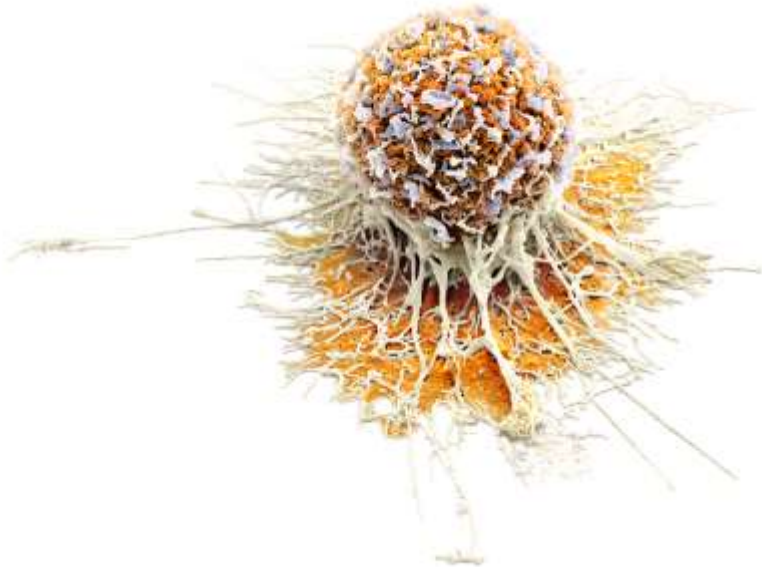


Cytostatika – mechanismus účinku, terapie a rezistence

~~Cytostatika – mechanismus účinku, terapie a rezistence~~

Látky s protinádorovým účinkem



Jiří Petrák
BIOCEV, 1. LF UK
jpetr@lf1.cuni.cz

Cytostatika – mechanismus účinku, terapie a rezistence

- Nádory, nádorové buňky a terapie
- **Klasická cytostatika**
 - Genotoxické látky
 - Alkylační činidla a deriváty platiny
 - **Interkalační látky a Inhibitory topoizomeráz**
 - **Látky způsobující rozštěpení DNA**
 - **Antimetabolity a hydroxymočovina**
 - Antimitotika
 - Inhibitory syntézy a degradace proteinů
 - Epigenetická cytostatika
 - Hormonální terapie
 - Diferenciační a fotodynamická terapie
- **Cílená a biologická terapie**
 - Inhibitory tyrozinkináz
 - Inhibitory mTOR
 - Inhibitory proteinů bez kinázové aktivity
 - Terapeutické protilátky a konjugáty
 - Vakcíny
 - CAR-T, buněčná terapie
 - další....
- **Mechanismy rezistence nádorových buněk na terapii**

Klasická Cytostatika

*genotoxické
látky
a
antimetaboly*

Účinek na
DNA

Účinek na mitotické
vřeténko

Účinek na
receptorech pro
steroidní
hormony

Poškození DNA nebo inhibice
syntézy

Agonisté

Antagonisté

Alkylace
s jiné
modifikace

Tvorba
volných
radikálů

Interkalace
a inhibice
topoisomeráz

Antimetaboly
a
hydroxyurea

Poškození existující DNA
(genotoxicita)

Poškození DNA při syntéze,
interference s ní a další efekty

GENOTOXICKÉ LÁTKY

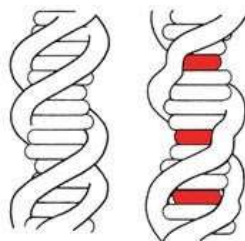
Alkylační činidla a deriváty platiny

Interkalační činidla, inhibitory DNA topoizomeráz

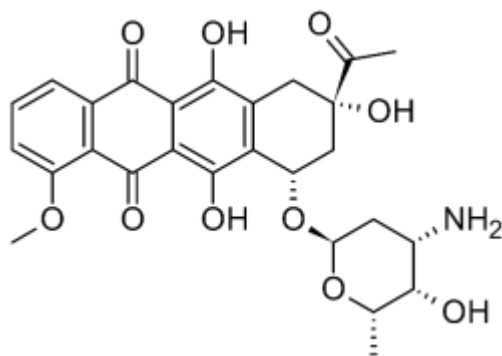
Látky způsobující rozštěpení DNA

Interkalační látky (antracykliny)

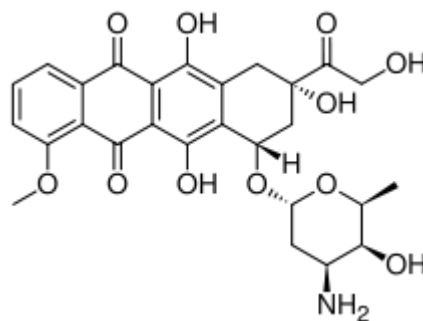
Antracykliny - Planární molekuly se 4 armoatickými jádry
(antibiotika izolovaná ze streptomycet 1960-1963 a jejich deriváty)



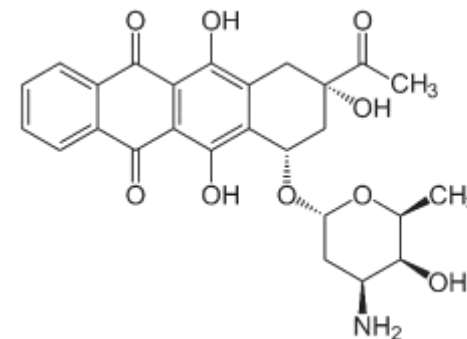
Daunorubicin



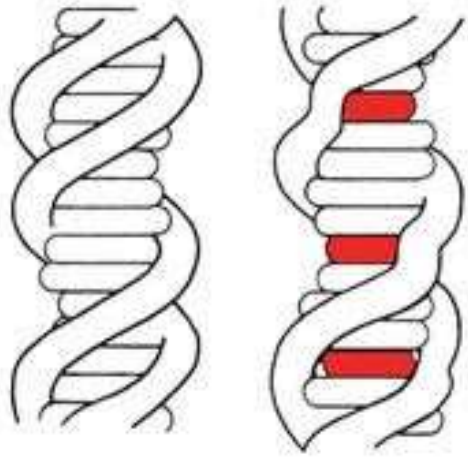
Doxorubicin
(Adriamycin)



Epirubicin
(Adriablastin)



Interkalace doxorubicinu do dsDNA



Doxorubicin

Doxorubicin-DNA structure

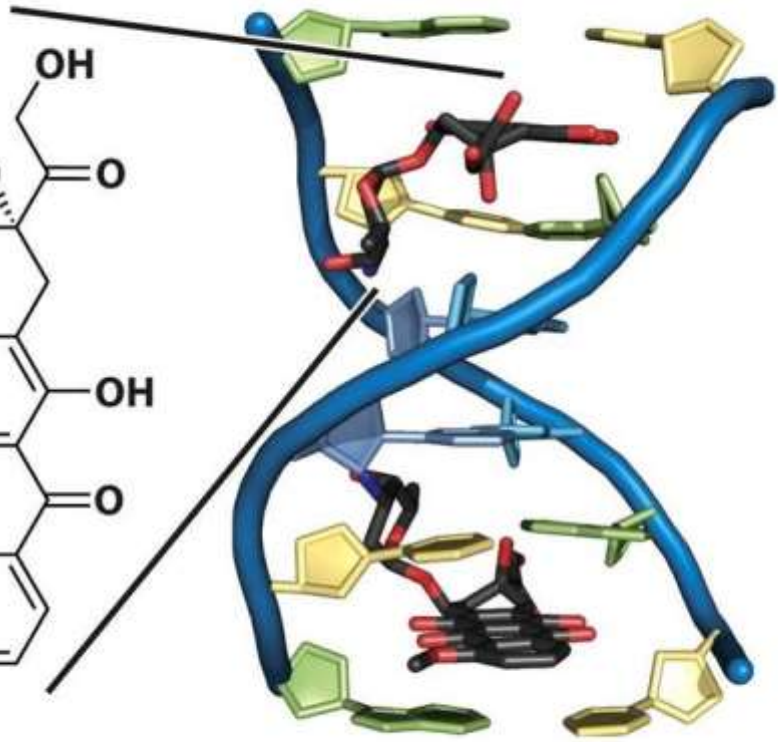
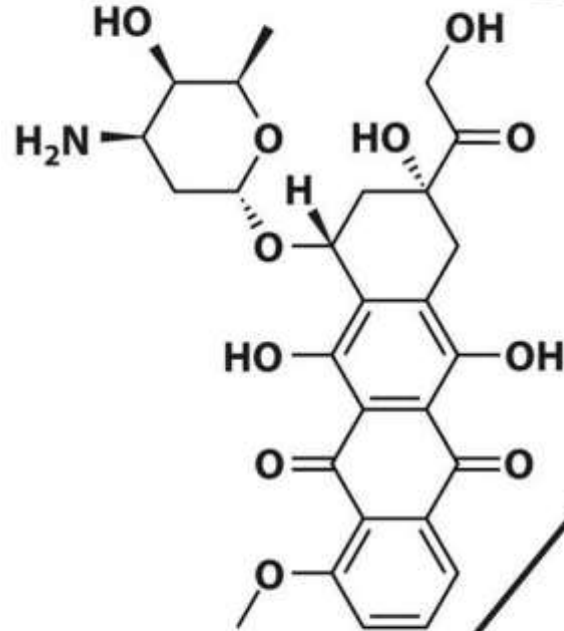
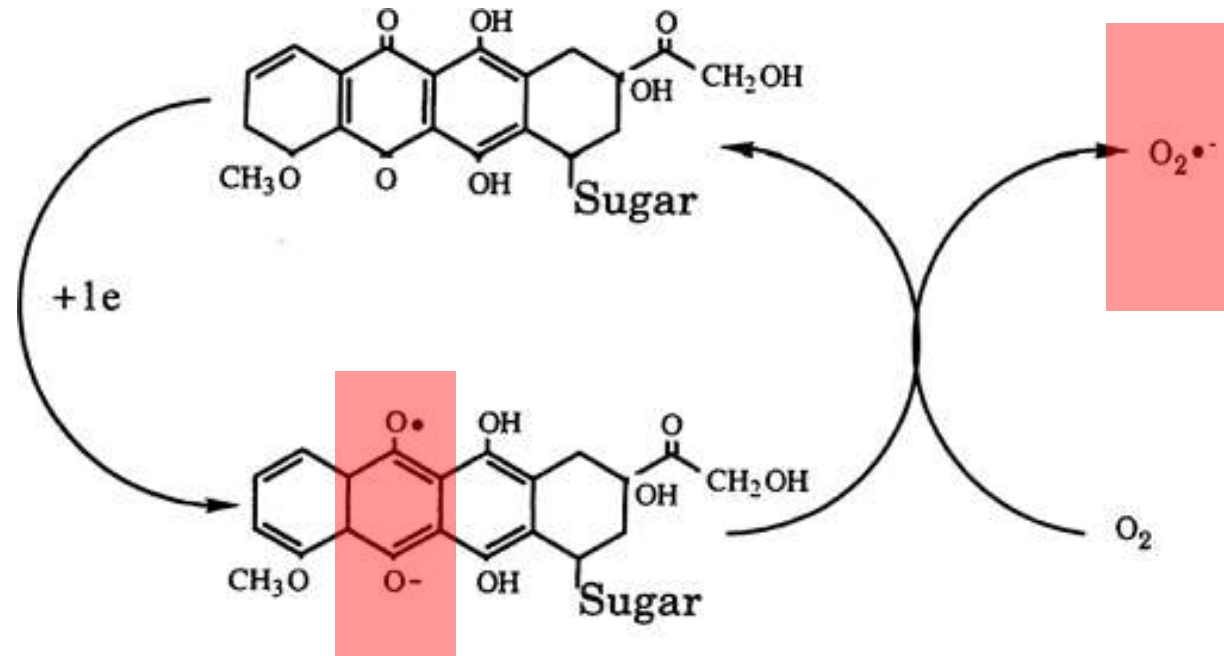


Figure 12-14c
Molecular Biology: Principles and Practice
© 2012 W. H. Freeman and Company

Generování volných radikálů antracykliny

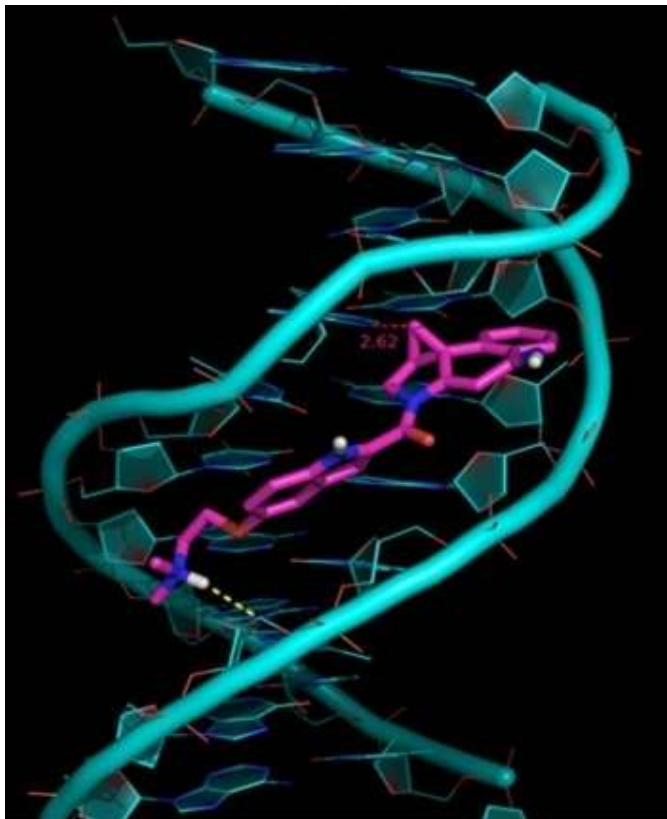
chinonová forma



semichinonová forma

O₂•⁻ = superoxide

Antracykliny – mechanismus účinku



- Interkalace molekuly do DNA způsobí inhibici transkripce a replikace
inhibici topizomerázy II → **dvouřetězcové zlomy**
- generují kyslíkové radikály
- vytěsňují histony z DNA a tak ovlivňují transkripci (účinnost nejen v S-fázi)

Table 1 – DNA topoisomerases

Topoisomerase I	Topoisomerase II
100 kDa	170 kDa; 180 kDa
Makes single-strand DNA breaks	Makes double-strand DNA breaks
ATP independent	ATP dependent
Genes located on chromosome 20q12	Gene located on chromosomes 17q21 and 3p24
	Two types, alpha and beta

Kardiotoxicita - poškozují srdeční sval

Inhibitory DNA topoizomeráz

Aktivita topoizomeráz – uvolnění nadšroubovicovitého vinutí při replikaci nebo transkripci.

Inhibicí aktivity topoizomeráz po rozštěpení řetězce DNA nedojde k opětovnému spojení řetězců vznikají tak **ss nebo ds zlomy, mechanismus není zcela jasný**

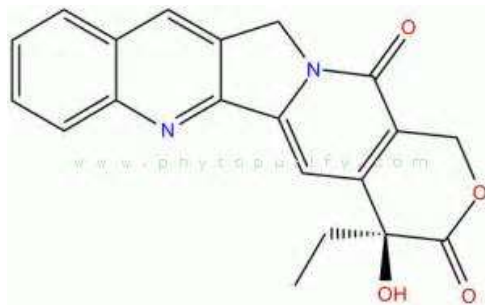
DNA topoisomerases	
Topoisomerase I	Topoisomerase II
100 kDa	170 kDa; 180 kDa
Makes <u>single-strand DNA breaks</u>	Makes <u>double-strand DNA breaks</u>
ATP independent	ATP dependent
Genes located on chromosome 20q12	Gene located on chromosomes 17q21 and 3p24
	Two types, alpha and beta



Topoizomeráza I a II **jsou přítomné prakticky jen v aktivně se dělících buňkách – vhodné cíle terapie**

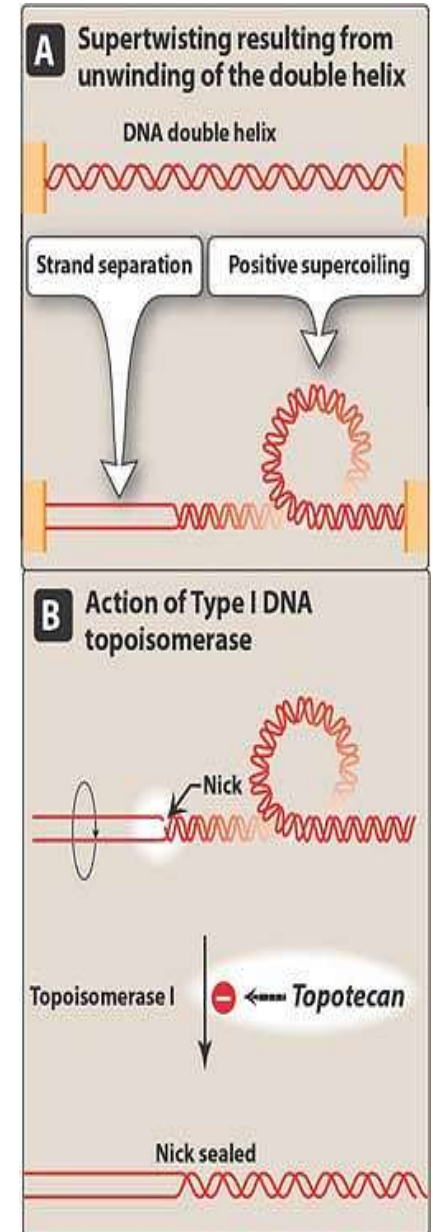
Inhibitory TOPOIZOMERÁZY I.

Deriváty **kamptothecinu** z kůry stromu *Camptotheca acuminata*
topotecan a irinotecan



kamptothecin

Vznik a kumulace jednořetězcových zlomů v DNA



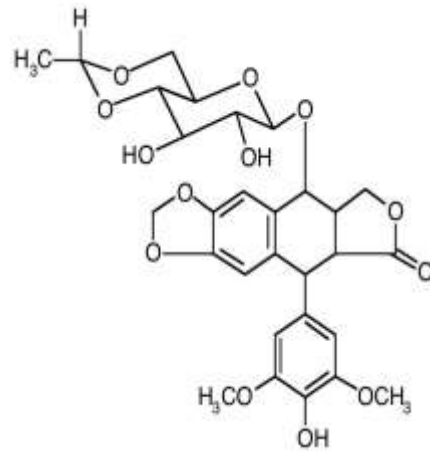
Inhibitory TOPOIZOMERÁZY II.

Deriváty epipodofylotoxinu z kořene

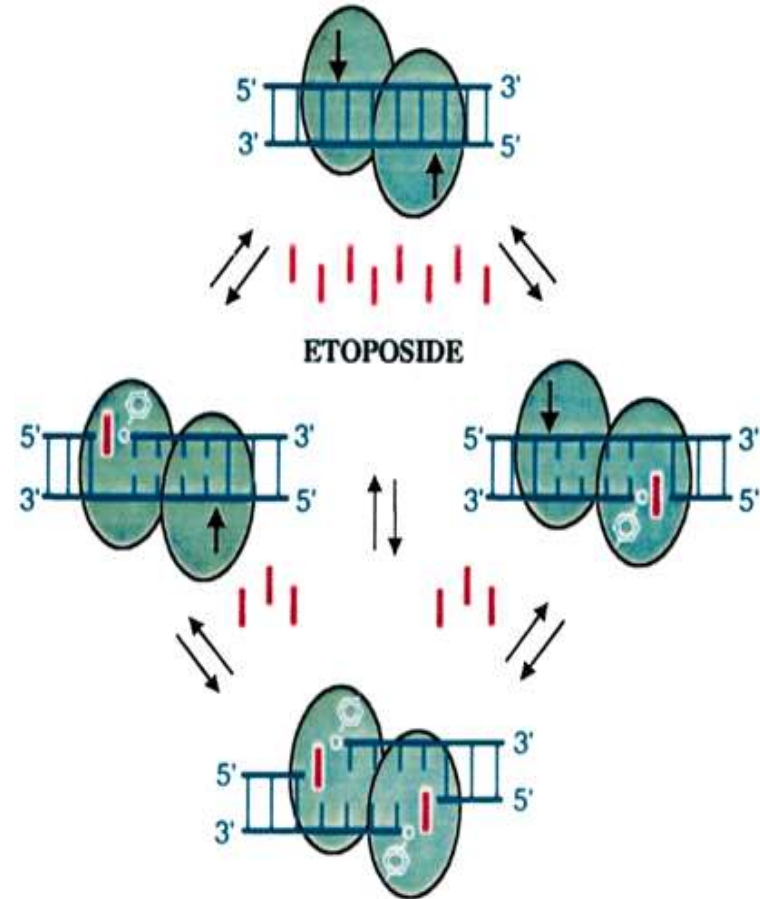
Podophyllum peltatum

(noholist štítnatý)

Etoposid, teniposid



Etoposid



Vznik ternárního komplexu s DNA a topizomerázou brání znovuspojení řetězců a vede ke kumulaci dvouřetězcových zlomů

GENOTOXICKÉ LÁTKY

Alkylační činidla a deriváty platiny

Interkalační činidla

Inhibitory DNA topoisomeras

Látky způsobující rozštěpení DNA

Klasická Cytostatika

*genotoxické
látky
a
antimetaboly*

Účinek na
DNA

Účinek na mitotické
vřeténko

Účinek na
receptorech pro
steroidní
hormony

Poškození DNA nebo inhibice
syntézy

Agonisté

Antagonisté

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s jiné
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volných
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topoisomeráz

Antimetaboly
a
hydroxyurea

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(genotoxicita)

Poškození DNA při syntéze,
interference s ní a další efekty

ANTIMETABOLITY a hydroxymočovina

antimetabolity

strukturní analogy vitaminů, regulačních látek nebo substrátů enzymů, blokující (obvykle mechanismem kompetice o vazebné místo) jejich působení.

Analogy kyseliny listové

Purinové antimetabolity

Pyrimidinové antimetabolity

Hydroxymočovina

Antimetabolity – analogy stavebních jednotek NA

- Inkorporace do DNA, inhibice replikace, indukce zlomů a inhibice oprav
 - Inhibice klíčových enzymů
 - Methylace DNA

Fungují především (ale ne výhradně) v S fázi

Analogy kyseliny listové

Metotrexát
(Inhibitor DFR)

Purinové analogy

Merkaptoguanin
(analog báze)

Fludarabin
(analog nukleosidu)

Pyrimidinové analogy

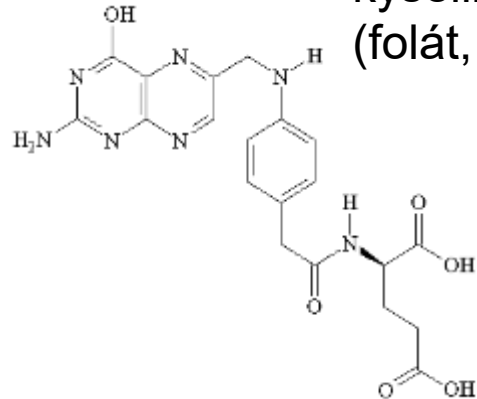
Fluoruracil
(analog báze)

Cytarabin
(analog nukleosidu)

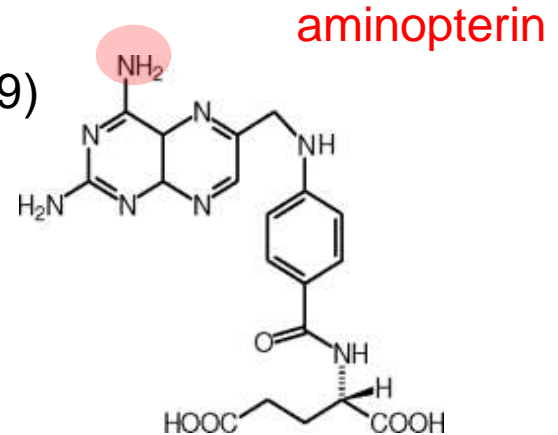
+ hydroxymočovina



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kyselina listová
(folát, vitamín B9)



aminopterin

1947 - **Sidney Farber** (Harvard Medical School)

Bylo známo, že podání **kyseliny listové** obnoví krvetvorbu při anemii z nedostatku folátu. Pokoušel se **kyselinou listovou** léčit leukemii u dětí – došlo k rychlé progresi onemocnění. Začal tedy hledat „anti-folát“ – použil **aminopterin** kterým dosáhl ústupu (remise) akutní lymfoblastické leukemie (ALL) u několika dětí.

