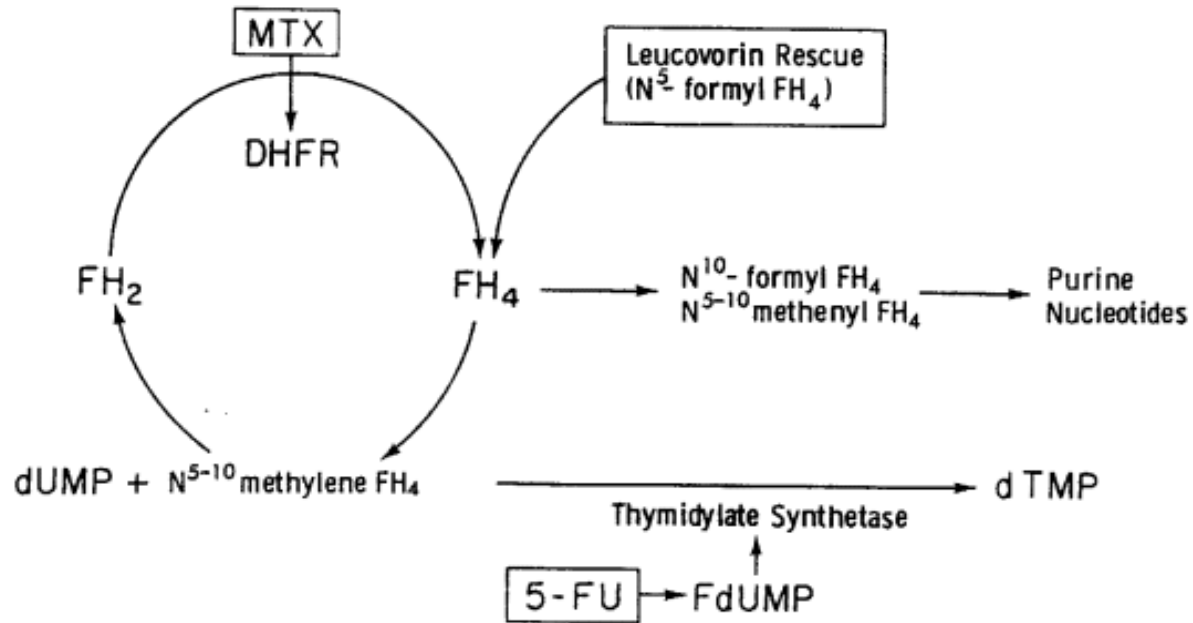


Antimetabolites



Antimetabolites

Flucytosine (Ancobon)



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Introduction

- A metabolite is the intermediate and product of metabolic reactions **inside the cell** (outside the cell is metabolic product)
- The term is usually restricted to small molecules that are vulnerable to chemical change.
- Metabolomics, a study of metabolites is now used to complement genomics and proteomics
- A metabolite retains most or all of its structure except if
 - It blends to form larger molecule e.g. amino acid → protein, glucose → glycogen, fatty acids → TG/membrane lipid and nucleotides → nucleic acids
 - Is reduced to smaller metabolites e.g. glucose oxidized → CO_2 , fatty acids → acetylCoA, xanthine → uric acid etc.

Classification of metabolites

1. Primary: synthesized by cells because they are needed for growth examples amino acids (e.g. glutamic acid), alcohols, vitamins (B2 & B12), polyols (e.g. glycerol), organic acids (e.g. acetic acid), nucleotides (IMP, GMP)
2. Secondary: produced but not required for primary metabolic processes e.g. pigments, resins, terpenes etc

Properties of metabolites

- Are found in the cells
- Are recognized and acted upon by enzymes
- Their products must be able to enter into subsequent reactions
- They have finite half-life; they do not accumulate in cells
- Many serve as regulators that control the pace of metabolism
- They must serve some useful biological functions in the cell

Functions of metabolites

- Metabolic fuel: glucose, Fatty acids
- Structure: membrane lipids
- Signalling: DAG, IP3, cAMP
- Stimulatory and inhibitory effect on enzymes: citrate activates acetylCoA carboxylase inhibited by epinephrine, heme inhibits ALAS
- As cofactor: TPP → pyruvate decarboxylase, biotin → acetylCoA carboxylase
- Defence: odorants, pigments
- Communication medium between organism: pheromones (hormone-like chemicals)

