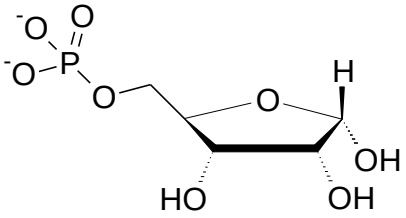
Αντιμεταβολίτες

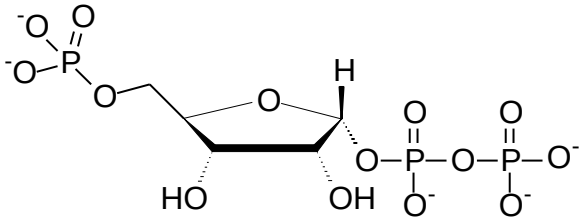
Ανταγωνιστές πουρινών

Ανταγωνιστές πυριμιδινών

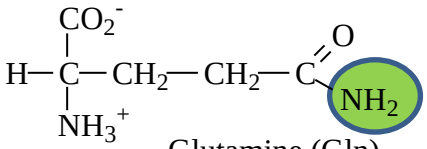


ribose-6-phosphate

ribose-6-phosphate pyrophosphokinase

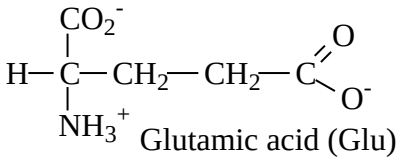


5-phosphoribosyl-1-pyrophosphate (PRPP)



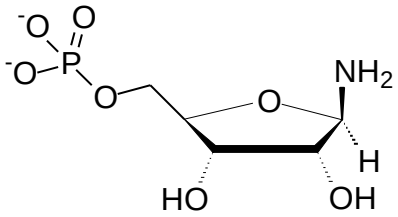
Glutamine (Gln)

amidophosphoribosyl transferase

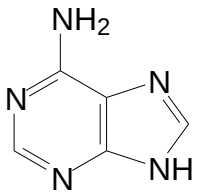


Glutamic acid (Glu)

PRPP amidotransferase



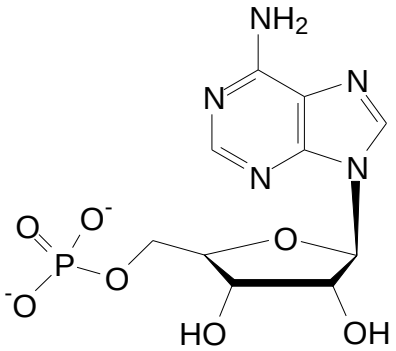
Salvage pathways



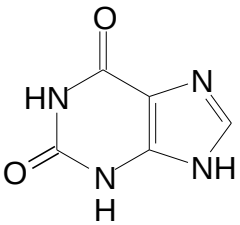
A (adenine)

adenine phosphoribosyl transferase (APRT)

PRPP



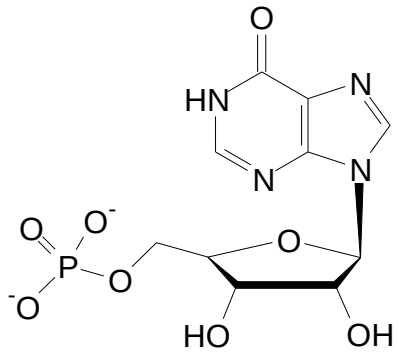
AMP



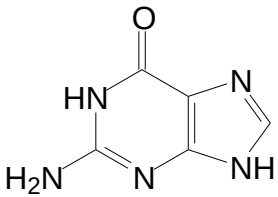
H (hypoxanthine)

hypoxanthine/guanine phosphoribosyl transferase (HGPRT)

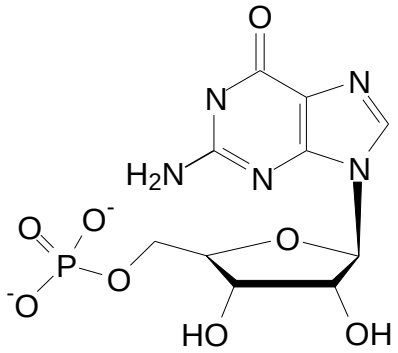
PRPP



IMP



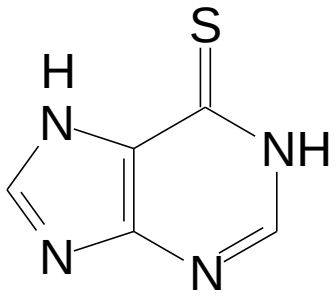
G (guanine)



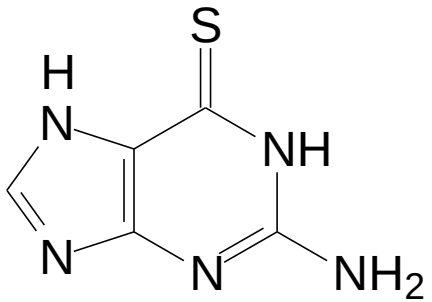
GMP

Ανταγωνιστές πουρινών

thiopurines

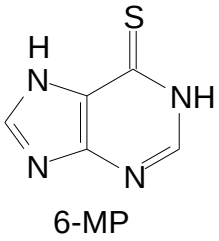


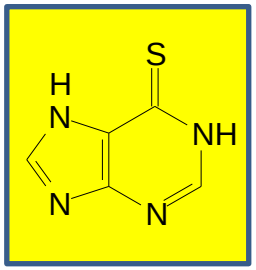
6-MP



6-TG

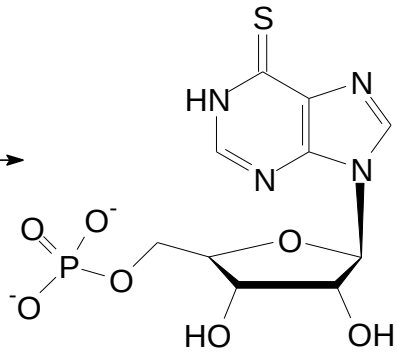
Και τα δύο οδηγούν στο ίδιο προϊόν, δρουν συνεργιστικά έναντι L1210