The New England Journal of Medicine

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Volume 238

JUNE 3, 1948

Number 23

TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

SIDNEY FARBER, M.D.,† LOUIS K. DIAMOND, M.D.,‡ ROBERT D. MERCER, M.D.,§
ROBERT F. SYLVESTER, JR., M.D.,¶ AND JAMES A. WOLFF, M.D.||

BOSTON

Sufficient encouragement was obtained from these observations to justify further studies on the effect of more powerful antagonists to folic acid on the course of acute leukemia in children. Since November, 1947, when a sufficiently pure substance became available, to the time of this writing (April 15, 1948) we have made studies on 16 children with acute leukemia to whom the most powerful folic acid antagonist we have yet encountered, 4-aminopteroyl-glutamic acid (aminopterin††) was administered by intramuscular injection. Many of these children were moribund at the onset of therapy. Of 16 infants and children with acute leukemia treated with aminopterin 10 showed clinical, hematologic and pathological evidences of improvement of important

nature of three months' duration at the time of this report. Six patients did not respond well; 4 of these are now dead, and 2 were unimproved. This paper presents detailed clinical, hematologic and bone-marrow studies in 5 children selected from these 10 who showed evidences of important improvement—the course in the other cases was essentially similar. The patients are selected for the purpose of illustrating some of the problems concerned with the use of aminopterin and because they demonstrate the best results that we have

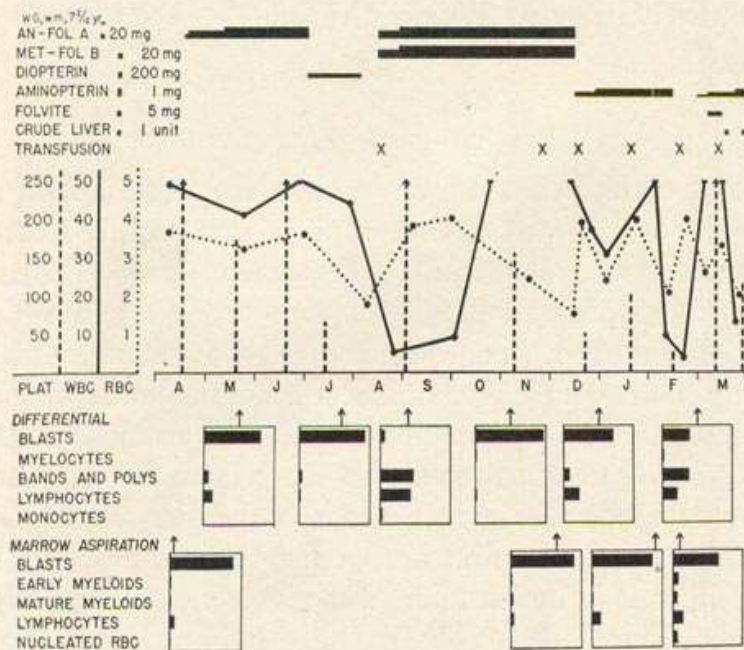


FIGURE 1. Course of Leukemia in Case 1.

observed. The toxic effects are stressed in these histories, and the temporary nature of the remissions is emphasized.

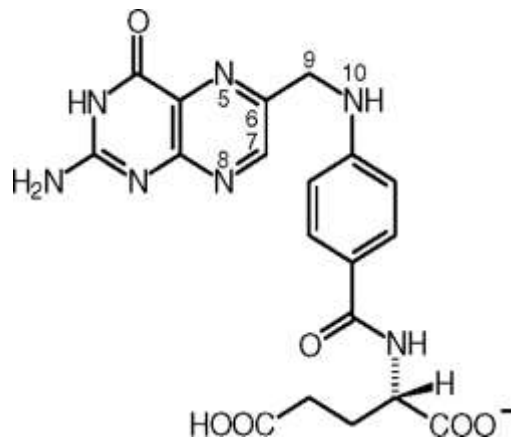


Nature Reviews | Cancer

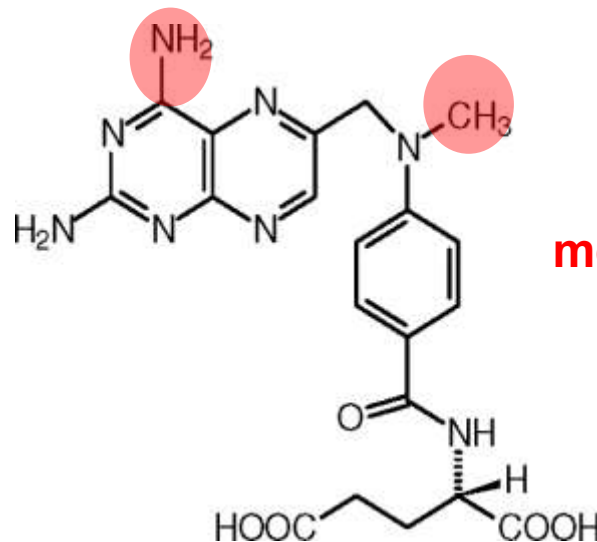
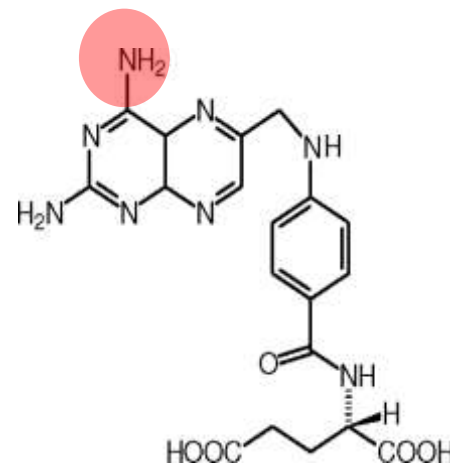
Sidney Farber

1953 -
aminopterin nahrazen
metotrexátem (MTX)
a schválen FDA.

kyselina listová
(folát)



aminopterin

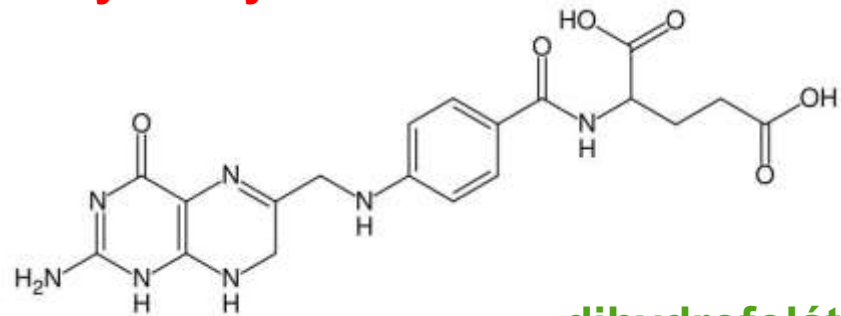
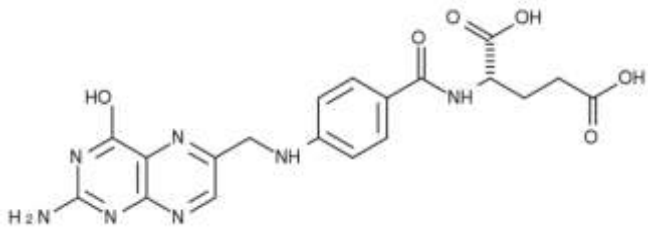


metotrexát (MTX)

KYSELINA LISTOVÁ

Donor jednouhlíkatých zbytků

kyselina listová
(folát)



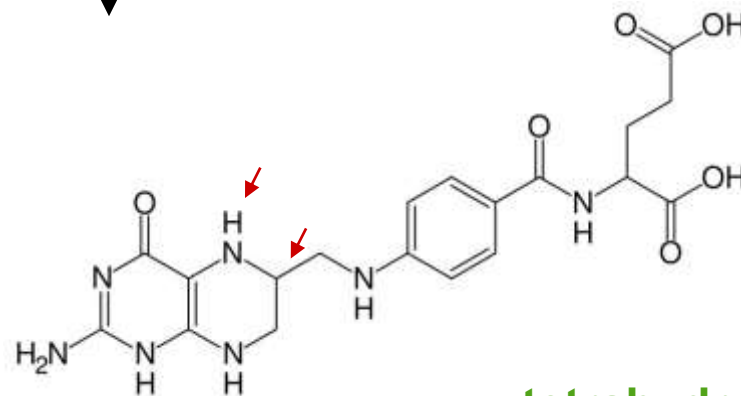
dihydrofolát

NADPH

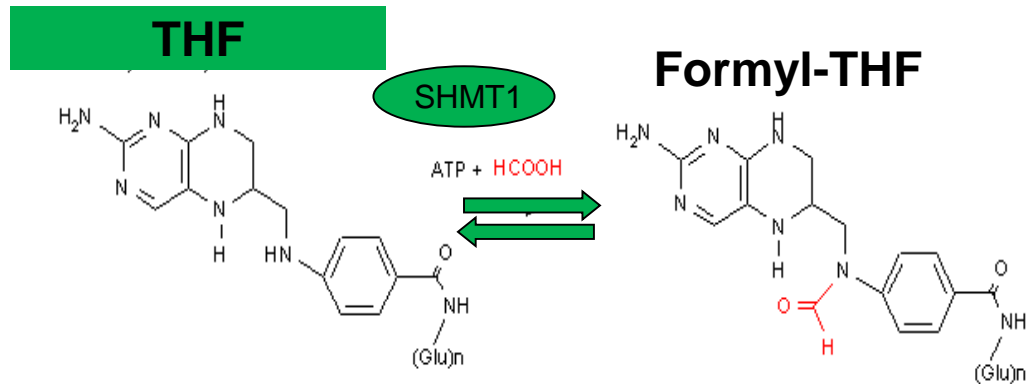


NADP+

Dihydrofolát
reduktáza
(DHFR)

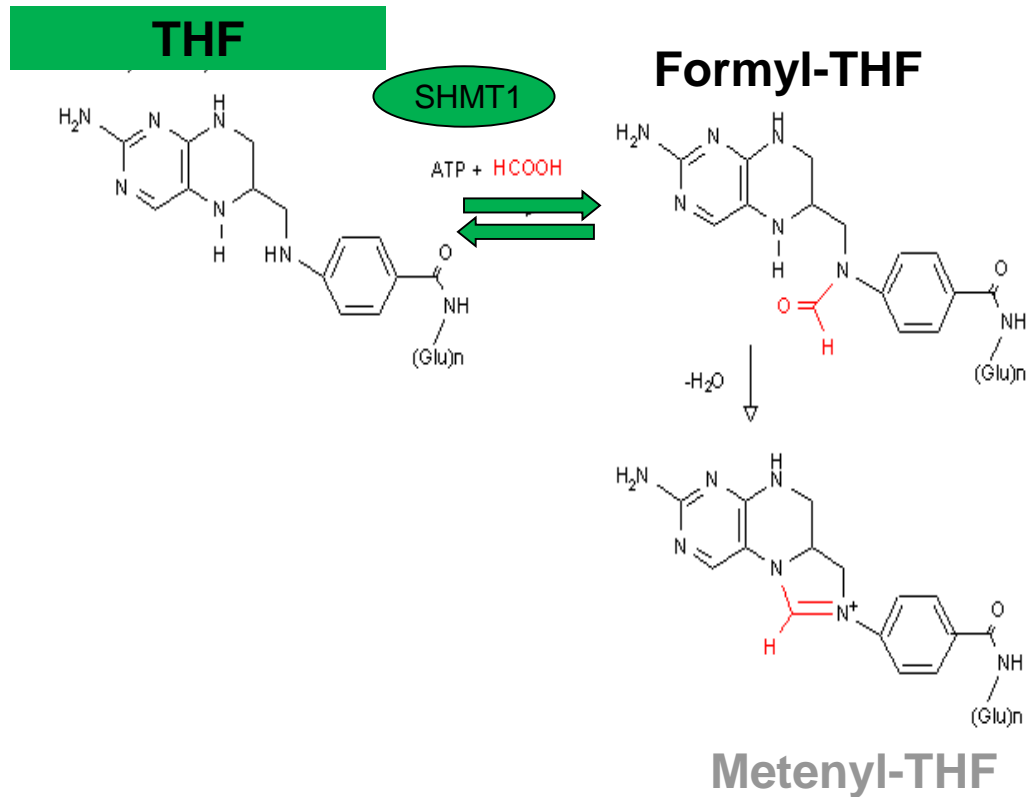


tetrahydrofolát



THF je donor jednouhlíkových zbytků (nesených N5 a N10) pro několik biochemických reakcí

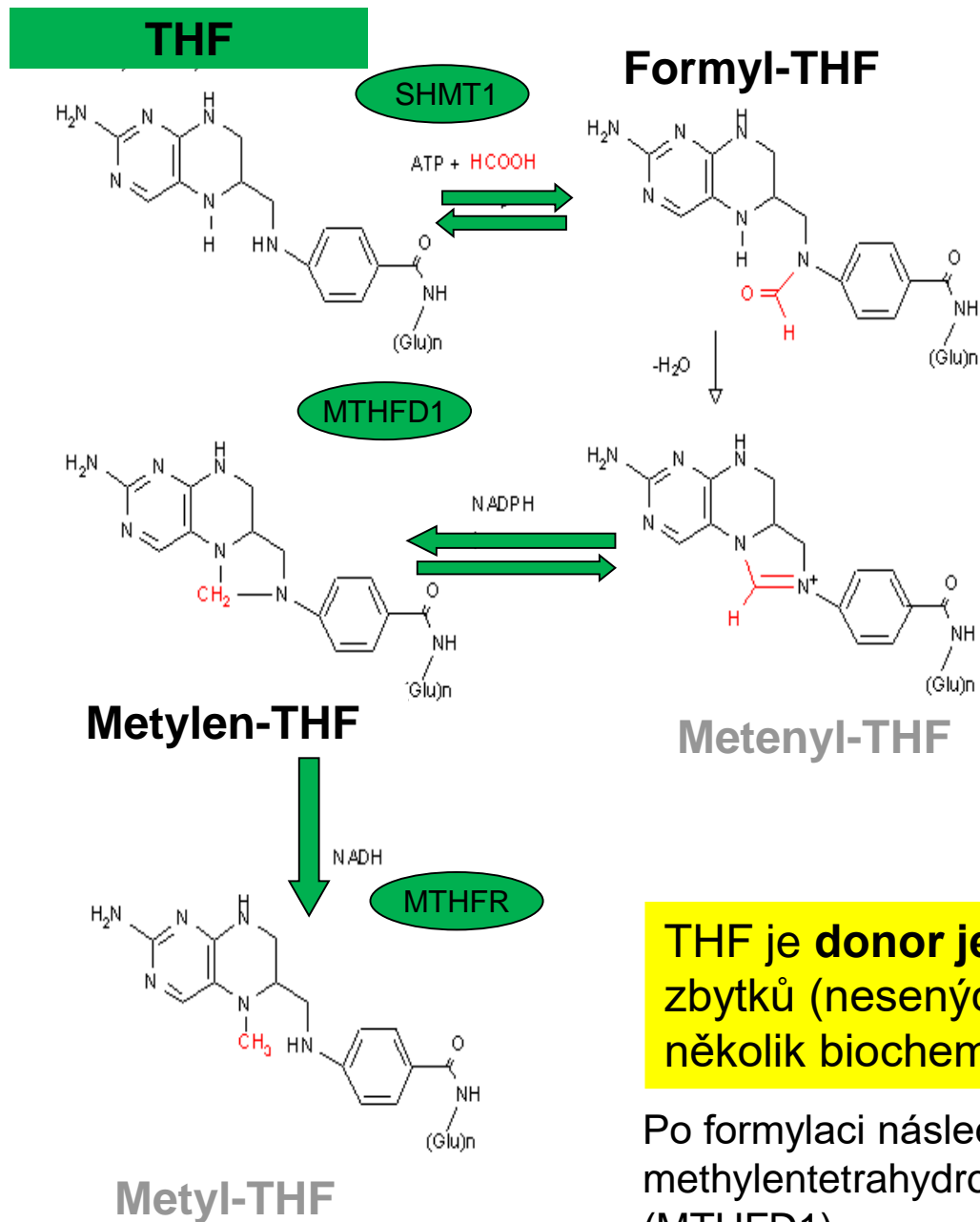
Po formylaci následuje **postupná redukce** methylenetetrahydrofolát dehydrogenázou (MTHFD1) a metylenetetrahydrofolát reduktázou (MTHFR)



THF je donor jednouhlíkových zbytků (nesených N5 a N10) pro několik biochemických reakcí

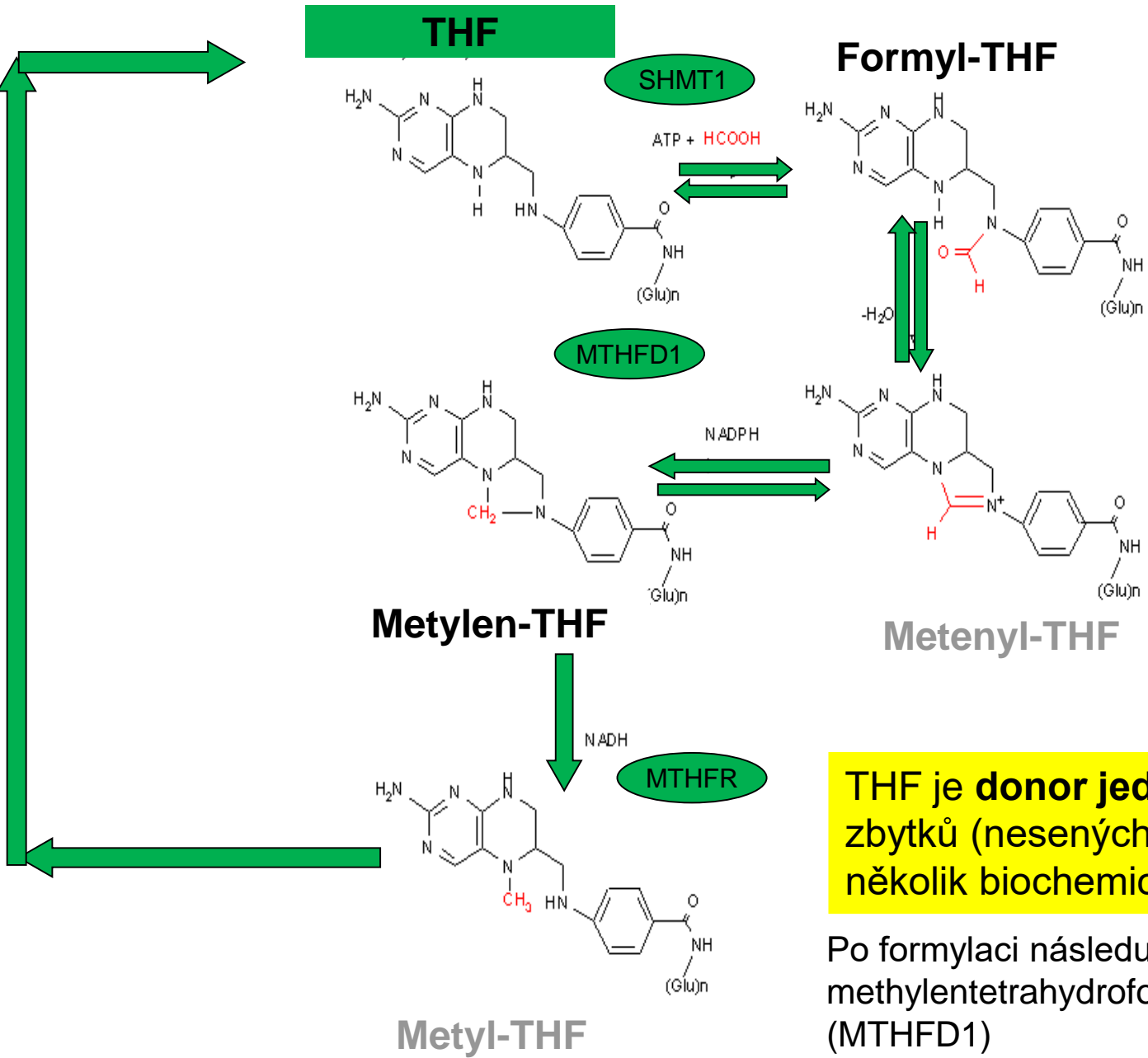
Po formylaci následuje **postupná redukce** methylenetetrahydrofolát dehydrogenázou (MTHFD1)

a metylenetetrahydrofolát reduktázou (MTHFR)



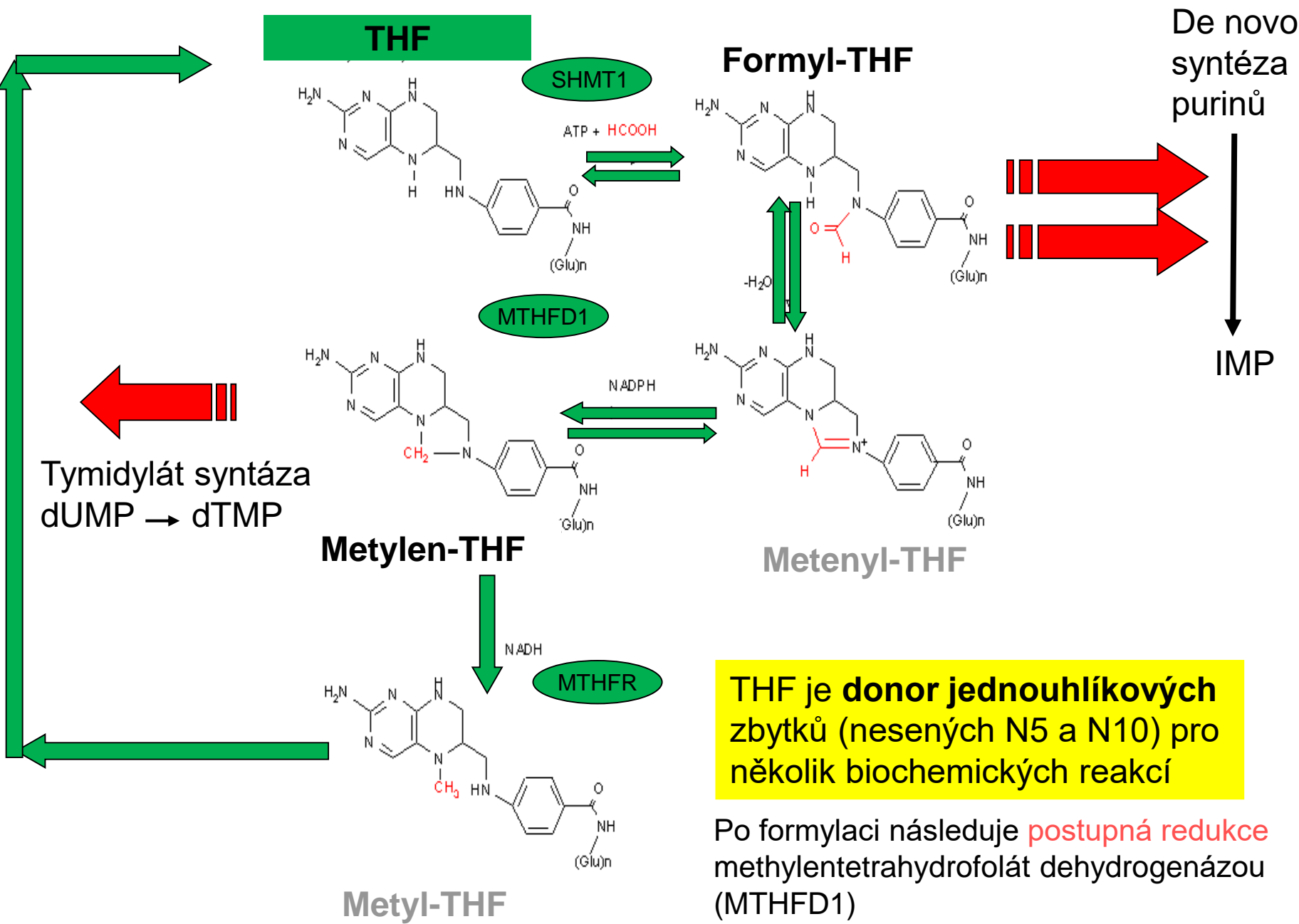
THF je **donor jednouhlíkových zbytků** (nesených N5 a N10) pro několik biochemických reakcí

