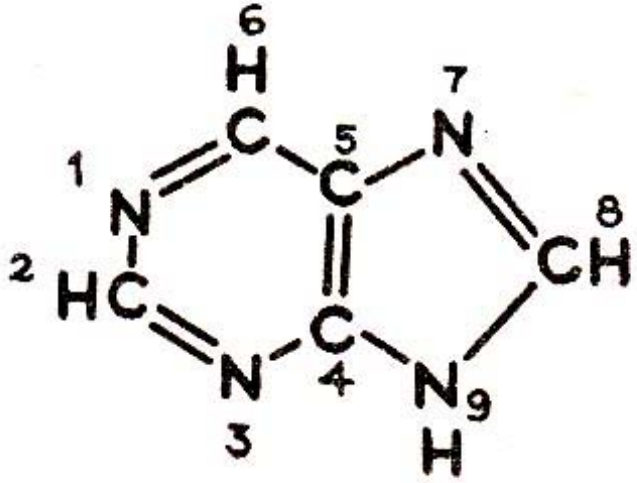
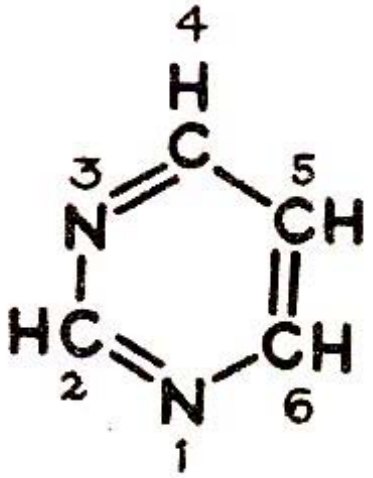
Metabolismo de Nucleótidos



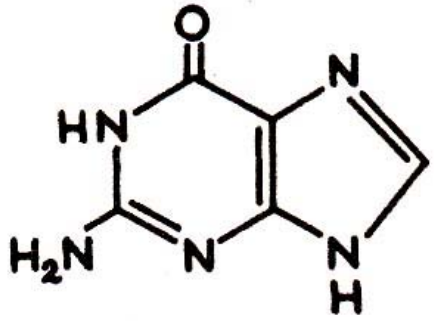
Purina



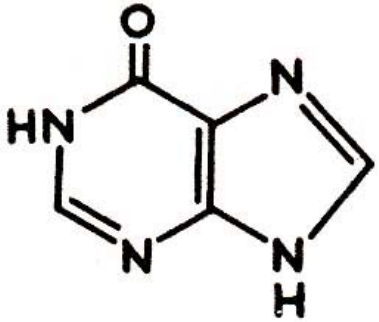
Pirimidina

Fig. 34–1. Estructuras de purina y pirimidina con las posiciones de los elementos numeradas de acuerdo con el sistema internacional.

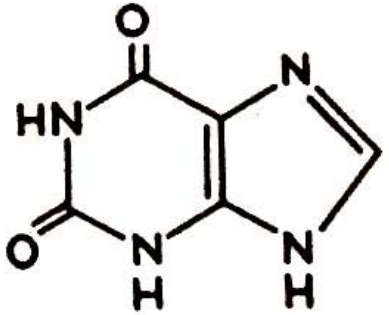
Adenina
(6-aminopurina)



Guanina
(2-amino-6-oxipurina)

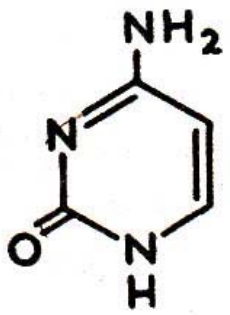


Hipoxantina
(6-oxipurina)

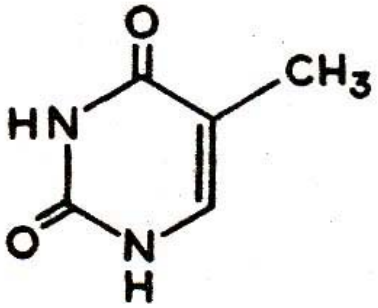


Xantina
(2,6-dioxipurina)

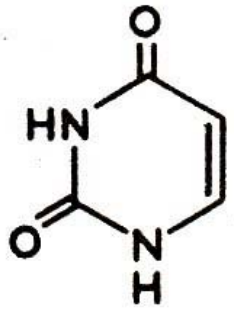
Fig. 34–3. Principales bases purínicas presentes en los nucleótidos.



Citosina
(2-oxi-4-aminopirimidina)

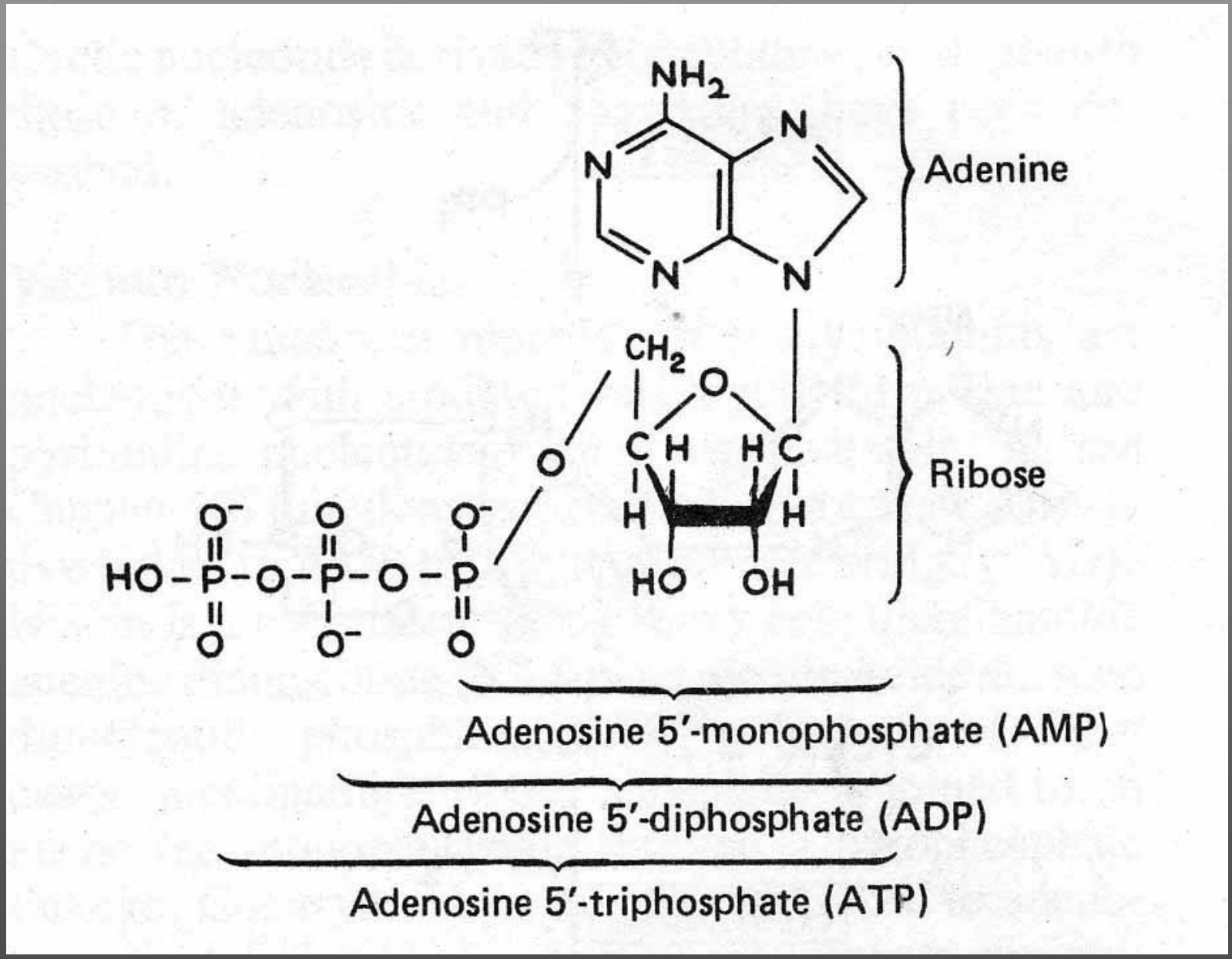


Timina
(2,4-dioxi-5-
metilpirimidina)



Uracilo
(2,4-dioxipi-
rimidina)

Fig. 34–2. Las tres principales bases pirimidínicas que se encuentran en los nucleótidos.