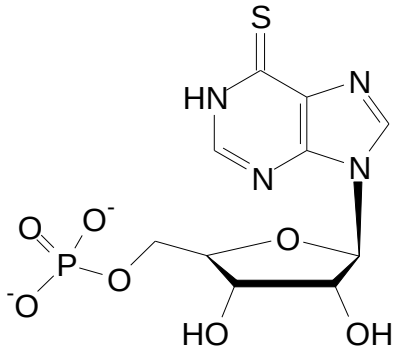
HGPRT

PRPP



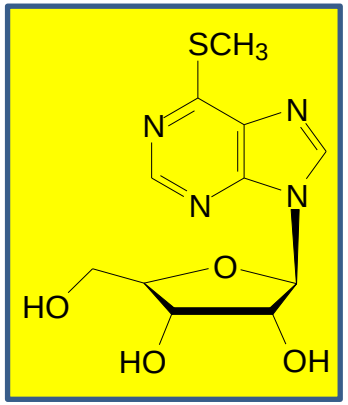
Αναστολή HGPRT

Αναστολή salvage pathways

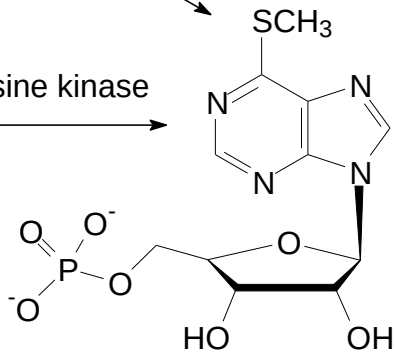


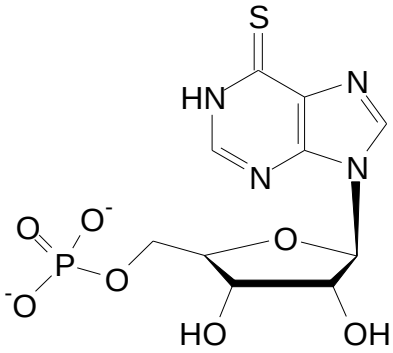
Αναστολή PRPP amidotransferase

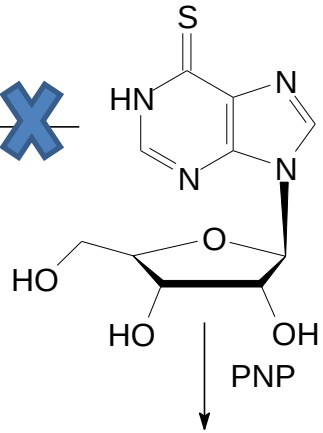
Αναστολή de novo σύνθεσης



adenosine kinase





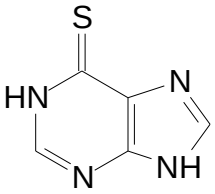


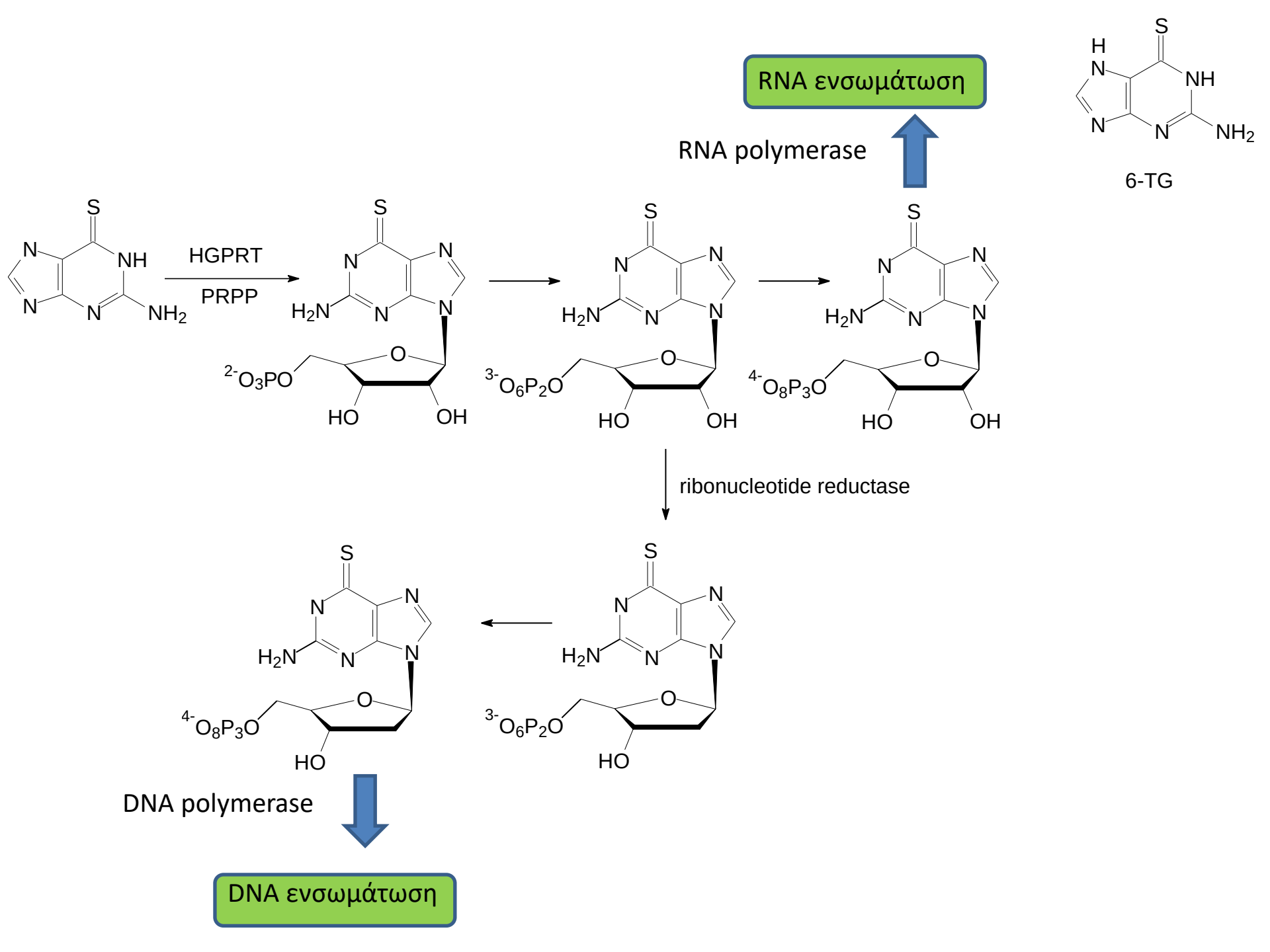
PNP

HGPRT

PRPP

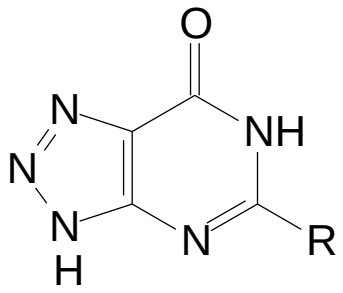
in vivo



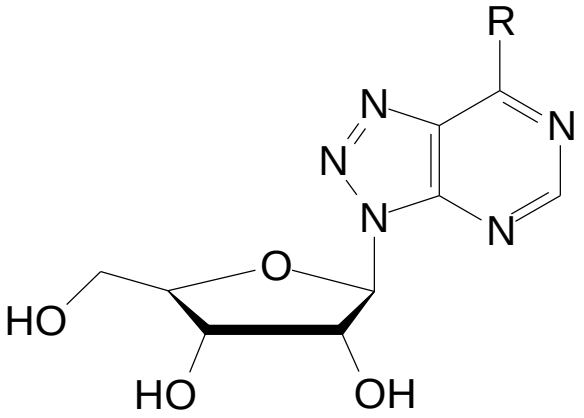

RNA ενσωμάτωση
RNA polymerase
6-TG
HGPRT
PRPP
ribonucleotide reductase
DNA polymerase
DNA ενσωμάτωση