Po formylaci následuje **postupná redukce** methylenetetrahydrofolát dehydrogenázou (MTHFD1) a metylenetetrahydrofolát reduktázou (MTHFR)



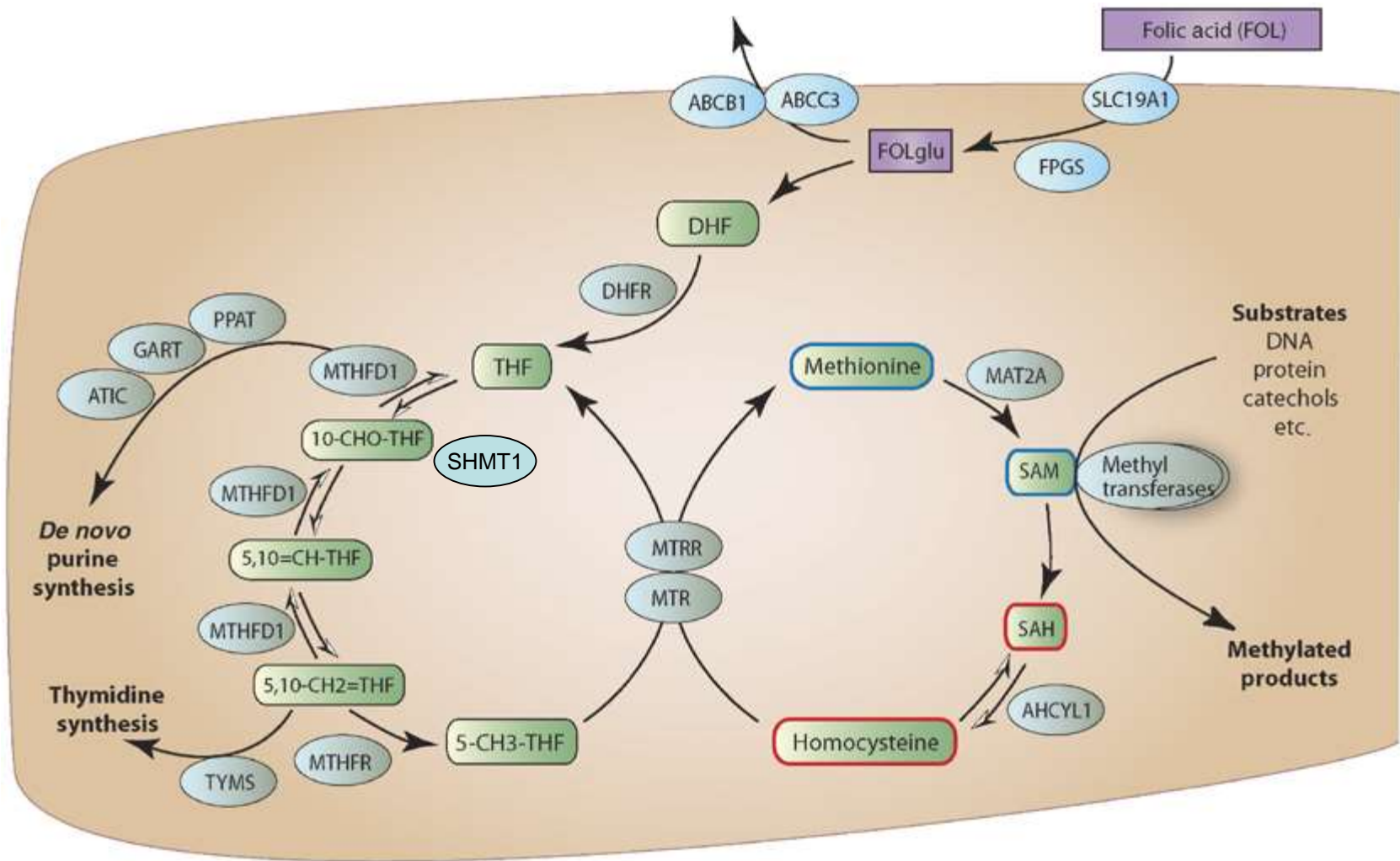
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THF je donor jednouhlíkových zbytků (nesených N5 a N10) pro několik biochemických reakcí

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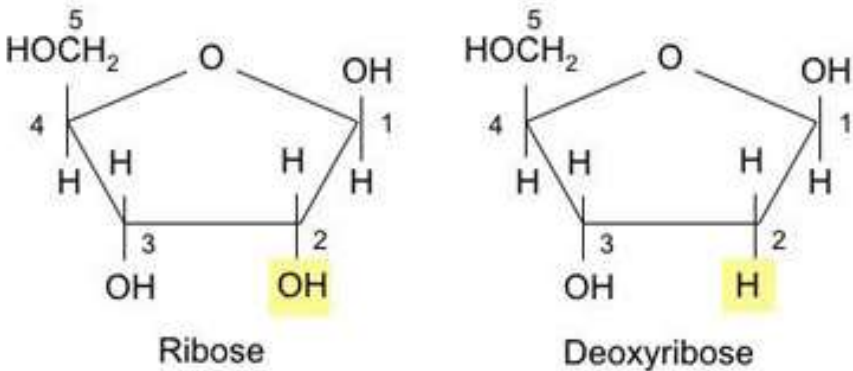
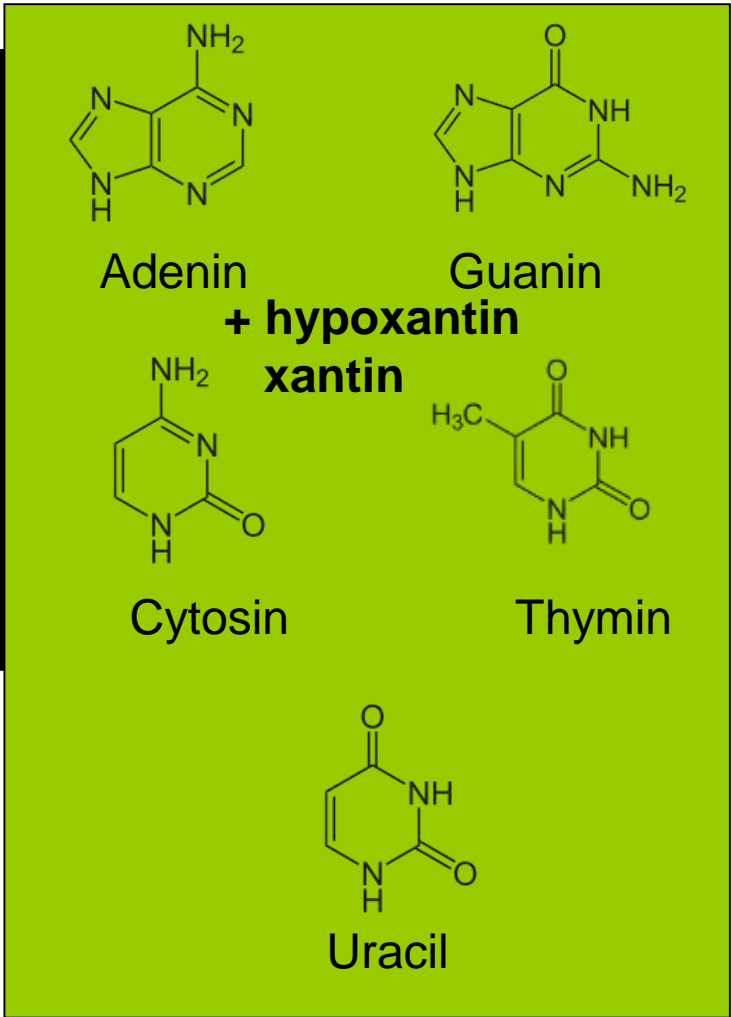
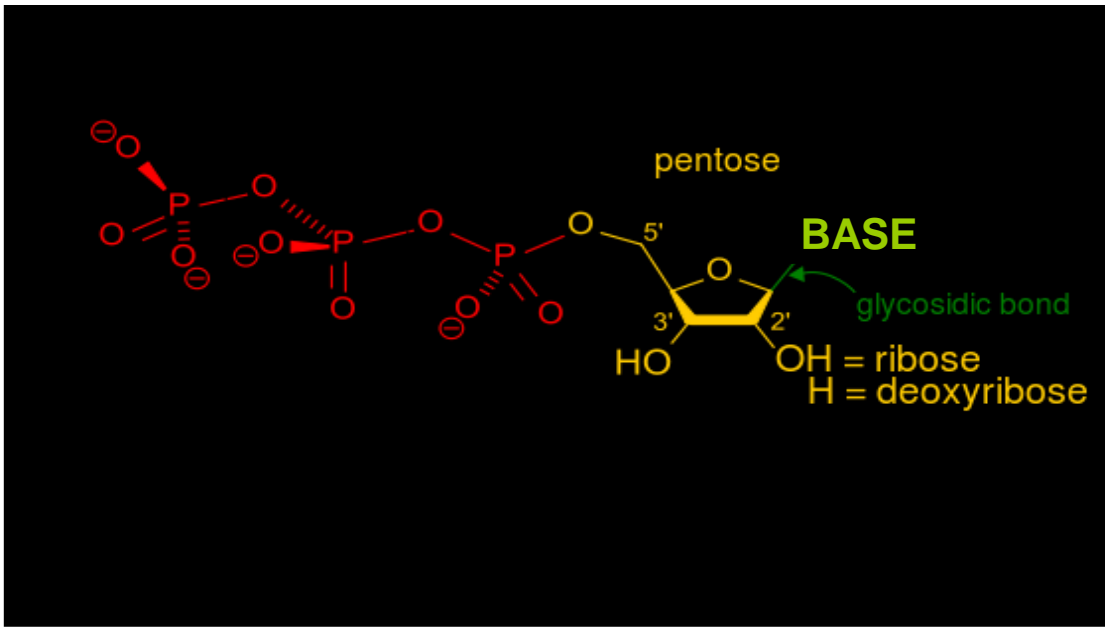


SHMT1 – serinhydroxymetyl transferáza

DHFR - dihydrofolát reduktáza

MTHFD1 - trifunkční methylenetetrahydrofolát dehydrogenáza

MTHF- methylenetetrahydrofolát reduktáza



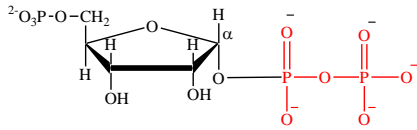
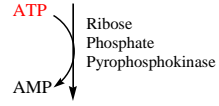
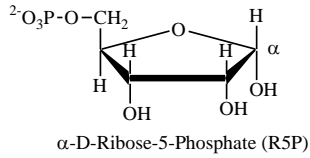
(deoxy)nukleosidy:
Adenosin, guanosin
cytidin, thymidin, uridin
+ inosin a xantosin

Syntéza a recyklace purinů a pyrimidinů a jejich nukleosidů

Syntéza de novo

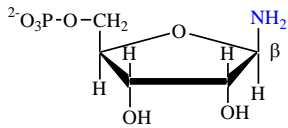
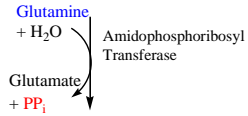
Salvage pathway (*šetřící dráha, záchranná dráha*)
především re-utilizace nukleosidů z buňky i z okolí

De novo syntéza purinů

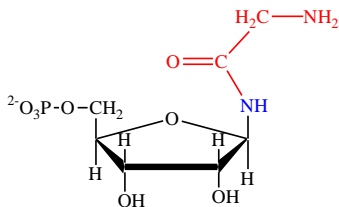
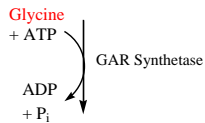


PRPP

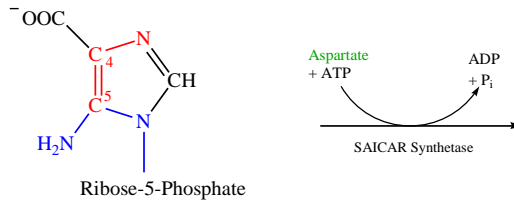
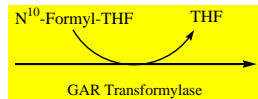
5-Phosphoribosyl- α -pyrophosphate (PRPP)



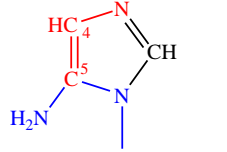
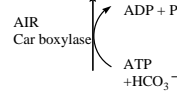
β -5-Phosphoribosylamine (PRA)



Glycinamide Ribotide (GAR)

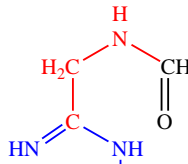
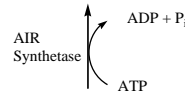


Carboxyamidoimidazole Ribotide (CAIR)



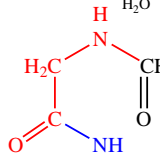
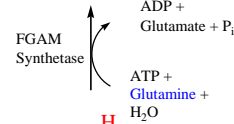
Ribose-5-Phosphate

5-Aminoimidazole Ribotide (AIR)



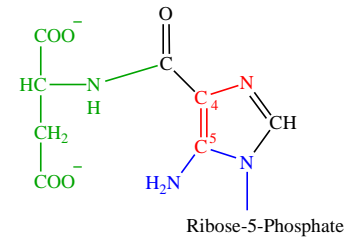
Ribose-5-Phosphate

Formylglycinamide ribotide (FGAM)

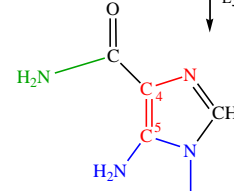
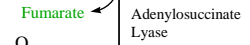


Ribose-5-Phosphate

Formylglycinamide ribotide (FGAR)

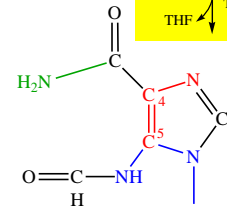
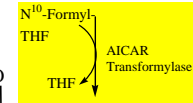


5-Aminoimidazole-4-(N-succinylcarboxamide) ribotide (SAICAR)



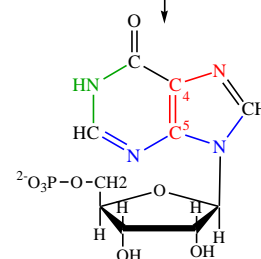
Ribose-5-Phosphate

5-Aminoimidazole-4-carboxamide ribotide (AICAR)



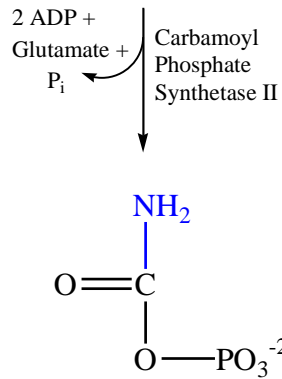
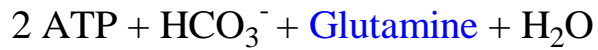
Ribose-5-Phosphate

5-Formaminoimidazole-4-carboxamide ribotide (FAICAR)

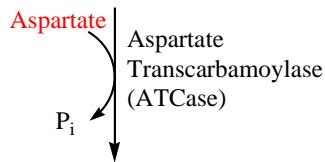


Inosine Monophosphate (IMP)

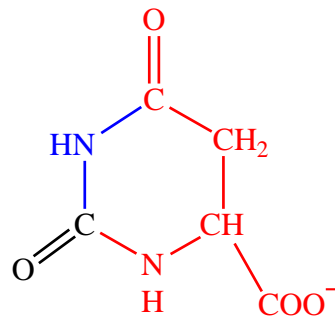
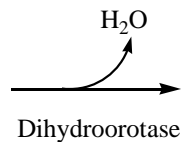
Pyrimidine Synthesis



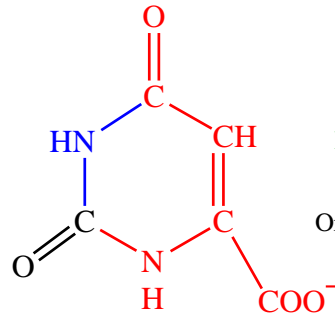
Carbamoyl Phosphate



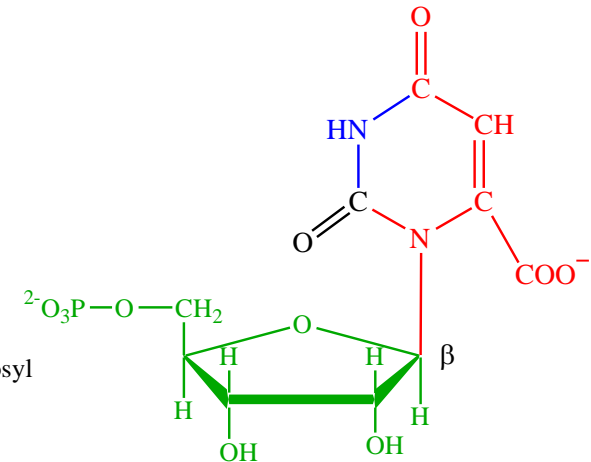
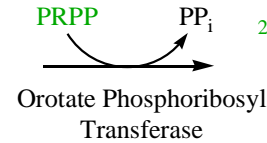
Carbamoyl Aspartate



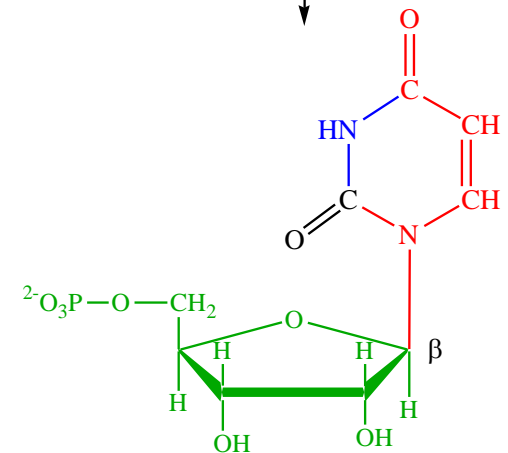
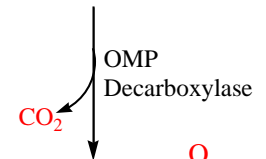
Dihydroorotate



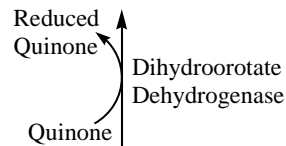
Orotate

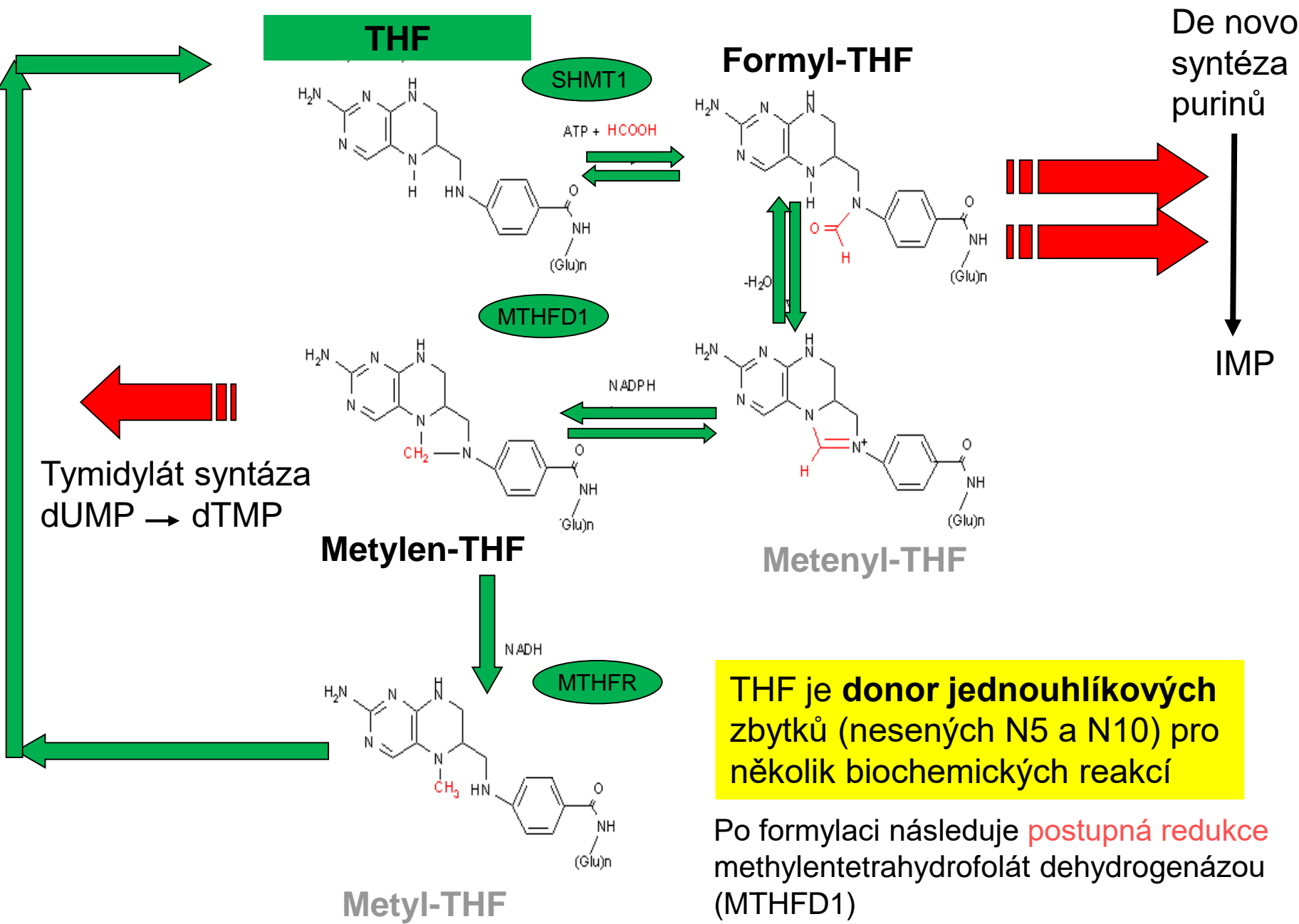


Orotidine-5'-monophosphate (OMP)



Uridine Monophosphate (UMP)



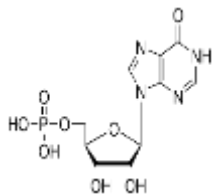


THF je donor jednouhlíkových zbytků (nesených N5 a N10) pro několik biochemických reakcí

Po formylaci následuje postupná redukce methylenetetrahydrofolát dehydrogenázou (MTHFD1) a metylenetetrahydrofolát reduktázou (MTHFR)