Antimetabolites

- An antimetabolite is a substance that interferes with the normal metabolic processes within cells
- By virtue of its similarity in structure (structural analogues) to a metabolite it
 - blocks metabolite action
 - Prevent combination of metabolite with specific enzyme
 - Combine with specific enzyme and transforms it
- Generally they act at the S-phase of cell cycle
- Antimetabolites are used in therapies such as
 - Neoplastic- cancer chemotherapy
 - Non-neoplastic- antimicrobial and antimalarial (sulfanamides), treatment of gout (Allopurinol), psoriasis, RA, Crohn's disease, immunosuppression, dermatomyositis,

Antimetabolites

- Antimetabolites general mechanism is they act by mimicking essential cellular molecules (e.g., purines, pyrimidines, folates)
 - thereby inhibiting key enzymes or being incorporated into DNA/RNA, leading to cytotoxic effects
- Since they act on cells with increased DNA synthesis; their toxicities are seen in rapidly growing cells of the body such as
 - mucous membranes of the mouth, git, white cells, red cells, part of skin causing hair loss.

Classification of antimetabolites

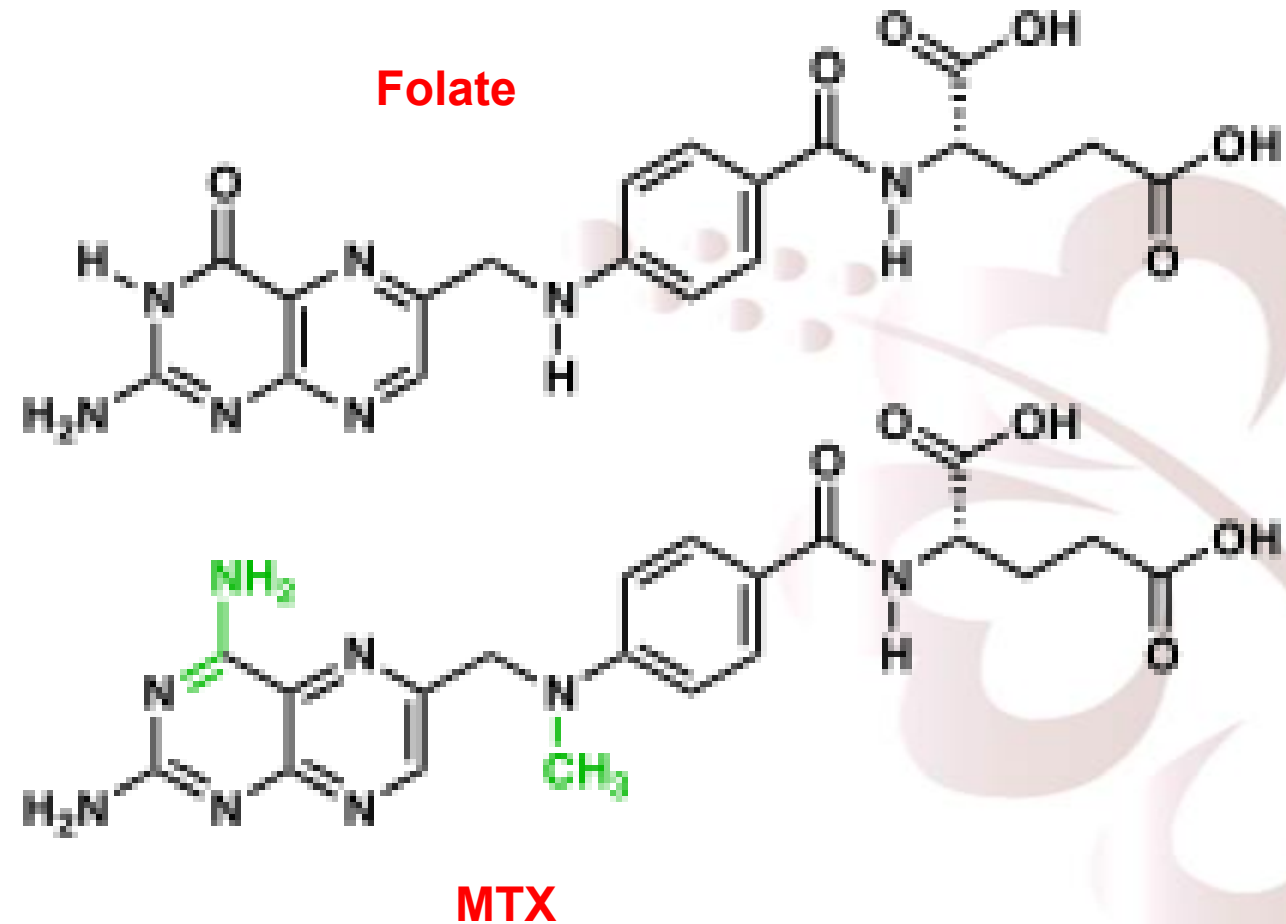
1. Folic acid/folate antagonists e.g. aminopterin, methotrexate, pemetrexed, raltitrexed, lometrexol, trimetrexate, pralatrexate, pyrimethamine, trimethoprim/sulfamethoxazole
2. Purine Analogs e.g. 6-mercaptopurine, azathioprine, 6-thioguanine, pentostatin, fludarabine phosphate, cladribine, clofarabine, nelarabine
3. Pyrimidine Analogs e.g. 5-fluorouracil, floxuridine, idoxuridine, capecitabine, cytarabine, 5-azacytidine, gemcitabine, decitabine