Ανταγωνιστές πουρινών

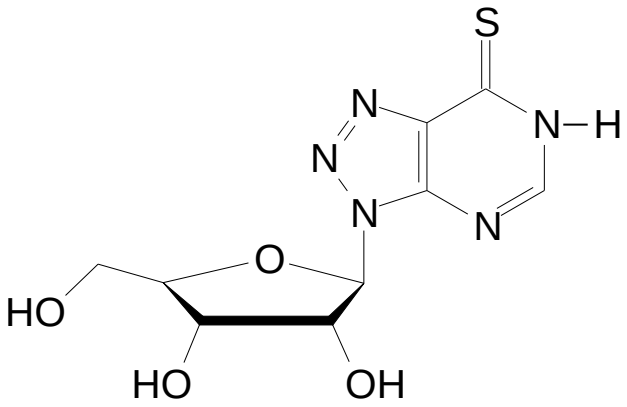
azapurines



R=NH_2 8-aza-G
R= H 8-azahypoxanthine



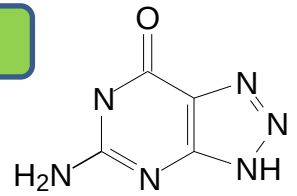
R=OH 8-azainosine
R= NH_2 8-aza-A



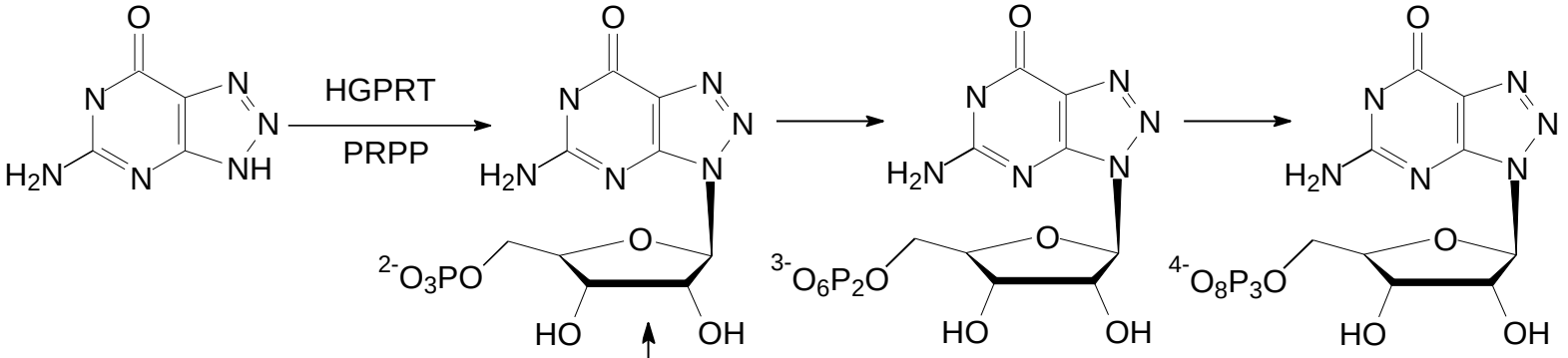
8-aza-6-thioinosine

RNA ενσωμάτωση

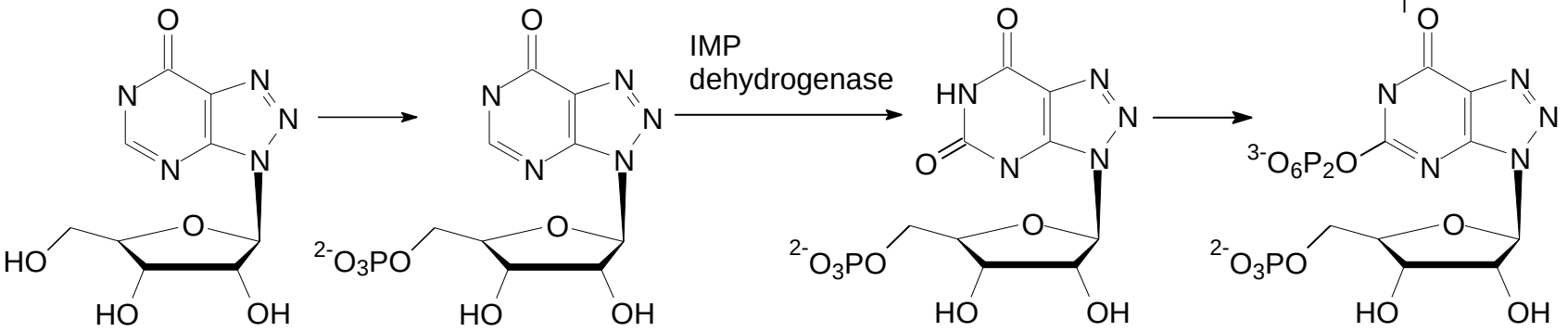
RNA polymerase



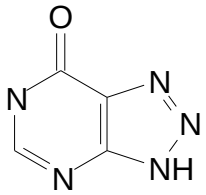
8-aza-G



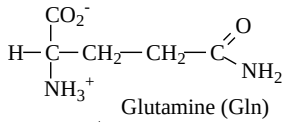
amidophosphoribosyl transferase



8-aza-I

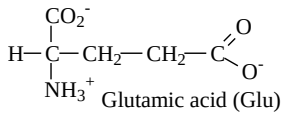


8-azahypoxanthine

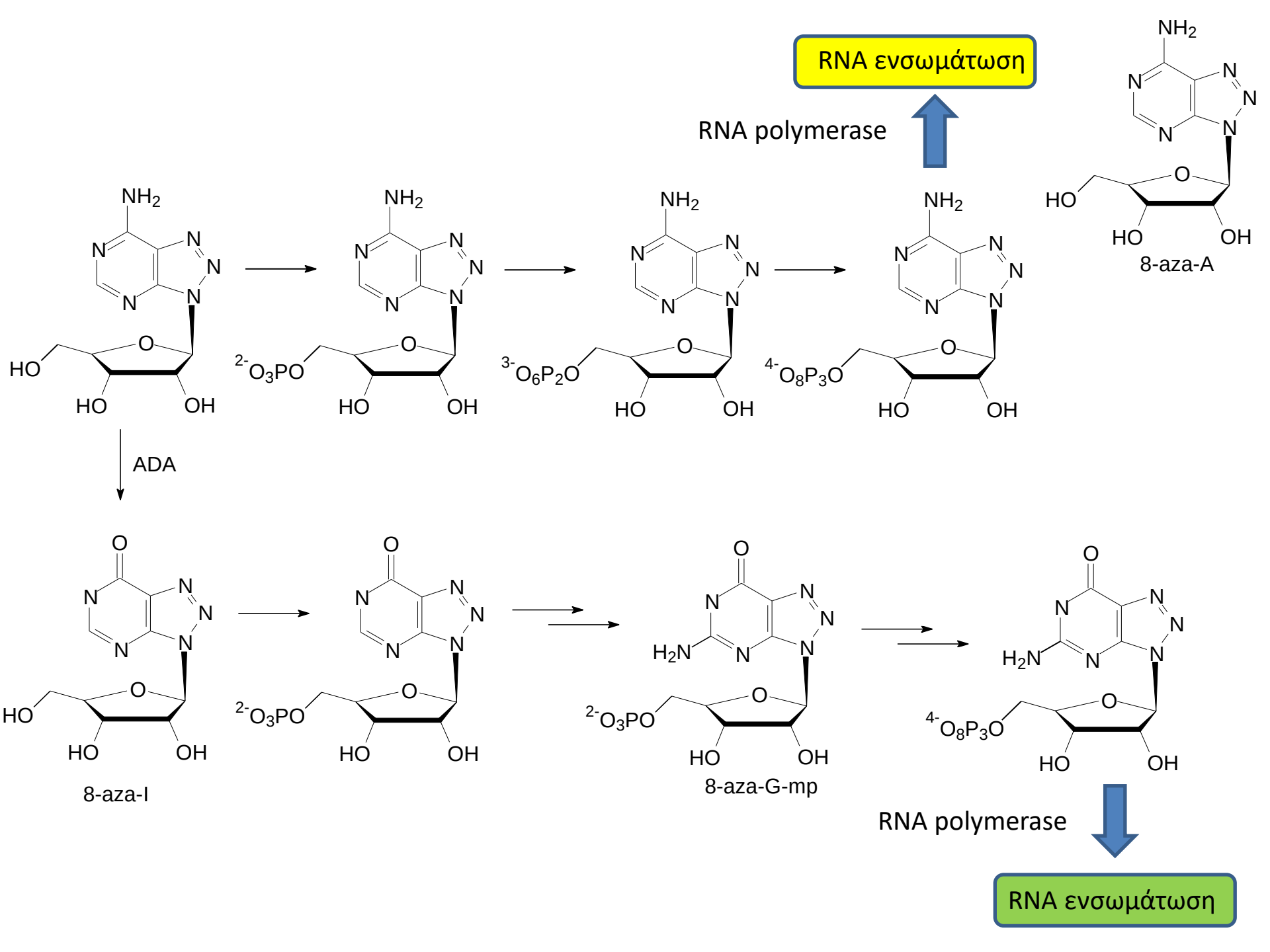


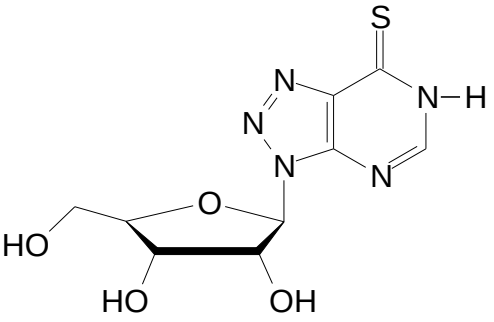
Glutamine (Gln)

amidophosphoribosyl transferase

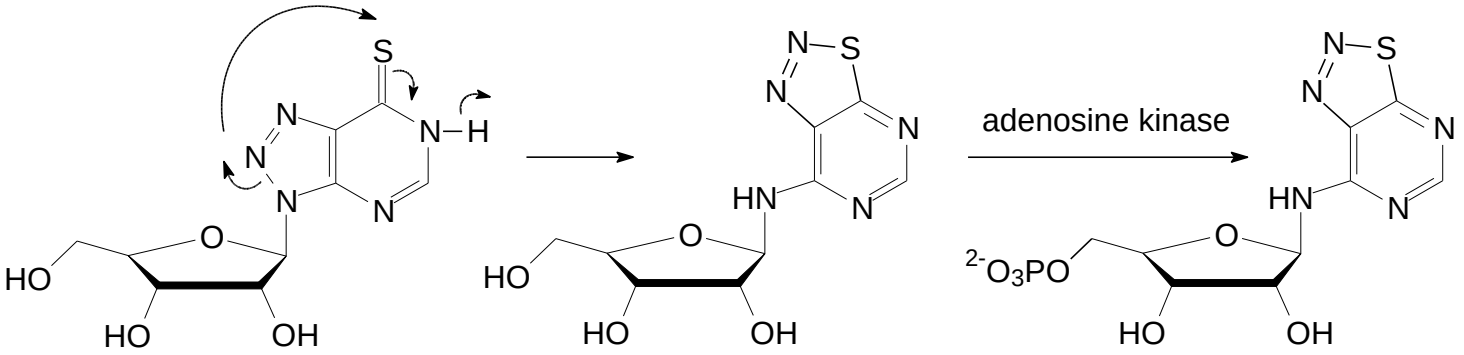


Glutamic acid (Glu)

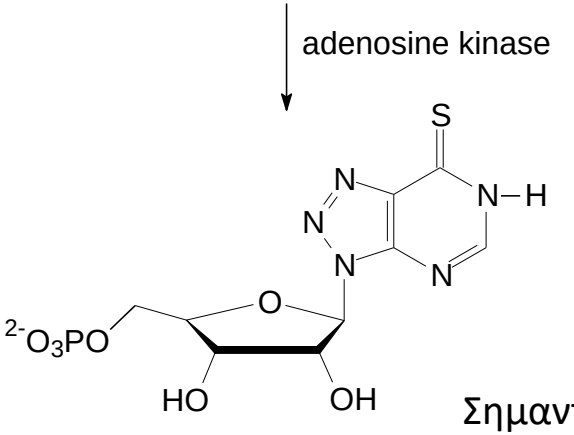

RNA ενσωμάτωση
RNA polymerase
8-aza-A
ADA
8-aza-I
8-aza-G-mp
RNA polymerase
RNA ενσωμάτωση



8-aza-6-thioinosine



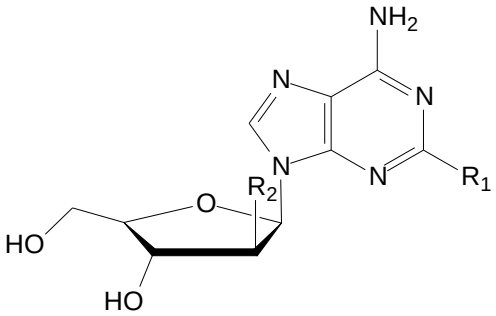
10πλάσια δραστικότητα



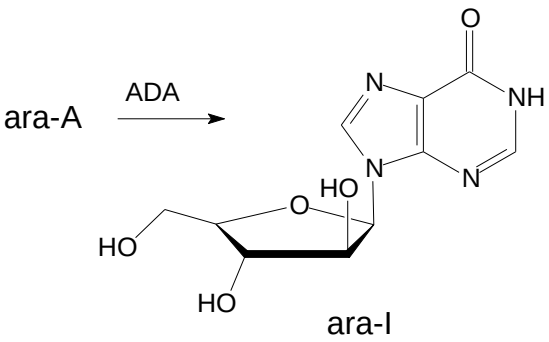
Σημαντική κυτταροτοξικότητα σε επιδερμικά καρκινικά κύτταρα