Adenine
Ribose
Adenosine 5′-monophosphate (AMP)
Adenosine 5′-diphosphate (ADP)
Adenosine 5′-triphosphate (ATP)

Base	Nucleoside (Base + Sugar)	Nucleotide (Base + Sugar + Phosphoric Acid)
Purines		
Adenine (6-aminopurine)	Adenosine Deoxyadenosine	Adenylic acid Deoxyadenylic acid
Guanine (2-amino-6-oxypurine)	Guanosine Deoxyguanosine	Guanylic acid Deoxyguanylic acid
Hypoxanthine (6-oxypurine)	Inosine (hypoxanthine riboside) Deoxyinosine (hypoxanthine deoxyriboside)	Inosinic acid (hypoxanthine ribotide) Deoxyinosinic acid (hypoxanthine deoxyribotide)
Xanthine (2,6-dioxypurine)	Xanthosine	Xanthinylic acid
Pyrimidines		
Cytosine (2-oxy-4-aminopyrimidine)	Cytidine Deoxycytidine	Cytidylic acid Deoxycytidylic acid
Thymine (2,4-dioxy-5-methylpyrimidine)	Thymidine (thymine deoxyriboside)	Thymidylic acid (thymine deoxyribotide)
Uracil (2,4-dioxypyrimidine) Uracil	Uridine Pseudouridine (5-ribosyl linkage)	Uridylic acid Pseudouridylic acid

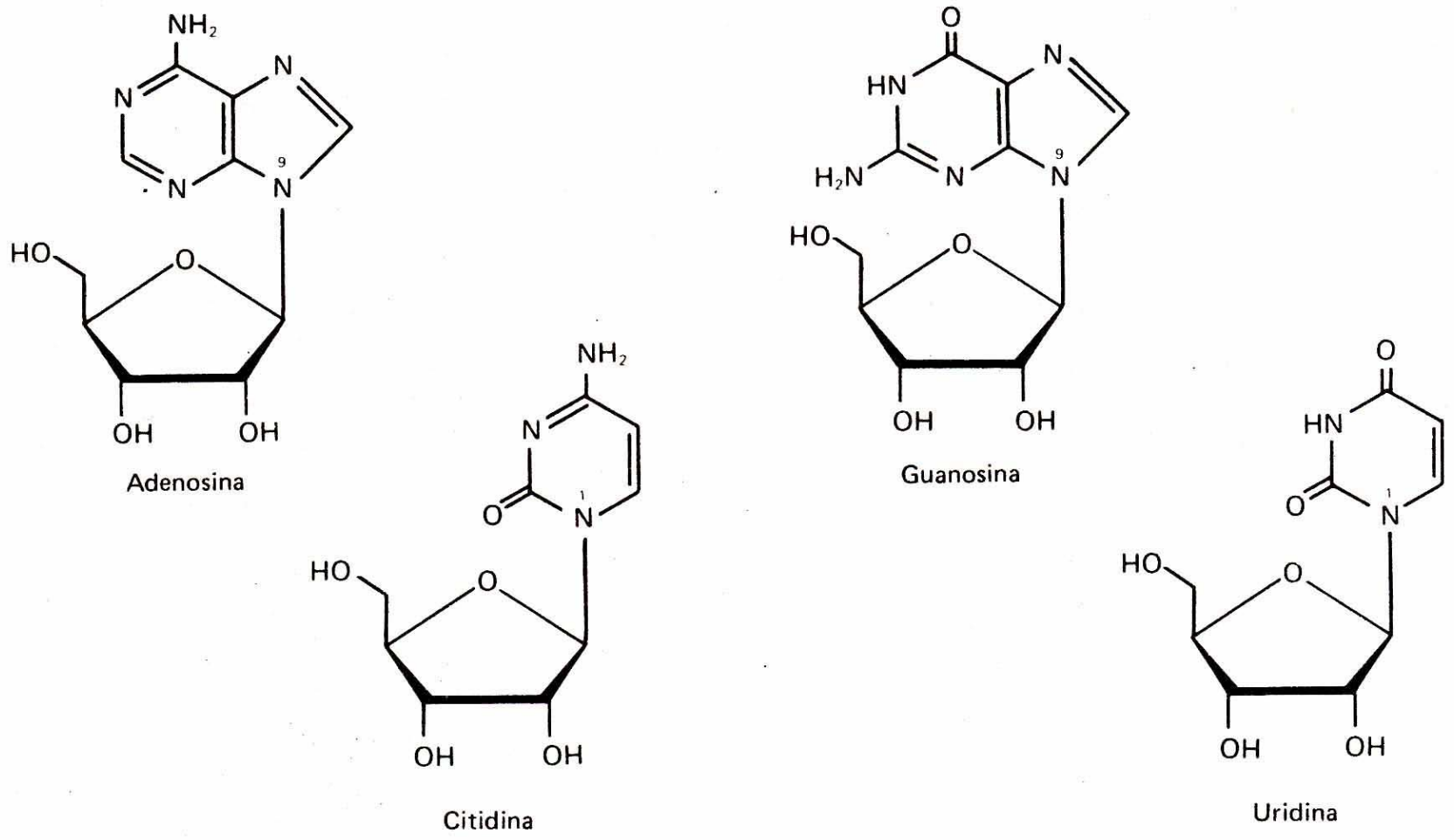


Fig. 34–8. Estructuras de ribonucleósidos.