Folic acid antagonists

- They are called antifolate
- They are structural analogues of folic acid
- They competitively inhibit dihydrofolate reductase enzyme
 - Preventing formation of THF
 - Hence affect biosynthesis of purines, pyrimidines → affect Nucleic acids formation → failure in cell proliferation
- Common antifolate drugs include aminopterin, methotrexate, pyrimethamine, trimethoprim/sulfamethoxazole
- Used in the treatment of Leukemias, breast cancer, autoimmune diseases (in low doses).

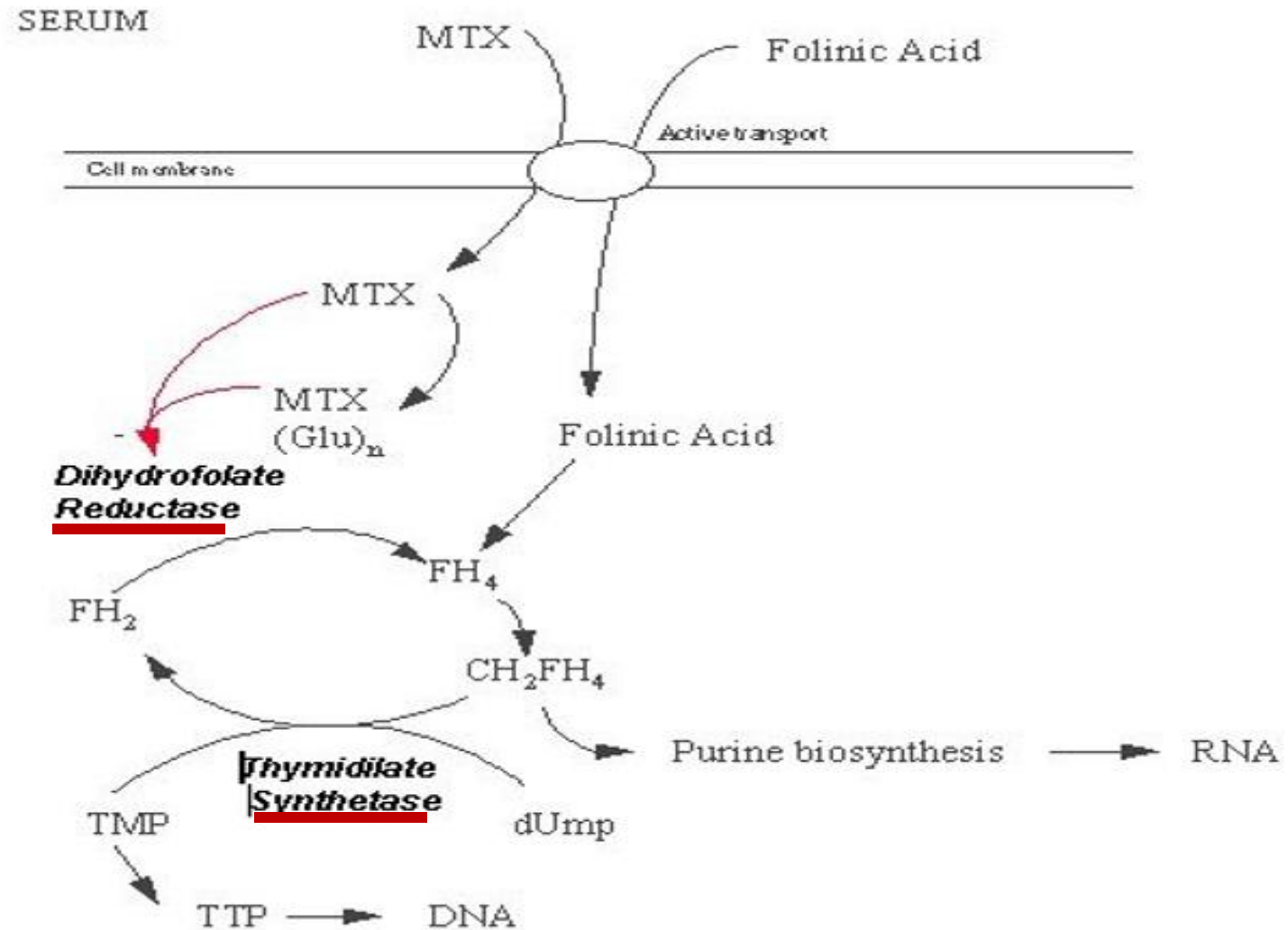
Methotrexate (MTX)