Ανταγωνιστές πουρινών

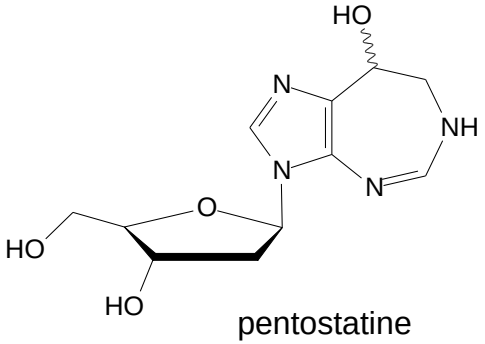
ara-adenosine



R_1= H, R_2= OH ara-A
R_1= F, R_2=OH 2-F-ara-A
R_1= H, R_2= N_3

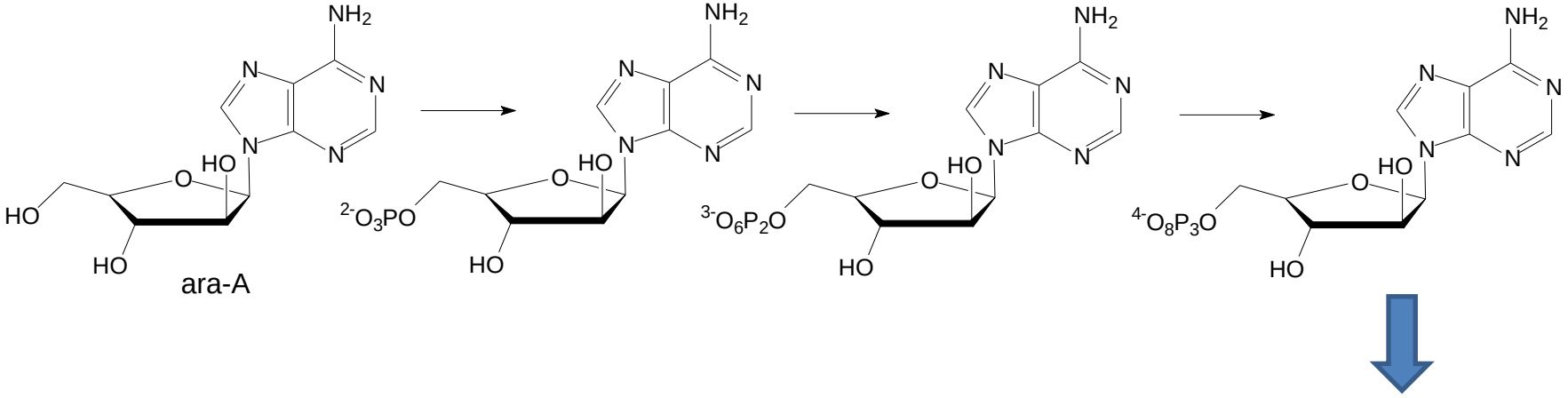


ara-I



pentostatine

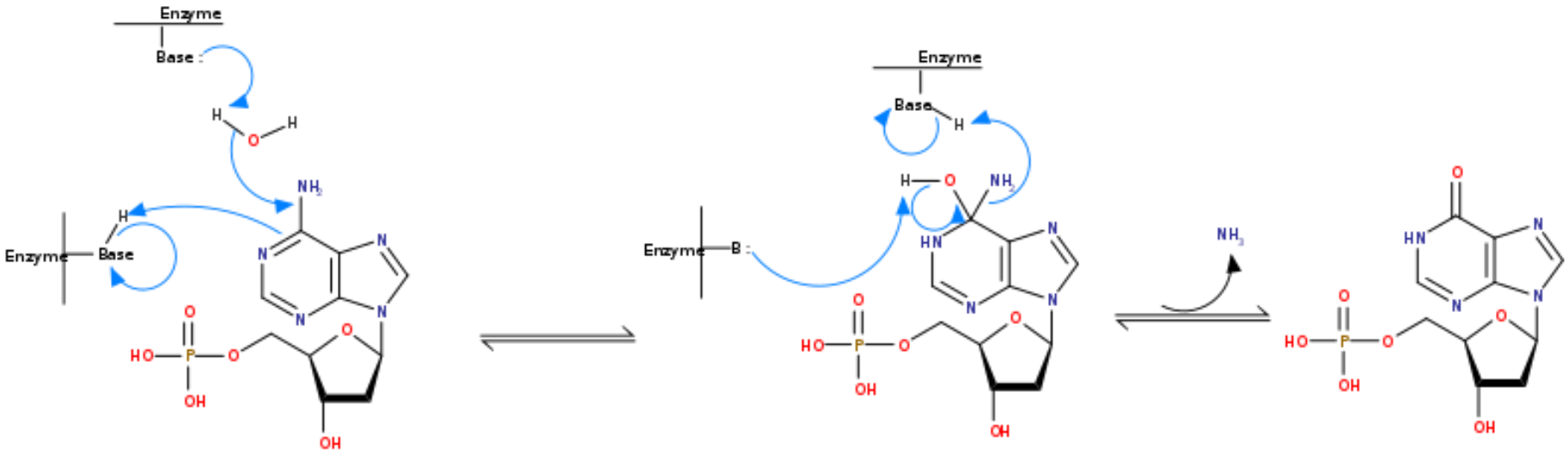
ADA inhibitor



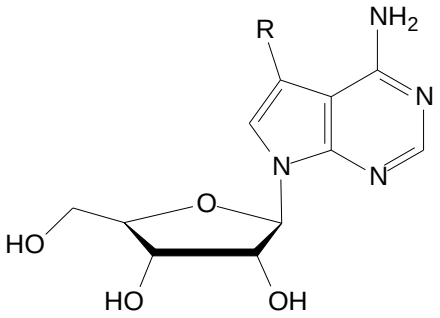
αναστολέας της DNA πολυμεράσης

Το Ara-A αναστέλλει επιπλέον το ribonucleotide reductase, επομένως αναστέλλεται η δημιουργία 2-δεοξυνουκλεοτιδίων