PURINY

Syntéza De novo



IMP

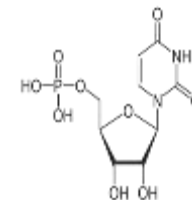
PRPP

Ribózo 5-P

karbamoyl fosfát

PYRIMIDINY

Syntéza De novo



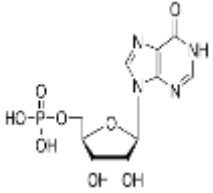
UMP

P_Pi



PURINY

Syntéza De novo



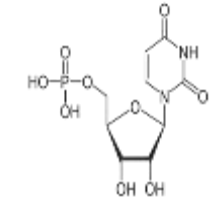
IMP

PRPP

Ribózo 5-P

PYRIMIDINY

Syntéza De novo



UMP

karbamoyl fosfát

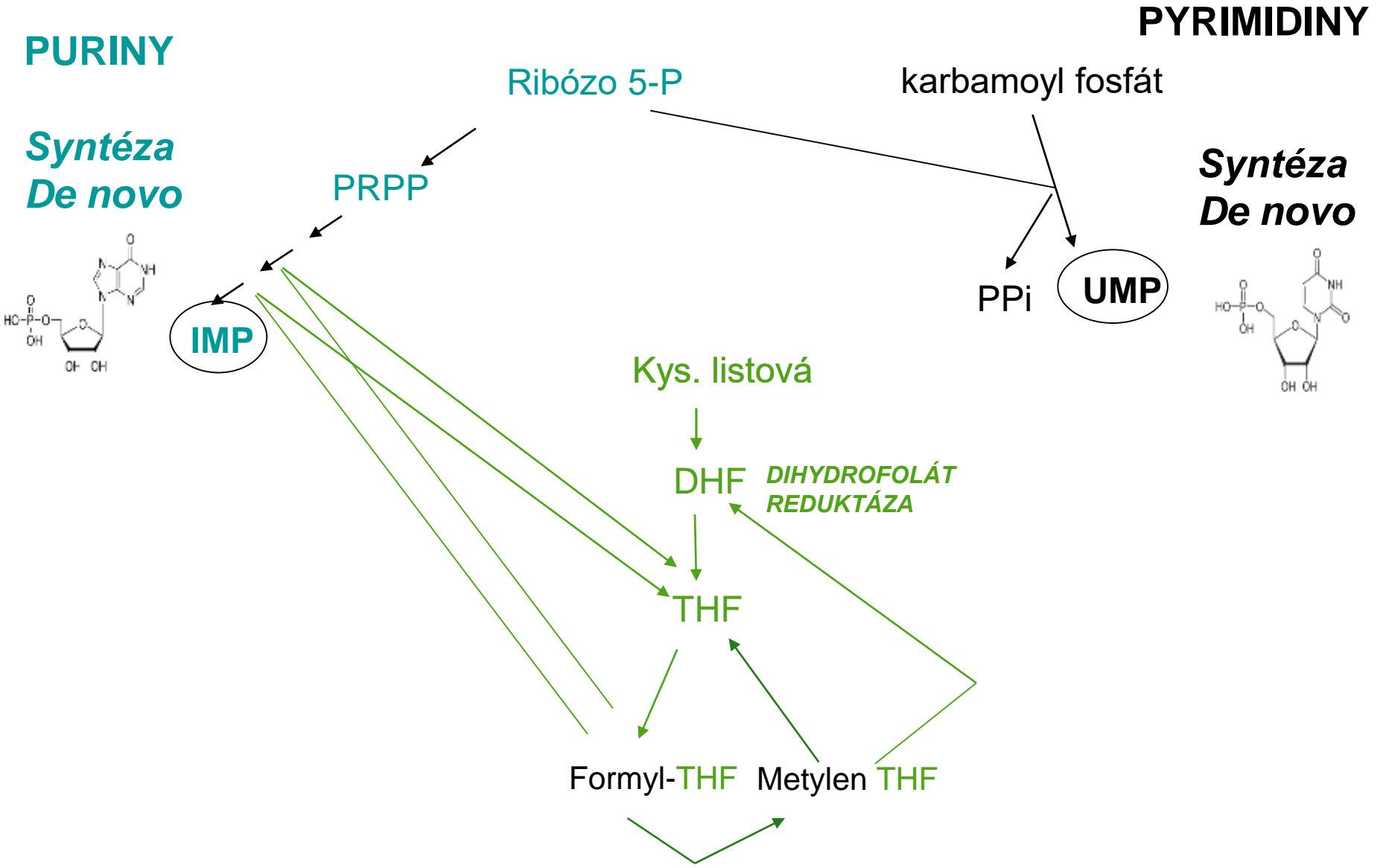
P_Pi

Kys. listová

DHF *DIHYDROFOLÁT REDUKTÁZA*

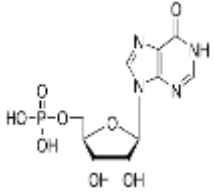
THF

Formyl-THF Metylen THF



PURINY

Syntéza De novo



IMP

AMP

GMP

ADP

GDP

ATP

GTP

PRPP

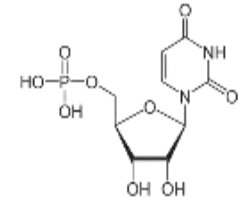
Ribózo 5-P

karbamoyl fosfát

P_Pi

UMP

Syntéza De novo



Kys. listová

DHF

*DIHYDROFOLÁT
REDUKTÁZA*

THF

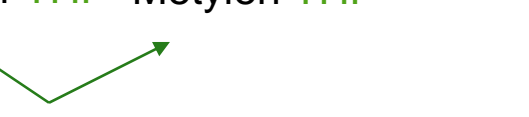
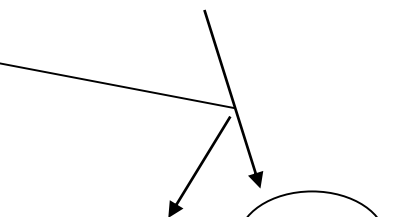
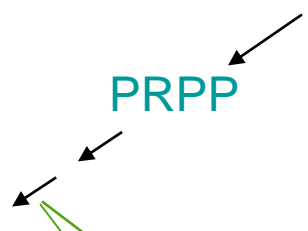
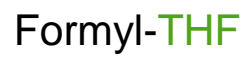
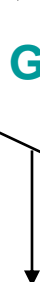
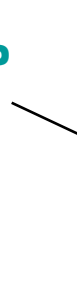
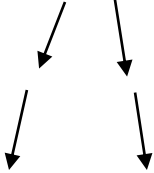
Formyl-THF

Metylen THF

*RIBONUKLEOTID
REDUKTÁZA*

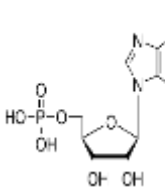
dGDP

dADP



PURINY

Syntéza De novo



IMP

AMP

GMP

ADP

GDP

ATP

GTP

PRPP

Ribózo 5-P

Kys. listová

DHF

DIHYDROFOLÁT
REDUKTÁZA

THF

Formyl-THF

Metylen-THF

dGDP
RIBONUKLEOTID
REDUKTÁZA

dADP

karbamoyl fosfát

PPi

UMP

UDP

dUMP

UTP

CTP
SYNTÁZA

CTP

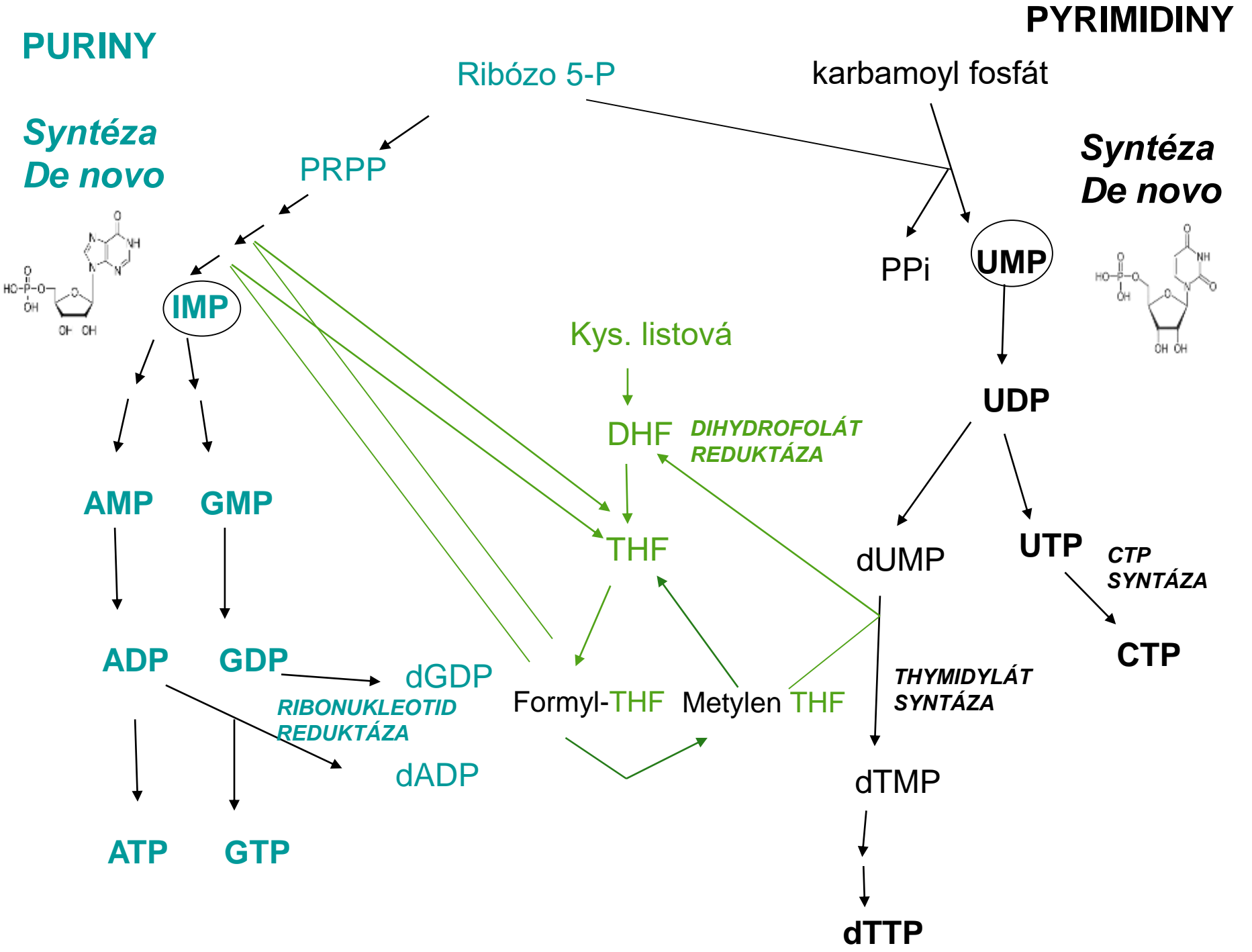
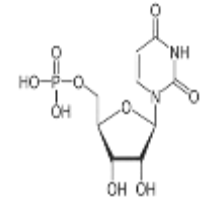
THYMIDYLÁT
SYNTÁZA

dTMP

dTTP

PYRIMIDINY

Syntéza De novo

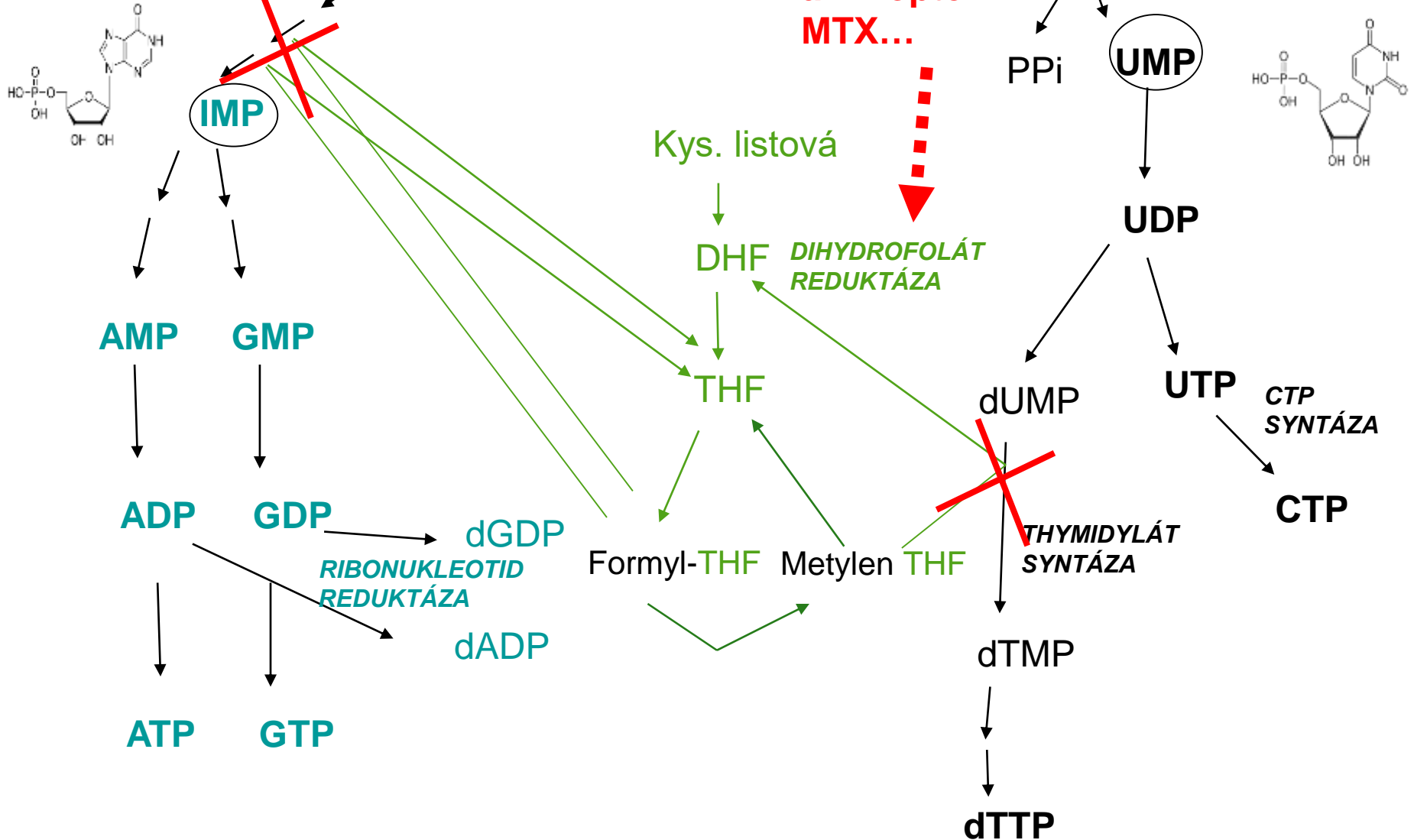


PURINY

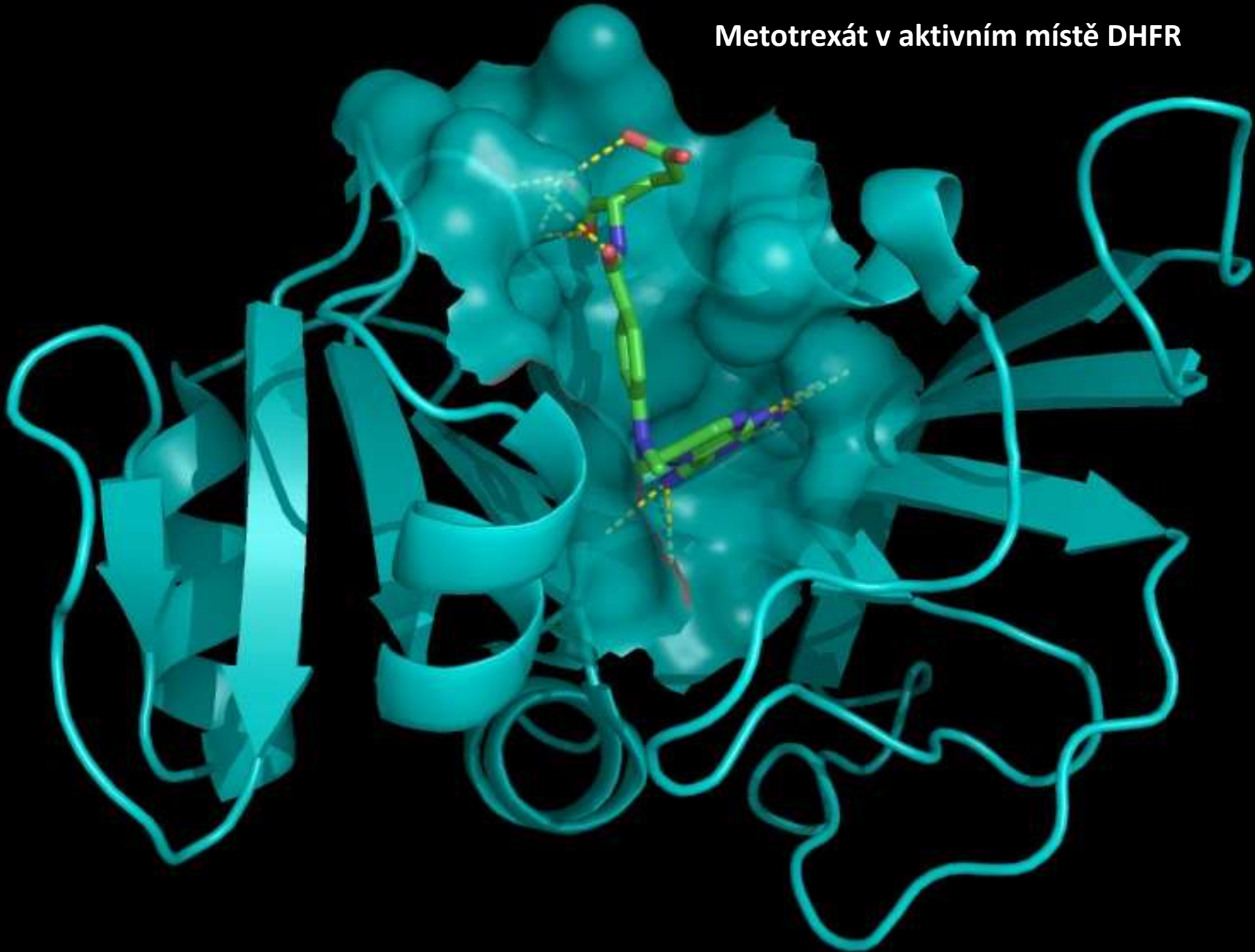
PYRIMIDINY

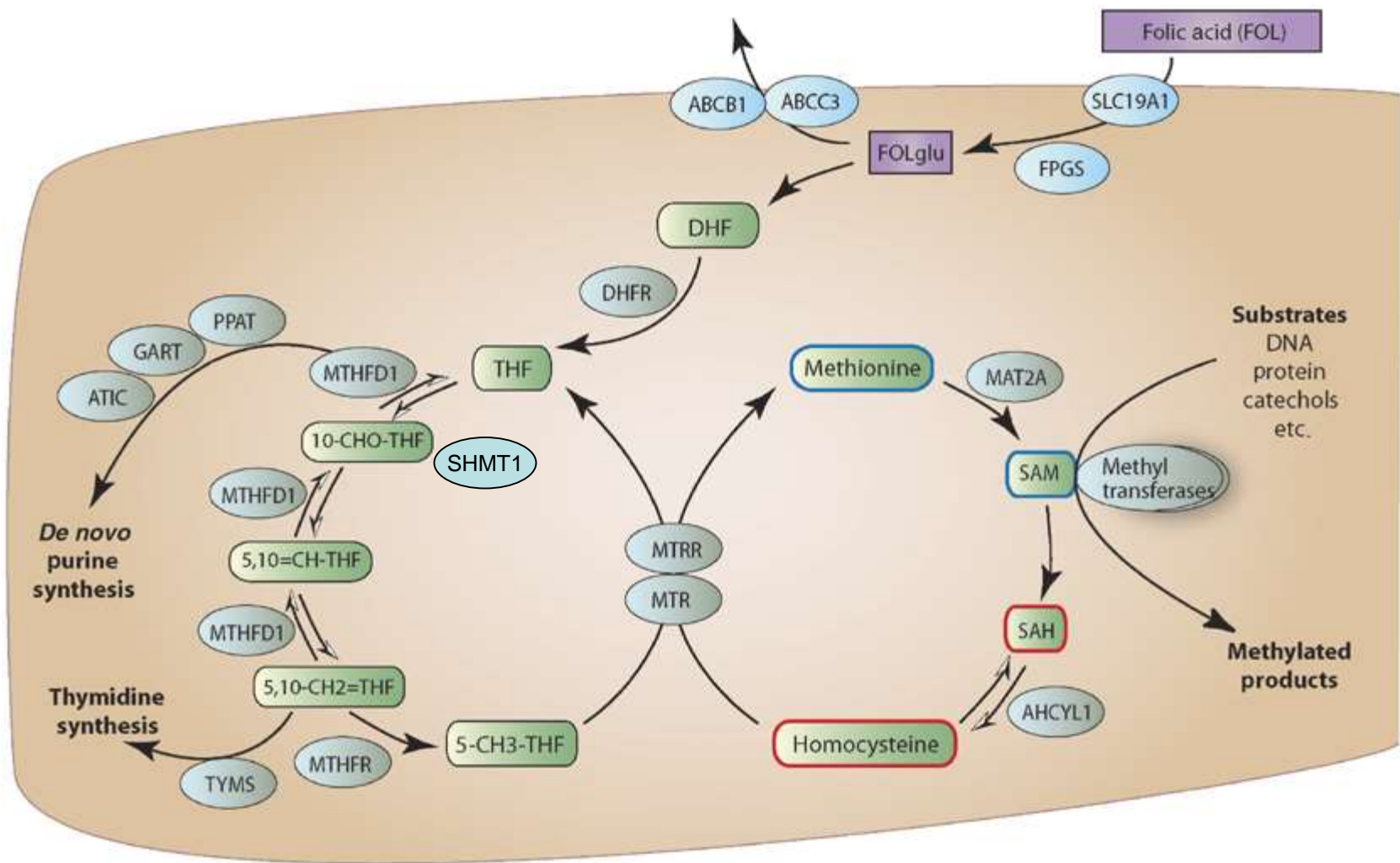
Syntéza De novo

Syntéza De novo



Metotrexát v aktivním místě DHFR



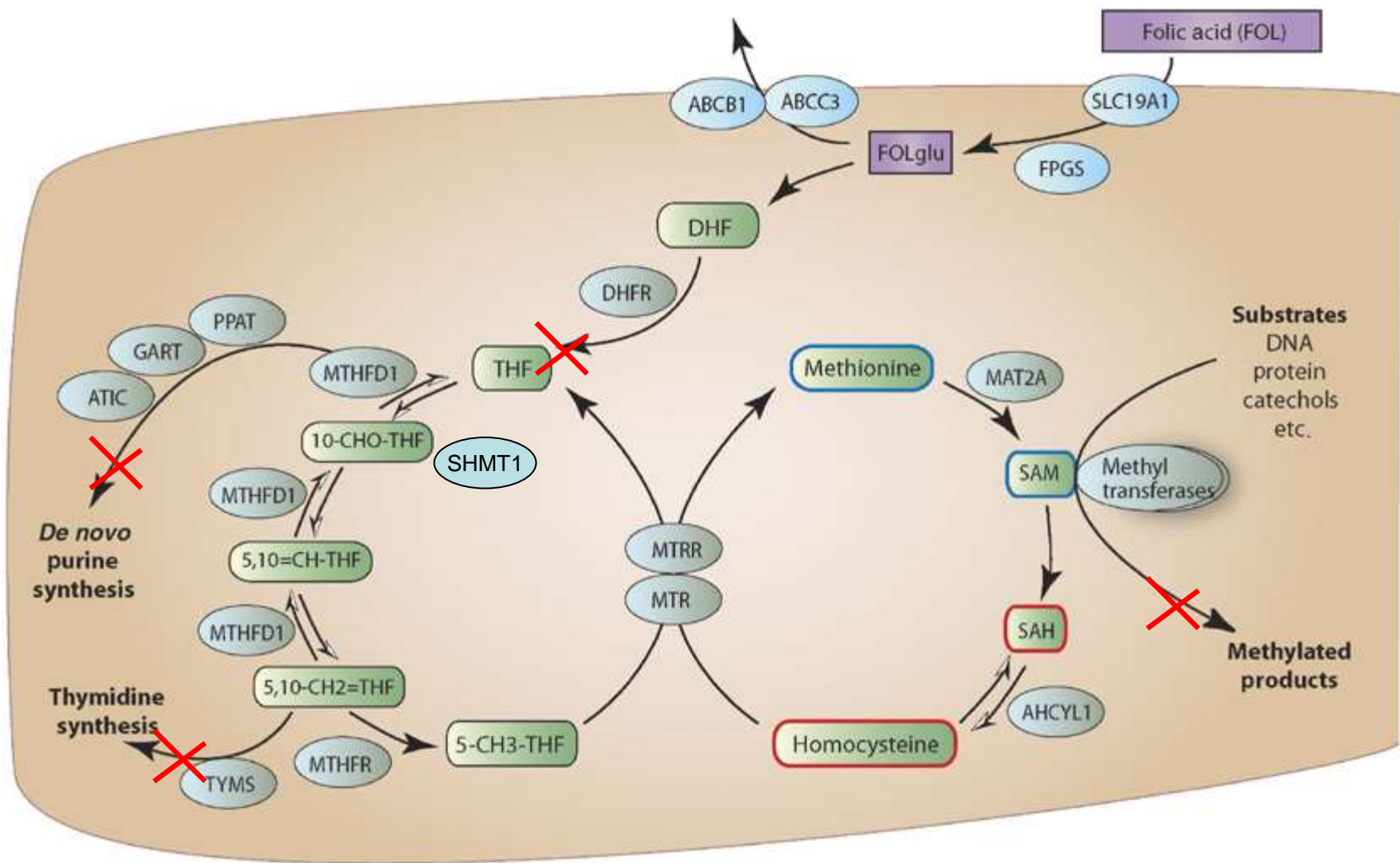


SHMT1 – serinhydroxymetyl transferáza

DHFR - dihydrofolát reduktáza

MTHFD1 - trifunkční methylenetetrahydrofolát dehydrogenáza

MTHF- methylenetetrahydrofoláte reduktáza



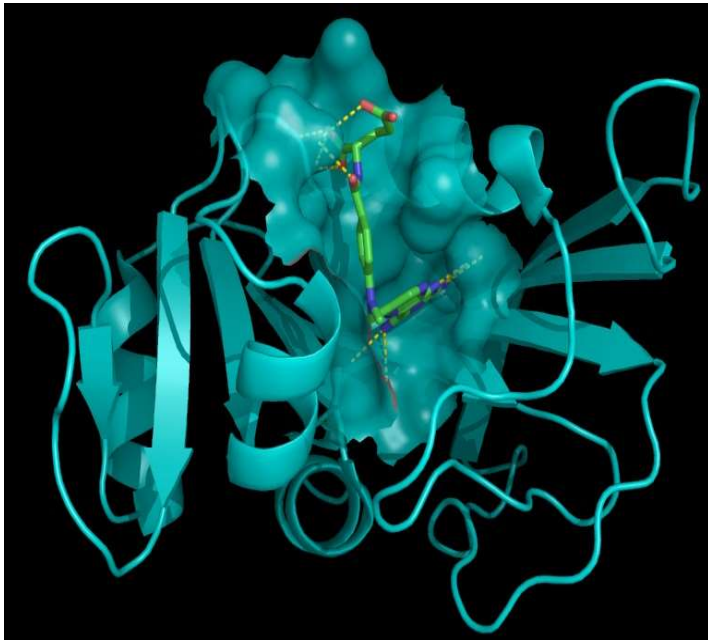
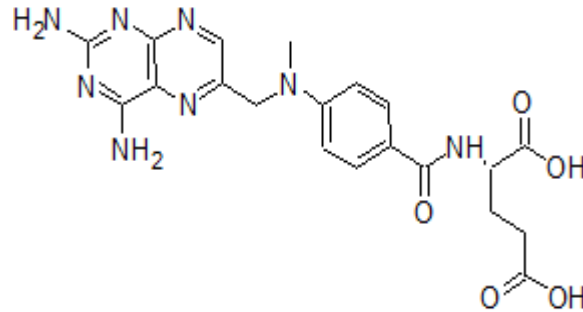
SHMT1 – serinhydroxymetyl transferáza

