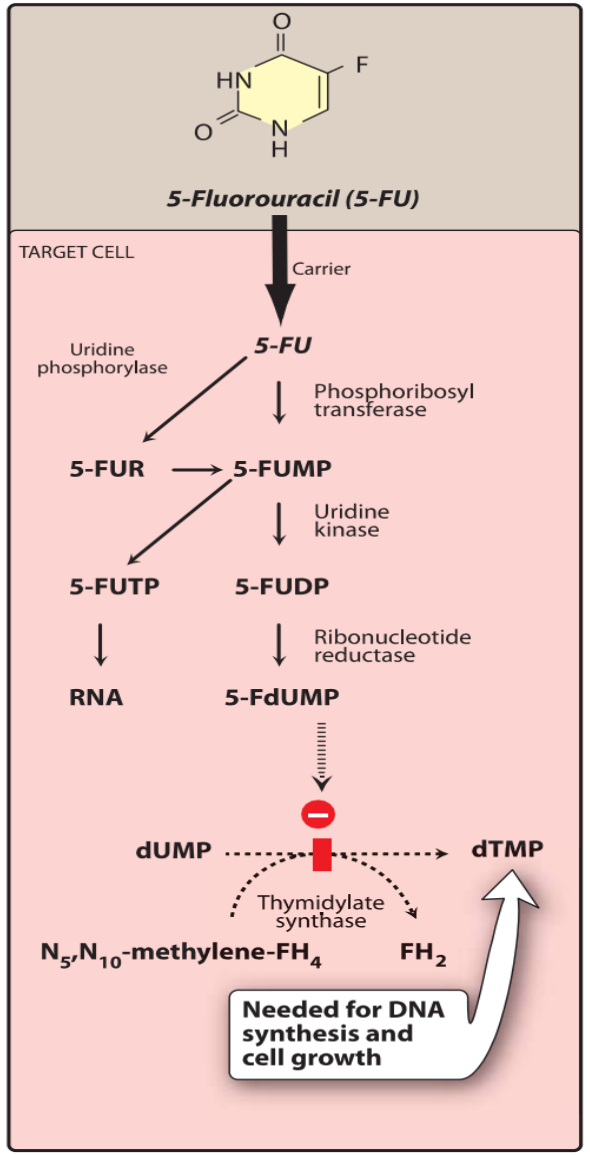
- 5-FU itself is **devoid** of **antineoplastic** activity.
- It **enters** the cell through a **carrier-mediated** transport system and is **converted** to **5-FdUMP**, which competes with **dUMP** for **thymidylate synthase**, thus inhibiting its action.
- **DNA** synthesis **decreases** due to **lack of thymidine**, leading to imbalanced cell growth and "**thymidine-less death**" of rapidly dividing cells.



1. 5-Fluorouracil

1. Mechanism of action:

- **Note: Leucovorin** is administered **with 5-FU** because the **reduced folate coenzyme** is required in the **thymidylate synthase inhibition**.
- For example a standard regimen for **advanced colorectal cancer** is **irinotecan plus 5-FU/leucovorin**.
- **5-FU** is also incorporated into **RNA**, and **low levels** have been detected in **DNA**.
- In the latter case, a **glycosylase** excises the 5-FU, damaging the DNA.
- 5-FU produces anticancer effect in the **S phase** of the cell cycle.



