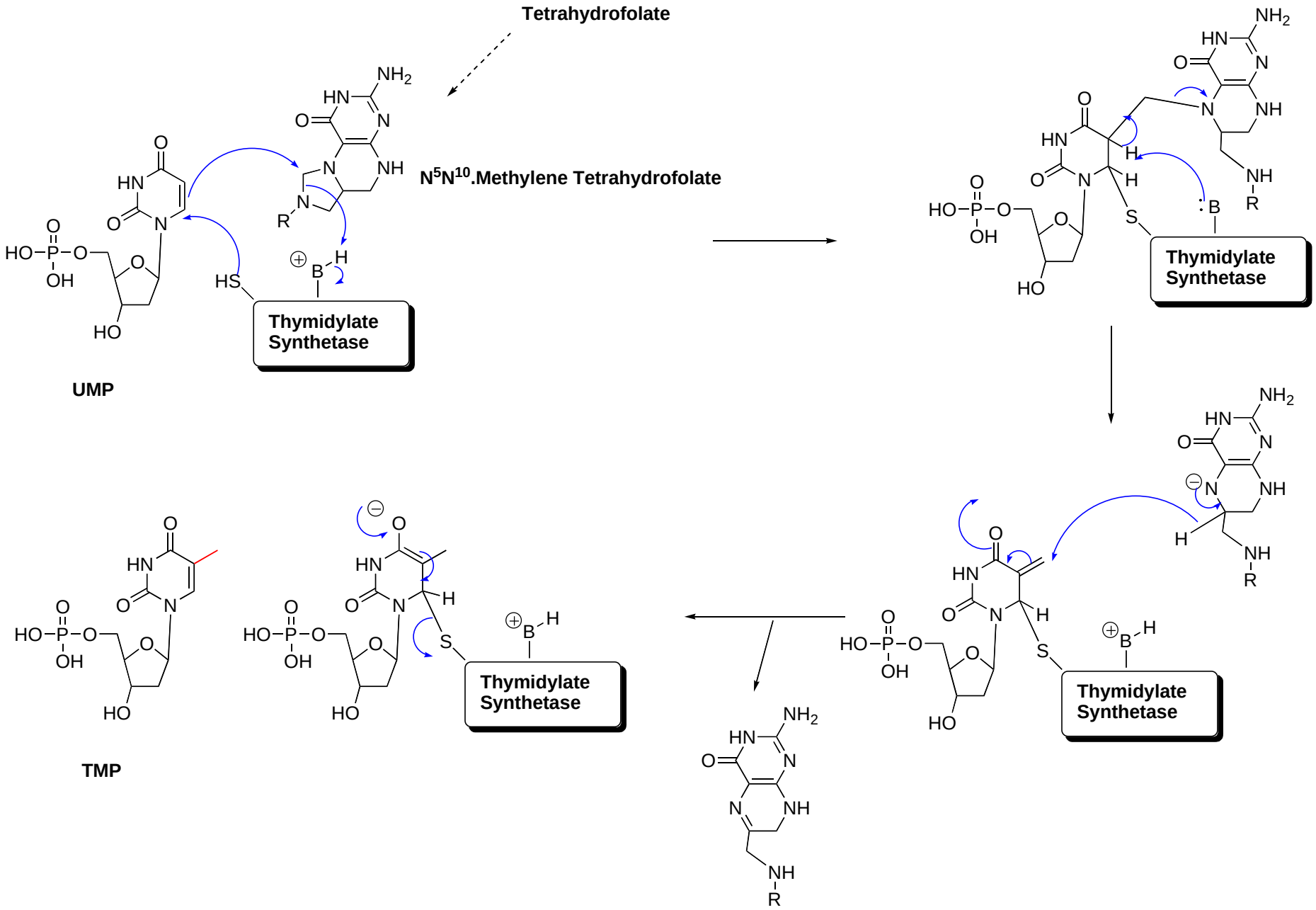
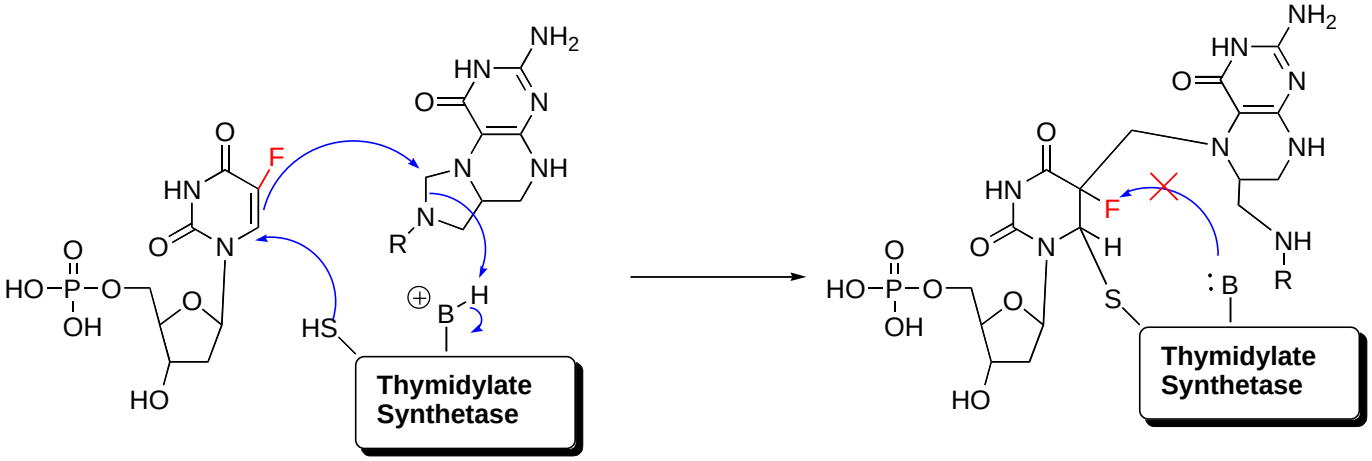
Pyrimidine antagonists

Acts through inhibition the synthesis of pyrimidine nucleotide especially deoxythymine monophosphate(dTMP).