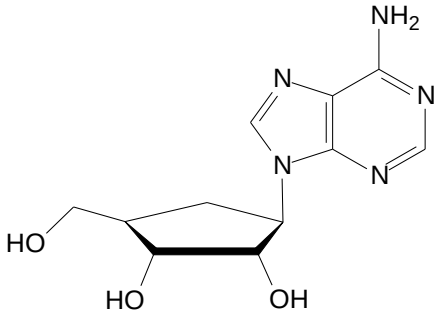
Adenosine deaminase (ADA) mechanism



Άλλα παράγωγα

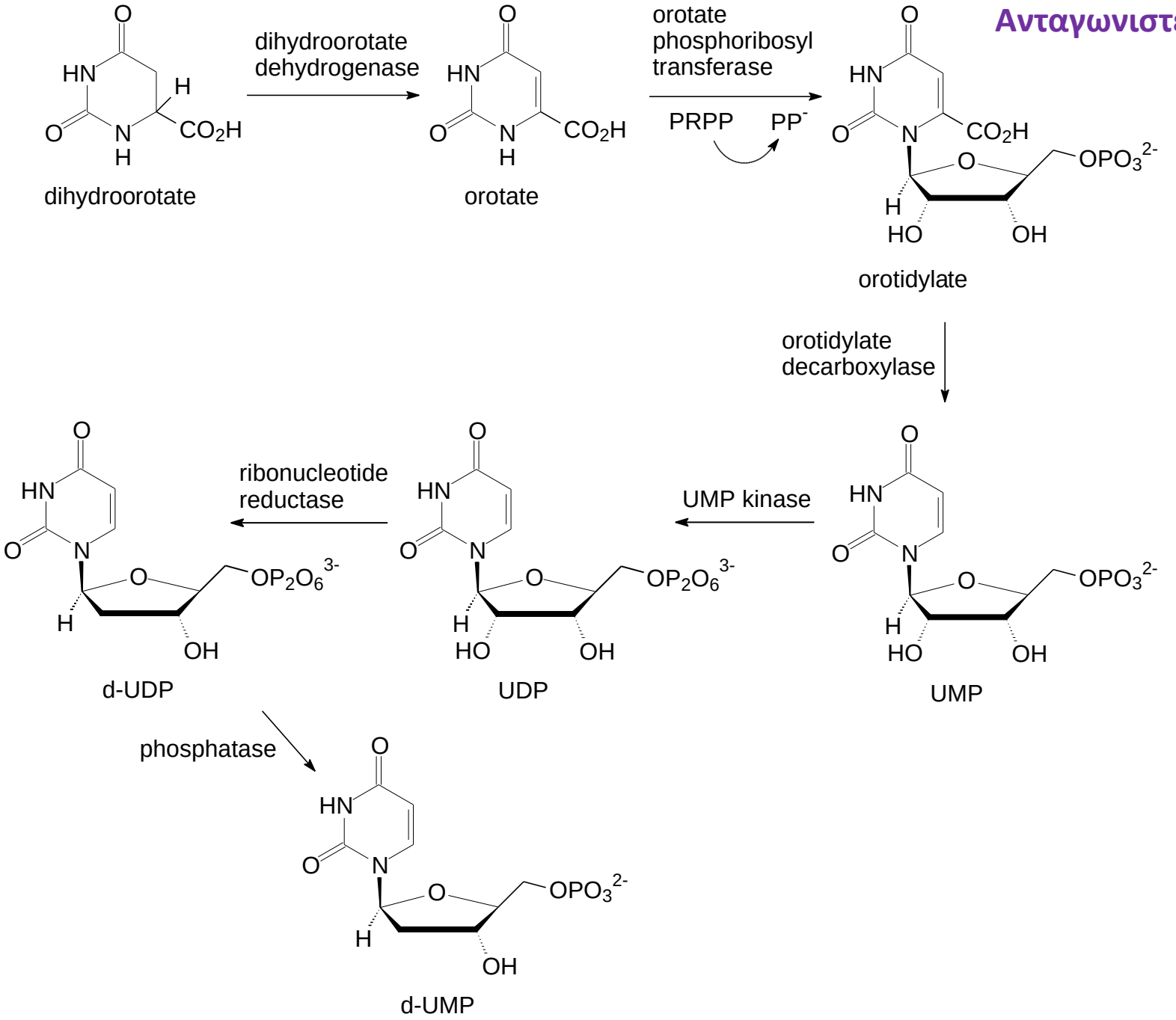


R= H tubercidin
R= $CONH_2$ sangivamycin
R= CN toyocamycin



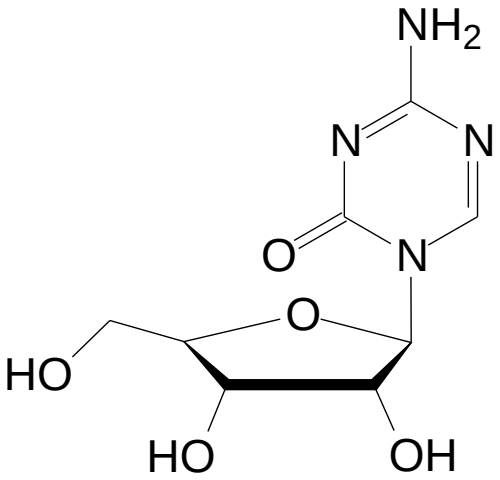
aristeromycin

Ανταγωνιστές πυριμιδινών

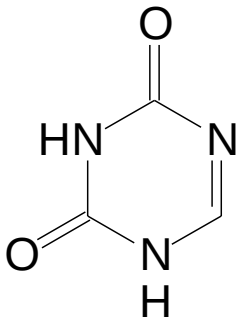


Ανταγωνιστές πυριμιδινών

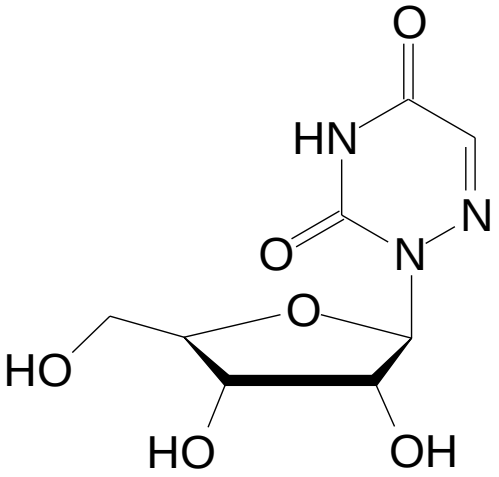
azapyrimidines



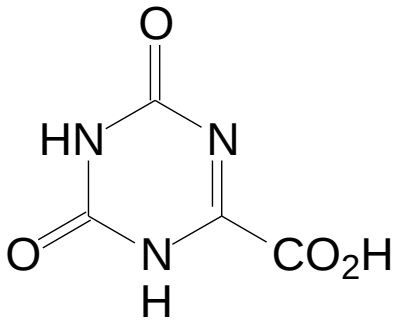
5-azaC



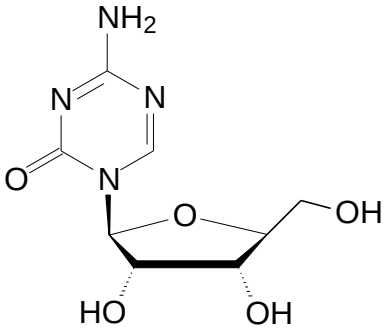
5-azaU



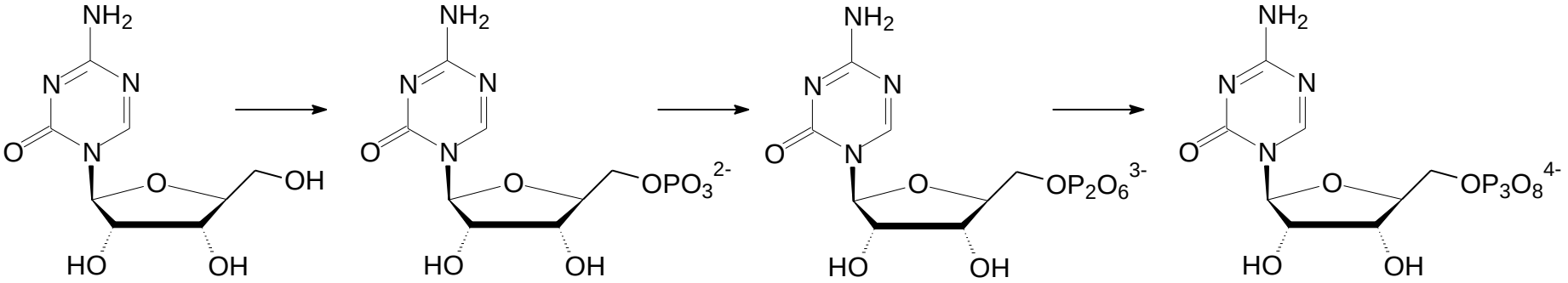
6-azaU



5-azaorotic acid

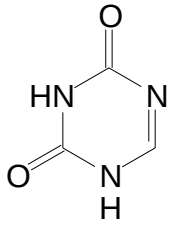


5-azaC

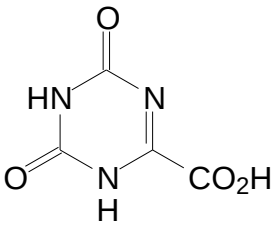


5-azaC

- Αναστέλλει τη σύνθεση m-RNA
- Ενσωματώνεται σε t-RNA και προκαλεί λάθος μετάφραση

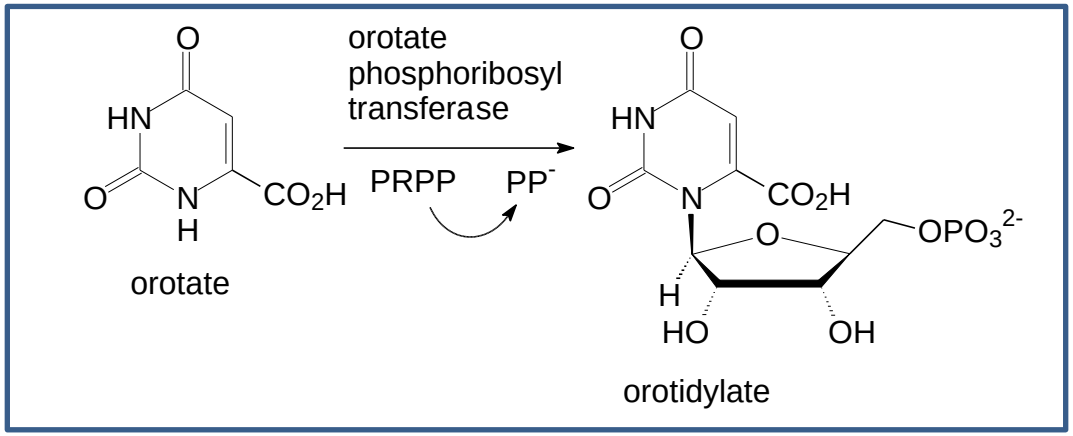


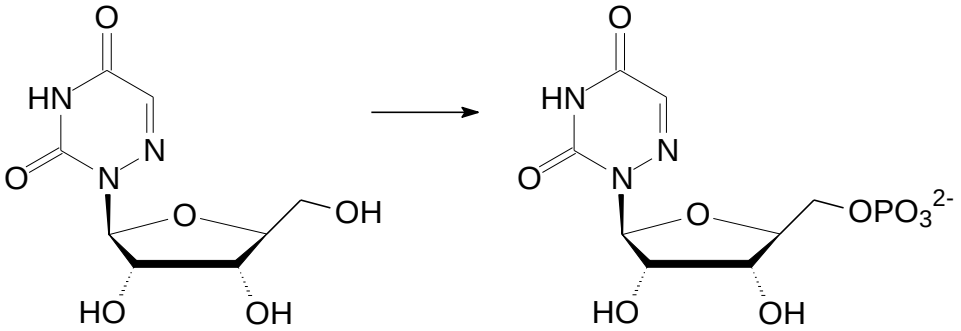
5-azaU



5-azaorotic acid

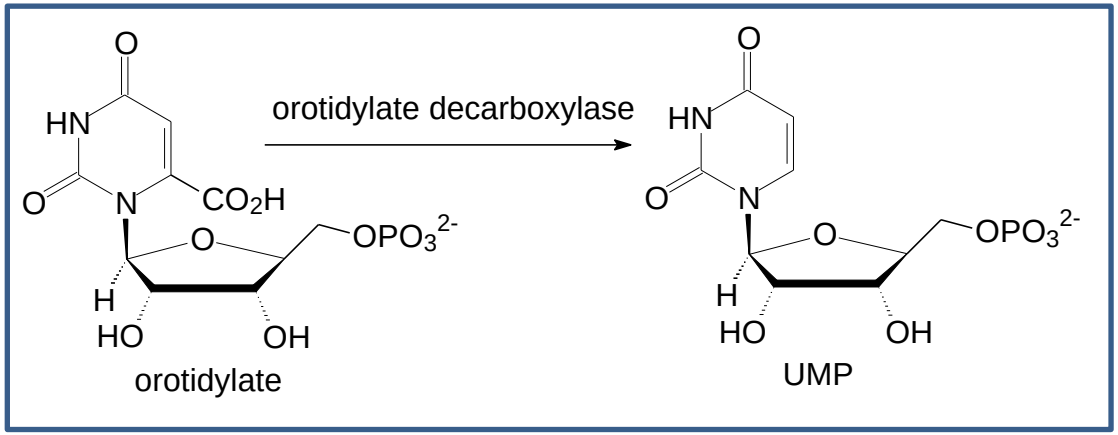
Αναστολείς του orotate phosphoribosyl transferase





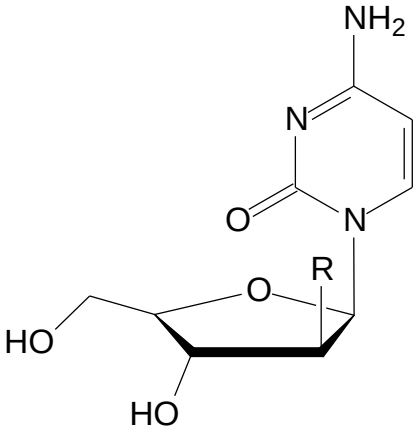
6-azaU

Αναστολέας του orotidylate decarboxylase

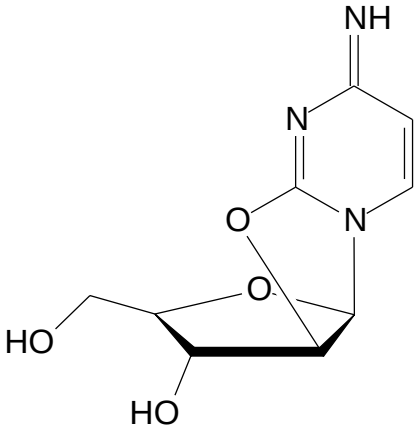


Ανταγωνιστές πυριμιδινών

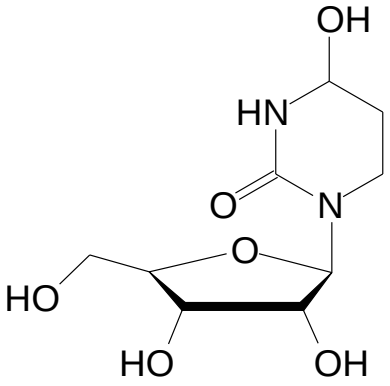
ara-cytidine



R= OH ara-C
R= N_3
R= NH_2



anhydro-araC

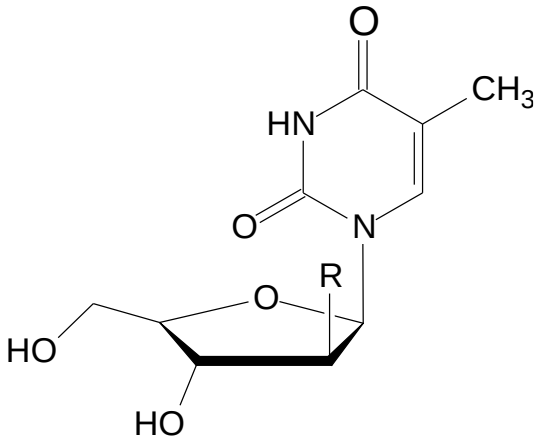


tetrahydro U

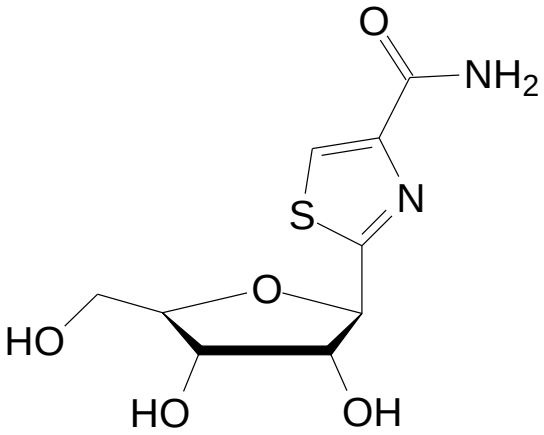
Αναγνωρίζεται και μετατρέπεται προς ara-CTP, που είναι υπόστρωμα του DNA polymerase και *ενσωματώνεται στο DNA, αλλά και στο RNA*