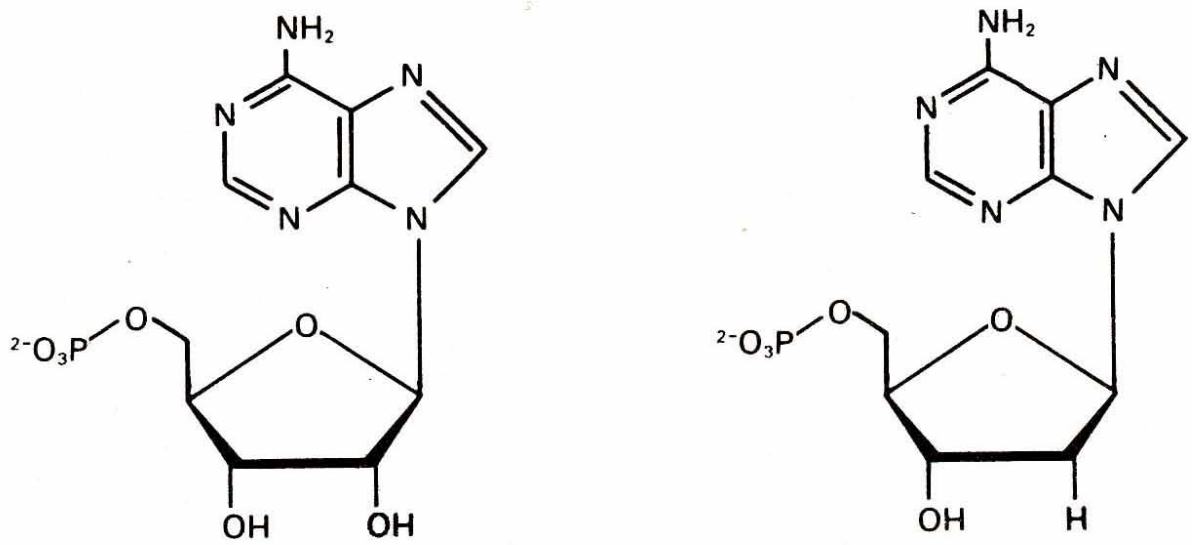
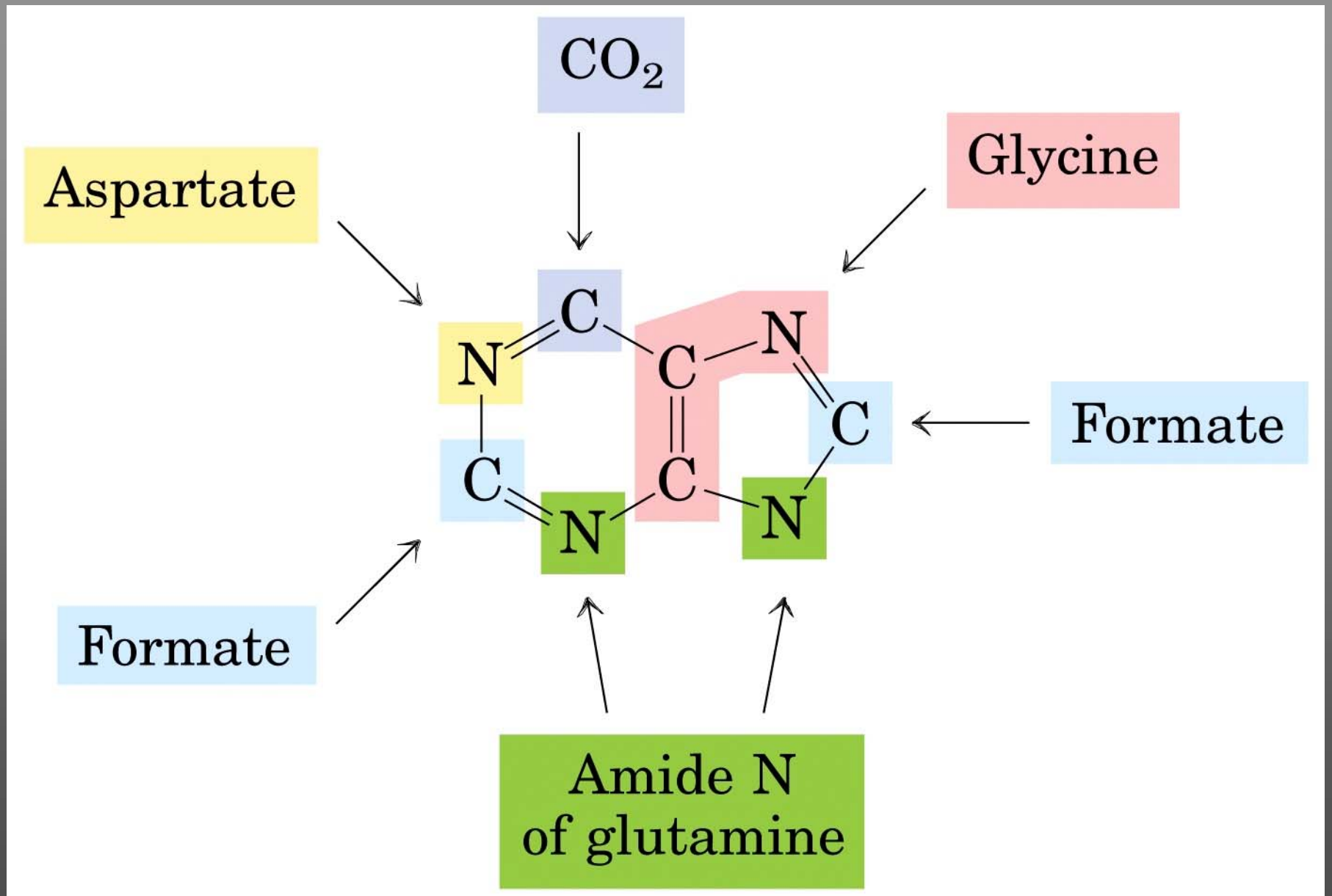
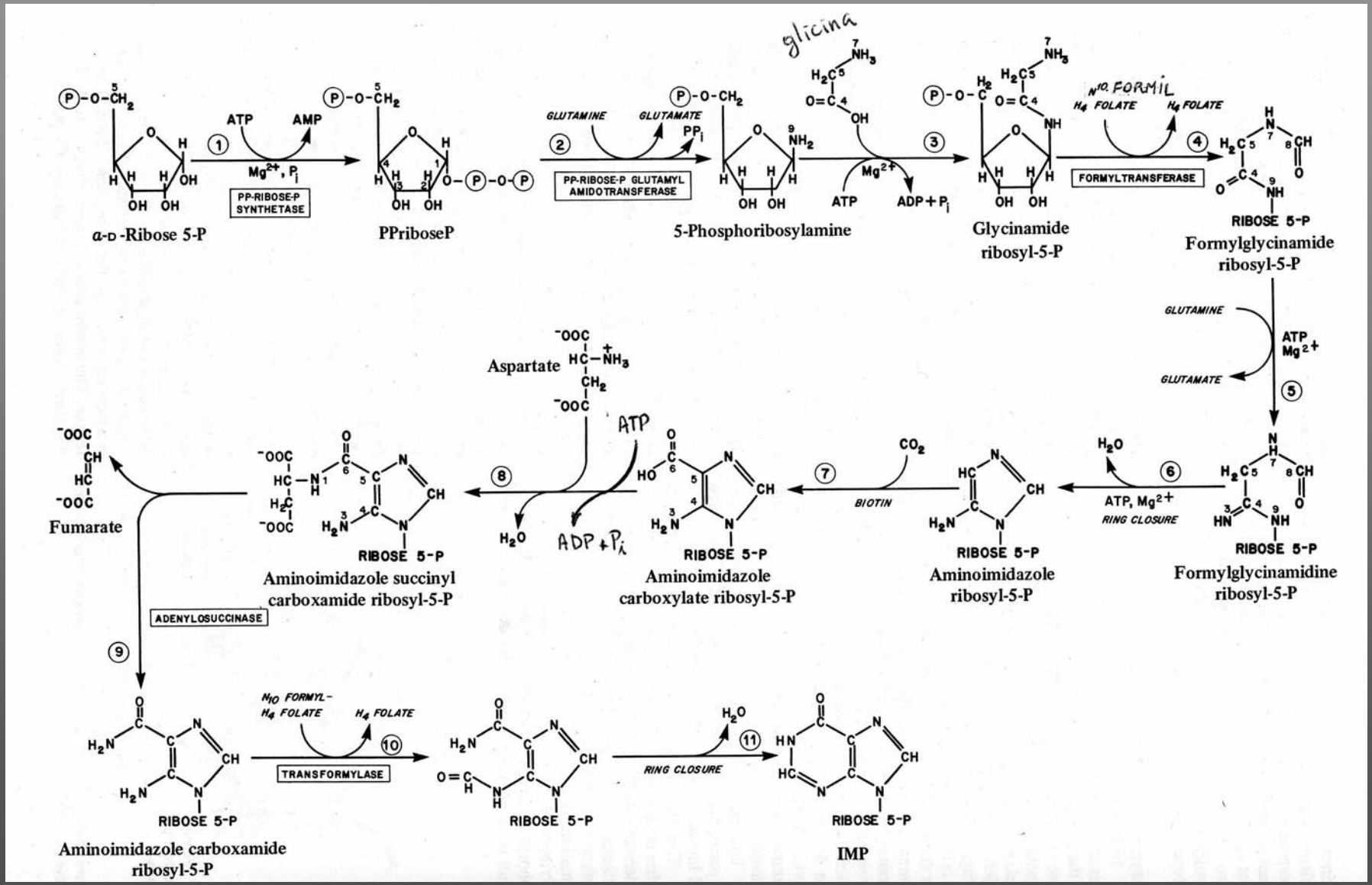
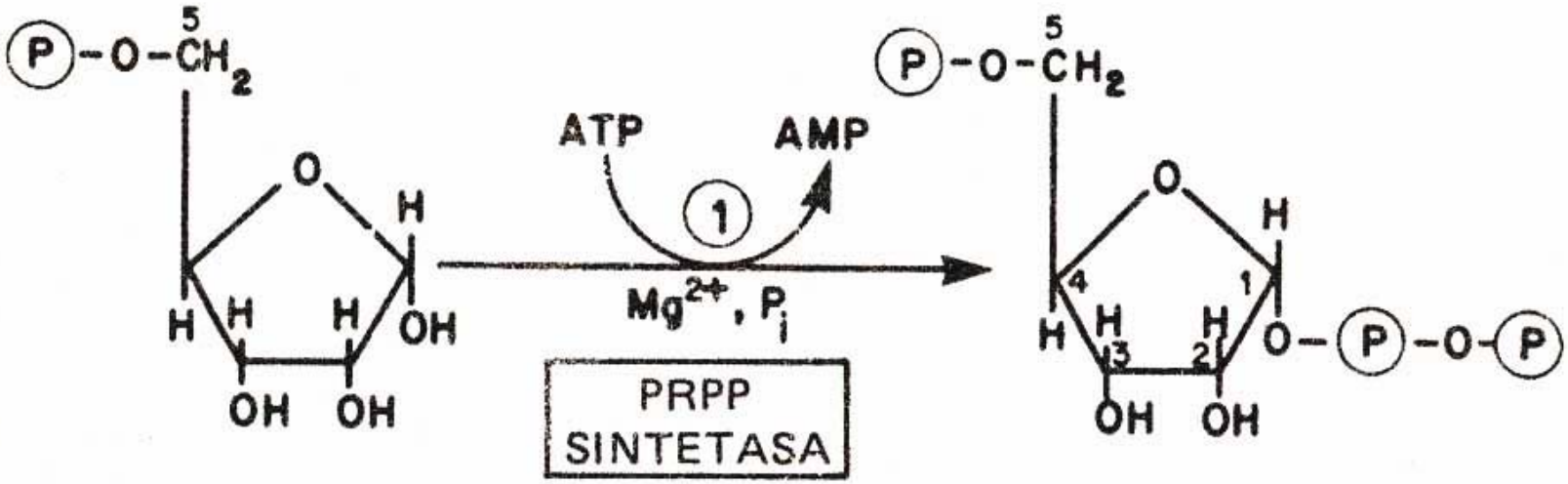
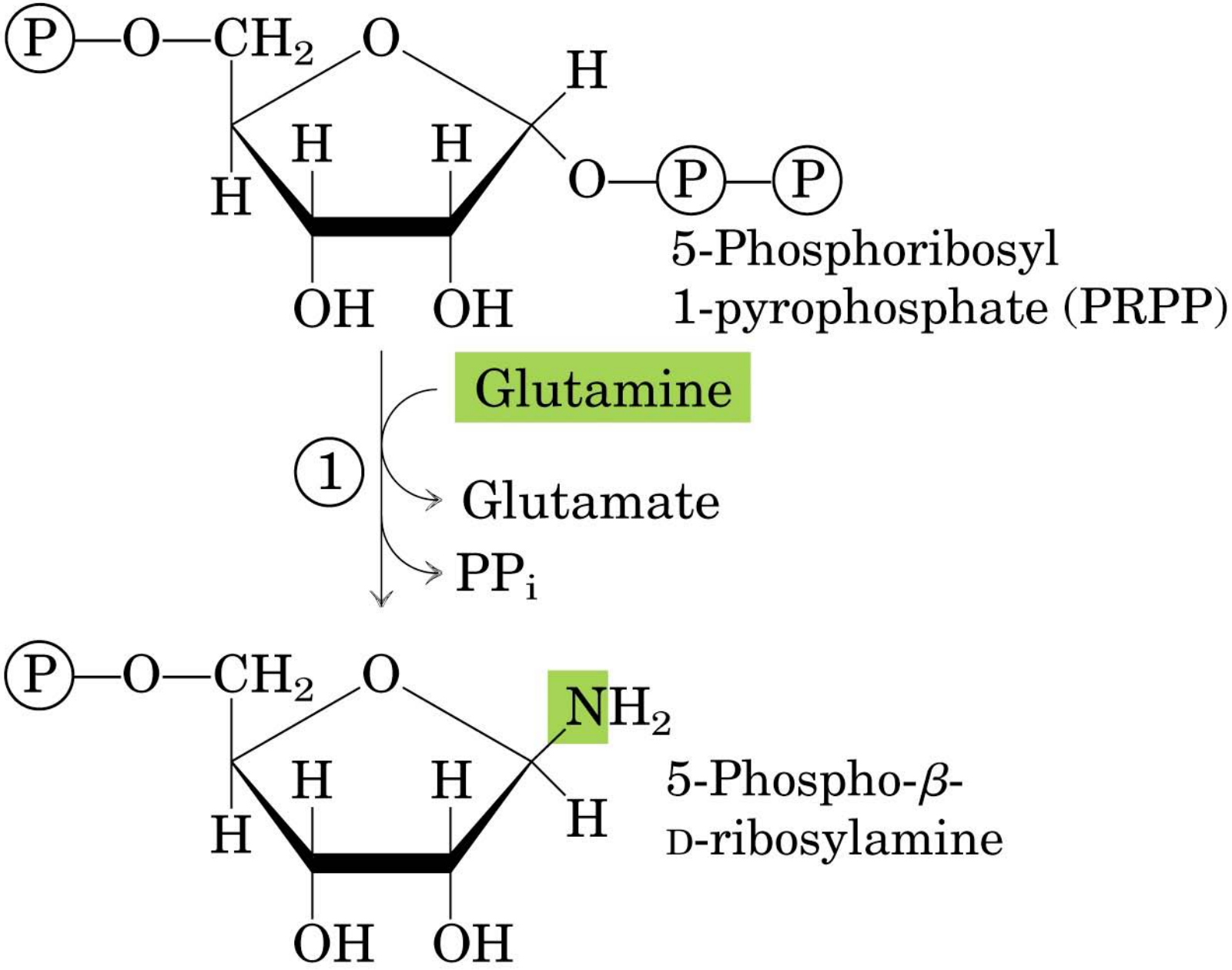