- Is on WHO essential drug list
- It is 4-amino-N¹⁰-methyl folic acid
- MTX has long been used in the treatment of cancer



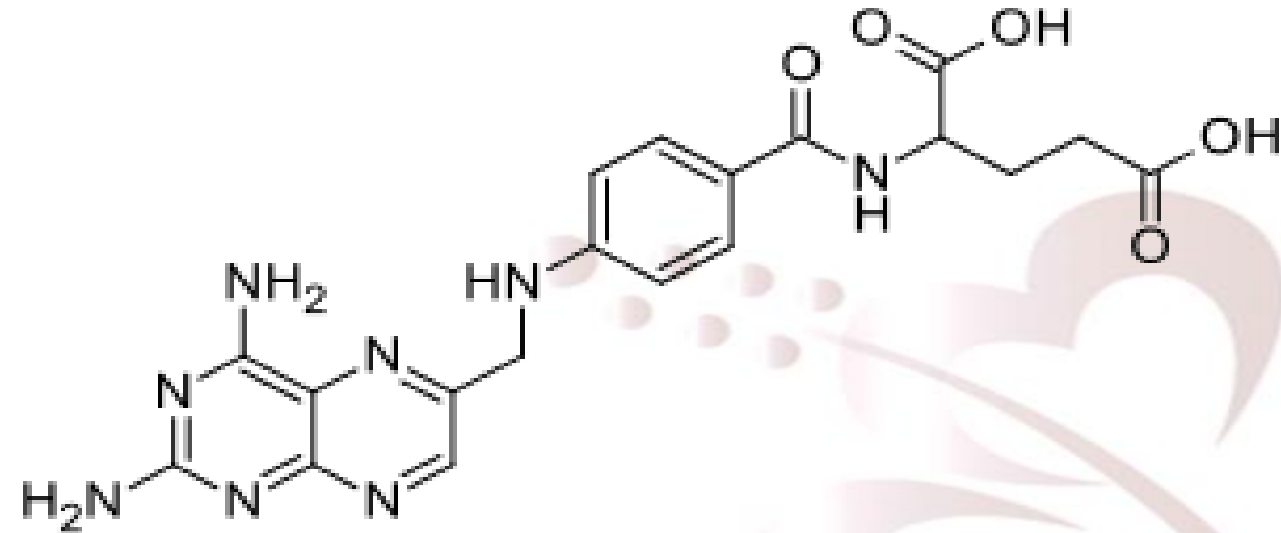
Mechanism of action of MTX

- MTX inhibits dihydrofolate reductase
- It also inhibits thymidylate synthetase
- Note: In addition it blocks formation of T cells
- Used in the treatment of Choriocarcinoma, ALL in children, Burkitt's lymphoma, Ca breast, AML