DHFR - dihydrofolát reduktáza

MTHFD1 - trifunkční methylen tetrahydrofolát dehydrogenáza

MTHFR- methylen tetrahydrofolát reduktáza

Metotrexát



Inhibuje dihydrofolát reduktázu DHFR

THF je zdroj jednouhlíkových zbytků
Uhlíkový zbytek je využíván thymidilát syntázou (TS) a dvěma enzymy de novo syntézy purinů
glycinamid ribonukleotid –formyl transferázou
(GARFT) a AICAR (amino imidazolkarboxamid
ribonukleotid-formyl transferáza).

Inhibice obou *de novo* syntéz vede k nedostatku
stavebních prvků pro syntézu DNA a indukci vnitřní
(mitochondriální) dráhy apoptózy nebo nekrózy (záleží
na koncentraci)

ANTIMETABOLITY a hydroxymočovina

Analogy kyseliny listové

Analogy bází

Analogy nukleosidů

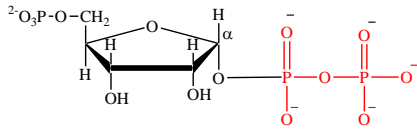
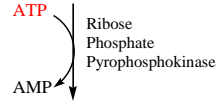
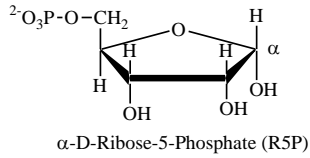
Hydroxymočovina

Syntéza a recyklace purinů a pyrimidinů a jejich nukleosidů

**Syntéza de novo - puriny (syntetizované na ribóze, *PRPP-IMP*)
pyrimidiny (nejdříve báze, pak až vazba na cukr
karbamoylfosfát-UMP)**

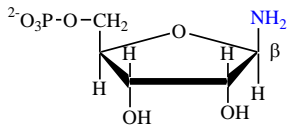
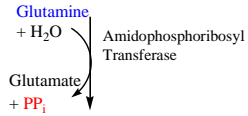
**Salvage pathway - (šetřící dráha, záchranná dráha)
*interkonverze a reutilizace bazí a nukleosidů z buňky i z okolí***

De novo syntéza purinů

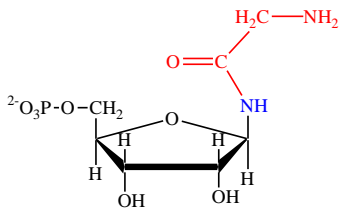
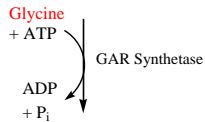


PRPP

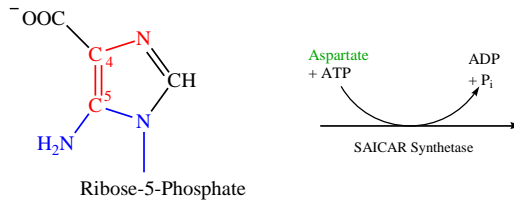
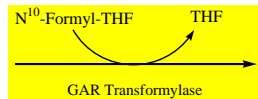
5-Phosphoribosyl- α -pyrophosphate (PRPP)



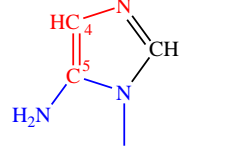
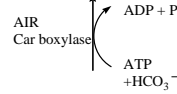
β -5-Phosphoribosylamine (PRA)



Glycinamide Ribotide (GAR)

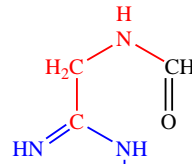
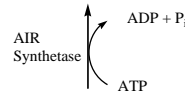


Carboxyamidoimidazole Ribotide (CAIR)



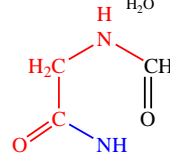
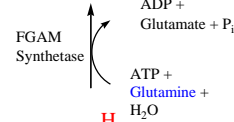
Ribose-5-Phosphate

5-Aminoimidazole Ribotide (AIR)



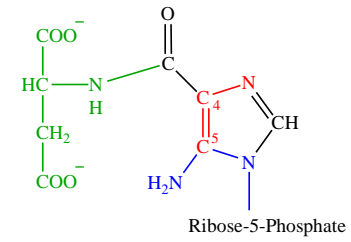
Ribose-5-Phosphate

Formylglycinamide ribotide (FGAM)

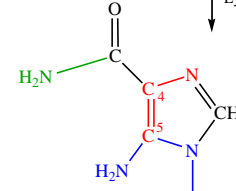
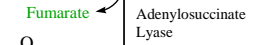


Ribose-5-Phosphate

Formylglycinamide ribotide (FGAR)

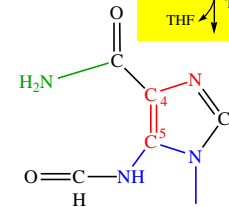
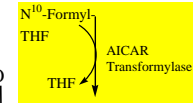


5-Aminoimidazole-4-(N-succinylcarboxamide) ribotide (SAICAR)



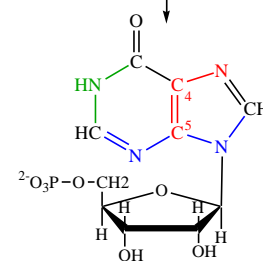
Ribose-5-Phosphate

5-Aminoimidazole-4-carboxamide ribotide (AICAR)



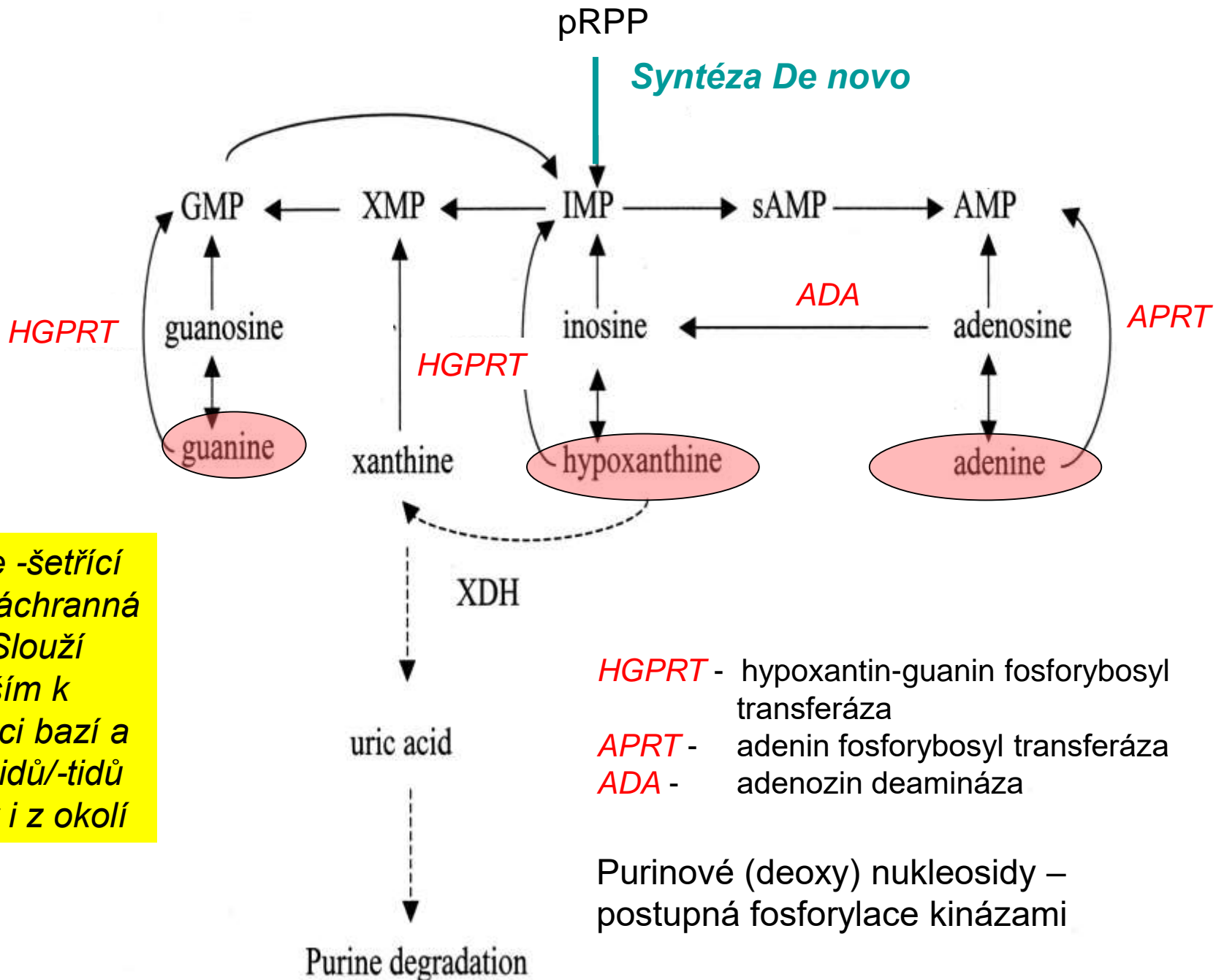
Ribose-5-Phosphate

5-Formaminoimidazole-4-carboxamide ribotide (FAICAR)



Inosine Monophosphate (IMP)

Purinová „salvage“ dráha



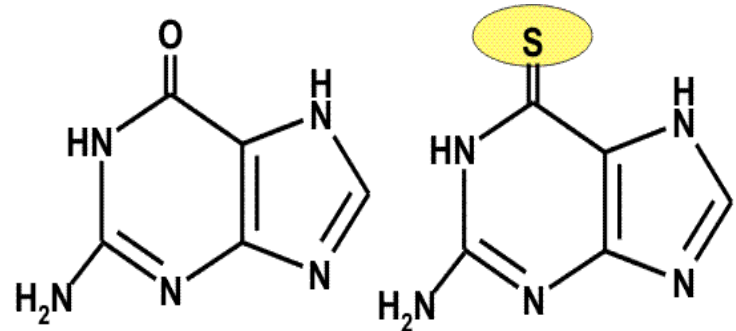
ANTIBÁZE (antipuriny)

thioguanin

(analog guaninu, inhibuje salvage dráhu)

Terapie leukemií

1950s



Guanine

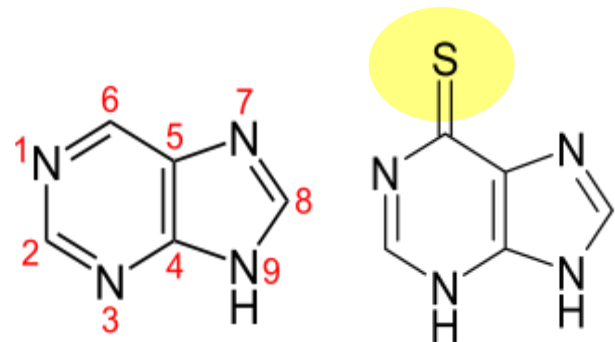
6-Thio-Guanine

6-merkaptopurin

(analog hypoxantinu, inhibuje salvage dráhu)

Terapie ALL u dětí

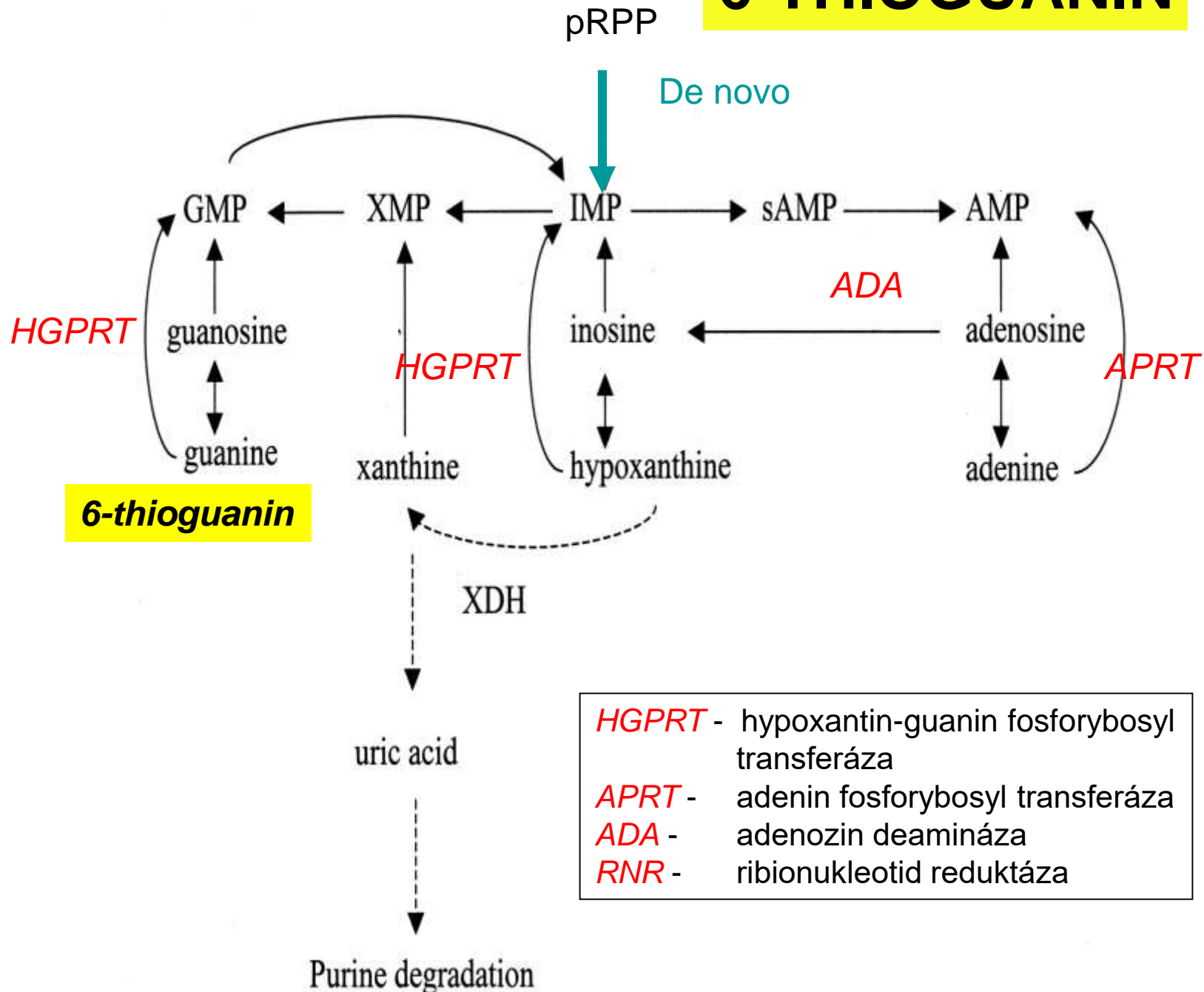
1950s



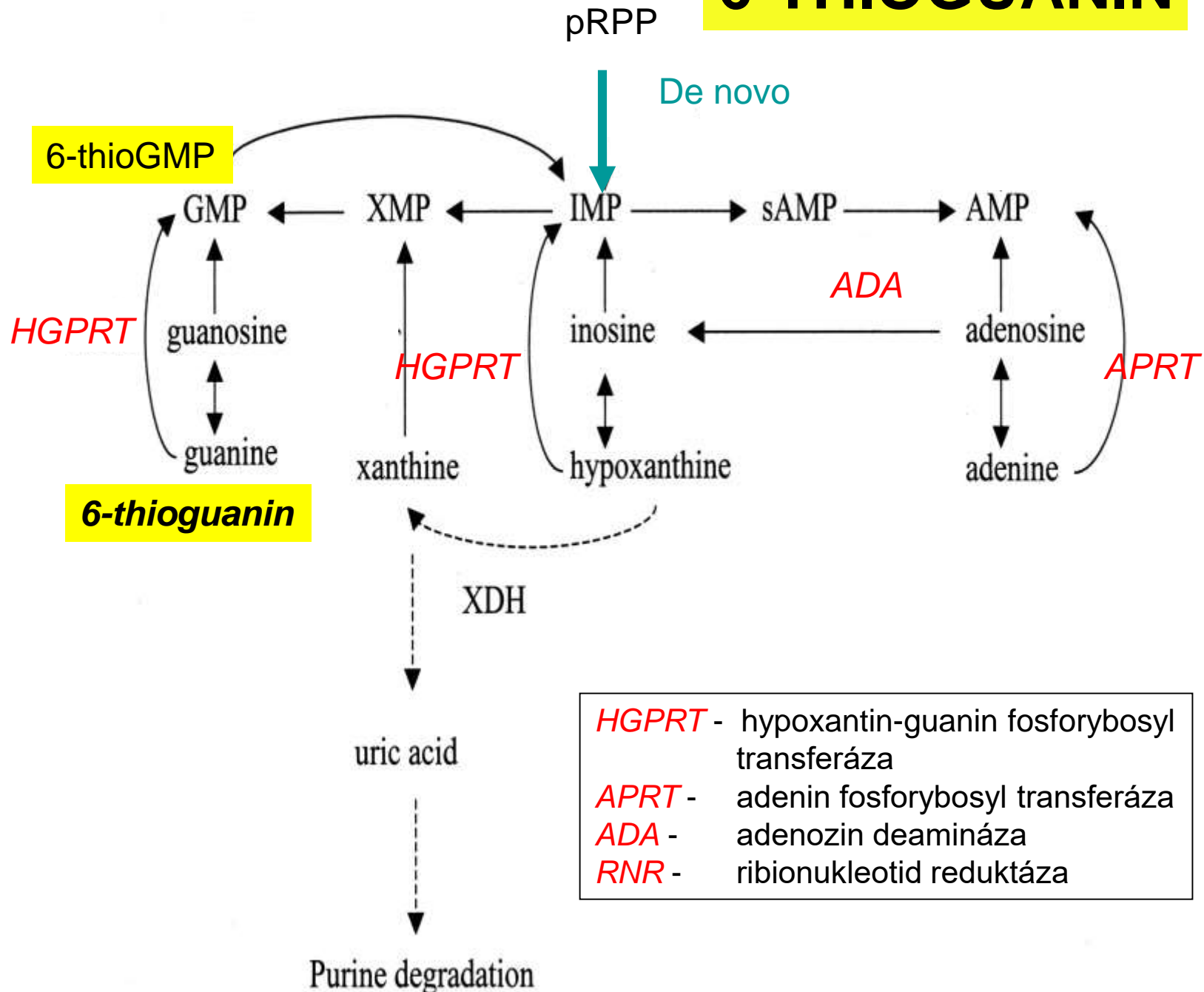
PURIN

6-merkaptopurin

6-THIOGUANIN



6-THIOGUANIN



- HGPRT** - hypoxantin-guanin fosforybosyl transferáza
- APRT** - adenin fosforybosyl transferáza
- ADA** - adenzin deamináza
- RNR** - ribionukleotid reduktáza