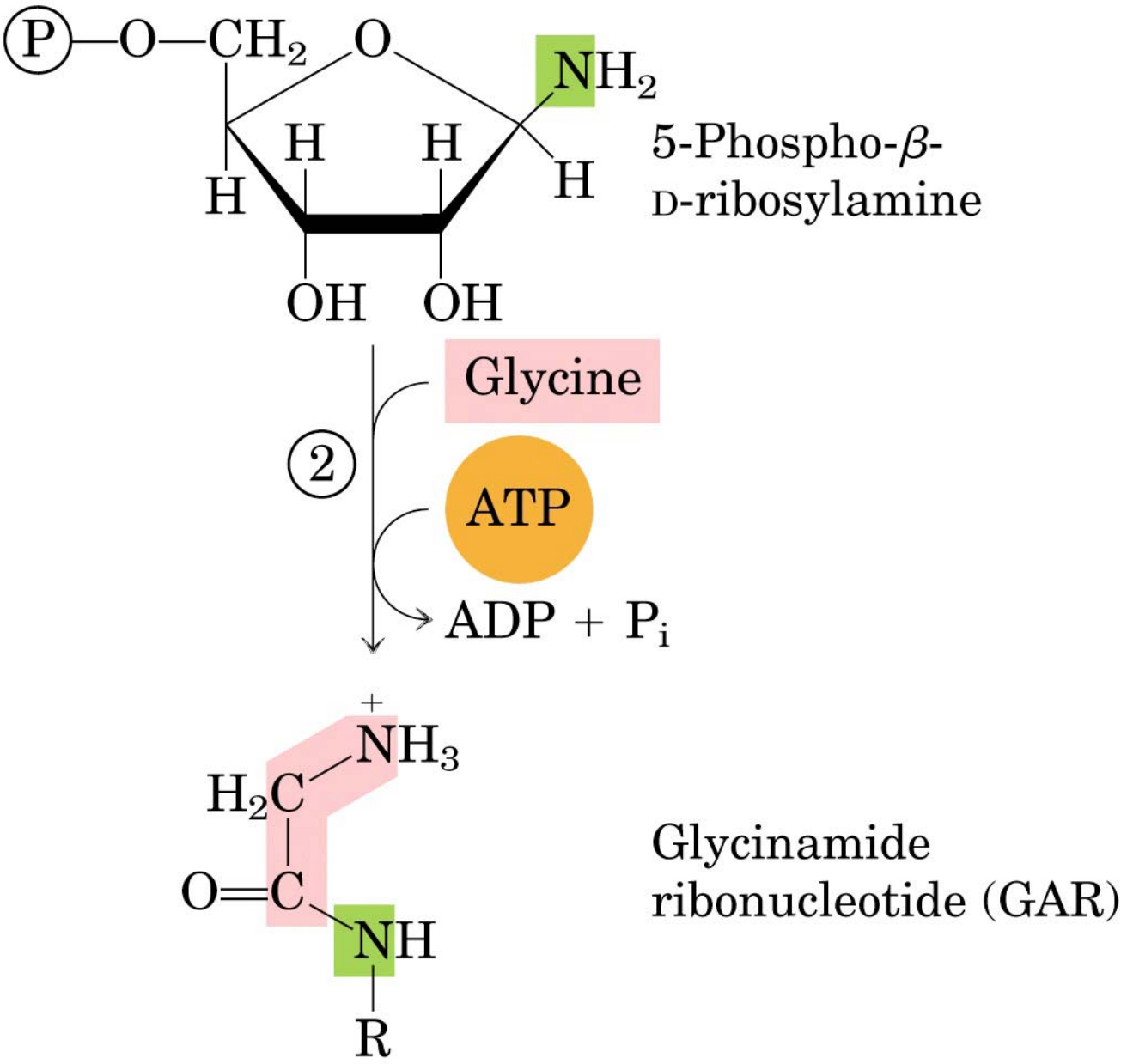
Fig. 34–10. Estructuras del ácido adenílico (adenilato; AMP) **(izquierda)** y del ácido 2′-desoxiadenílico (desoxiadenilato; dAMP) **(derecha).**