Synth. thymine nucleotide from uracil nucleotide by thymidylate synthetase

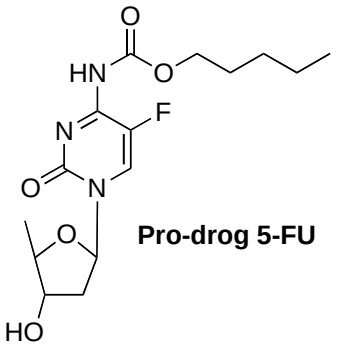




5-FU metabolite

Enzyme inhibition

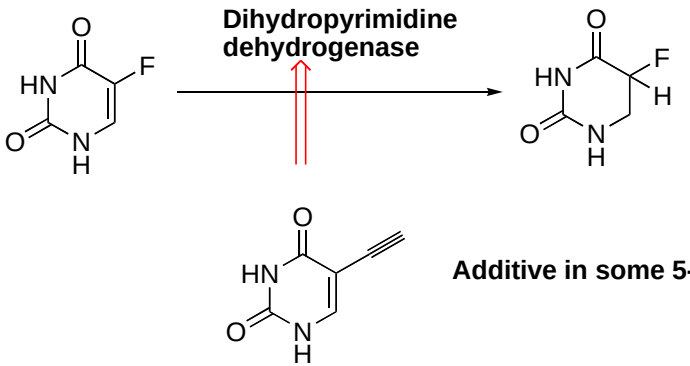
Kapecitabin
Xelodar®,



Pro-drog 5-FU

Additional mechanisms: Incorp. DNA / RNA

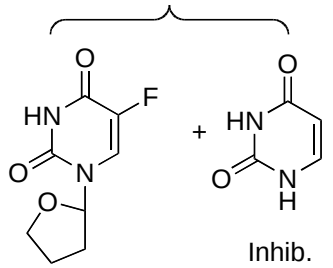
5-FU metabolism



Inactive metabolite

Additive in some 5-FU preparates (Not in N)