6-THIOGUANIN

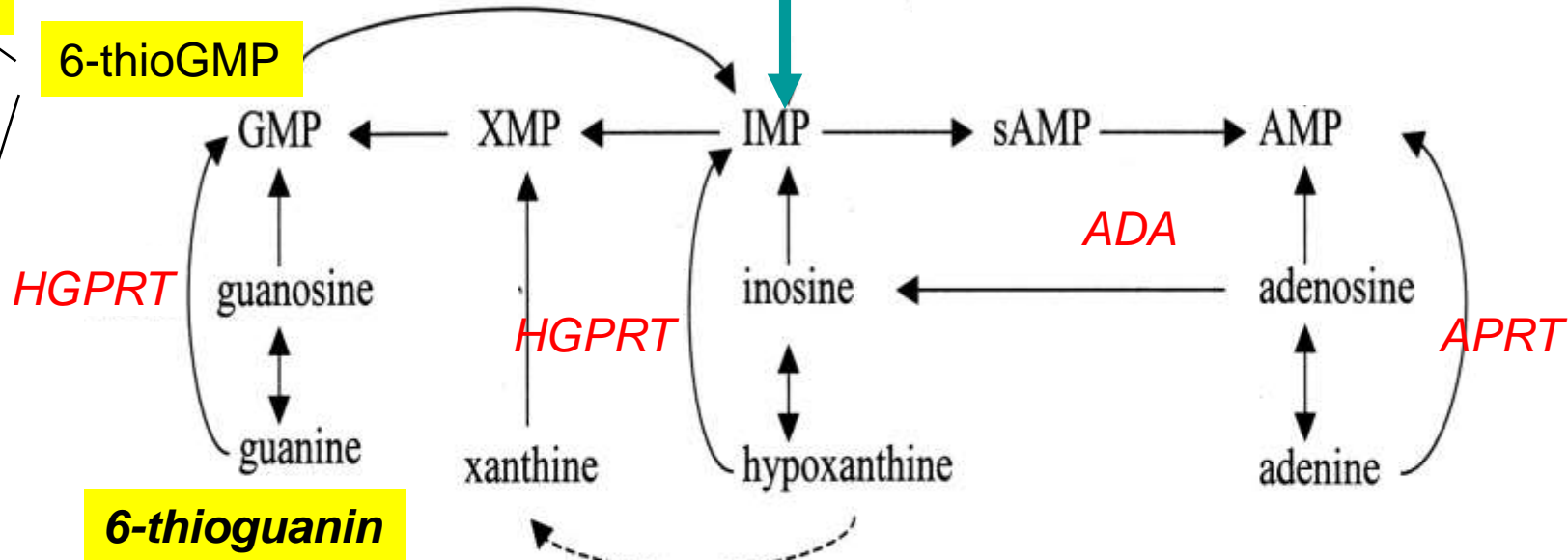
Inkorporace do RNA

6-thio
GTP

6-thioGMP

pRPP

De novo



RNR

HGPRT

HGPRT

ADA

APRT

6-thioguanin

XDH

6-thio dGTP

uric acid

Purine degradation

HGPRT - hypoxantin-guanin fosforybosyl transferáza

APRT - adenin fosforybosyl transferáza

ADA - adenzin deamináza

RNR - ribionukleotid reduktáza

Inkorporace do DNA

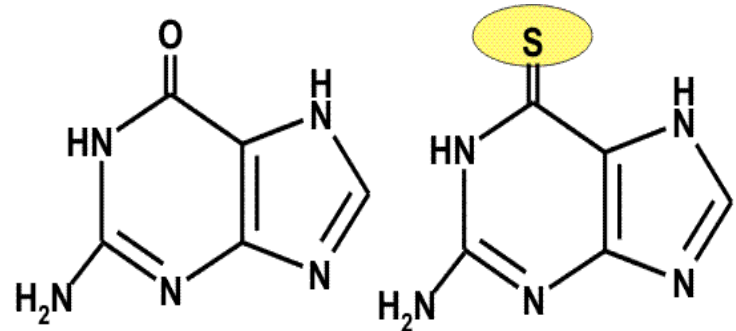
ANTIBÁZE (antipuriny)

thioguanin

(analog guaninu, inhibuje salvage dráhu)

Terapie leukemií

1950s



Guanine

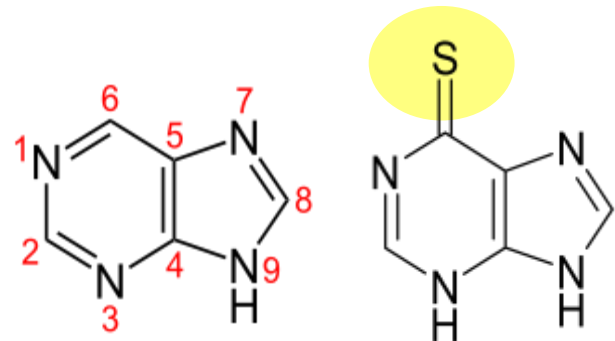
6-Thio-Guanine

6-merkaptopurin

(analog hypoxantinu, inhibuje salvage dráhu)

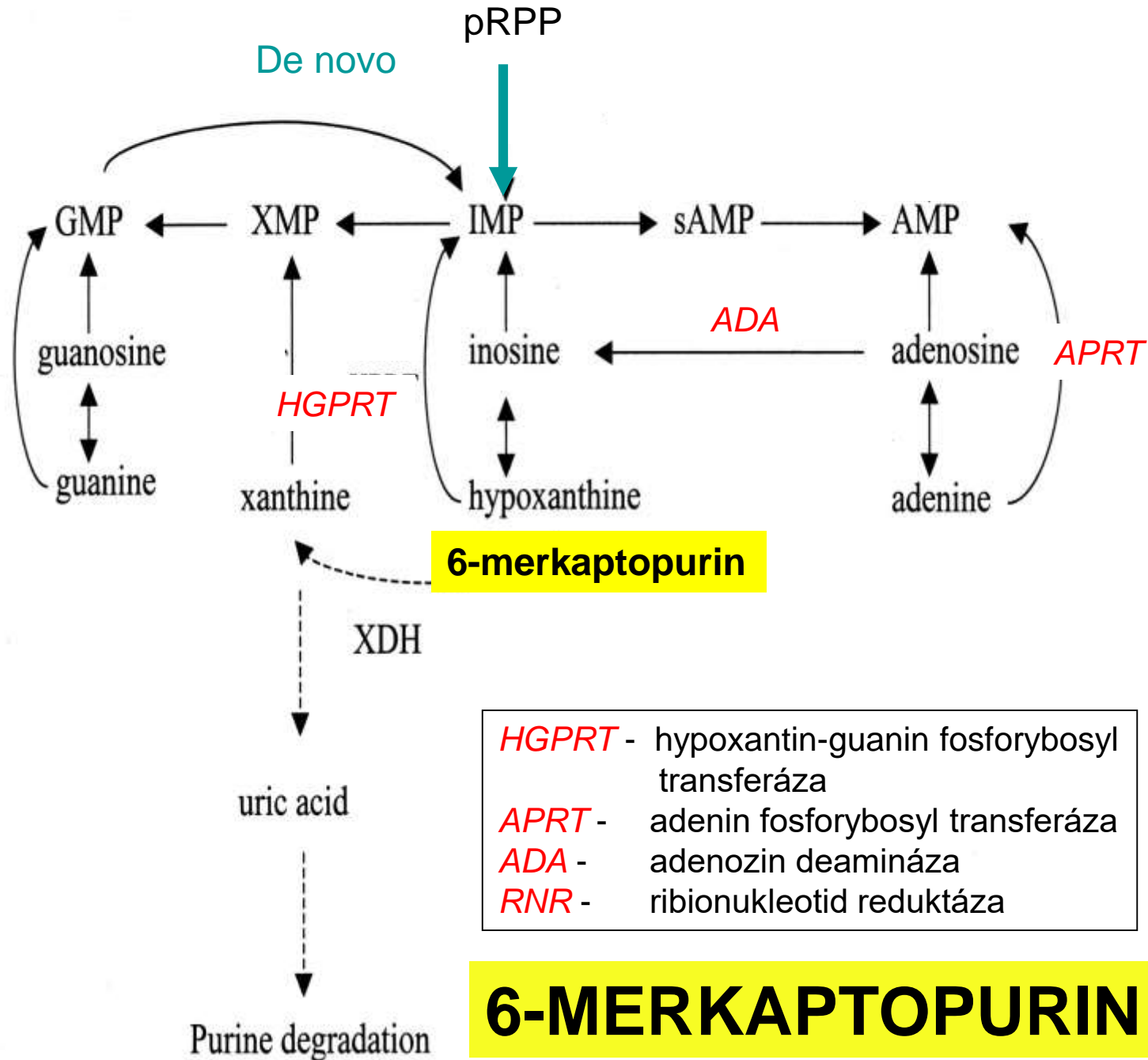
Terapie ALL u dětí

1950s



PURIN

6-merkaptopurin



HGPRT - hypoxantin-guanin fosforybosyl transferáza
APRT - adenin fosforybosyl transferáza
ADA - adenzin deamináza
RNR - ribionukleotid reduktáza

6-MERKAPTAPURIN

Inkorporace do RNA

6-thio
GTP

6-thioGMP

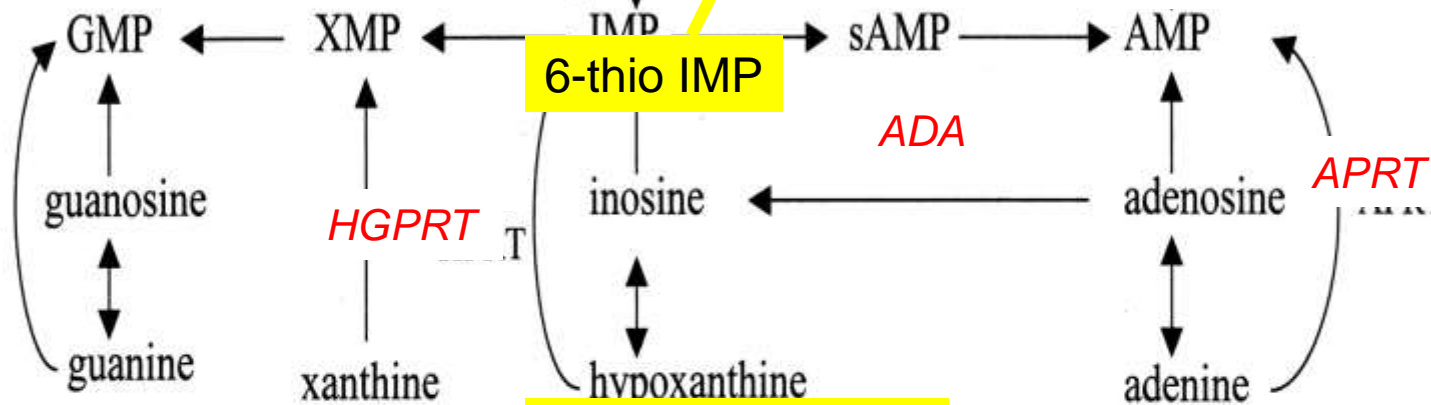
De novo

pRPP

Inhibice fosforibosyl pyrofosfát amidotransferázy

RNR

HGPRT



6-thio dGTP

Inkorporace do DNA

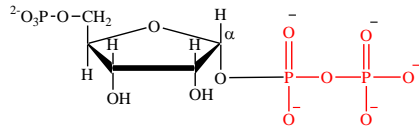
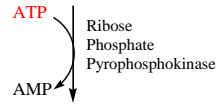
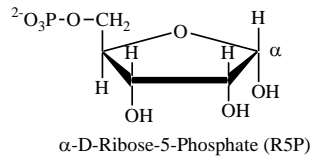
6-merkaptopurin

- HGPRT** - hypoxantin-guanin fosforybosyl transferáza
- APRT** - adenin fosforybosyl transferáza
- ADA** - adenzin deamináza
- RNR** - ribionukleotid reduktáza

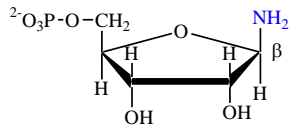
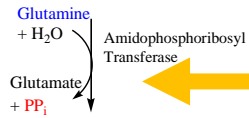
6-MERKAPTOPURIN

Purine degradation

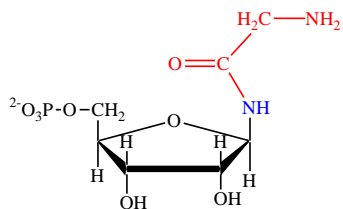
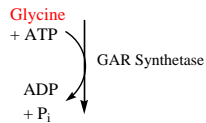
De novo syntéza purinů



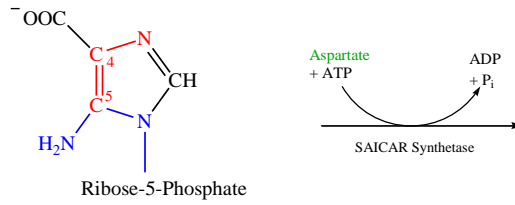
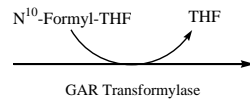
5-Phosphoribosyl- α -pyrophosphate (PRPP)



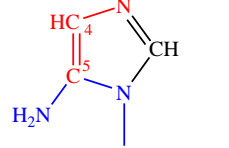
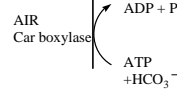
β -5-Phosphoribosylamine (PRA)



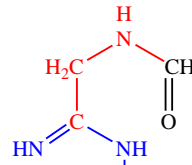
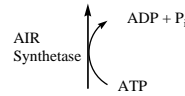
Glycinamide Ribotide (GAR)



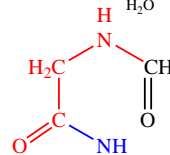
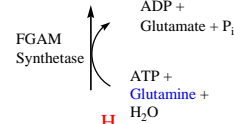
Carboxyamidoimidazole Ribotide (CAIR)



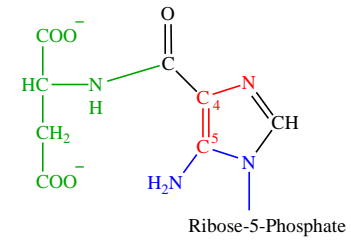
5-Aminoimidazole Ribotide (AIR)



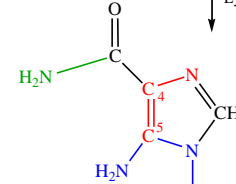
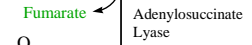
Formylglycinamide ribotide (FGAM)



Formylglycinamide ribotide (FGAR)

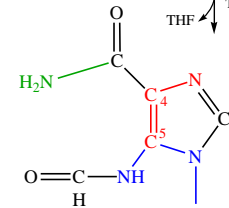
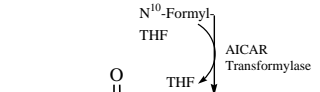


5-Aminoimidazole-4-(N-succinylcarboxamide) ribotide (SAICAR)

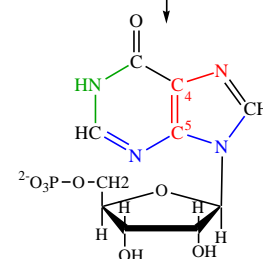


5-Aminoimidazole-4-carboxamide ribotide (AICAR)

5-Aminoimidazole-4-carboxamide ribotide (AICAR)



5-Formaminoimidazole-4-carboxamide ribotide (FAICAR)



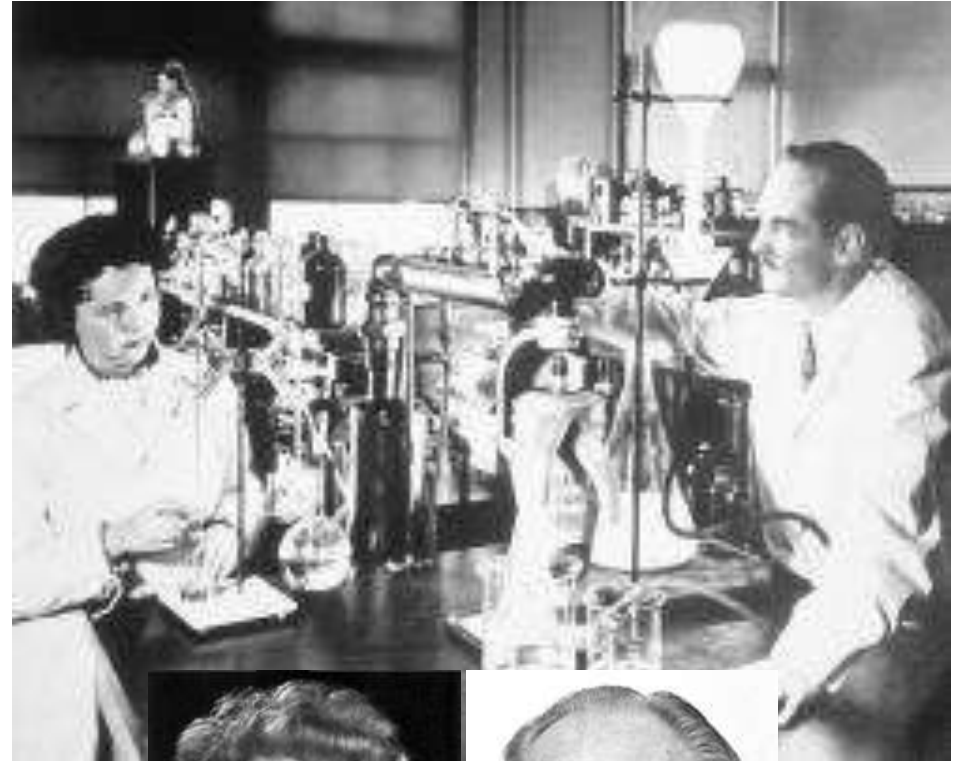
Inosine Monophosphate (IMP)

George Hitchings and Gertrude Elion

(Nobelova cena 1988 za fyziologii a medicínu)

6-merkaptopurin
Thioguanin

(1950s)

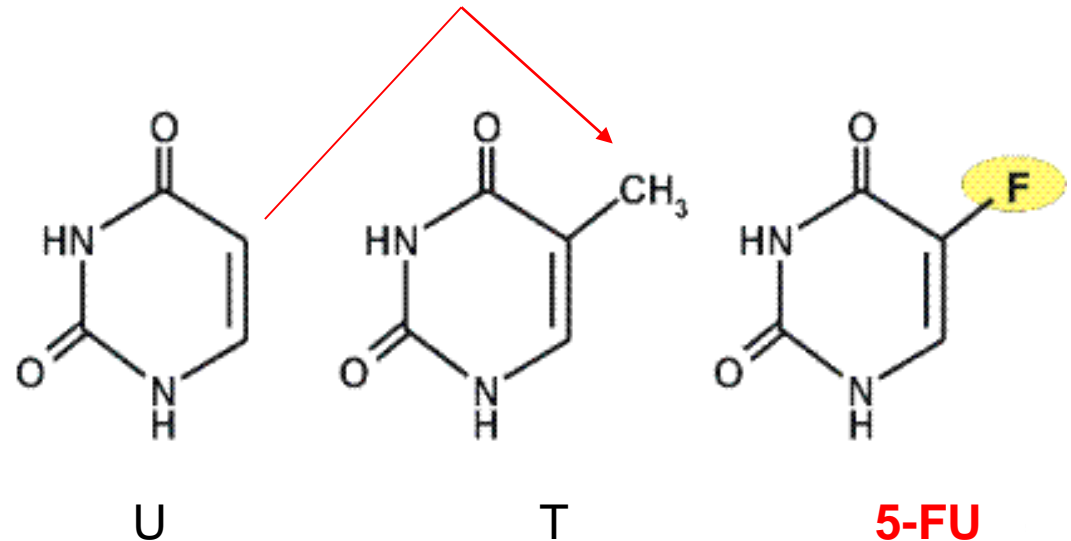


ANTIBÁZE (antipyrimidiny)

5-FU (5-fluorouracil)

Uracil je nádory intenzivně přijímán, atom fluoru má podobné rozměry jako H (van der Waals radius) 5-FU je tedy přijímán a metabolizován podobně.

Funguje jako **Inhibitor tymidylát syntázy**, která při reakci dUMP na dTMP nahrazuje vodík na pozici 5 metylovou skupinou.



Zaveden v 50-letech

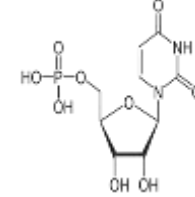
*Léčba solidních nádorů: **5-FU** nebo se podává se jako prodrug (musí být nejprve metabolizován) - **Kapecitabin, Tegafur***