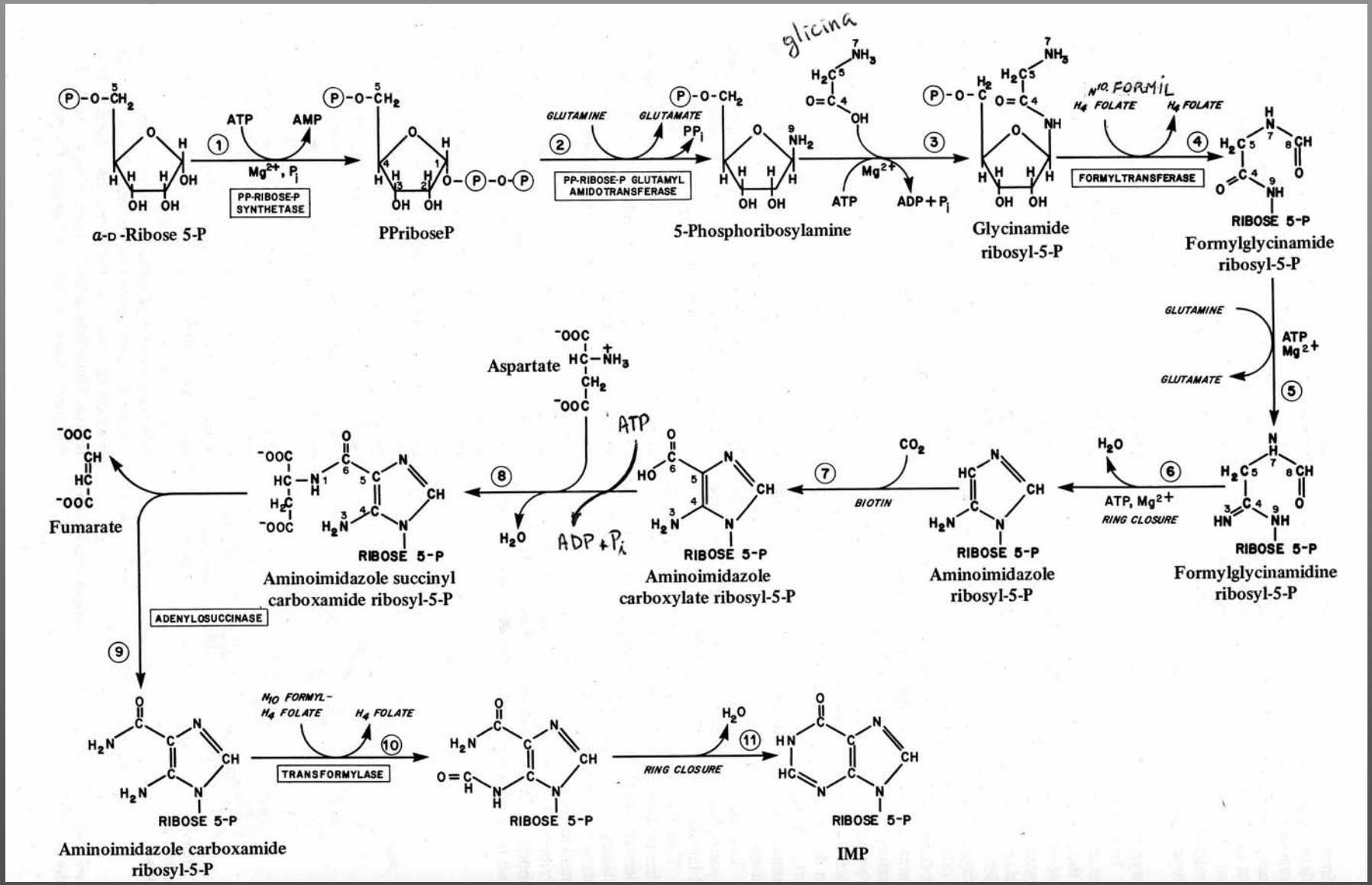

CO_2
Aspartate
Glycine
Formate
Formate
Amide N
of glutamine

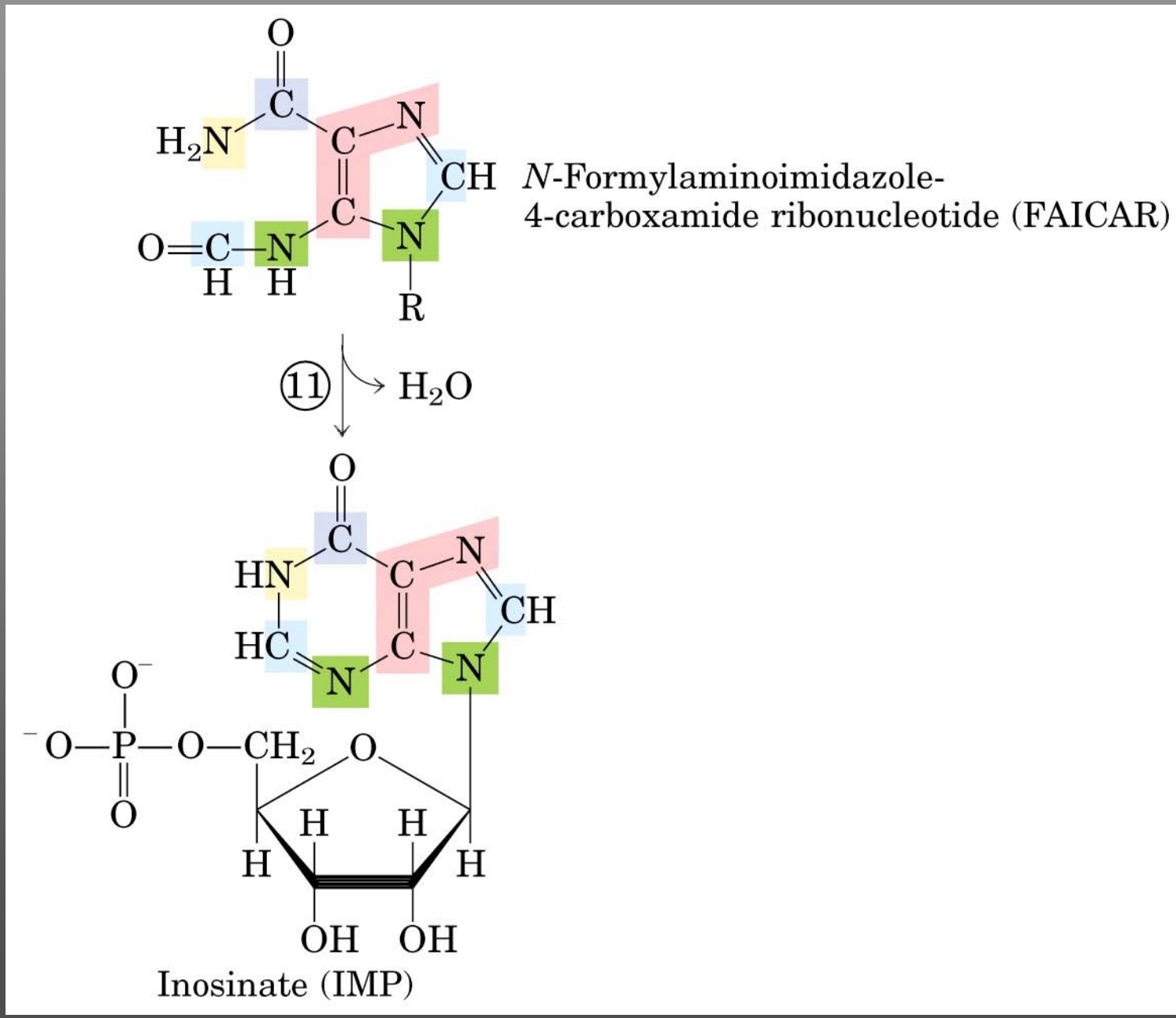

α-D-Ribose 5-P
ATP
AMP
Mg2+, Pi
PP-RIBOSE-P SYNTHETASE
PPriboseP
GLUTAMINE
GLUTAMATE
PPi
PP-RIBOSE-P GLUTAMYL AMIDOTRANSFERASE
glicina
5-Phosphoribosylamine
ATP
ADP + Pi
Glycinamide ribosyl-5-P
N10 FORMIL H4 FOLATE
H4 FOLATE
FORMYLTRANSFERASE
RIBOSE 5-P
Formylglycinamide ribosyl-5-P
GLUTAMINE
GLUTAMATE
ATP Mg2+
Formylglycinamidine ribosyl-5-P
H2O
ATP, Mg2+
RING CLOSURE
CO2
BIOTIN
Aminoimidazole ribosyl-5-P
Aminoimidazole carboxylate ribosyl-5-P
Aspartate
ATP
H2O
ADP + Pi
Aminoimidazole succinyl carboxamide ribosyl-5-P
Fumarate
ADENYLOSUCCINASE
N10 FORMYL-H4 FOLATE
H4 FOLATE
TRANSFORMYLASE
Aminoimidazole carboxamide ribosyl-5-P
RING CLOSURE
H2O
IMP


ATP
AMP
1
Mg^{2+}, P_i
PRPP
SINTETASA
α-D-Ribosa 5-P
PRPP


P—O—CH2
O
H
H
H
H
O—P—P
OH
OH
5-Phosphoribosyl
1-pyrophosphate (PRPP)
Glutamine
1
Glutamate
PPi
P—O—CH2
O
NH2
H
H
H
H
OH
OH
5-Phospho-β-
D-ribosylamine