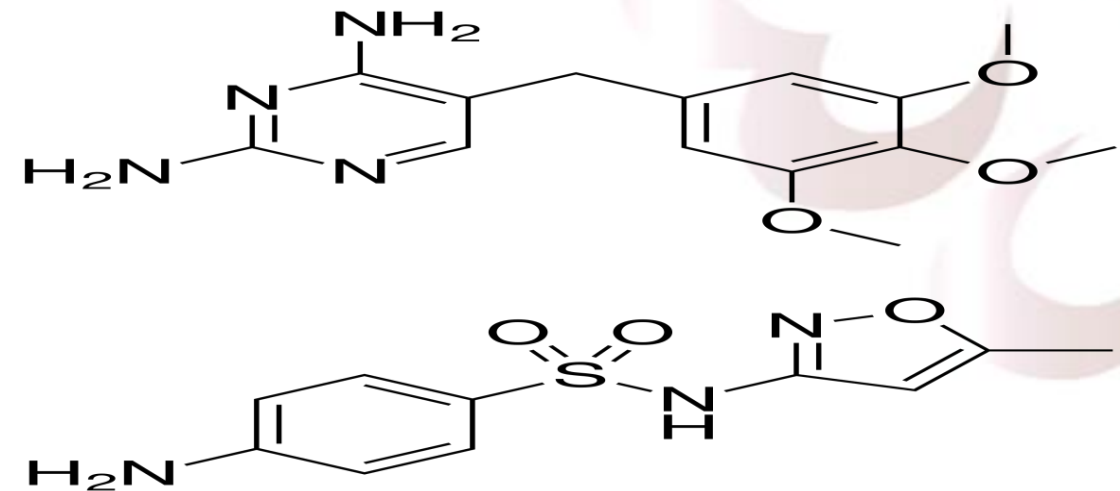
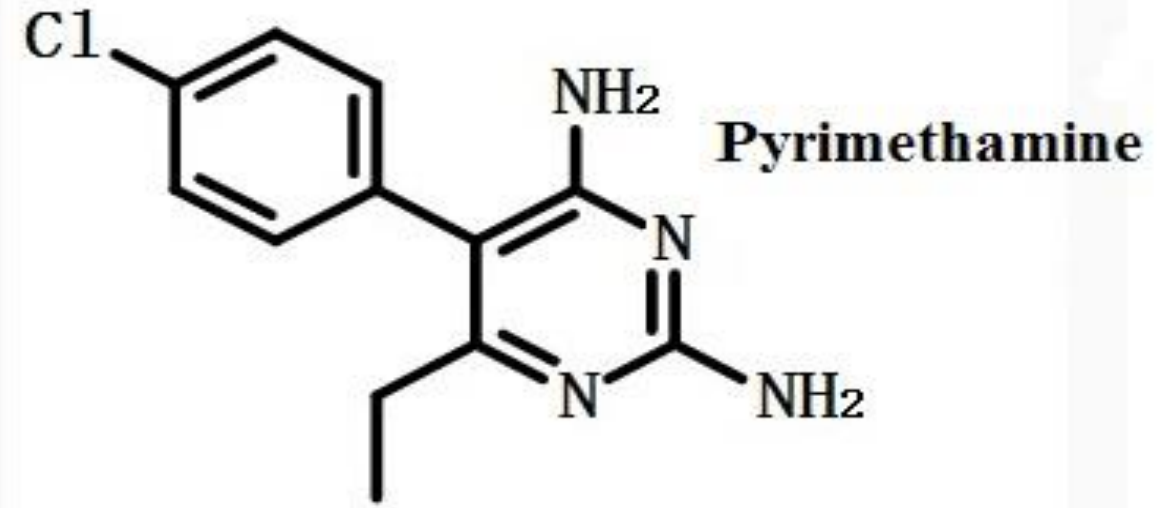
Aminopterin

- Is a 4-amino folic acid
- Like methotrexate, it is also a dihydrofolate reductase inhibitor



Pyrimethamine & trimethoprim/sulfamethoxazole

- Pyrimethamine is an antimalaria
 - has antifolate activity
 - It is also a dihydrofolate inhibitor in plasmodium parasite
- Trimethoprim/sulfamethoxazole is an antibacterial.
 - inhibits dihydrofolate reductase in bacteria