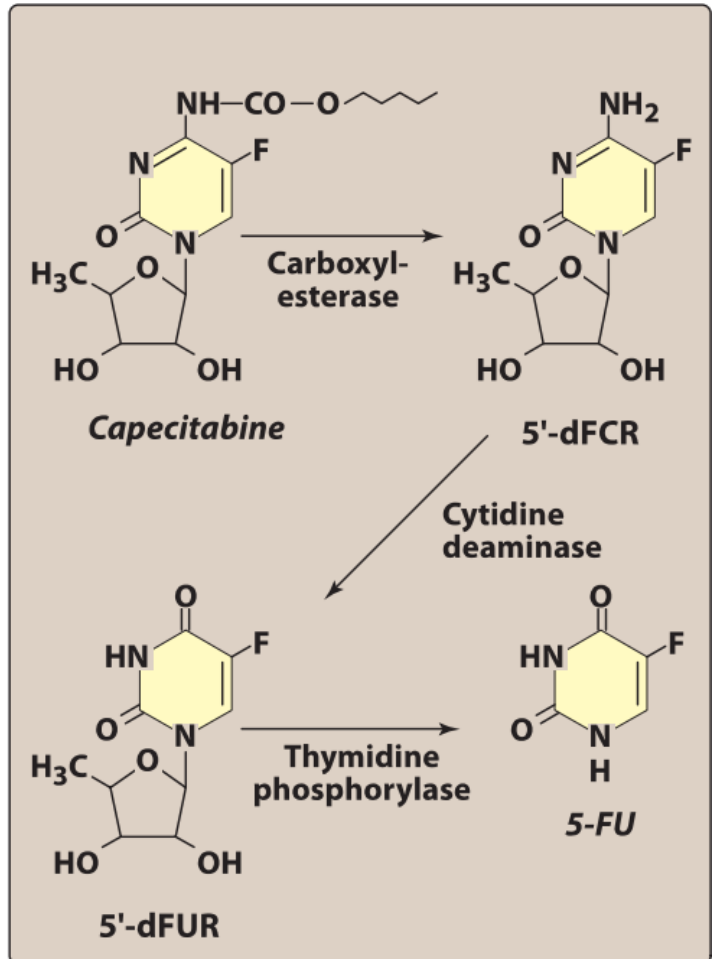
1. 5-Fluorouracil

2. Pharmacokinetics:

- Because of severe **toxicity to the GIT**, 5-FU is administered **IV** or, in the case of skin cancer, **topically**.
- The drug penetrates well into **all tissues**, including the **CNS**.
- 5-FU is **rapidly metabolized** in the liver, lung, and kidney and eventually converted to **fluoro-β-alanine**, which is removed in the **urine**.
- Elevated levels of **dihydro-pyrimidine dehydrogenase** (DPD) can **increase** the rate of 5-FU **catabolism** and **decrease** its **bioavailability**.
- The level of **DPD varies** from individual to individual and may **differ** by as much as **six-fold** in the general population.
- Patients with **DPD deficiency** may experience **severe toxicity** manifested by **pancytopenia, mucositis, and life-threatening diarrhea**.
- **Knowledge** of **DPD** activity in an individual should allow **more appropriate dosing** of 5-FU.

2. Capecitabine

- Capecitabine is a **fluoropyrimidine carbamate**.
- It is used in the treatment of **colorectal and metastatic breast cancer**.
- Capecitabine is **well absorbed** following **oral** administration.
- **After** being absorbed, capecitabine, which is **itself nontoxic**, undergoes a series of enzymatic reactions, the **last** of which is **hydrolysis to 5-FU**.
- This step is **catalyzed by thymidine phosphorylase**, an enzyme that is **concentrated** primarily in **tumors**.
- Thus, the **cytotoxic** activity of **capecitabine** is the **same** as that of **5-FU** and is **tumor specific**.
- The most **important enzyme** inhibited by 5-FU (and, thus, capecitabine) is **thymidylate synthase**.



Cytidine analogs

- These pyrimidine inhibitors are **cytidine analogs** with antineoplastic action include:
  - ✓**Cytarabine**
  - ✓**Azacytidine**
  - ✓**Gemcitabine**

1. Cytarabine

- Cytarabine is an **analog** of **2'-deoxycytidine** in which the natural ribose residue is replaced by o-arabinose.
- Cytarabine acts as a **pyrimidine antagonist**.
- The major clinical use of cytarabine is in **acute nonlymphocytic (myelogenous) leukemia (AML)**.
- Cytarabine **enters** the cell by a **carrier-mediated** process and, like the other purine and pyrimidine antagonists, must be **sequentially phosphorylated by deoxycytidine kinase** and **other** nucleotide kinases to the **nucleotide form** (cytosine arabinoside triphosphate or ara-CTP) to be **cytotoxic**.
- **Ara-CTP** is an **effective inhibitor of DNA polymerase**.
- The nucleotide is also **incorporated into nuclear DNA** and can **terminate chain elongation**.
- It is, therefore, **S phase** (and, hence, cell cycle) **specific**.