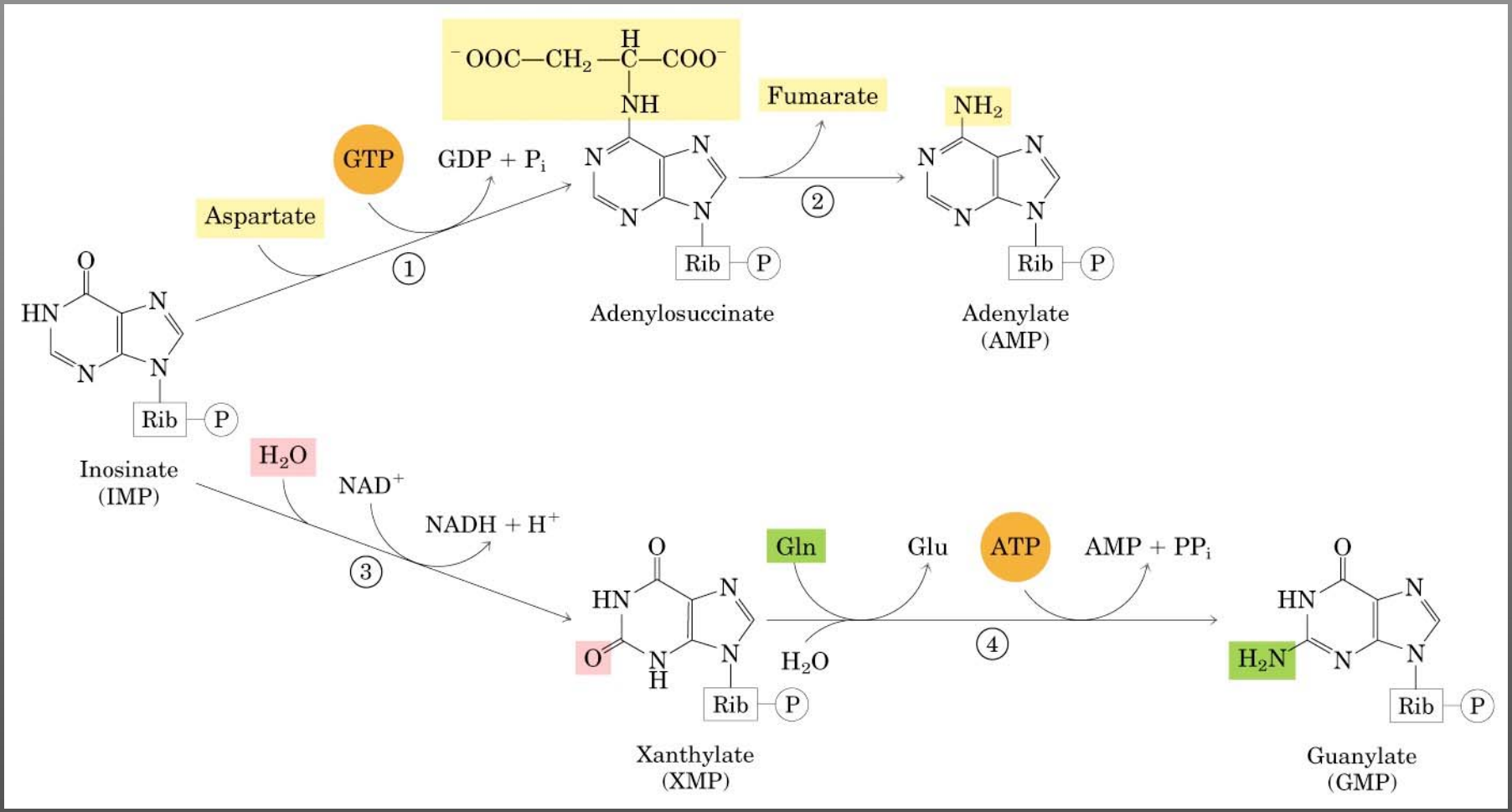

P—O—CH2
O
NH2
H
H
H
H
OH
OH
5-Phospho-β-
D-ribosylamine
Glycine
2
ATP
ADP + Pi
+
NH3
H2C
O=C
NH
R
Glycinamide
ribonucleotide (GAR)

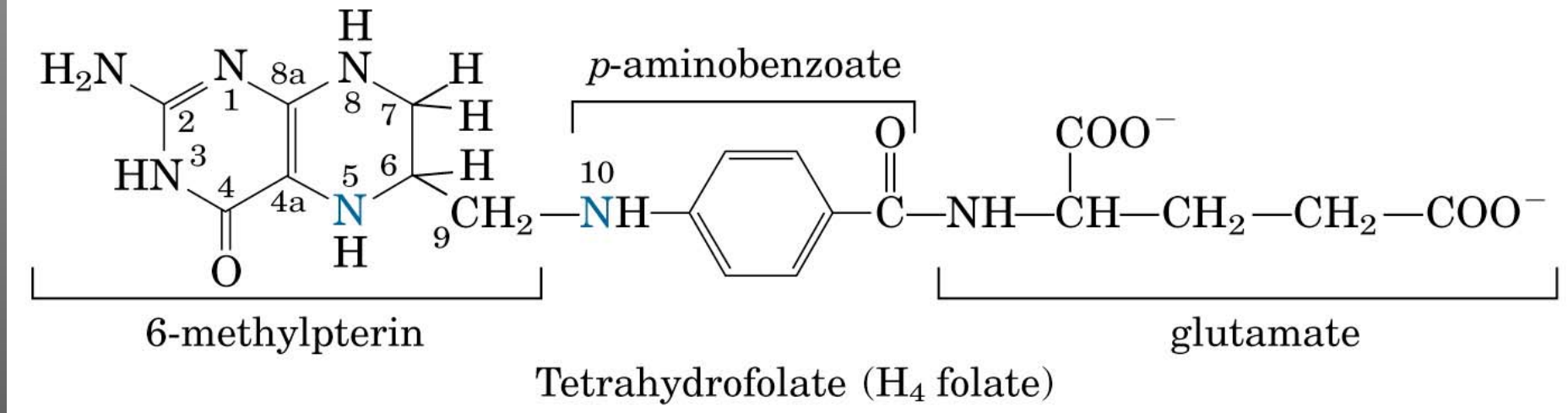

α-D-Ribose 5-P
ATP
AMP
Mg2+, Pi
PP-RIBOSE-P SYNTHETASE
PPriboseP
GLUTAMINE
GLUTAMATE
PPi
PP-RIBOSE-P GLUTAMYL AMIDOTRANSFERASE
glicina
5-Phosphoribosylamine
ATP
ADP + Pi
Glycinamide ribosyl-5-P
N10 FORMIL H4 FOLATE
H4 FOLATE
FORMYLTRANSFERASE
RIBOSE 5-P
Formylglycinamide ribosyl-5-P
GLUTAMINE
GLUTAMATE
ATP Mg2+
Formylglycinamidine ribosyl-5-P
H2O
ATP, Mg2+
RING CLOSURE
CO2
BIOTIN
Aminoimidazole ribosyl-5-P
Aminoimidazole carboxylate ribosyl-5-P
Aspartate
ATP
H2O
ADP + Pi
Aminoimidazole succinyl carboxamide ribosyl-5-P
Fumarate
ADENYLOSUCCINASE
N10 FORMYL-H4 FOLATE
H4 FOLATE
TRANSFORMYLASE
Aminoimidazole carboxamide ribosyl-5-P
RING CLOSURE
H2O
IMP



N-Formylaminoimidazole-
4-carboxamide ribonucleotide (FAICAR)

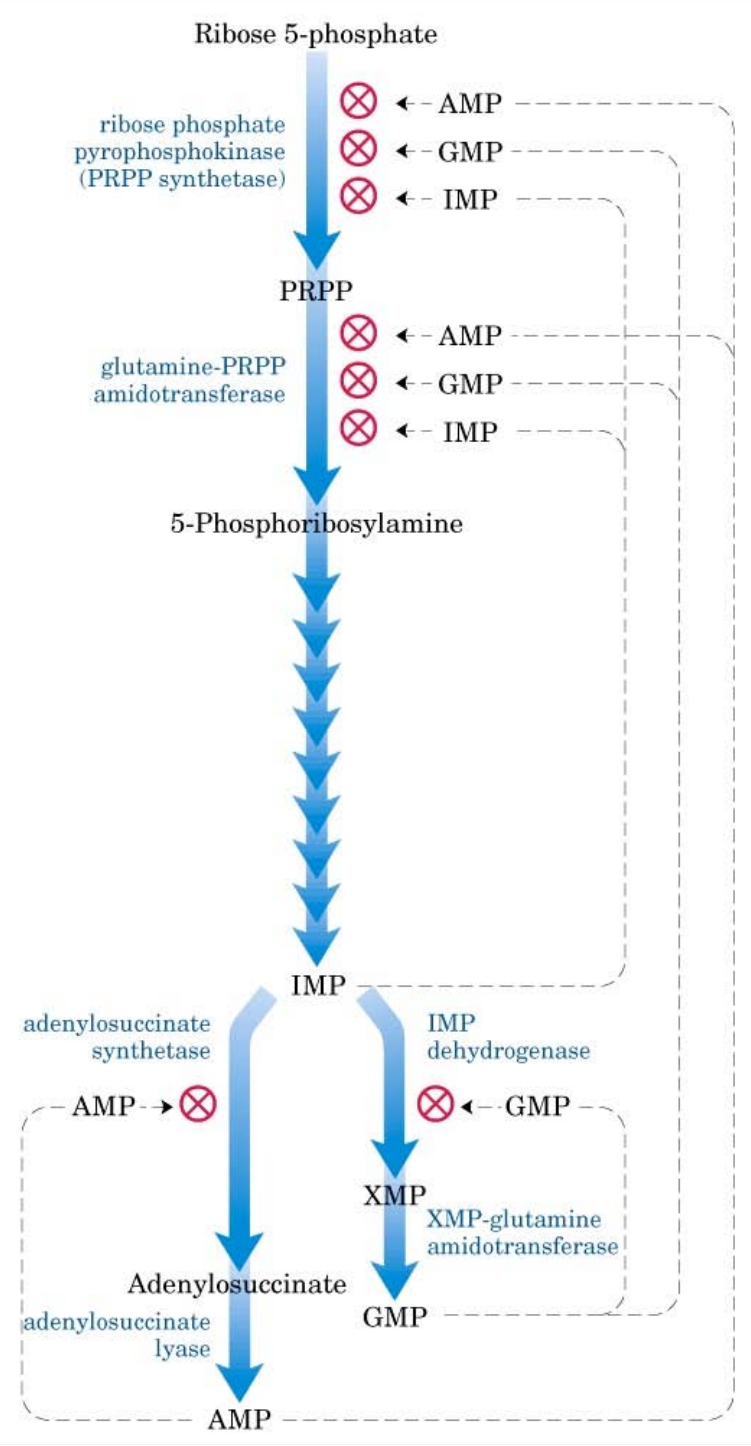
Inosinate (IMP)