PYRIMIDINY

Ribózo 5-P

karbamoyl fosfát

**Syntéza
De novo**



PPi

UMP

UDP

dUMP

UTP

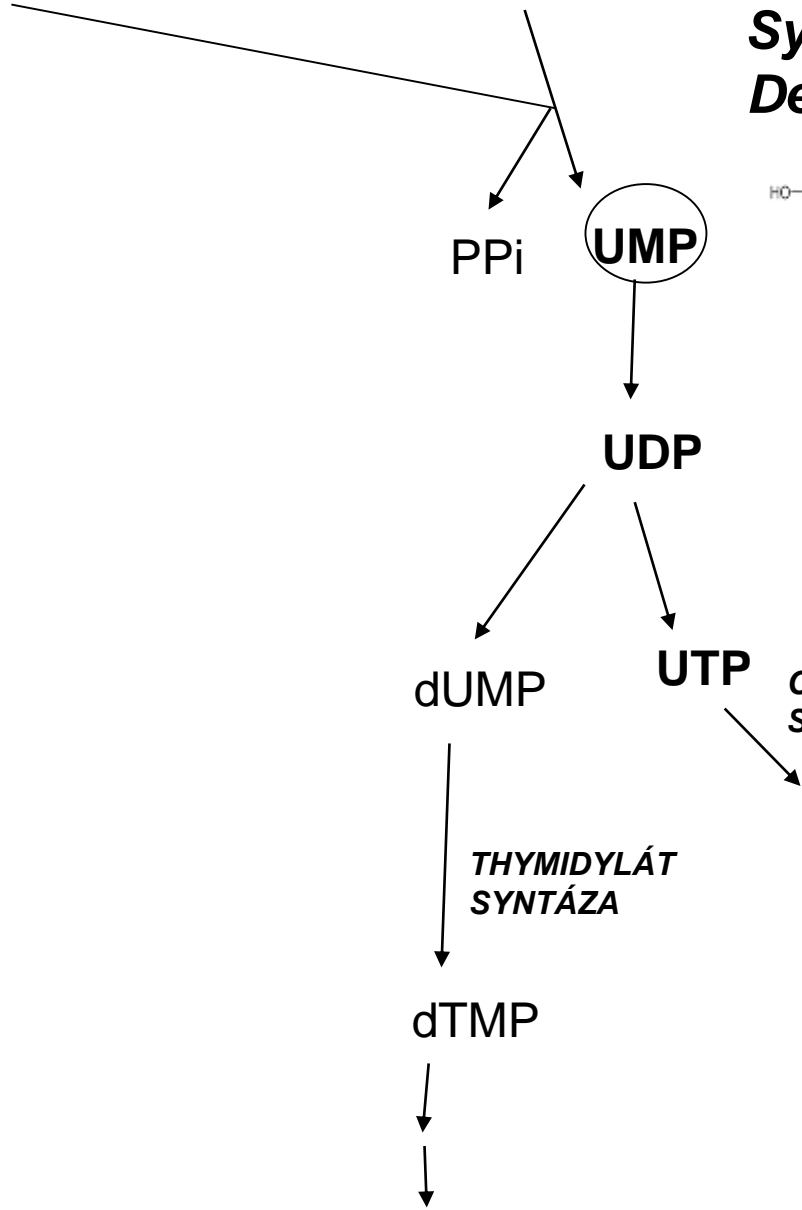
*CTP
SYNTÁZA*

CTP

*THYMIDYLÁT
SYNTÁZA*

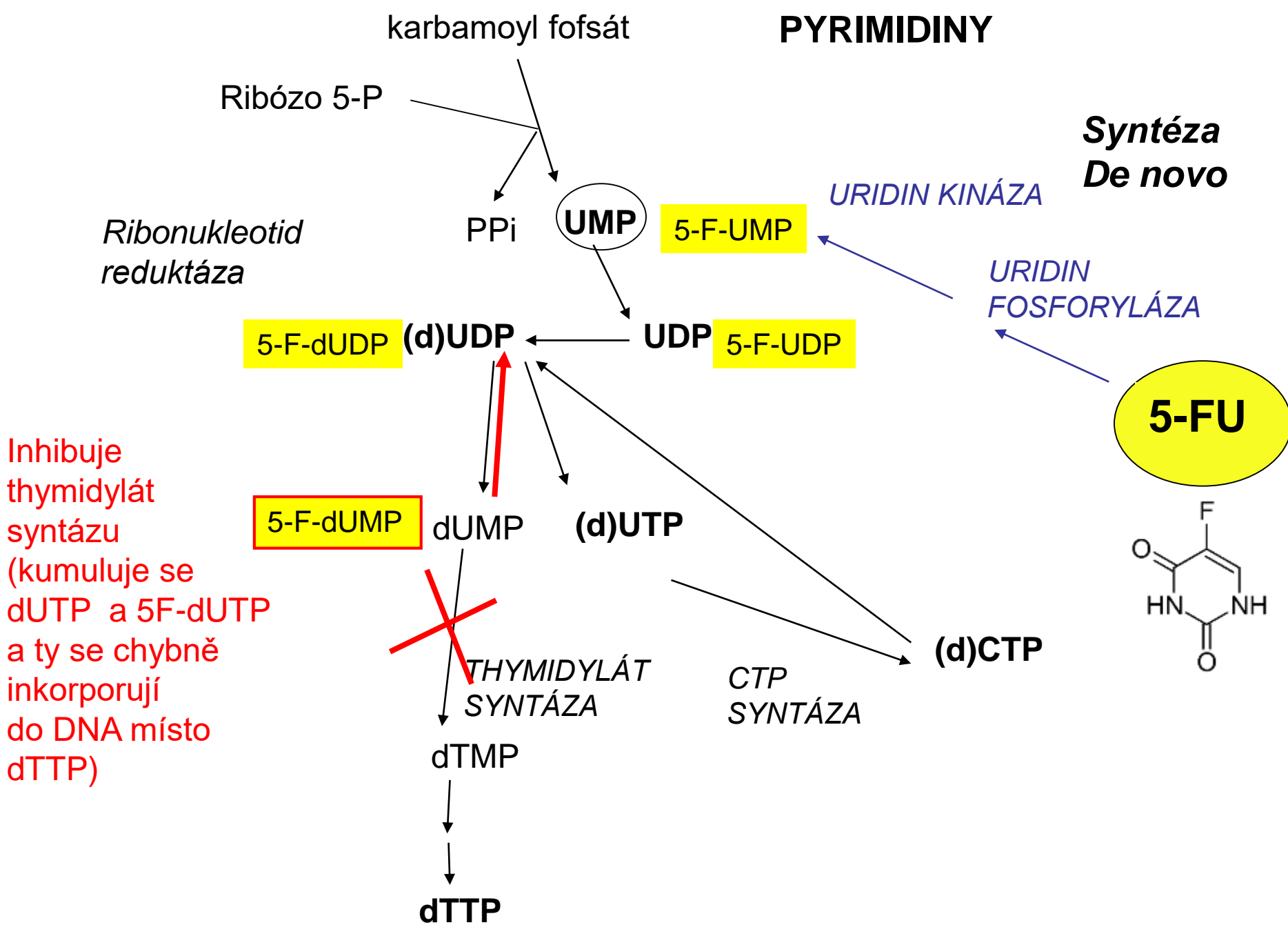
dTMP

dTTP

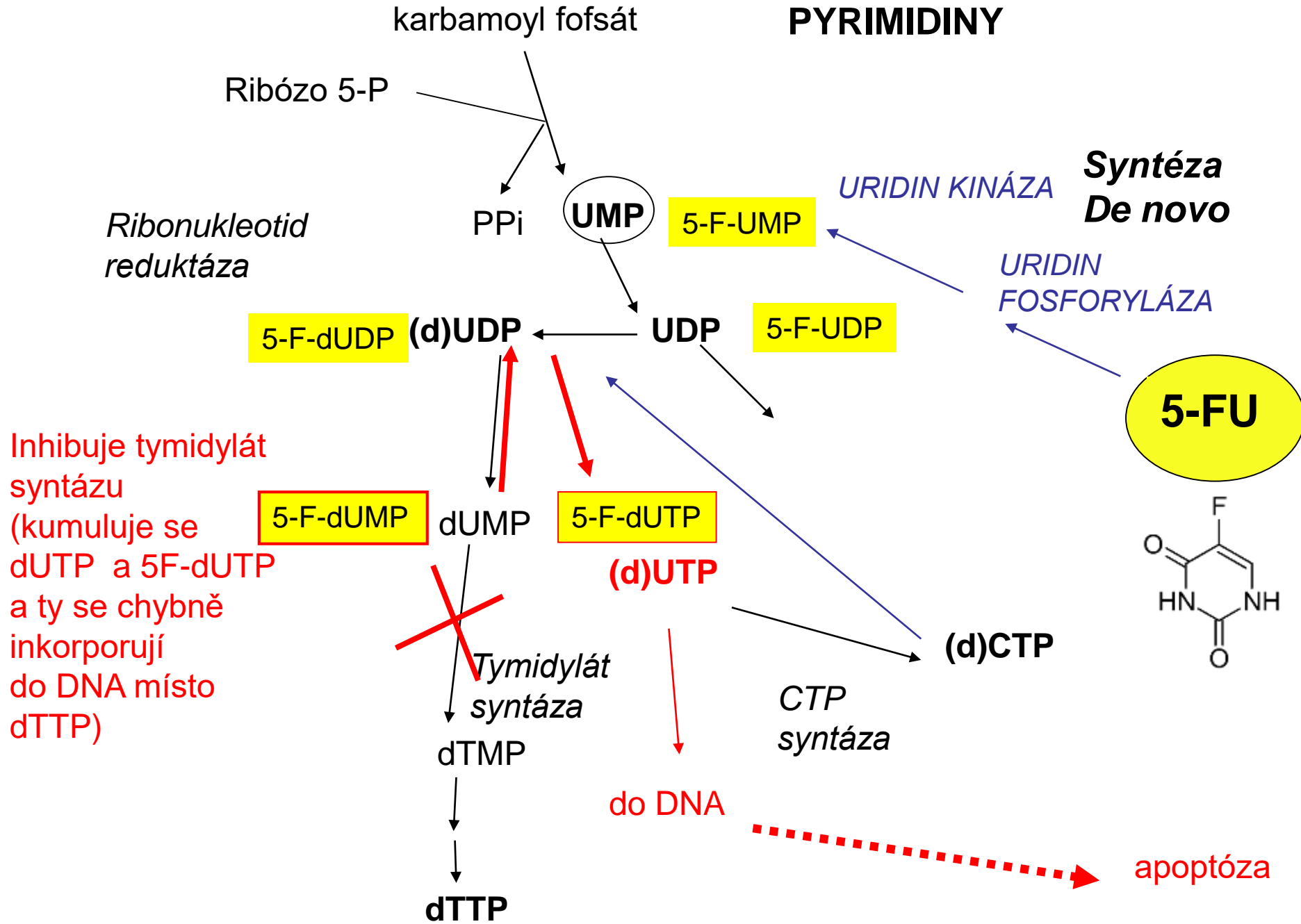


PYRIMIDINY

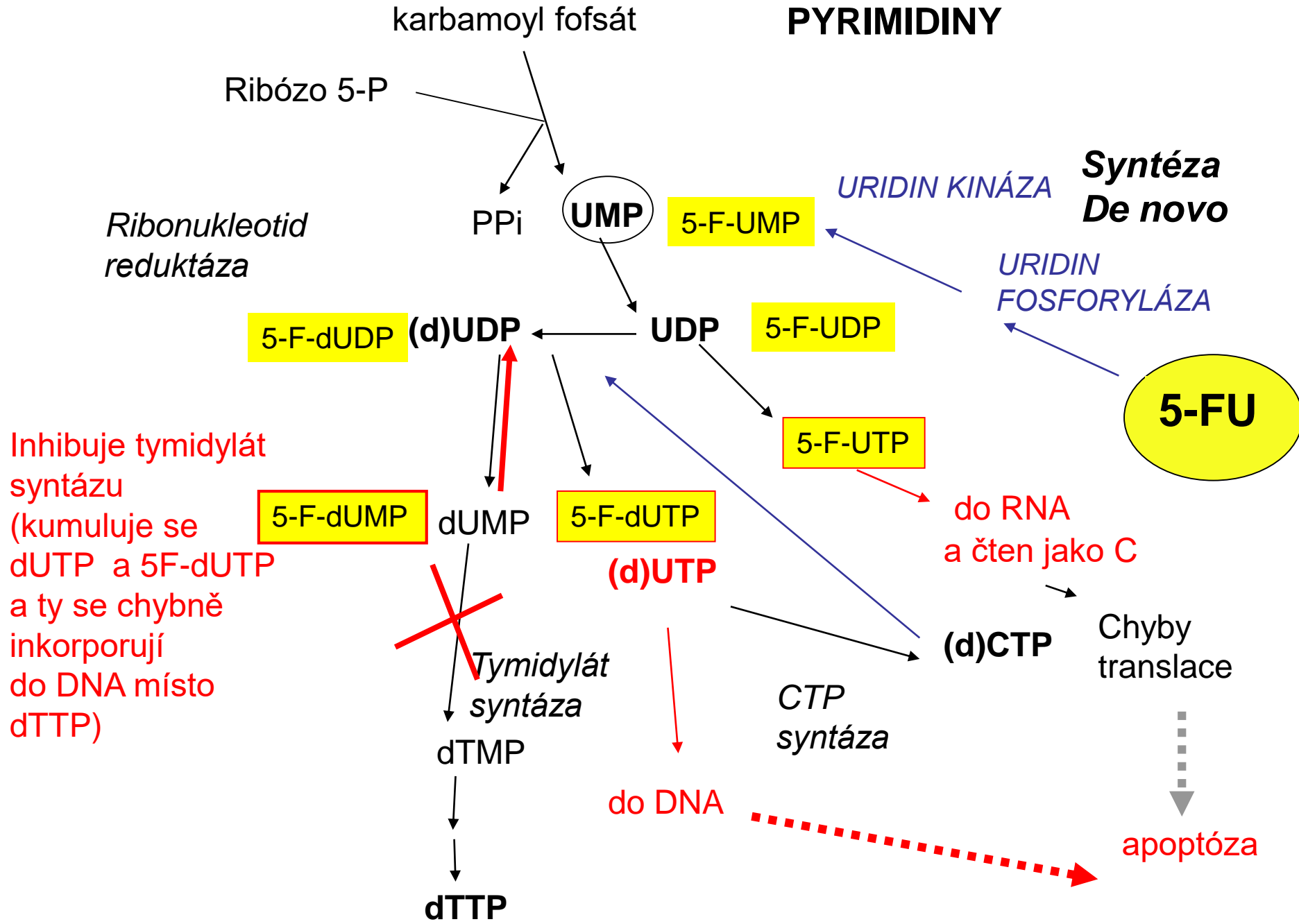
**Syntéza
De novo**



PYRIMIDINY



PYRIMIDINY



5-FU

Zaveden v 50-letech, využití: především léčba solidních nádorů

Podává se jako:

5-FU nebo jako prodrug (musí být nejprve metabolizován) - **Kapecitabin, Tegafur**

Využíván je rovněž 5-FU už navázaný na deoxyribózu - FUdR - **floxuridin**

Ten jen tymidin kinázou fosforylován na 5-FUdMP a funguje stejně



Aza-deriváty bazí budou probrány v rámci epigentických modifikátorů

ANTIMETABOLITY a hydroxymočovina

Analogy kyseliny listové

Analogy bází

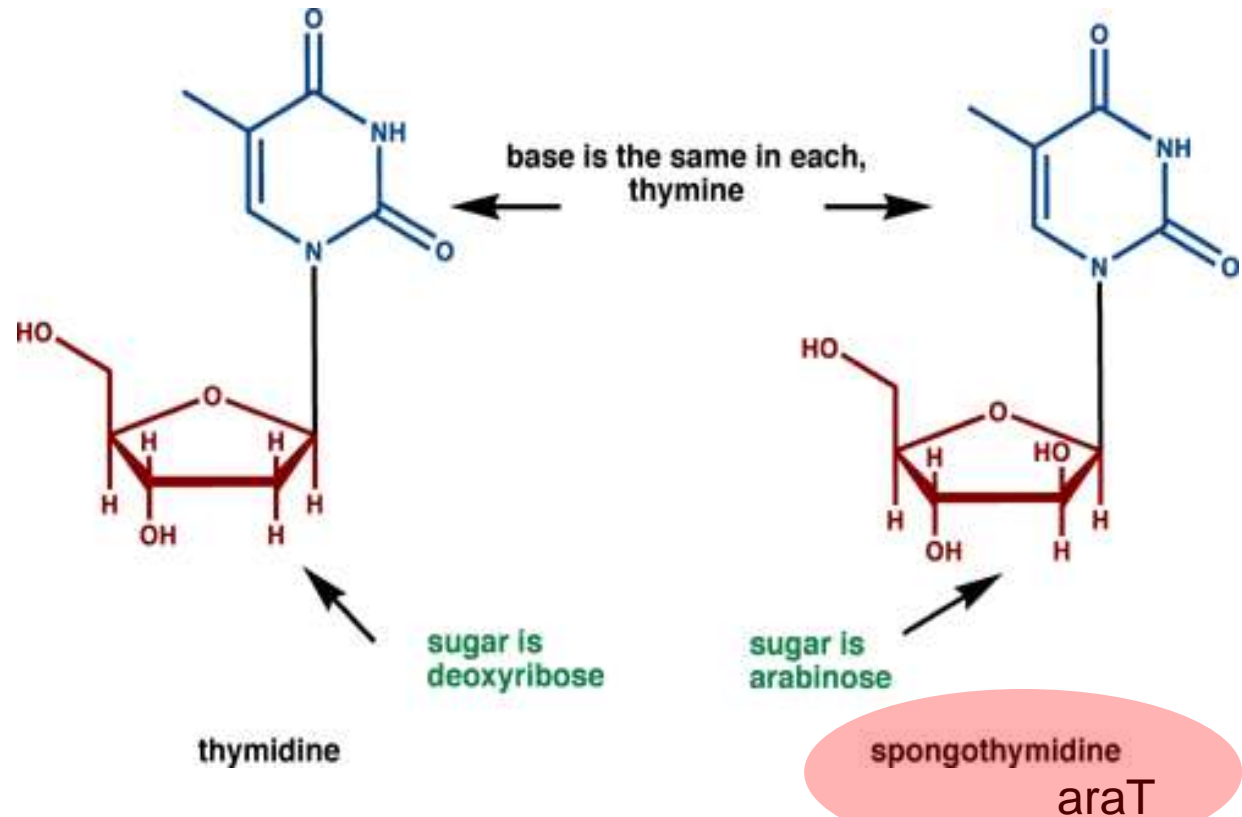
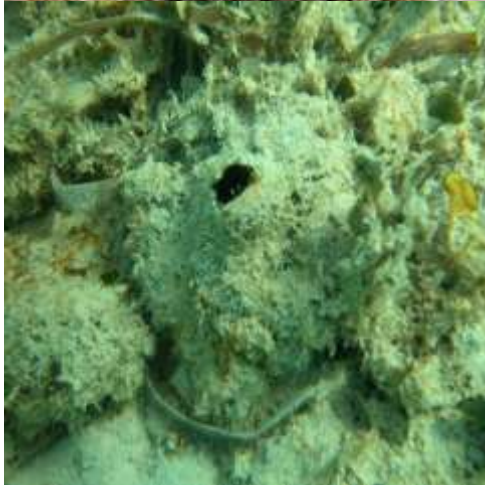
Analogy nukleosidů

Hydroxymočovina

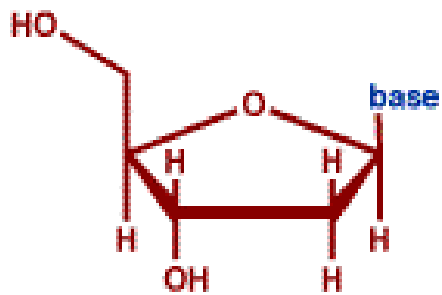
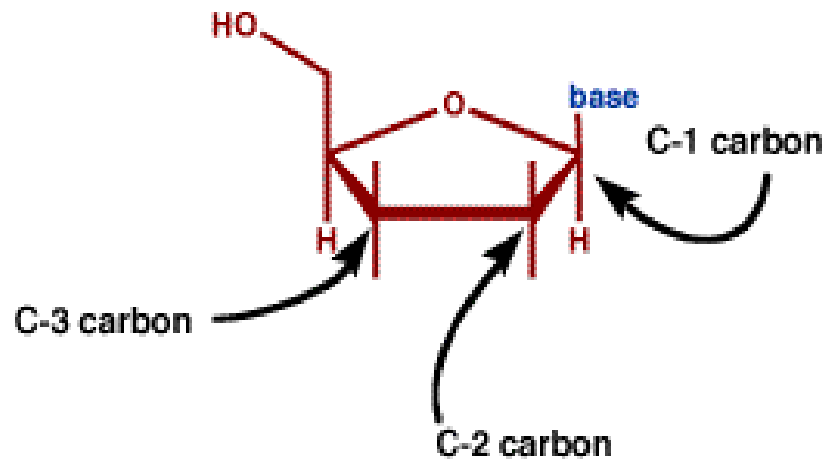
(DEOXY) NUKLEOSIDOVÉ ANTIMETABOLITY

Werner Bergmann (1945)

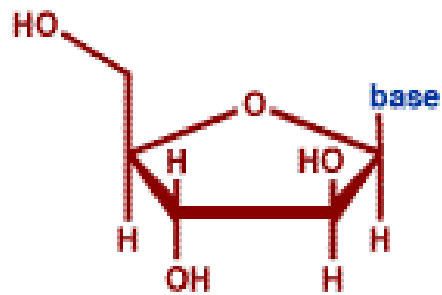
Snaha o izolace steroidů z mořské houby
Cryptotethia crypta- extrakce do acetonu
(získ velké množství čisté krystalické látky)



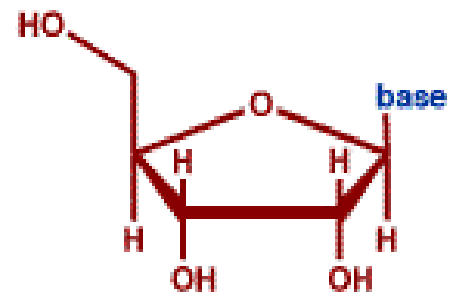
spongothymidine "3-beta-D-arabofuranosylthymine"
spongouridine is "3-beta-D-arabofuranosyluracil"



deoxyribose
DNA backbone



arabinose

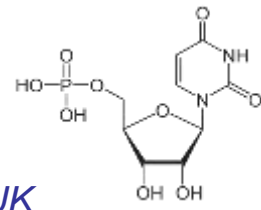


ribose
RNA backbone

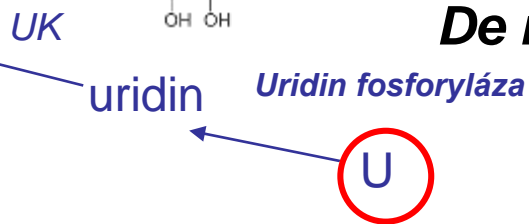
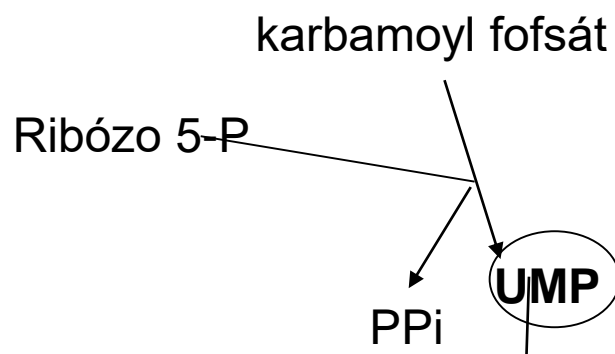
DEOXYNUKLEOSIDOVÉ ANTIMETABOLITY

(PYRIMIDINOVÉ)

PYRIMIDINY



Syntéza De novo



DCTP DEAMINÁZA

Salvage dráha



CTP syntáza



↑ NUKLEOTID DIFOSFÁT KINÁZA



↑ CYTIDYLÁT KINÁZA



↑ DEOXYCTIDIN KINÁZA



THYMIDYLÁT SYNTÁZA



TYMIDIN KINÁZA



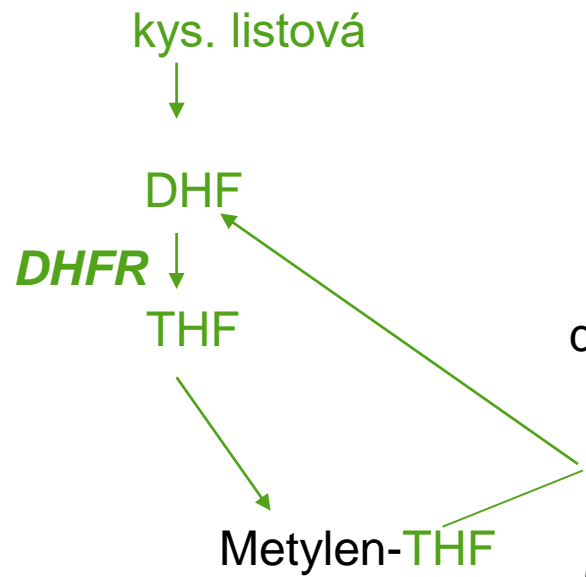
kys. listová



DHFR



Metylen-THF



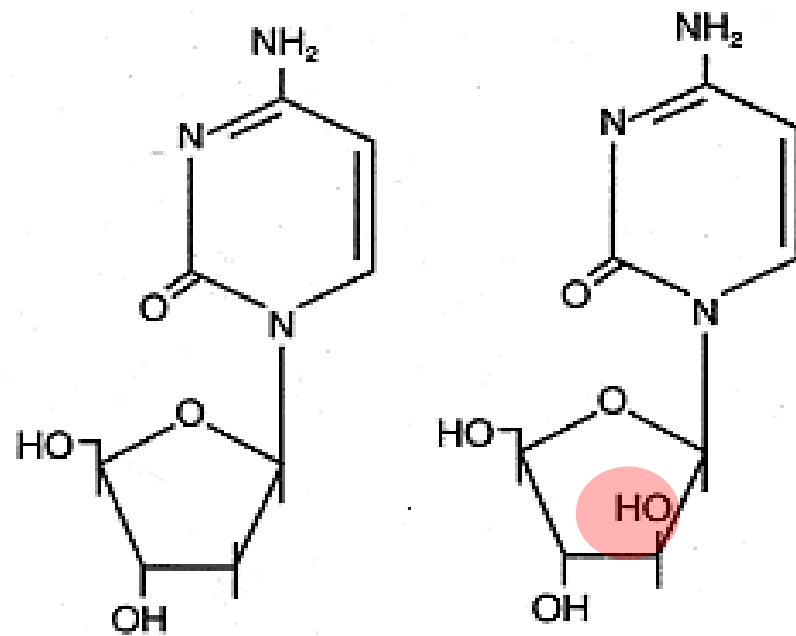
Cytarabin (araC, cytosinarabinosid)

V praxi cca od roku 1965

Terapie leukemií a některých lymfomů

Vstup do buňky přes membránu
nebo transportérem.