Tegafur
UFT®

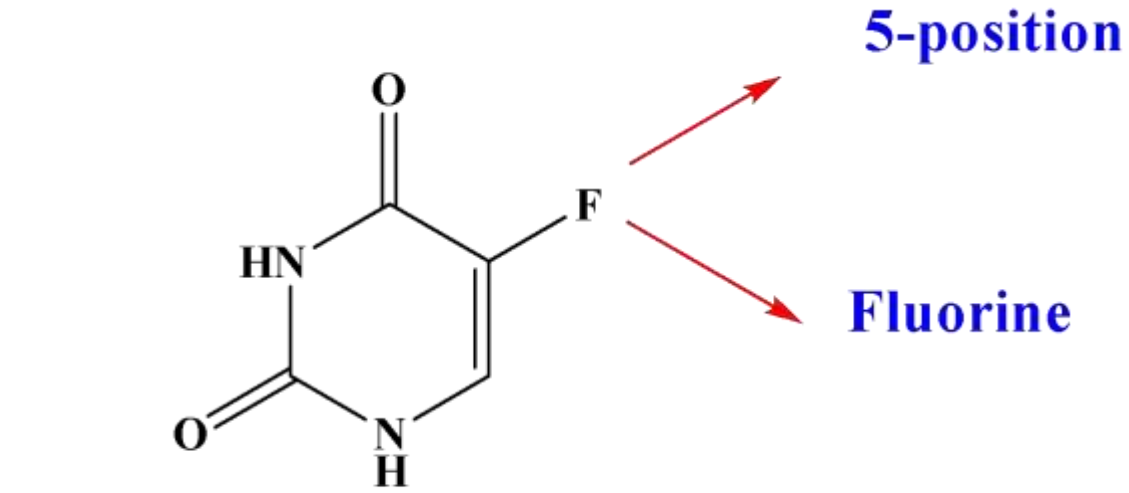


5-FU prodrug

Inhib.
Dihydropyrimidine dehydrogenase

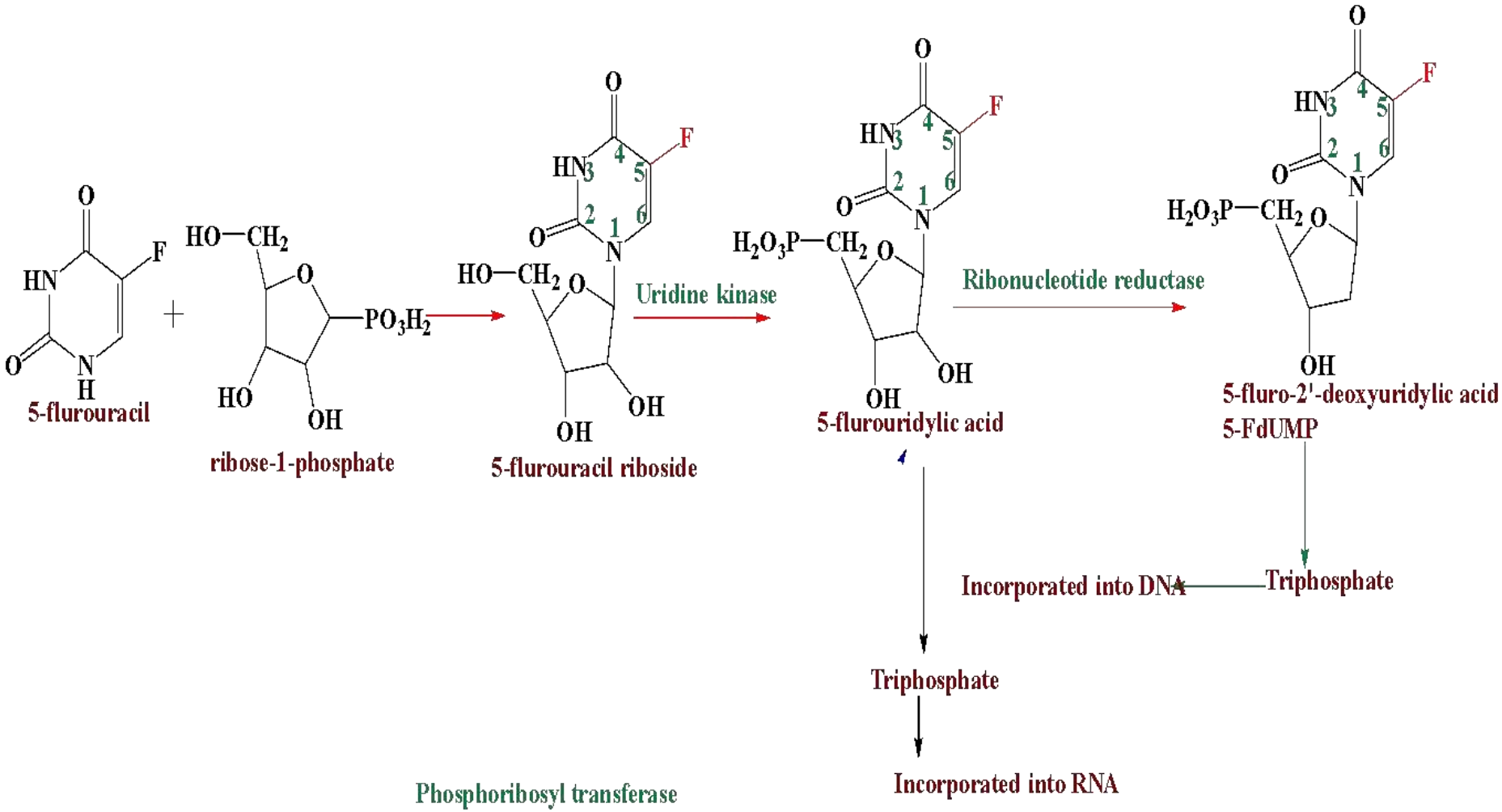
Pyrimidine antagonists products (uracil Derivative)