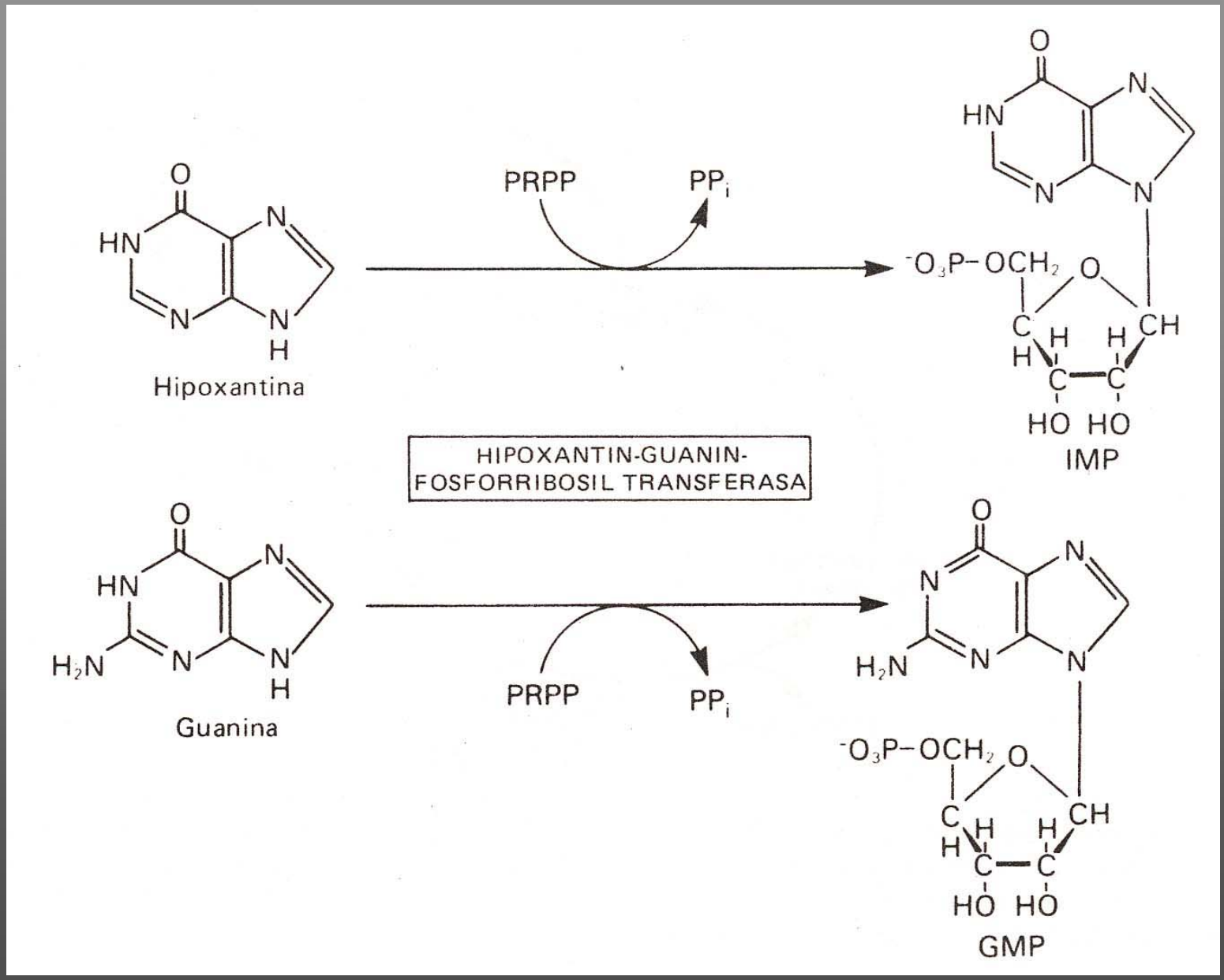

⁻OOC—CH₂—C(H)(NH)—COO⁻
GTP
GDP + Pi
Aspartate
Fumarate
NH2
1
2
Rib
P
Adenylosuccinate
Adenylate
(AMP)
Inosinate
(IMP)
H2O
NAD+
NADH + H+
3
Gln
Glu
ATP
AMP + PPi
4
Xanthylate
(XMP)
Guanylate
(GMP)