Το Ara-C (όπως και το Ara-A) αναστέλλει το ribonucleotide reductase, επομένως αναστέλλεται η δημιουργία 2-δεοξυνουκλεοτιδίων

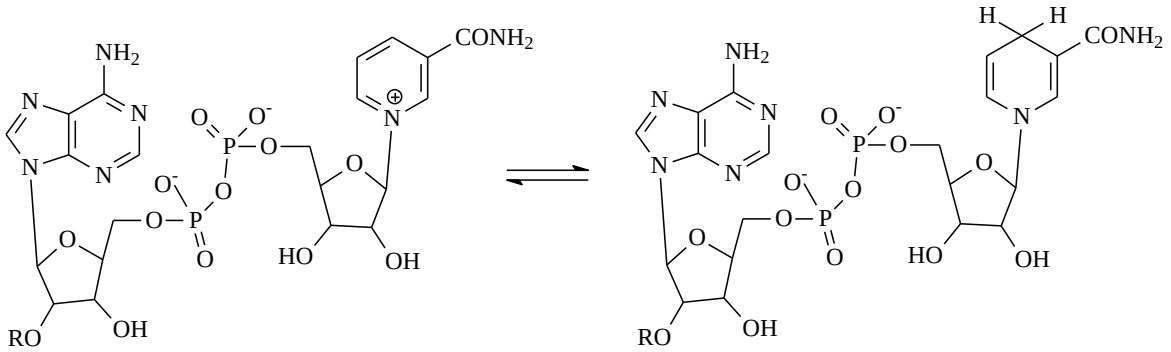
Άλλα παράγωγα



R= OH ara-T
R= F FMAU



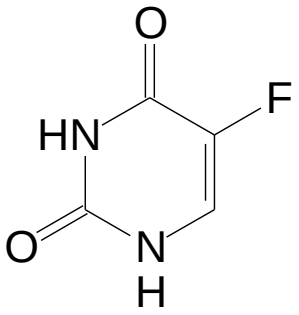
tiazofurin



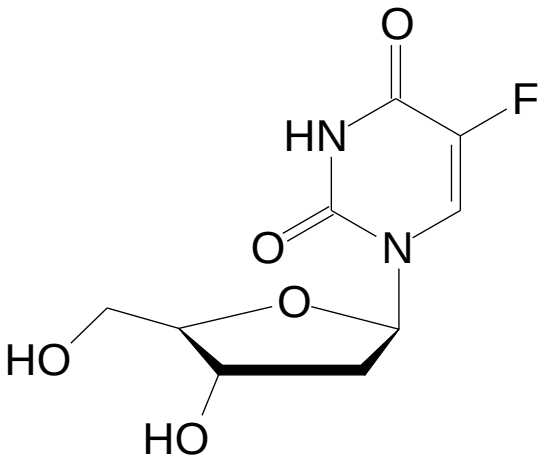
NAD, R= H
NADP, R= PO_3H_2

Ανταγωνιστές πυριμιδινών

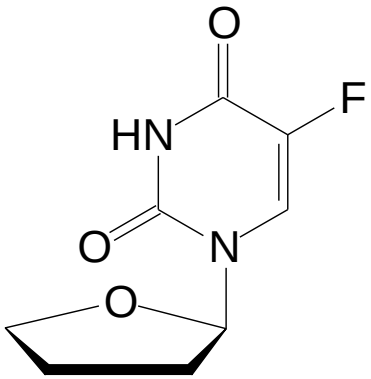
fluoropyrimidines

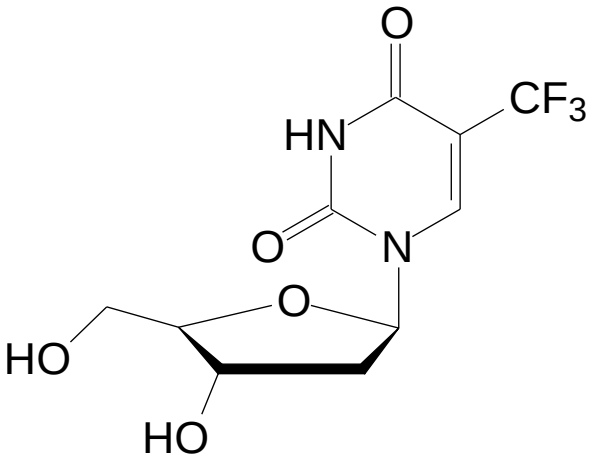


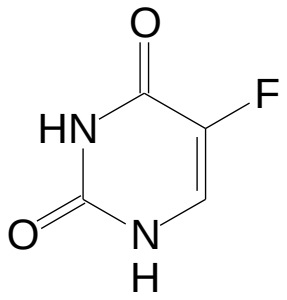
FU



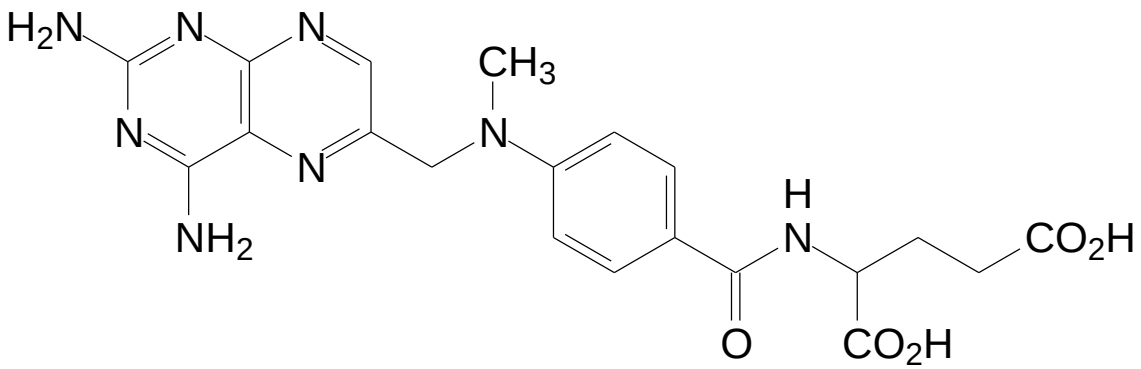
FUdR



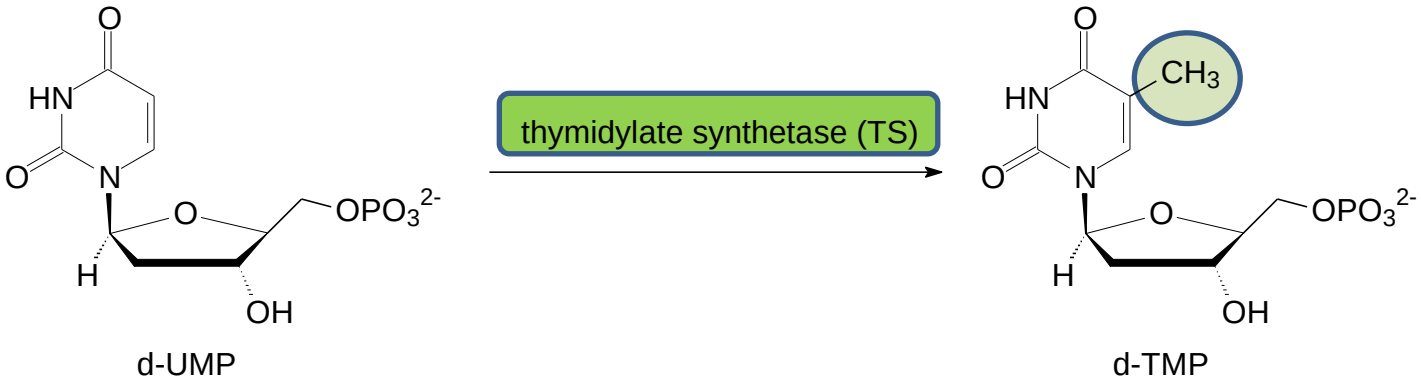


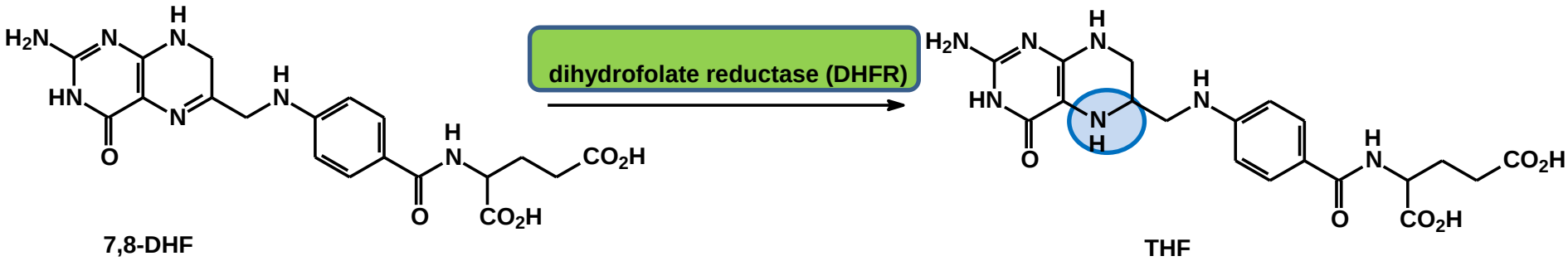


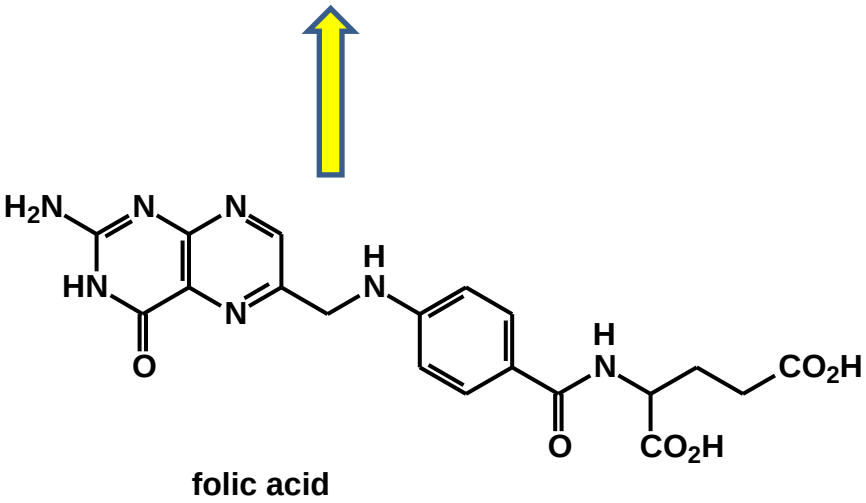