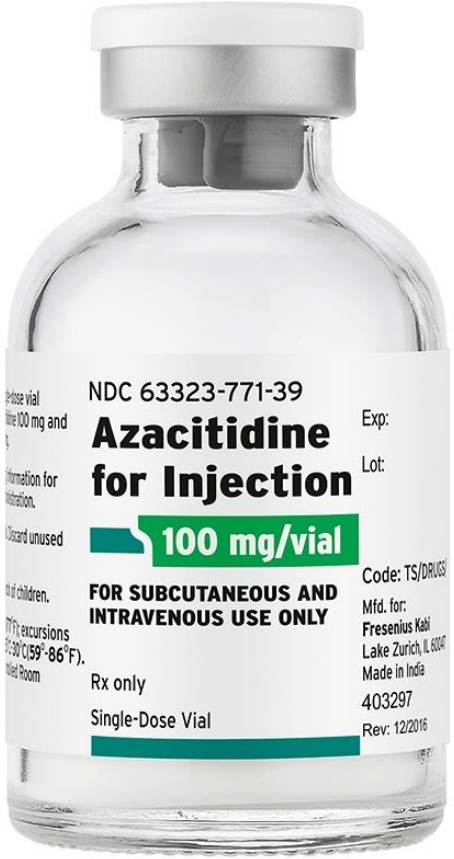
1. Cytarabine

Pharmacokinetics:

- Cytarabine is **not effective when given orally**, because of **deamination to the noncytotoxic** ara-U by **cytidine deaminase** in the **intestinal mucosa and liver**.
- Given **IV**, it distributes throughout the body but does **not penetrate the CNS** in sufficient amounts, **therefore**, it may also be injected **intrathecally**.
- Cytarabine undergoes **extensive oxidative deamination** in the body to ara-U, a pharmacologically **inactive metabolite**.
- **Both** cytarabine and ara-U are excreted in **urine**.

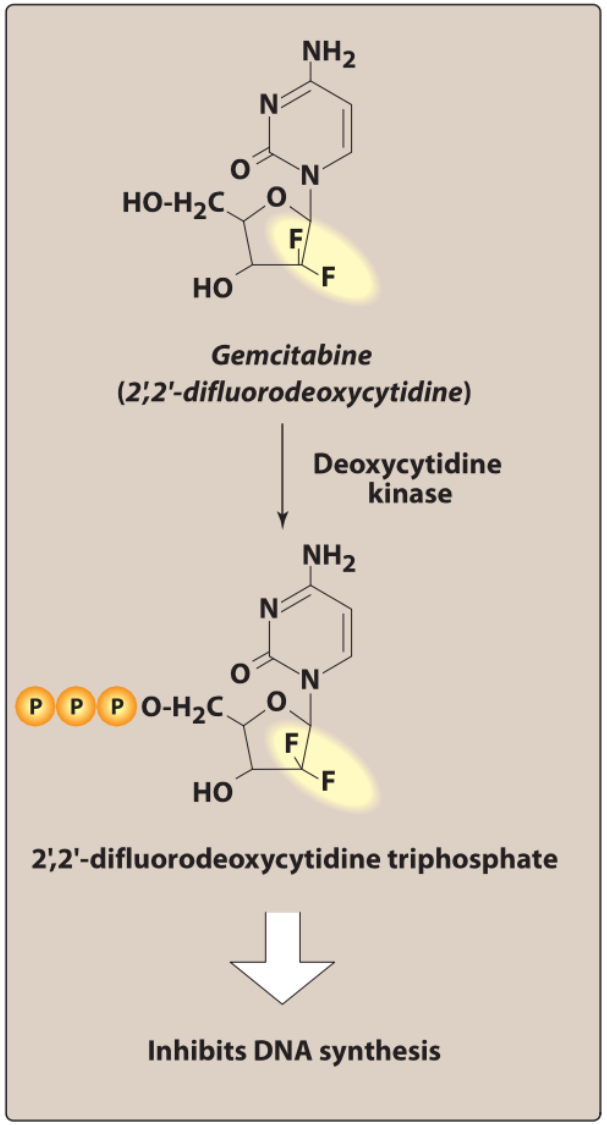
2. Azacitidine

- Azacitidine is a **pyrimidine** nucleoside analog of **cytidine**.
- It is used for the treatment of **myelodysplastic syndromes and AML**.
- **Azacitidine** undergoes **activation to** the nucleotide metabolite **azacitidine triphosphate** and gets **incorporated** into **RNA** to **inhibit** RNA processing and function.
- It is **S-phase** cell-cycle **specific**.



3. Gemcitabine

- Gemcitabine is an **analog** of the nucleoside **deoxycytidine**.
- It is used most commonly for **pancreatic cancer and non-small cell lung cancer**.
- Gemcitabine is a **substrate for deoxycytidine kinase**, which **phosphorylates** the drug to **2',2'-difluoro-deoxycytidine triphosphate**.
- Gemcitabine is administered by **IV** infusion.
- It is **deaminated** to **di-fluoro-deoxyuridine**, which is **not cytotoxic**, and is **excreted** in urine.



THANK YOU FOR YOUR ATTENTION