Mechanism of resistance to antifolates

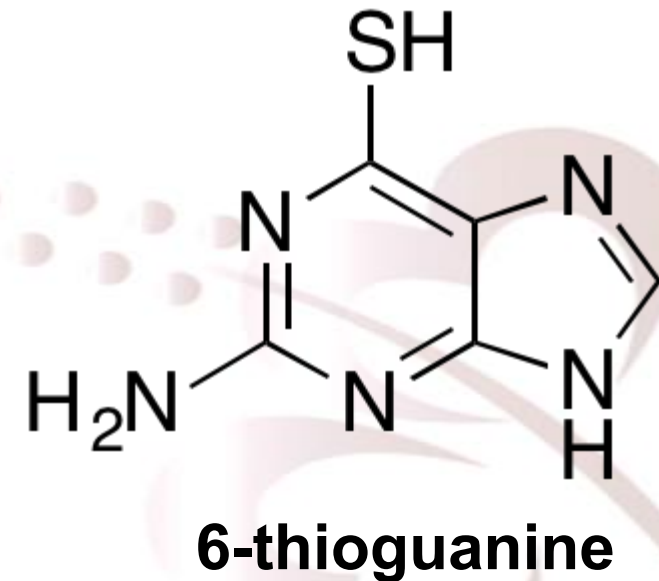
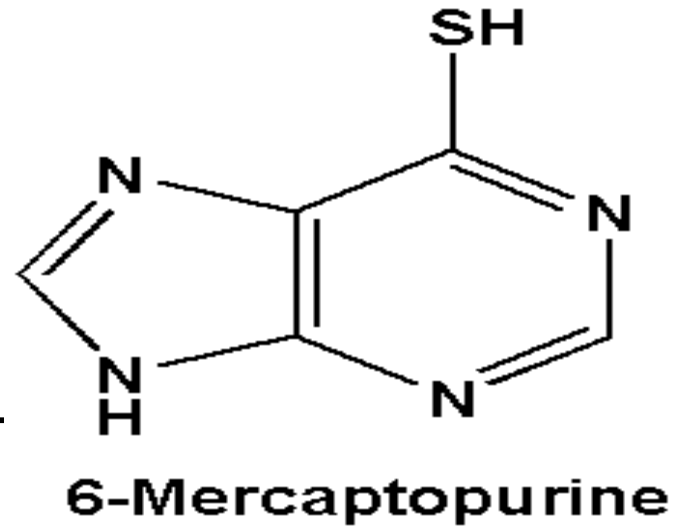
- Impaired transport to cells
- Increased expression of multidrug resistant proteins e.g. ATP binding cassette subfamily C member 2 (ABCC2), canalicular multispecific organ anion transporter 1 (cMOAT1), P-glycoprotein 1
- Decreased ability to synthesise polyglutamate form e.g. MtxPG
- Synthesis of increased levels of DHFR through gene amplification
- Altered DHFR with reduced affinity to drug e.g. Mtx.

Purines antagonists

- Introduced by George Hitchings and Gertrude Elion in 1942
- Drugs in this group include 6-mercaptopurine, azathioprine, 6-thioguanine, pentostatin, fludarabine phosphate, cladribine, clofarabine, nelarabine
 - 6-mercaptopurine and 6-thioguanine are first to be found
- They are used in the treatment of cancer, autoimmune diseases, organ transplant rejection and some viral infections