FU

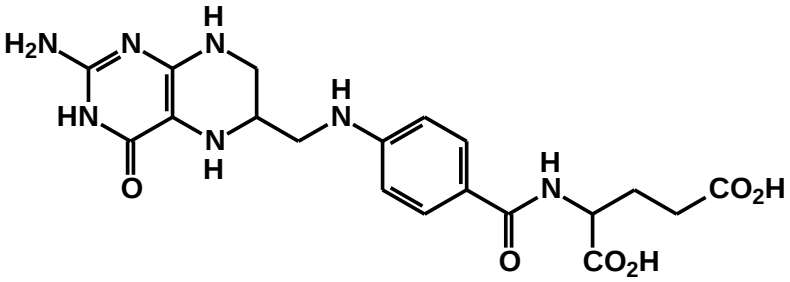


methotrexate

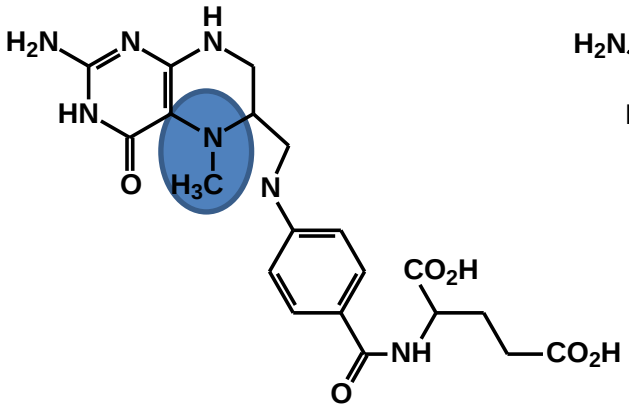

thymidylate synthetase (TS)
d-UMP
d-TMP

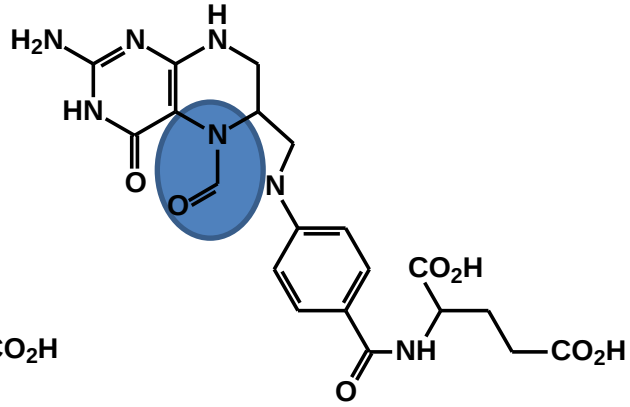

dihydrofolate reductase (DHFR)
7,8-DHF
THF

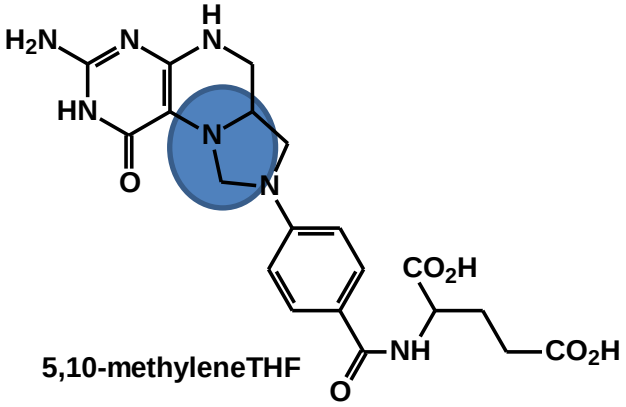

folic acid



THF

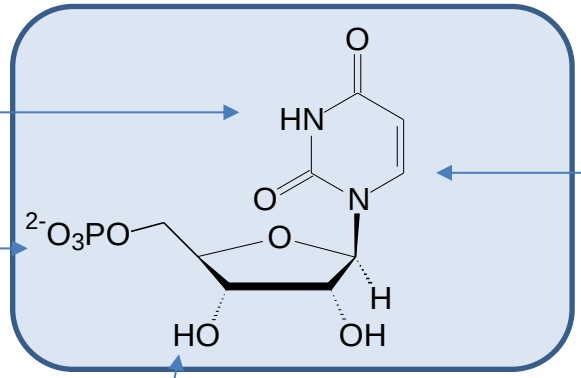




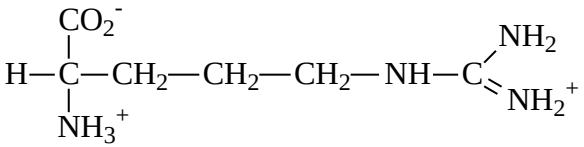


5,10-methyleneTHF

Thymidilate synthase key residues

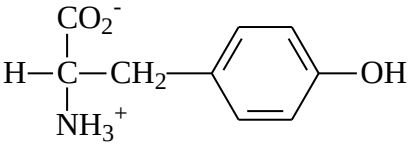


Arg 23



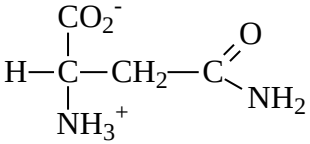
5’-phosphate

Tyr 261



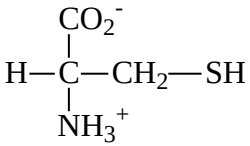
3’-OH

Asn 229



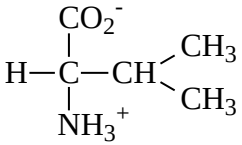
N_3-H

Cys 198