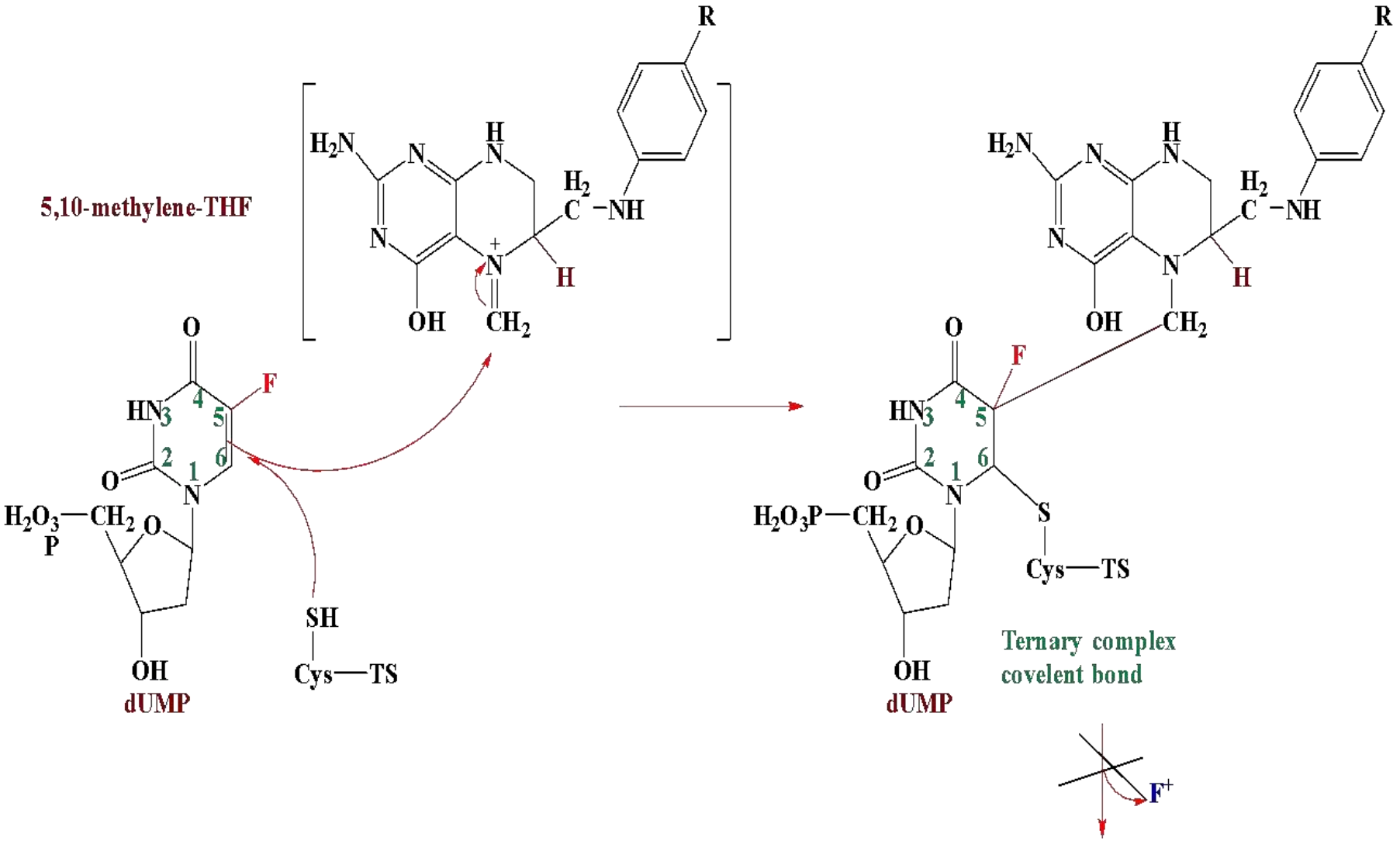
- **Fluorouracil (5-FU)**



5-fluropyrimidine-2,4(1H,3H)dione

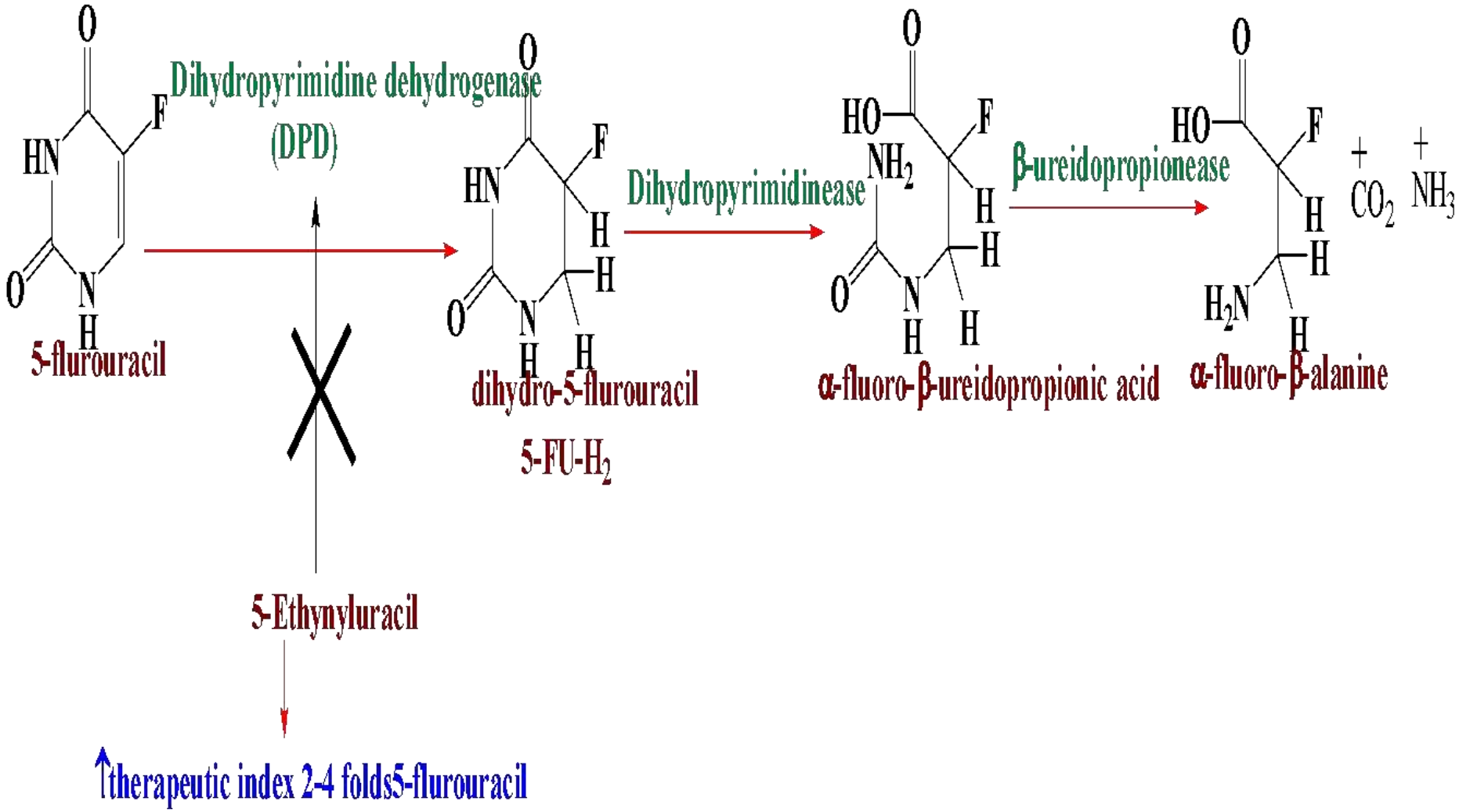
Anabolism of 5-FU



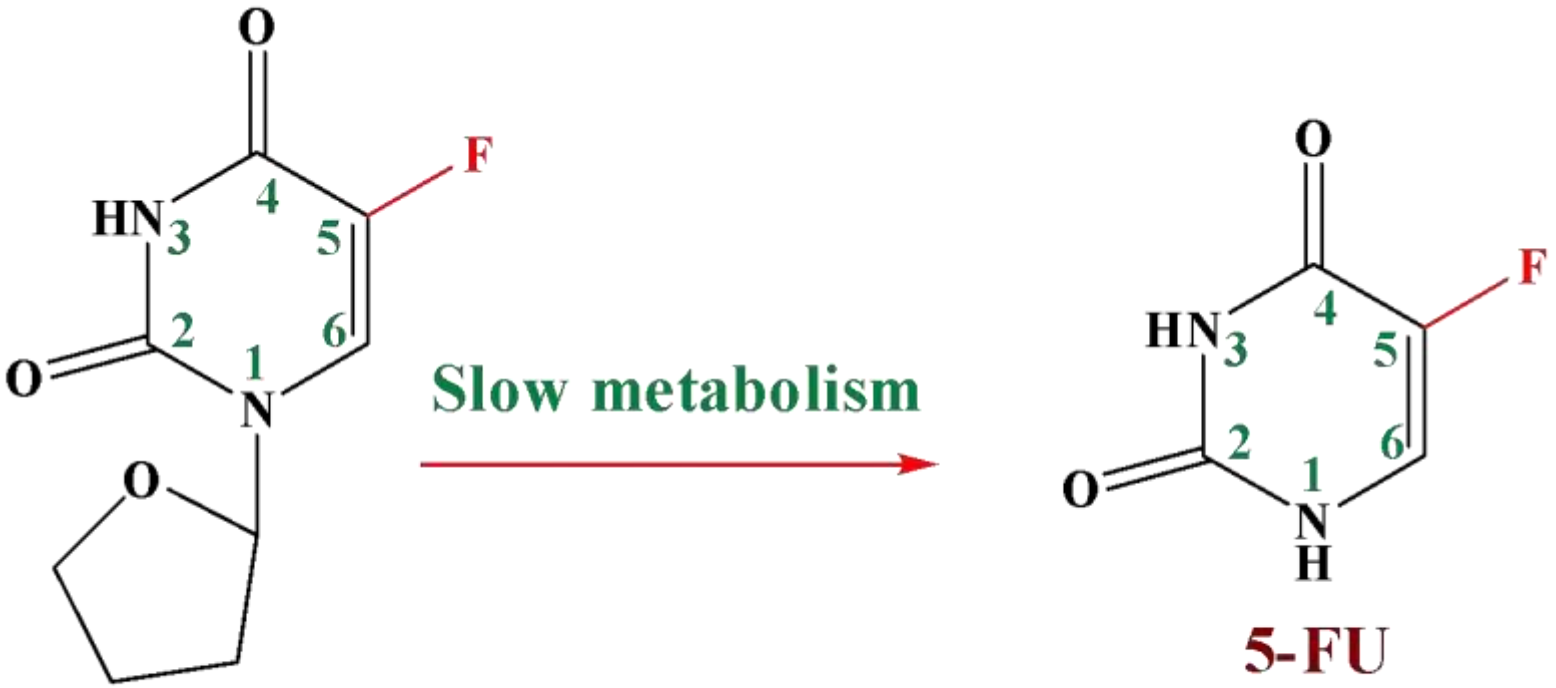

5,10-methylene-THF
dUMP
SH
Cys—TS
dUMP
Ternary complex
covelent bond

No oxidative breakdown of ternary complex, due the inability of the cofactor to abstract F from its position and this resultin-:

No dTMP formation.
No release of DHF (irreversible inhibitor).
No regeneration of thymidylate synthetase.
No DNA formation.


Dihydropyrimidine dehydrogenase
(DPD)
5-flurouracil
dihydro-5-flurouracil
5-FU-H2
Dihydropyrimidinase
α-fluoro-β-ureidopropionic acid
β-ureidopropionease
α-fluoro-β-alanine
+ CO2
+ NH3
5-Ethynyluracil
↑therapeutic index 2-4 folds5-flurouracil