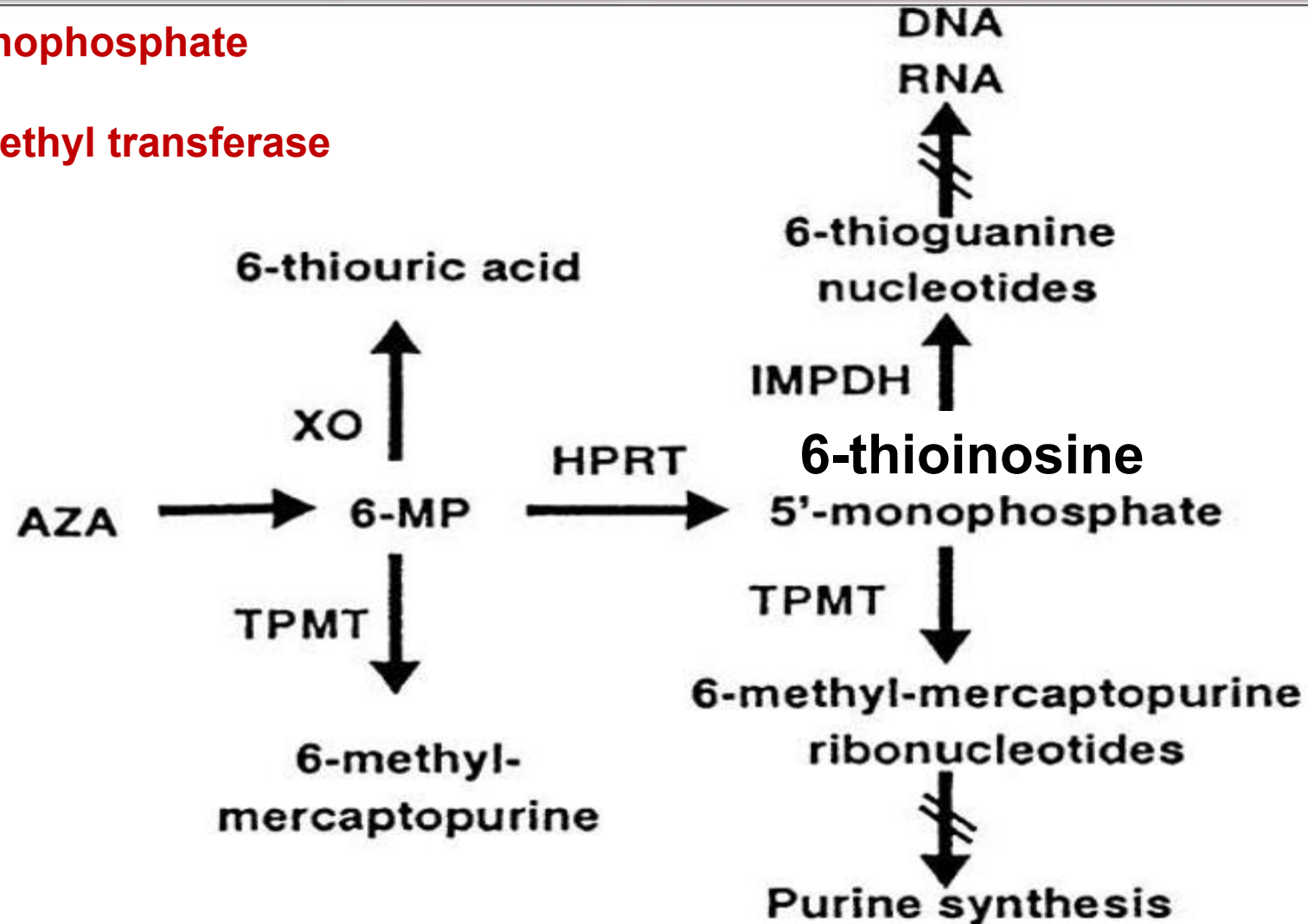
6-mercaptopurine and 6-thioguanine

- 6-mercaptopurine is an analogue of hypoxanthine
- 6-thioguanine is an analogue of guanine
- Azathioprine is converted to 6-mercaptopurine
- These drugs are used in the treatment of ALL, paediatric non-Hodgkin's lymphoma and Crohn's disease