C_6 of dUMP

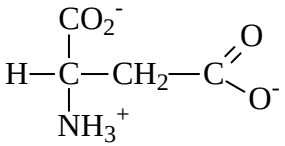
Val 316



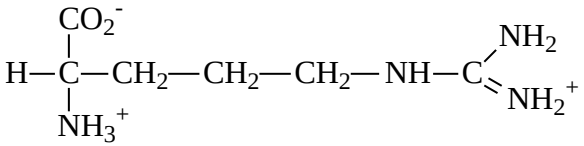
C-terminal

DHFR key residues

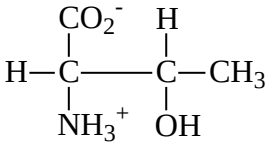
Asp 27



Arg 57



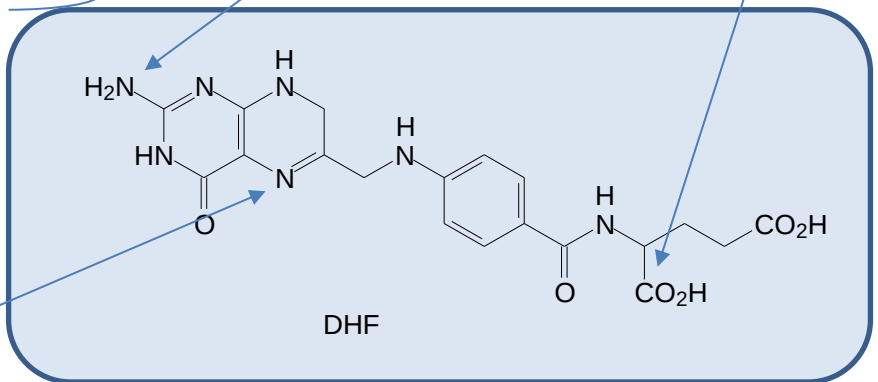
Thr 43

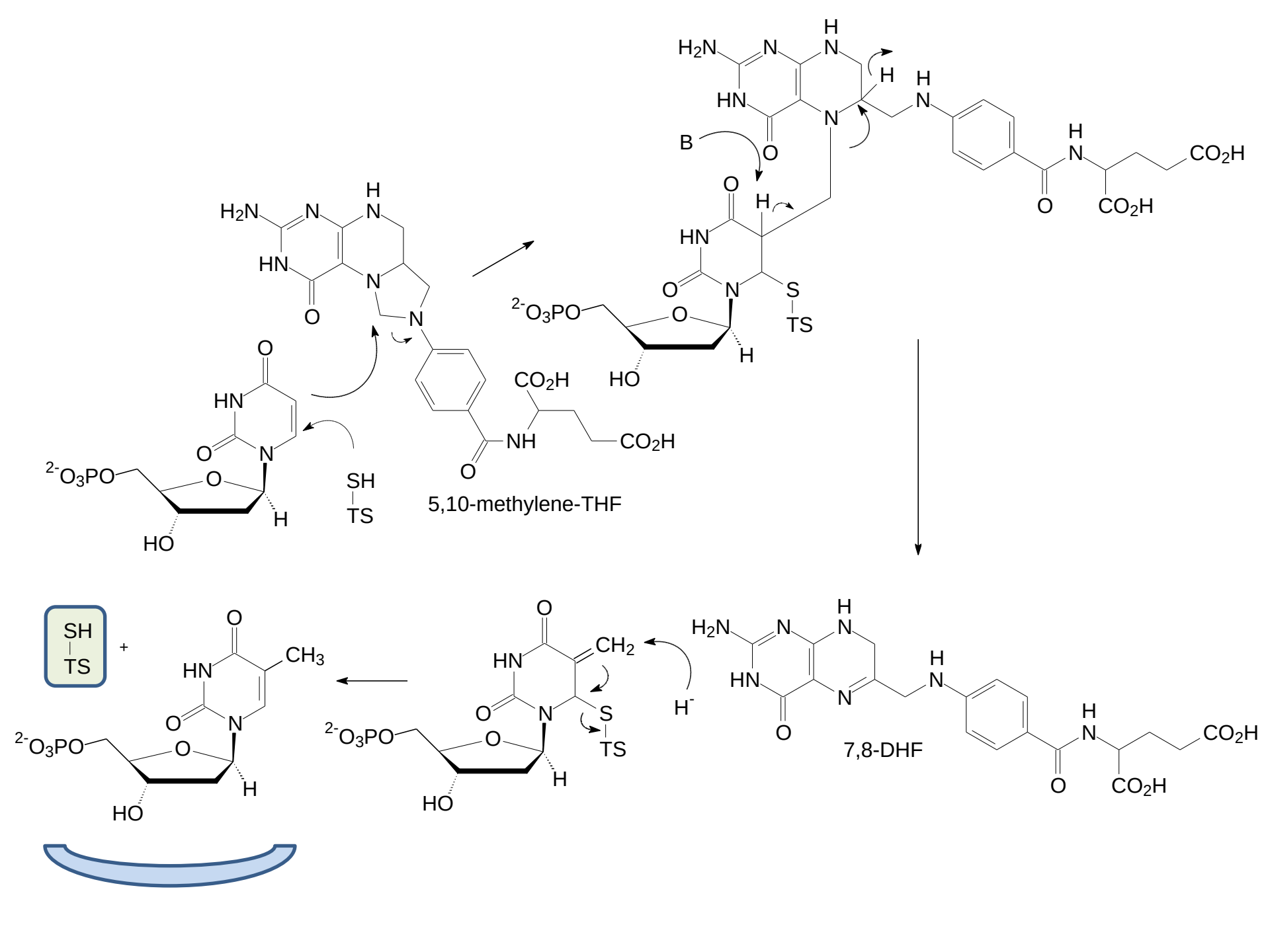


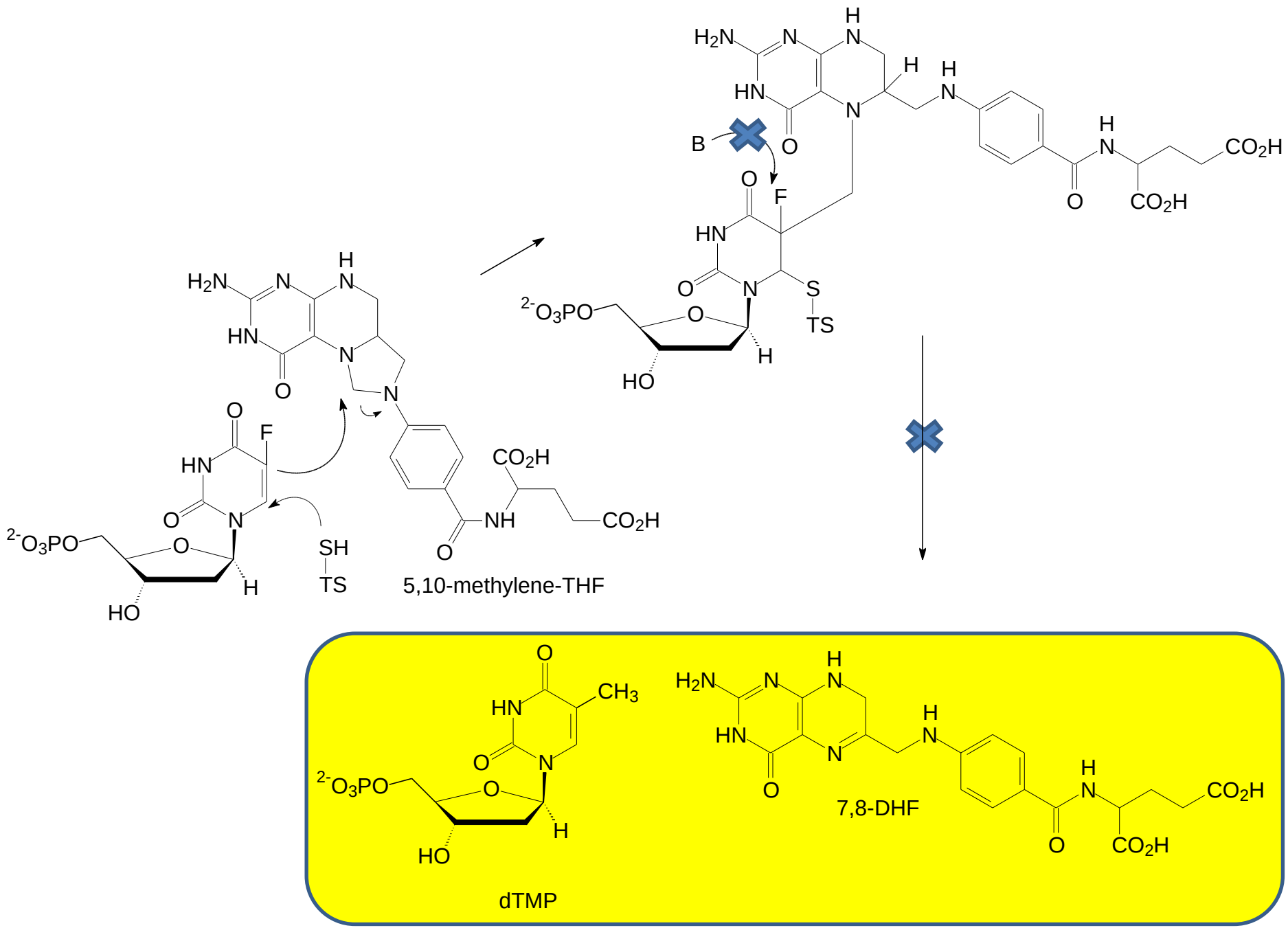
N_5 of DHF

α-COOH

$2\text{-}NH_2$ of DHF

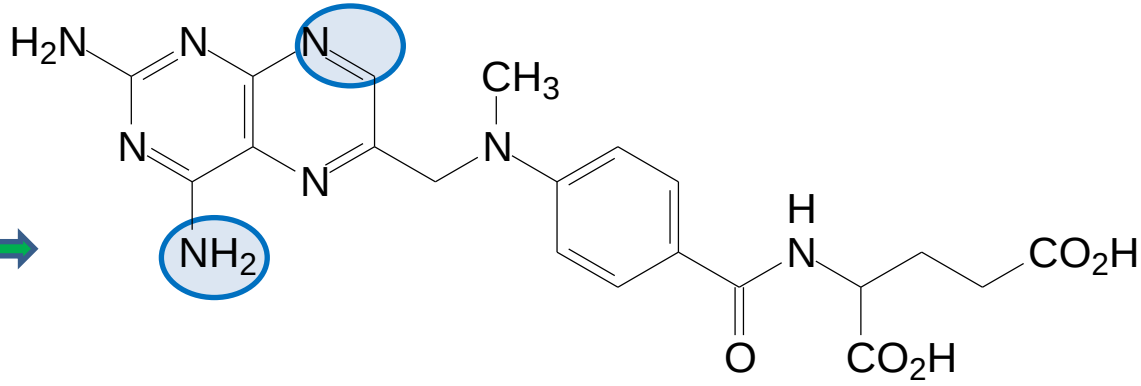



5,10-methylene-THF
7,8-DHF

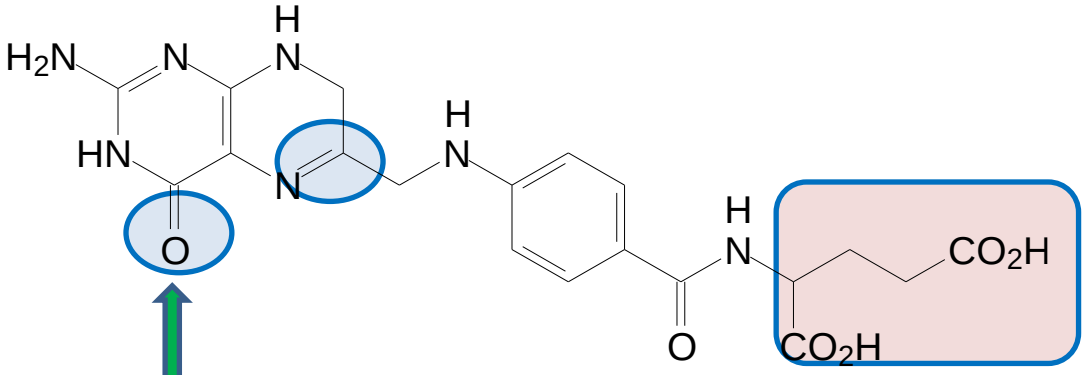

5,10-methylene-THF
dTMP
7,8-DHF

N_1 is the most basic N

e-donating



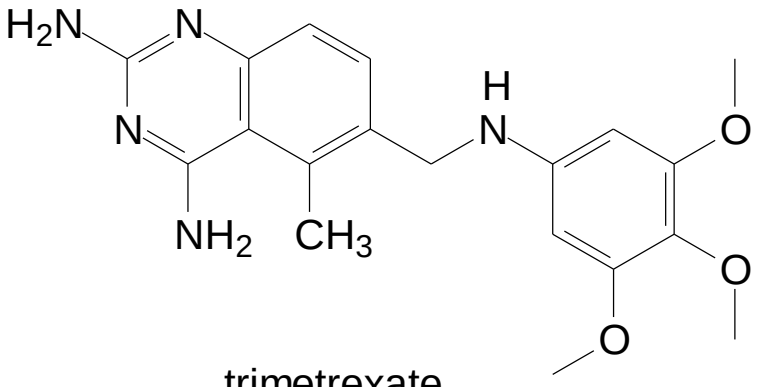
methotrexate



DHF

e-withdrawing

N_5 is the most basic N



trimetrexate