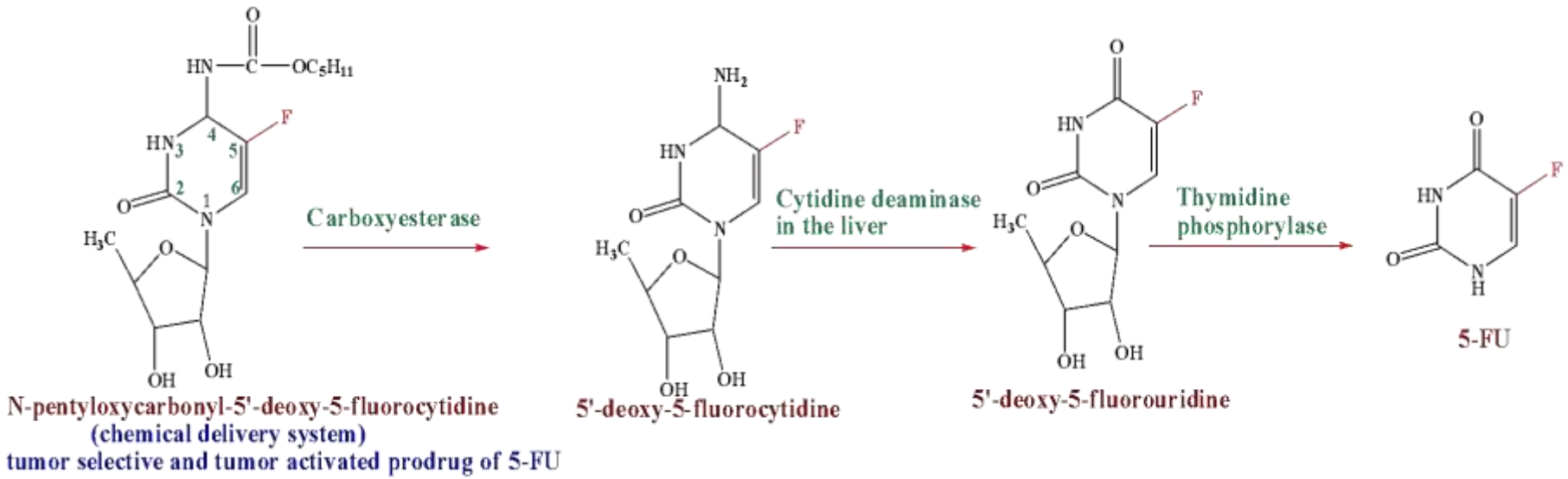
Tegafur



5-FU

Prodrug of 5-FU

Capecitabine



N-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine
(chemical delivery system)
tumor selective and tumor activated prodrug of 5-FU

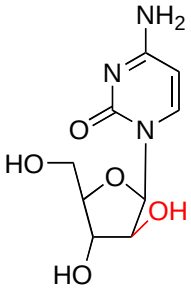
5'-deoxy-5-fluorocytidine

5'-deoxy-5-fluorouridine

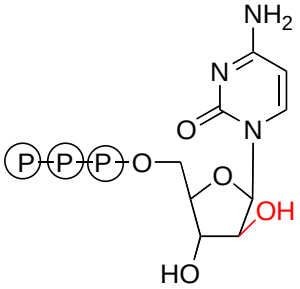
Used for treatment breast and colorectal cancer

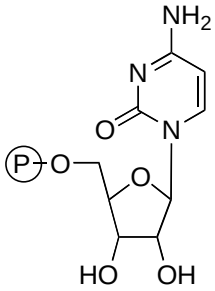
Cytarabine (ARA-C)

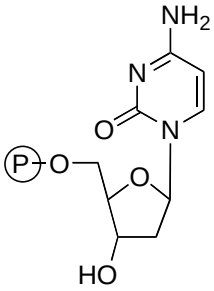
Cytarabin®, Cytosar®,



metabolic activation

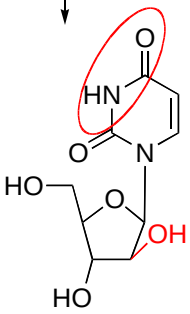






ARA-C

Metabolic inactivation (fast)