V buňce je postupně fosforylován
salvage dráze na araCTP



Deoxycytidine

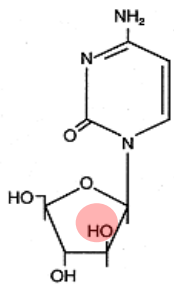
Cytarabine

Human equilibrative nucleoside transporter 1, 2

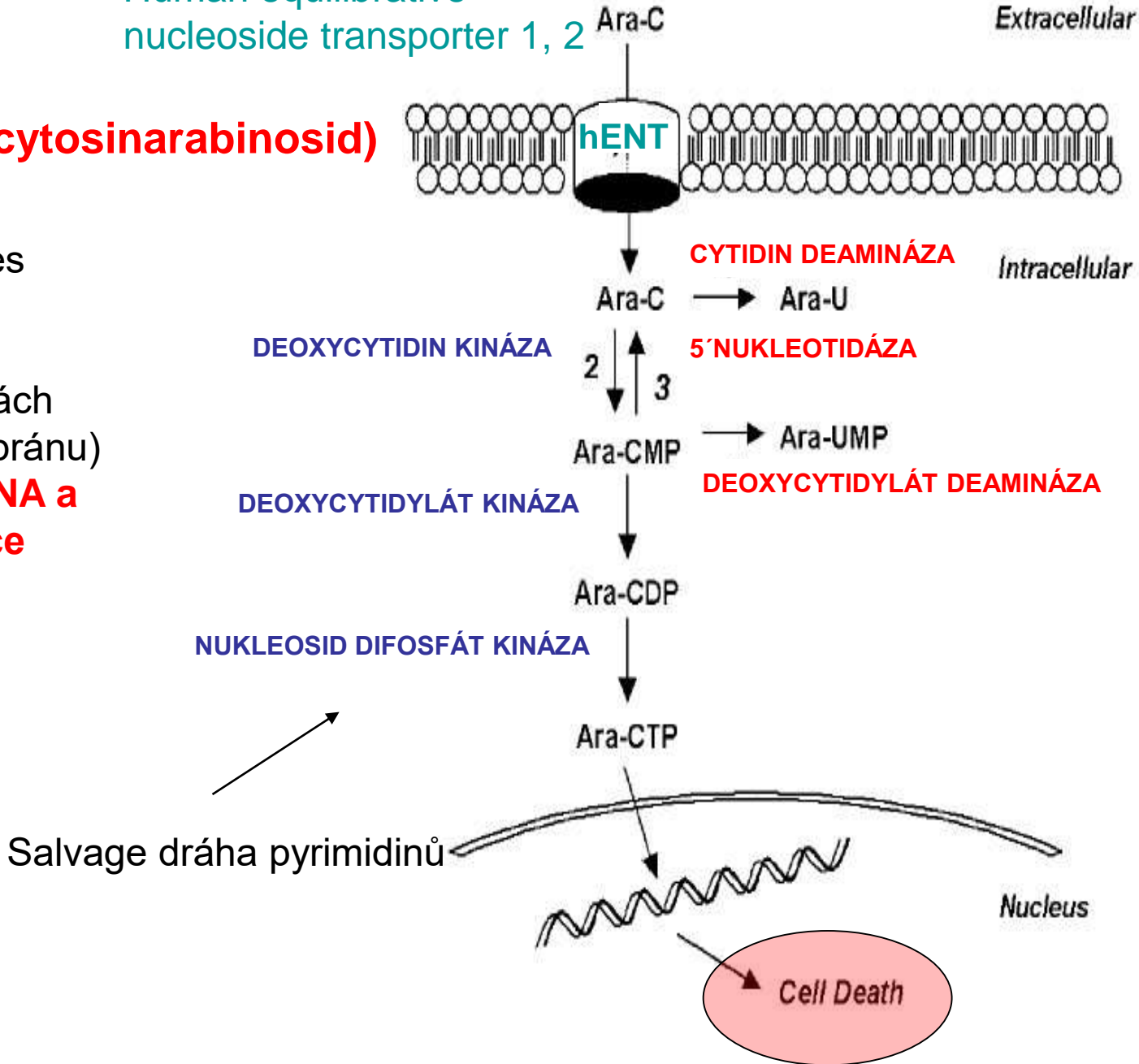
Cytarabin(araC, cytosinarabinosid)

Vstup do buňky přes hENT transportéry

(při vysokých dávkách pasivně přes membránu)
inkorporace do DNA a zastavení replikace



Cytarabine



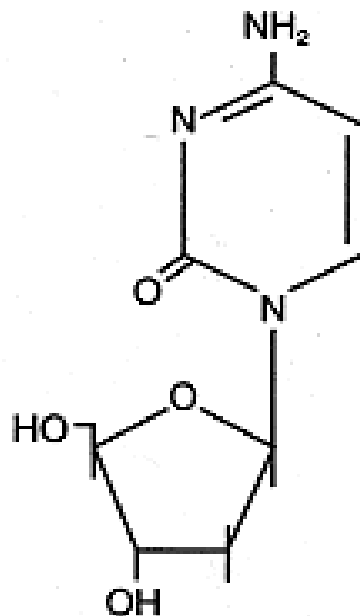
Gemcitabin (2,2 – difluordeoxycytidin, Gemzar)

di-fluorovaný analog deoxycytidnu

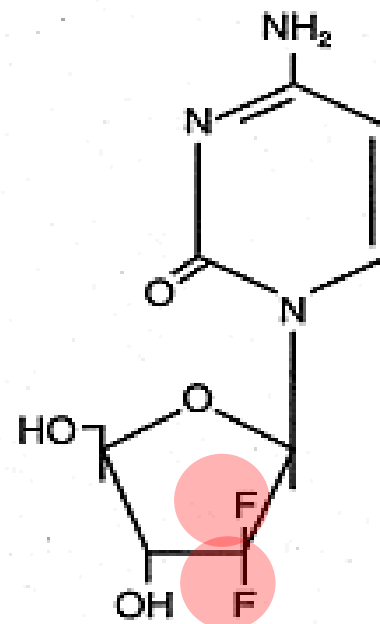
Aktivace stejná jako u araC.

DifluordeoxycytidinTP se **inkorporuje do DNA**

kromě toho **inhibuje ribonukleotid reduktázu**



Deoxycytidine



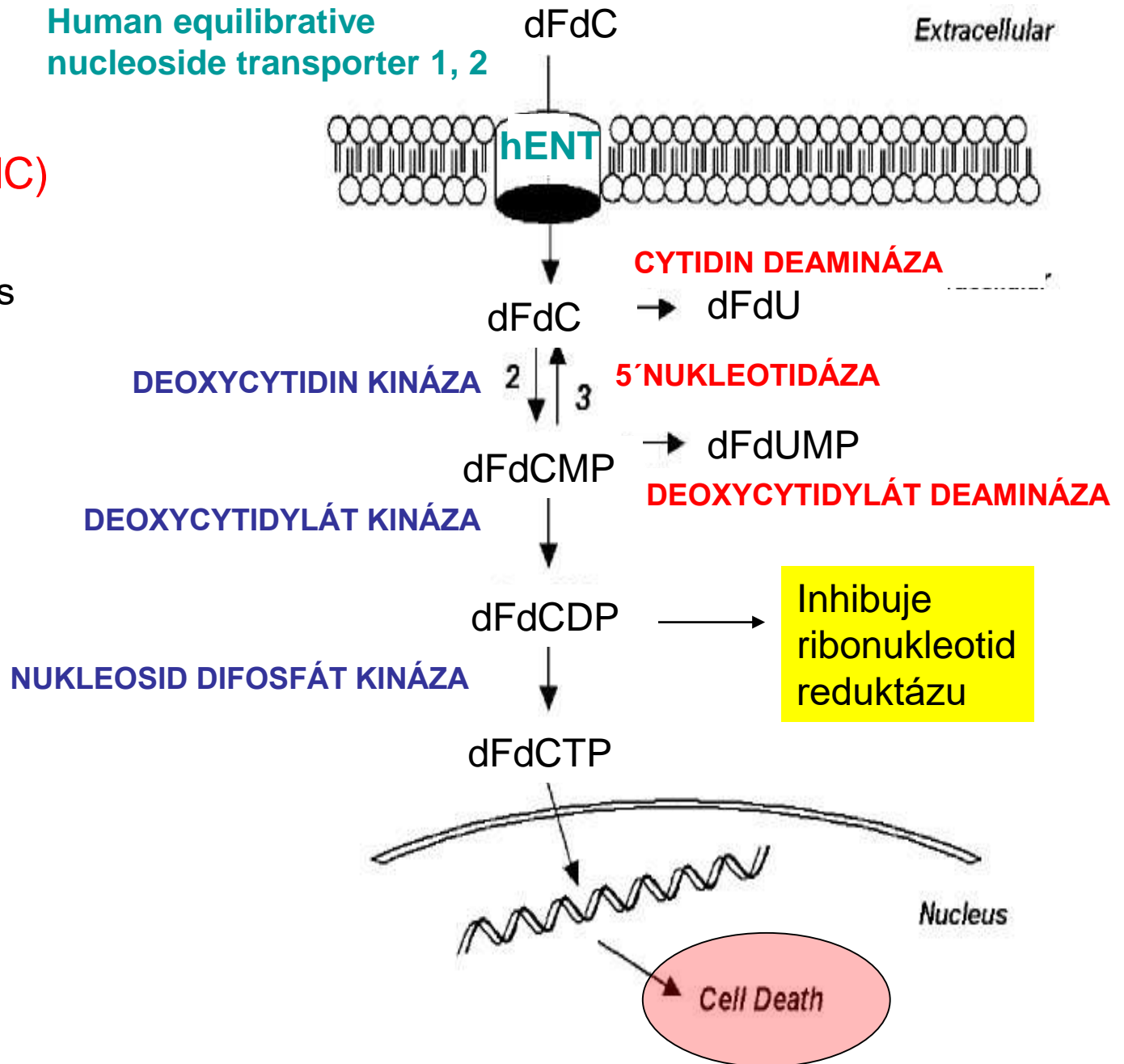
Gemcitabine

Gemcitabin (dFdC)

Vstup do buňky přes membránu (při vysokých dávkách) a/nebo hENT transportéry

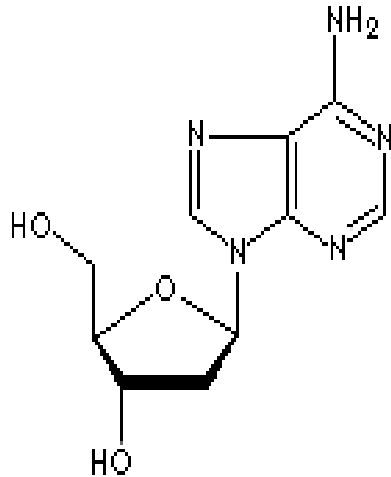
Inkorporace do DNA a zastavení replikace

Inibitor RNR

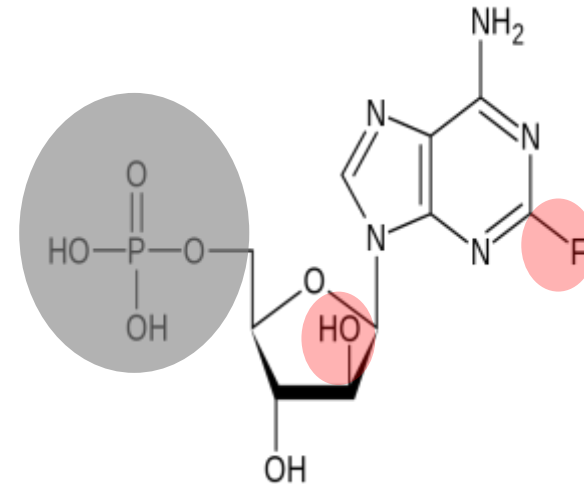


(DEOXY) NUKLEOSIDOVÉ ANTIMETABOLITY (PURINOVÉ)

Fludarabin (Fludara)



deoxyadenozin



Fludarabin (fosfát)

Díky F na bázi je **odolný vůči deaminaci adenosin deaminázou na inozin a je jejím inhibitorem.**

Fosforylovaný je lépe rozpustný (lze podávat orálně), je defosforylován plazmatickými fosfatázami (nebo na povrchu buněk) a vstupuje do buněk (HENT), kde je aktivován kinázami (podobně jako araC nebo gemcitabin).

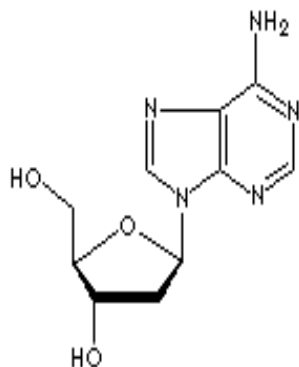
DCK je totiž promiskutiní a fosforyluje i puriny

Inkorporace do DNA zabrání elongaci. Inhibice DNA polymerázy, částečná inhibice RNR (málo dATP zvyšuje inkorporaci dF-araATP)

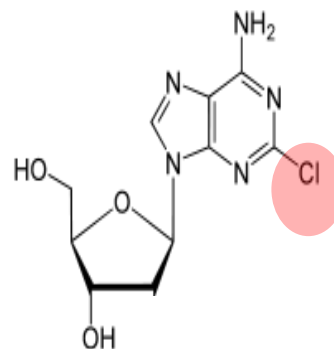
Kladribin

(Cl-A-dRIB-in)

1992



dA



Kladribin

Fosforylován na Clad-TP

Rezistentní vůči ADA

Inkorporace do DNA

Inhibice DNA pol

Inhibice RNR

Klofarabin

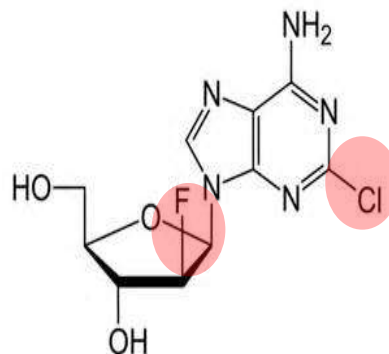
(Cl-F-araA)

F-dává cukru zvýšenou

odolnost proti pH a

bakteriální PNP

2004



Fosforylován na Klof-TP

Rezistentní vůči ADA

inkorporace do DNA

Inhibitor DNA

polymerázy a RNR

ANTIMETABOLITY+ hydroxymočovina

Analogy kyseliny listové

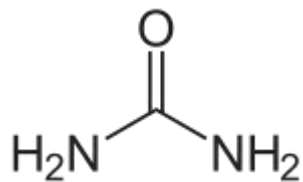
Analogy bází

Analogy nukleosidů

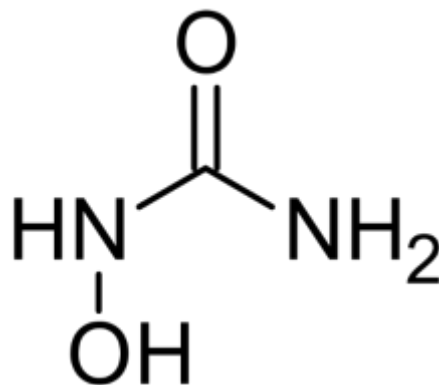
Hydroxymočovina

HYDROXYUREA (Hydroxymočovina)

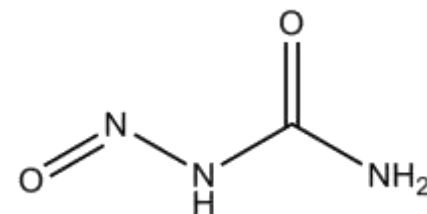
Někdy neprávem řazena mezi antimetaboly



Močovina



Hydroxymočovina

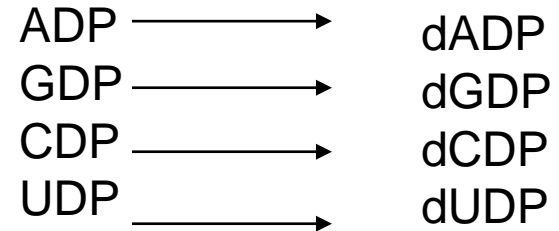
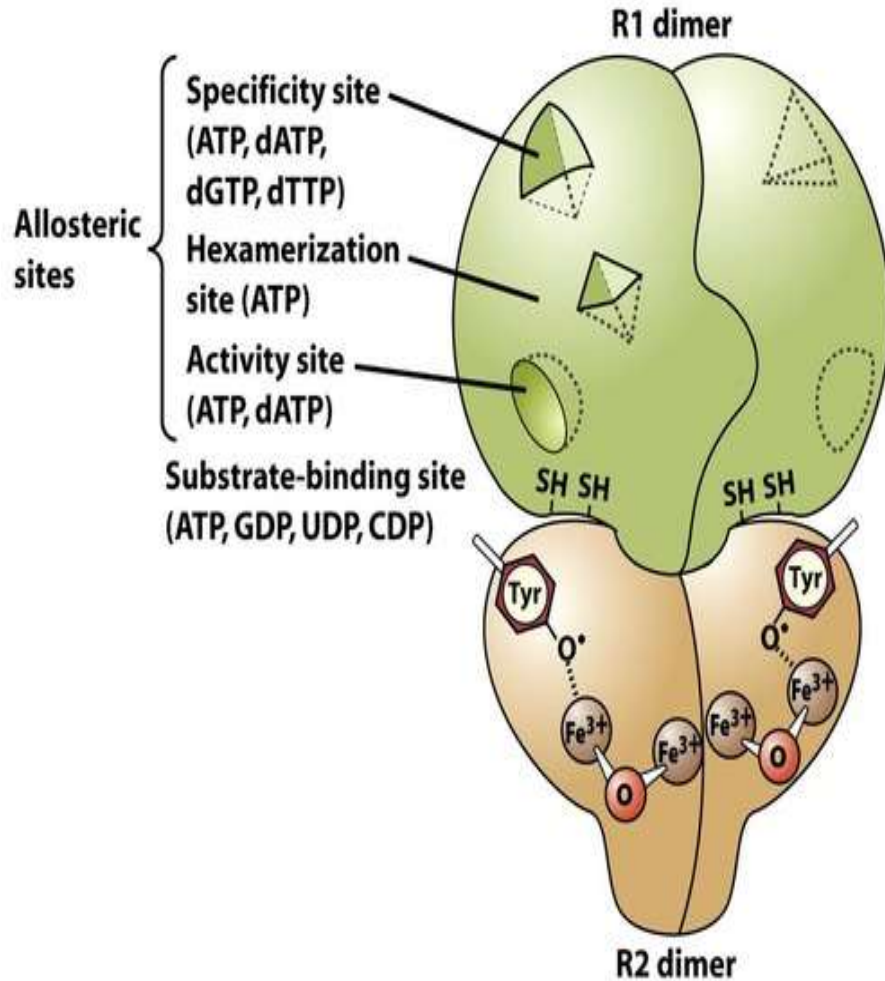


Neplést s nitrosoureou!

INHIBITOR RIBONUKLEOTID REDUKTÁZY

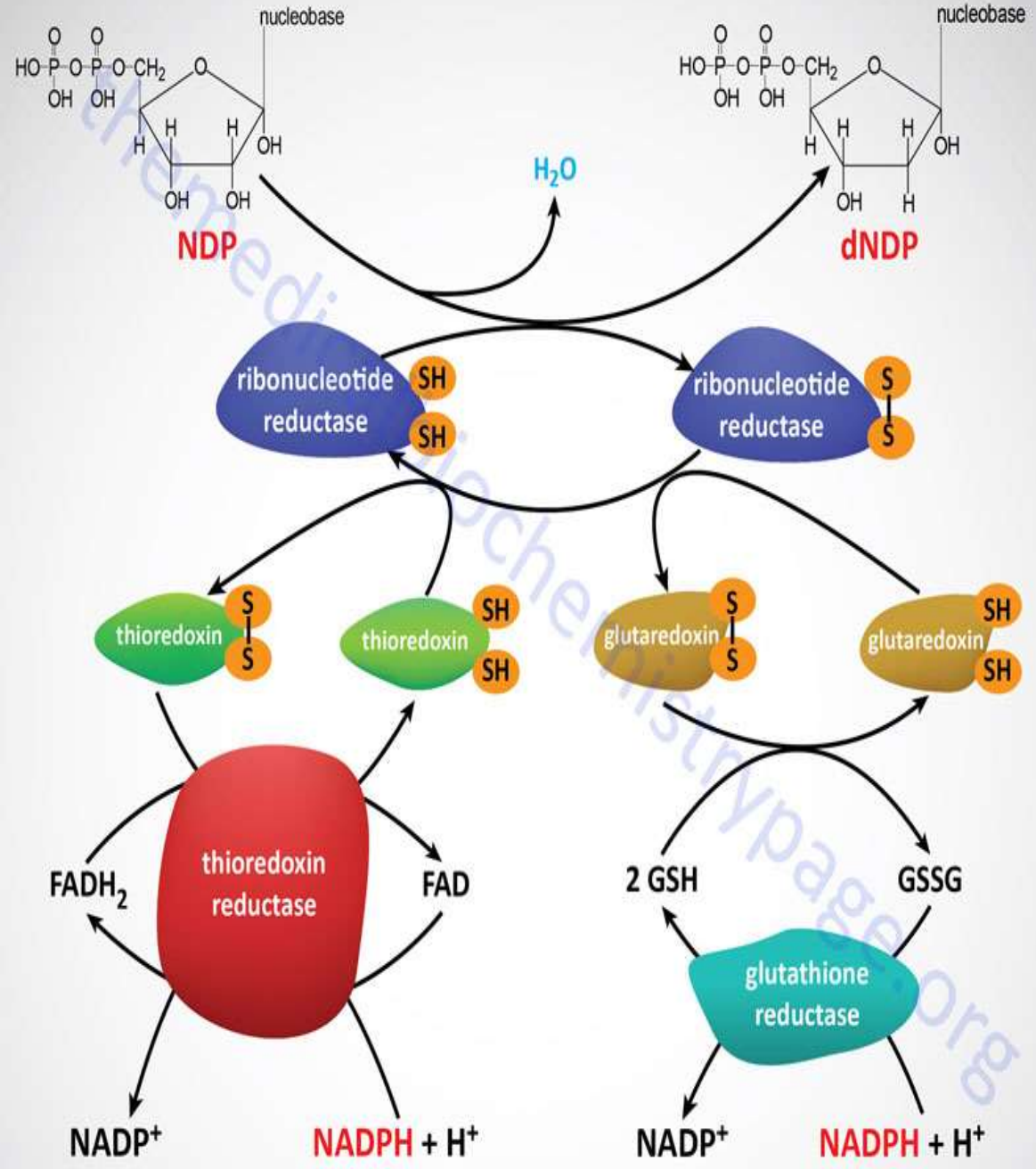
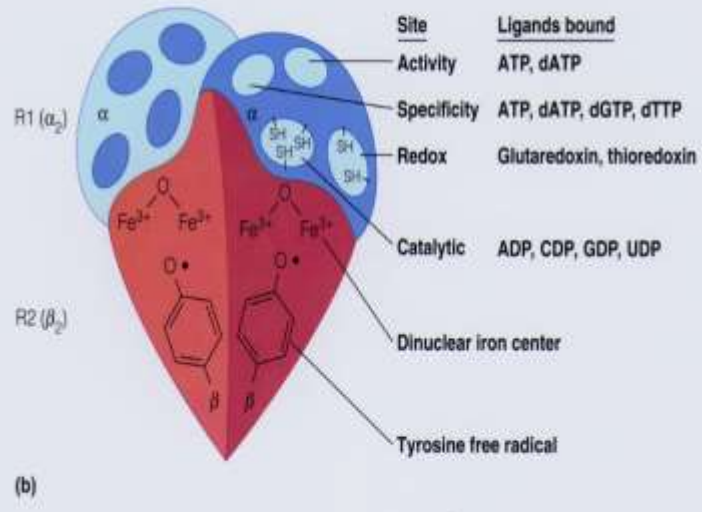
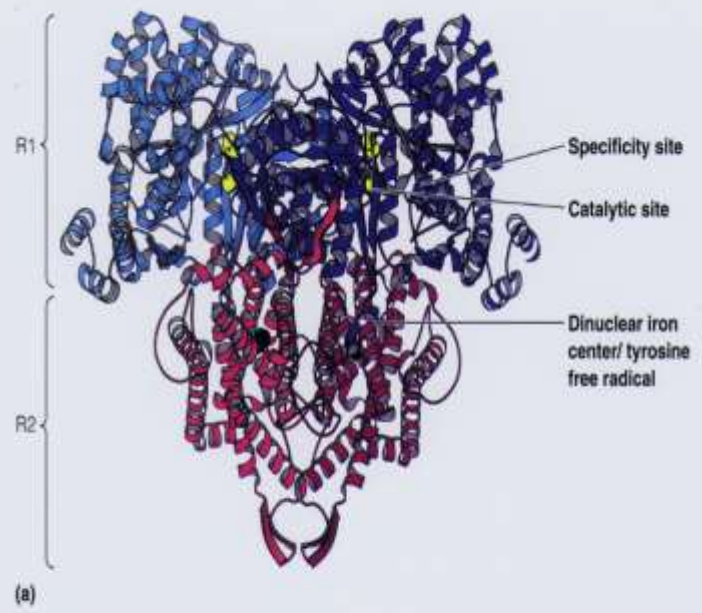
RIBONUKLEOTID REDUKTÁZA

RNR (heterodimerický tetramer) RNR1 a RNR2
 RNR2 má aktivní centrum s iontem železa



dTMP vzniká z dUMP tymidylát syntázou

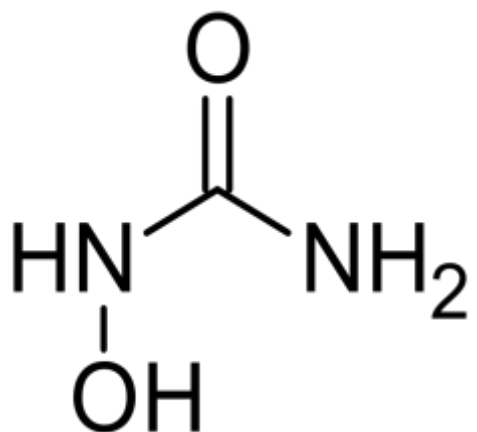
Figure 22.13 Structure of *E. coli* ribonucleoside diphosphate reductase



From Mathews and van Holde: Biochemistry 2/e. © The Benjamin/Cummings Publishing Co., Inc.

Hydroxyurea, Hydroxymočovina

Váže kovy (Fe v RNR) a inaktivuje tyrosylový radikál nutný pro redukci NDPs



Produkuje NO a tím stimuluje guanyl cyklázu a další enzymy