Mechanism of action of 6-mercaptopurine/Azathioprine

IMPDH= inosine monophosphate
dehydrogenase
TPMT= thiopurine methyl transferase

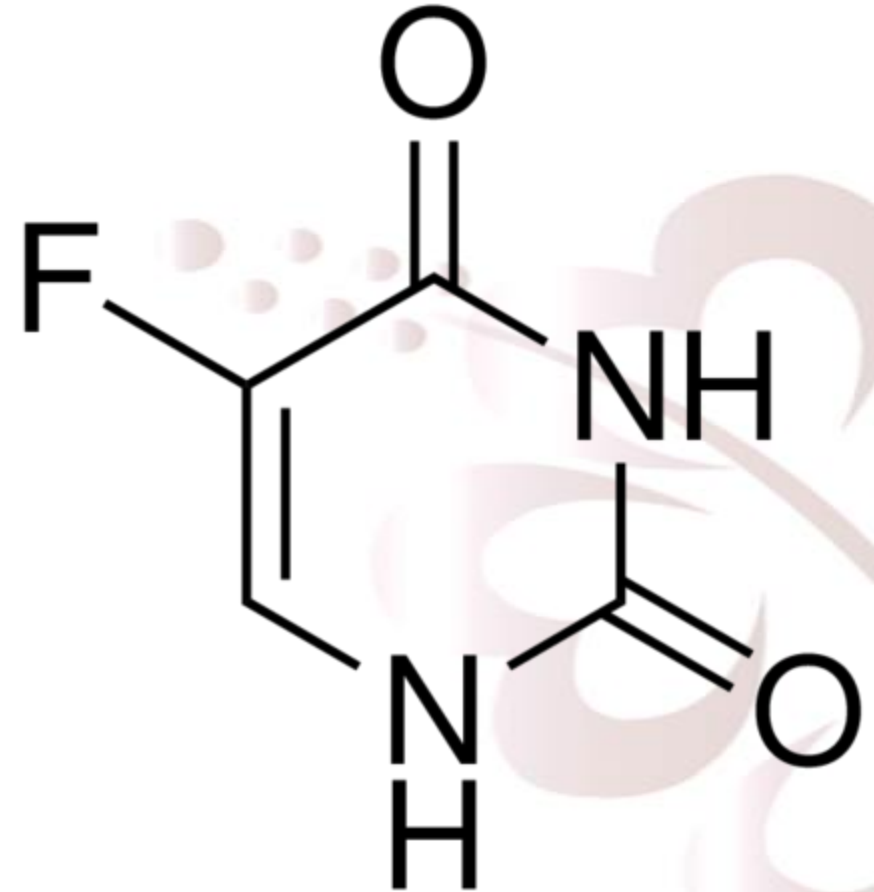


Pyrimidine antagonists

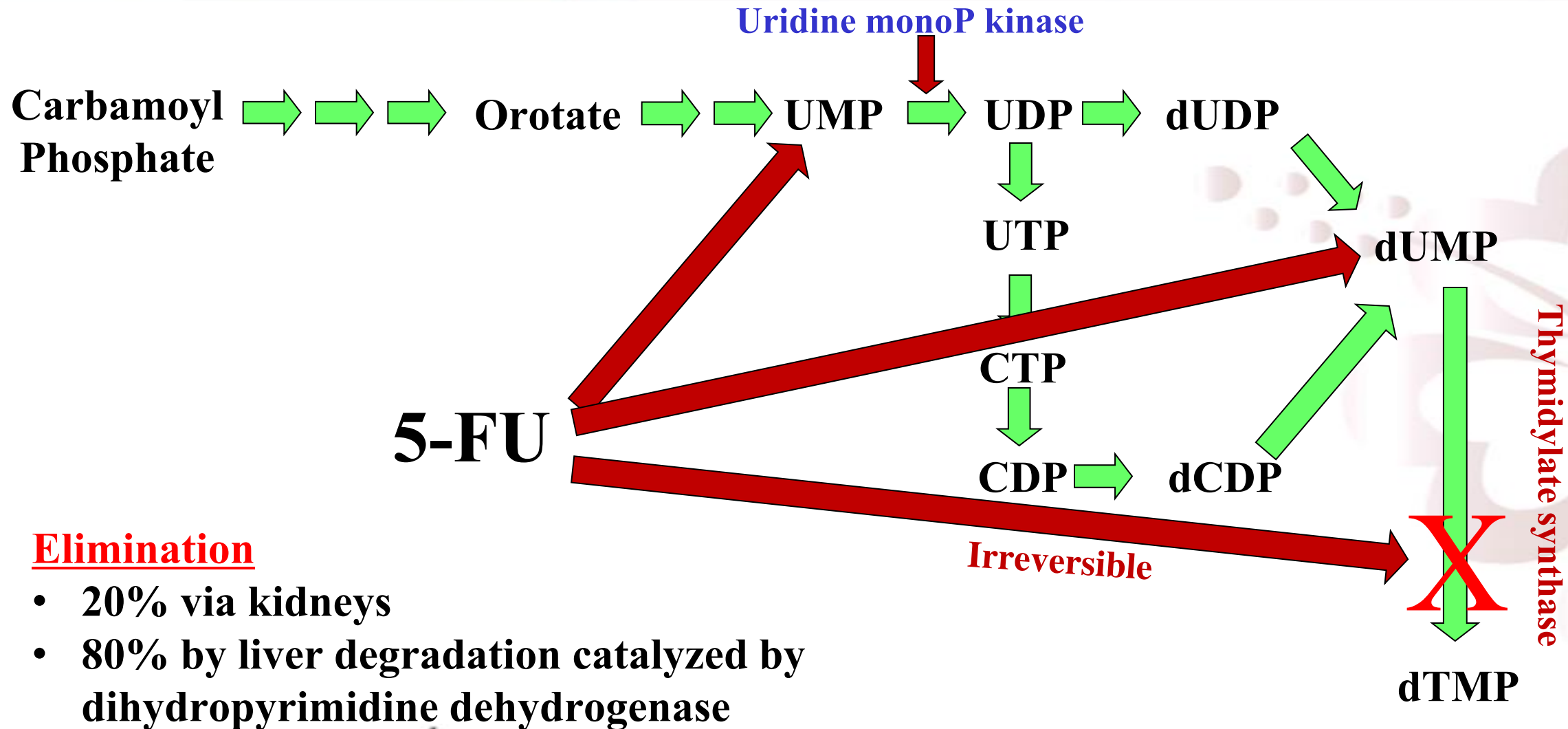
- Halogenated: 5 Fluorouracil, Floxuridine, Idoxuridine, Capecetabine
- Cytidine analogues: Cytarabine, 5 Azacytidine, Gemcitabine, Decitabine

5-fluorouracil

- Is the most important drug in the group
- Resembles uracil and thymine



Mechanism of action of 5-fluorouracil



Elimination

- 20% via kidneys
- 80% by liver degradation catalyzed by dihydropyrimidine dehydrogenase

Uses 5-fluorouracil

- Systemic:
 - Ca breast
 - Ca colon
 - Ca Bladder
 - Ca liver
 - Ca upper GIT
- Topical:
 - basal cell Ca
 - premalignant keratosis

THANK YOU