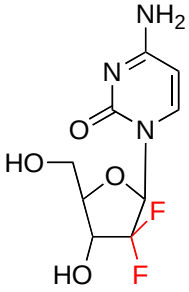
ARA-C

Inhib. DNA polymerase

Incorporation DNA/RNA; misreading

Gemcitasbin

Gemzar®,

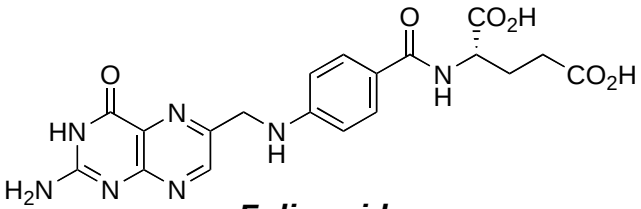


Metabolic activation (triphophate)
Incorp. DNA / RNA

Folic Acid analogs as antimetabolites

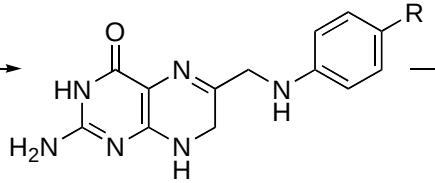
PABA

Microorganisms



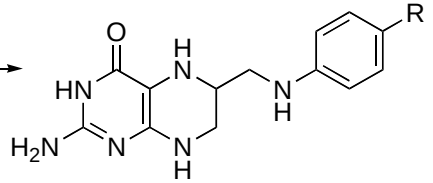
Folic acid

DHFR

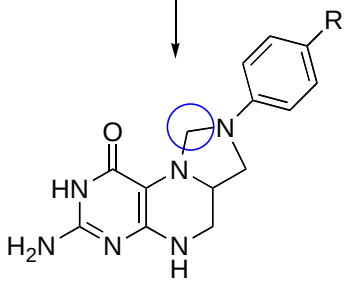


Dihydrofolate

DHFR



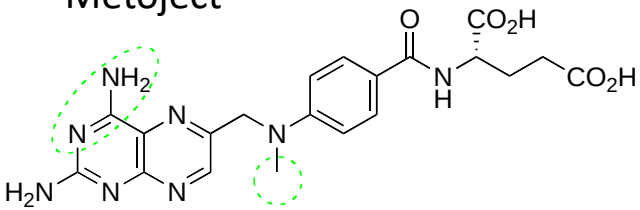
Tetrahydrofolate



Thymine synth

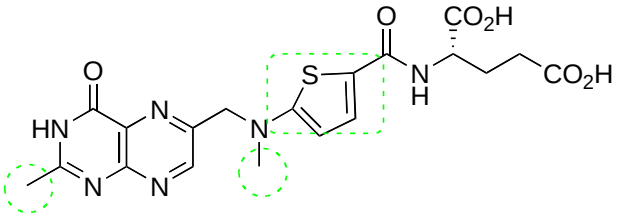
Metotreksat

Metoject®

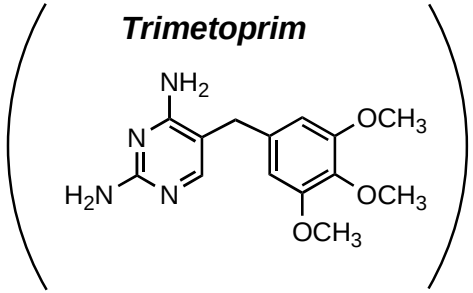


Raltitrexed

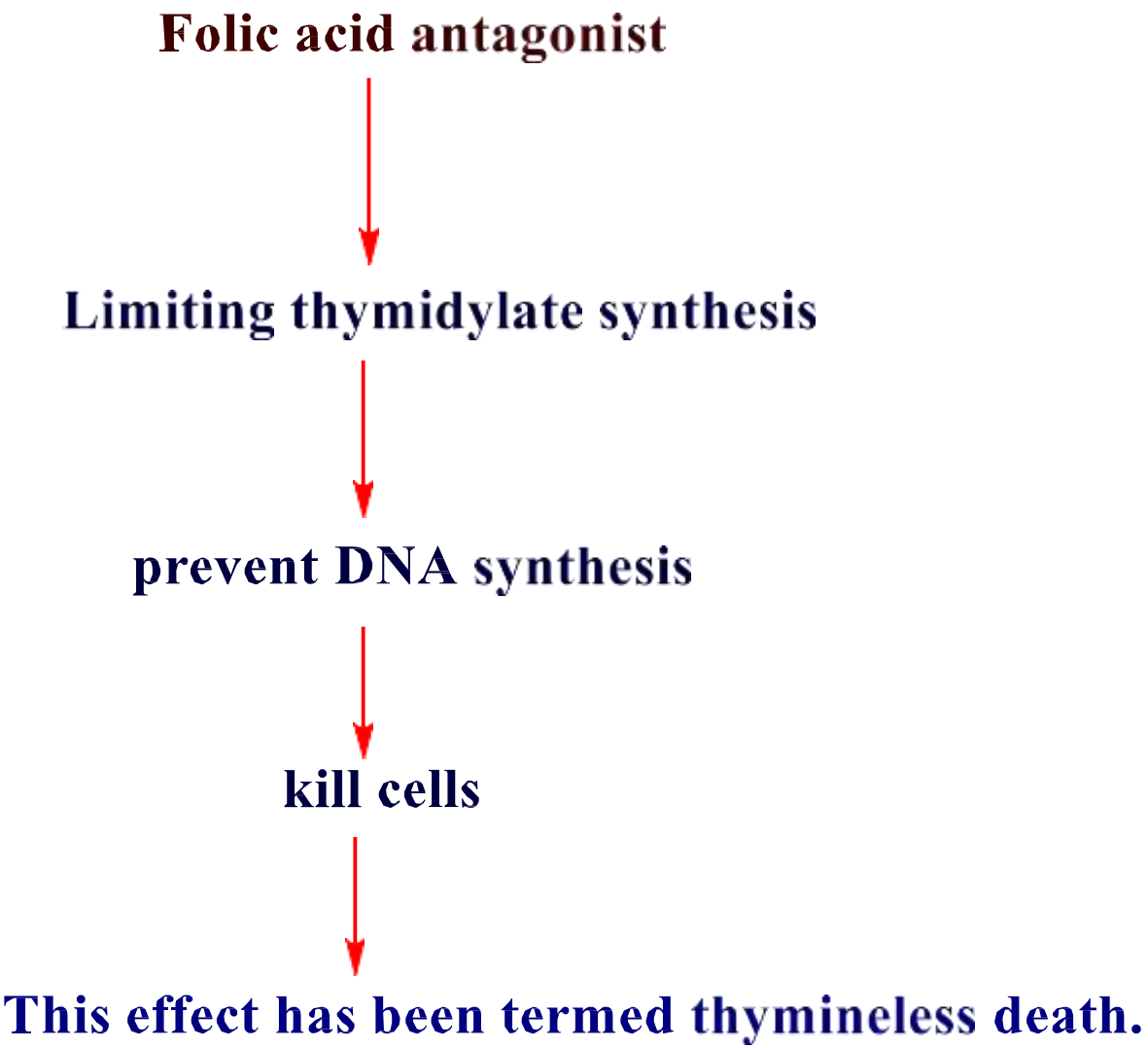
Tomudex®



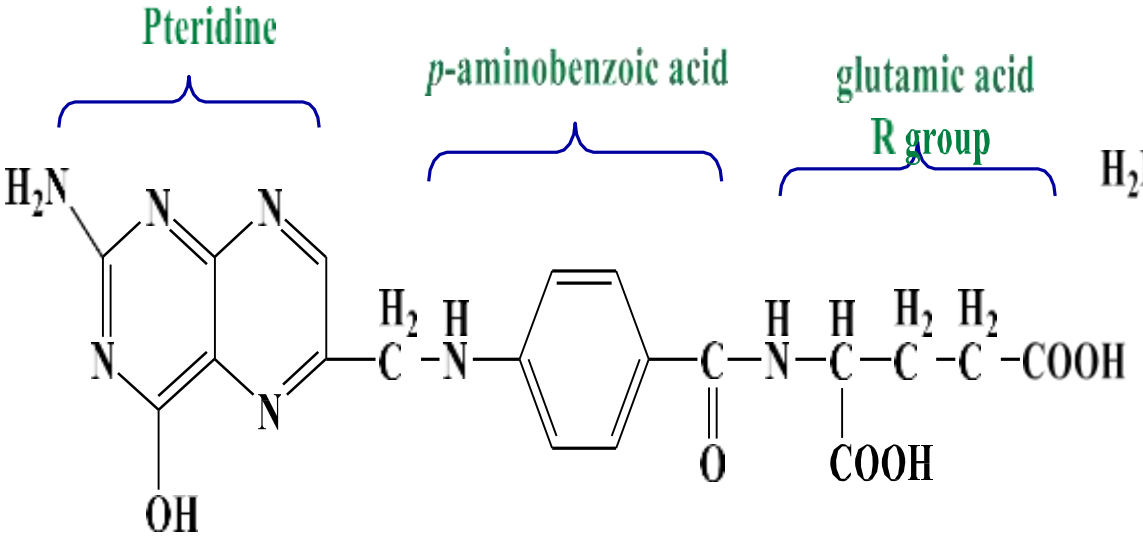
Trimetoprim



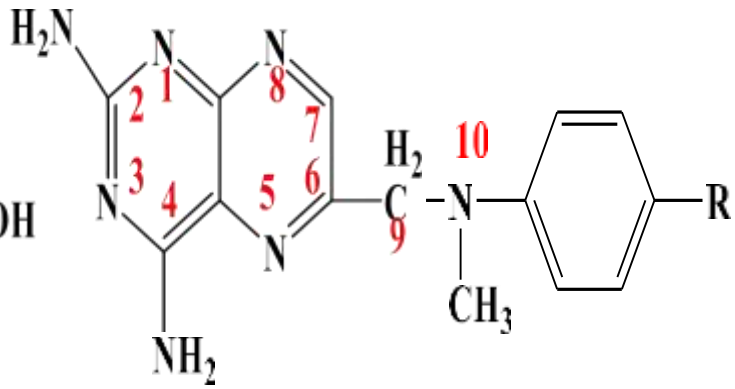
Mechanism of action of folic acid antagonist



Methotrexate(amethopterin)



Folic acid
Vit B9



Methotrexate
4-amino-N^{10}-methyl-pteroylglutamic acid

The mechanism of action of methotrexate

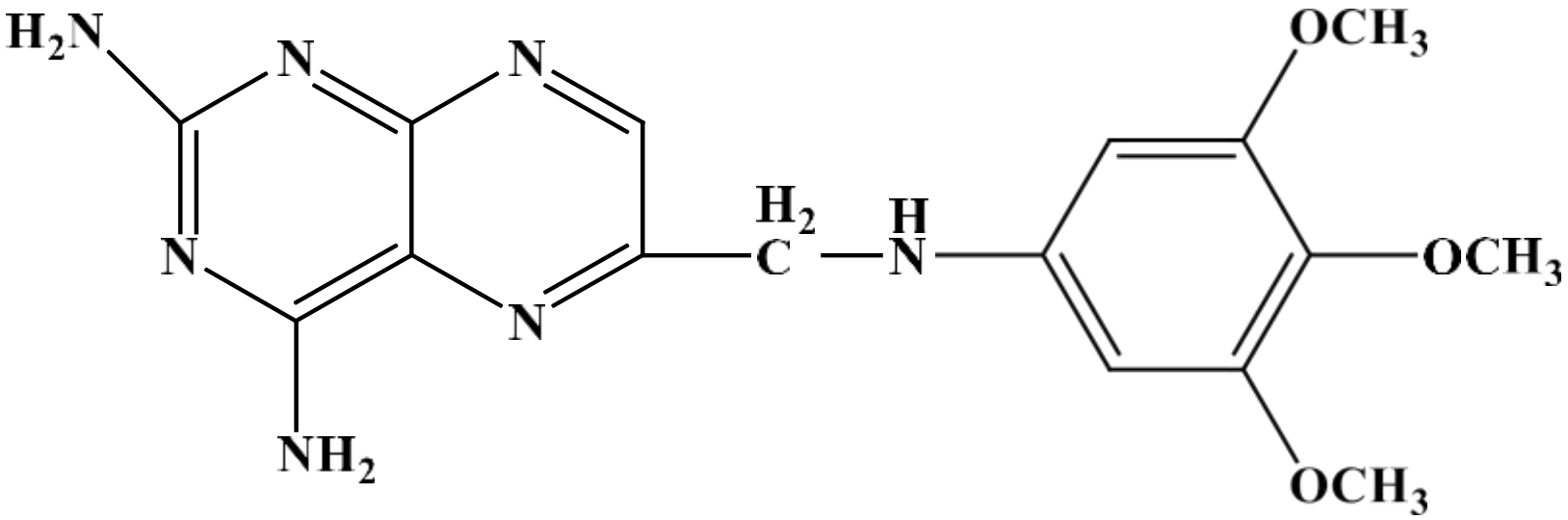
Methotrexate binds tightly to dihydrofolate reductase, blocking the reduction of dihydrofolate to tetrahydrofolate. It is specific for the S phase of the cell cycle.

Resistance to methotrexate can occur because of:-

Decreased carrier-mediated transport of drug into cells.
Increased expression of the target enzyme DHFR, due to amplification of the DHFR gene.
Impaired of polyglutamation.

Methotrexate undergoes polyglutamation intracellularly forming a pool of compounds that is retained for months.

Trimetrexate (use by IV inj only)•



The drug is used to treat colorectal cancer, head and neck cancer as well as nonsmall cell lung cancer (NSCLC).

The mechanism of action of trimetrexate involves folate antagonism and inhibition of thymidylate synthesis. Trimetrexate does not form intracellular polyglutamate adducts as does methotrexate and other related compounds. Resistance can occur by increased expression of the target enzyme, decreased binding affinity for the target enzyme, or decreased intracellular drug transport.

The major catabolic pathways involve O-demethylation followed by glucuronide conjugation.