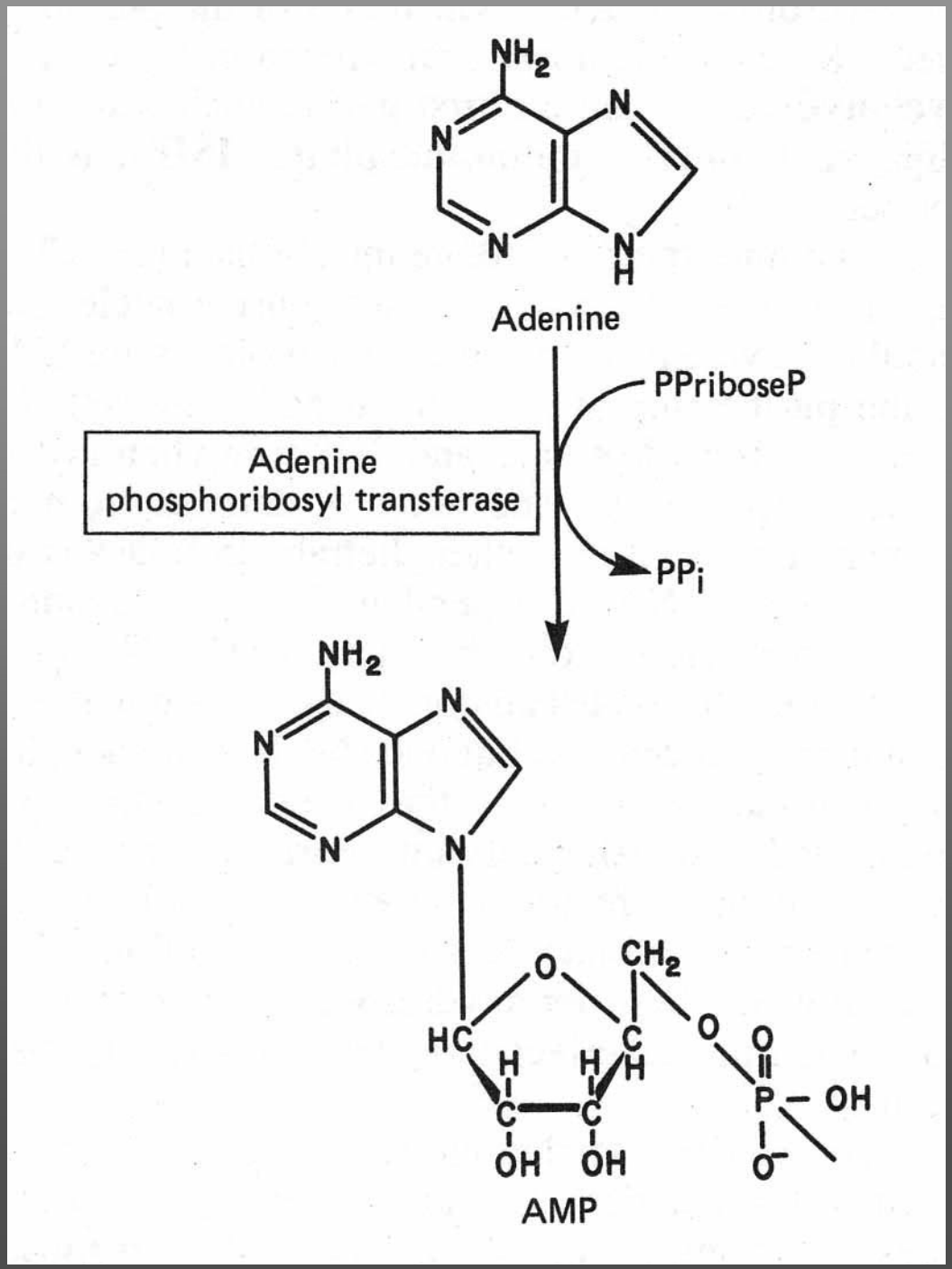


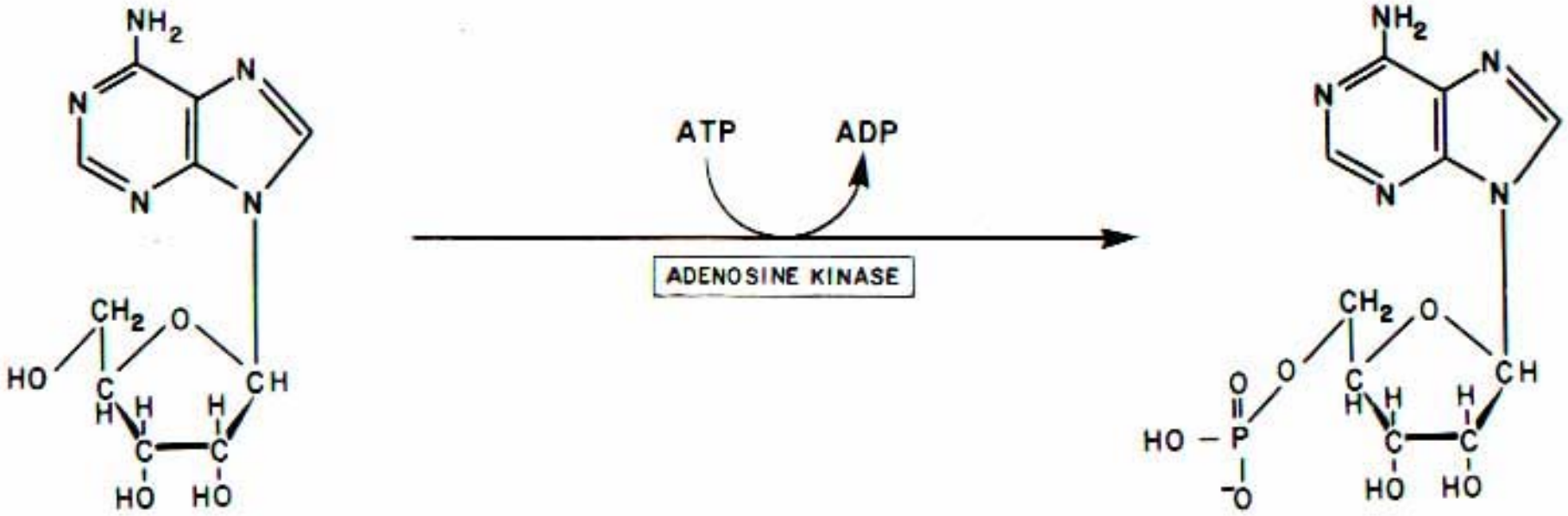
Tetrahydrofolate (H_4 folate)

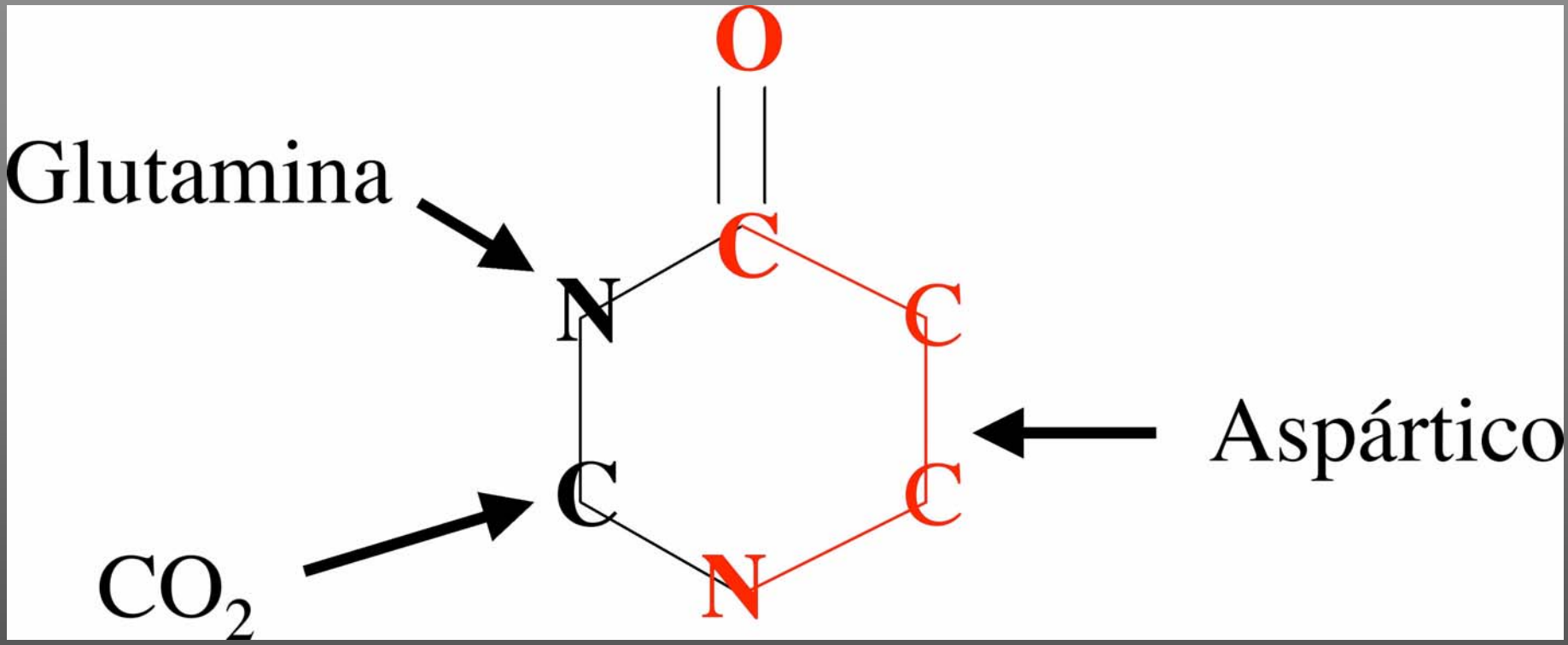

ATP
ADP
Nucleosido-
monofosfato
quinasa
Nucleosido-
difosfato
ATP
ADP
quinasa
Nucleosido-
trifosfato

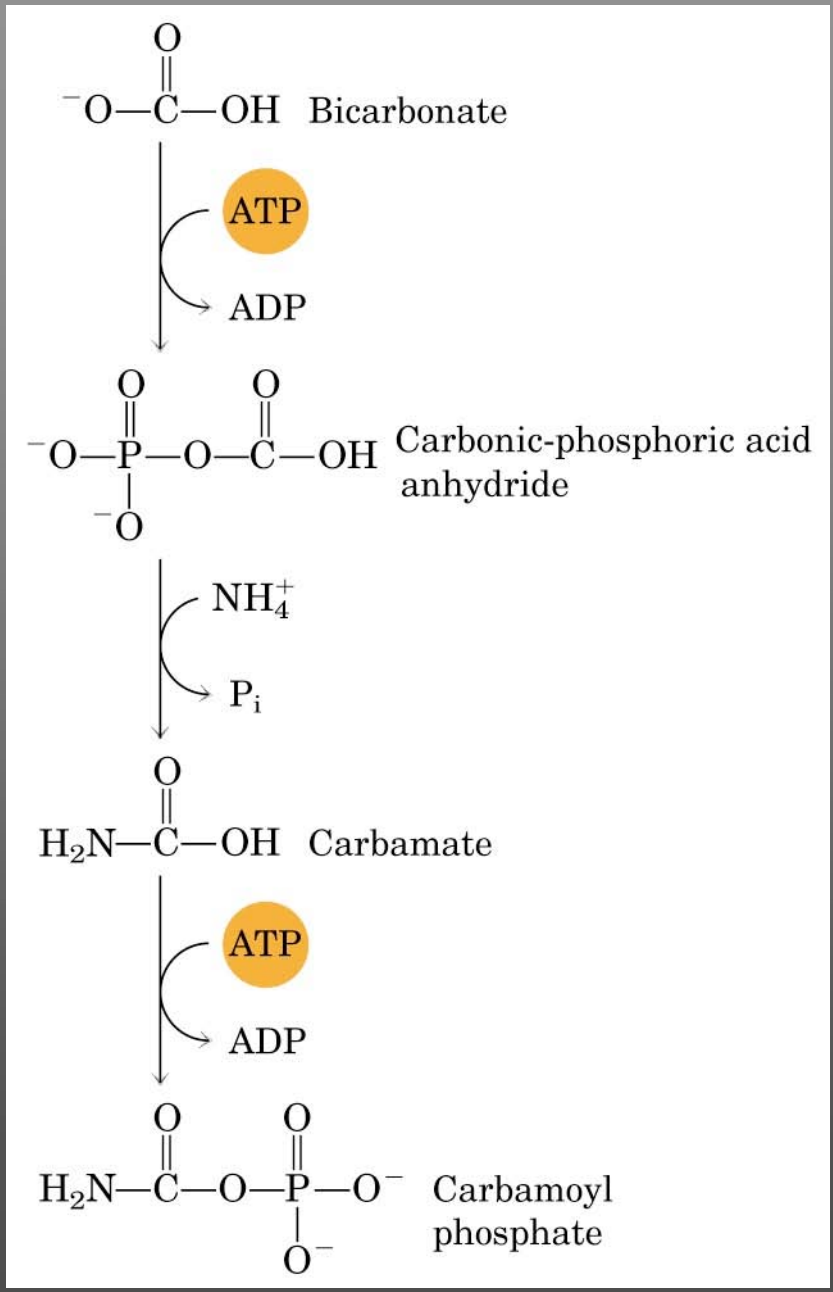

Ribose 5-phosphate
ribose phosphate pyrophosphokinase (PRPP synthetase)
AMP
GMP
IMP
PRPP
glutamine-PRPP amidotransferase
AMP
GMP
IMP
5-Phosphoribosylamine
IMP
adenylosuccinate synthetase
AMP
IMP dehydrogenase
GMP
XMP
XMP-glutamine amidotransferase
Adenylosuccinate
GMP
adenylosuccinate lyase
AMP

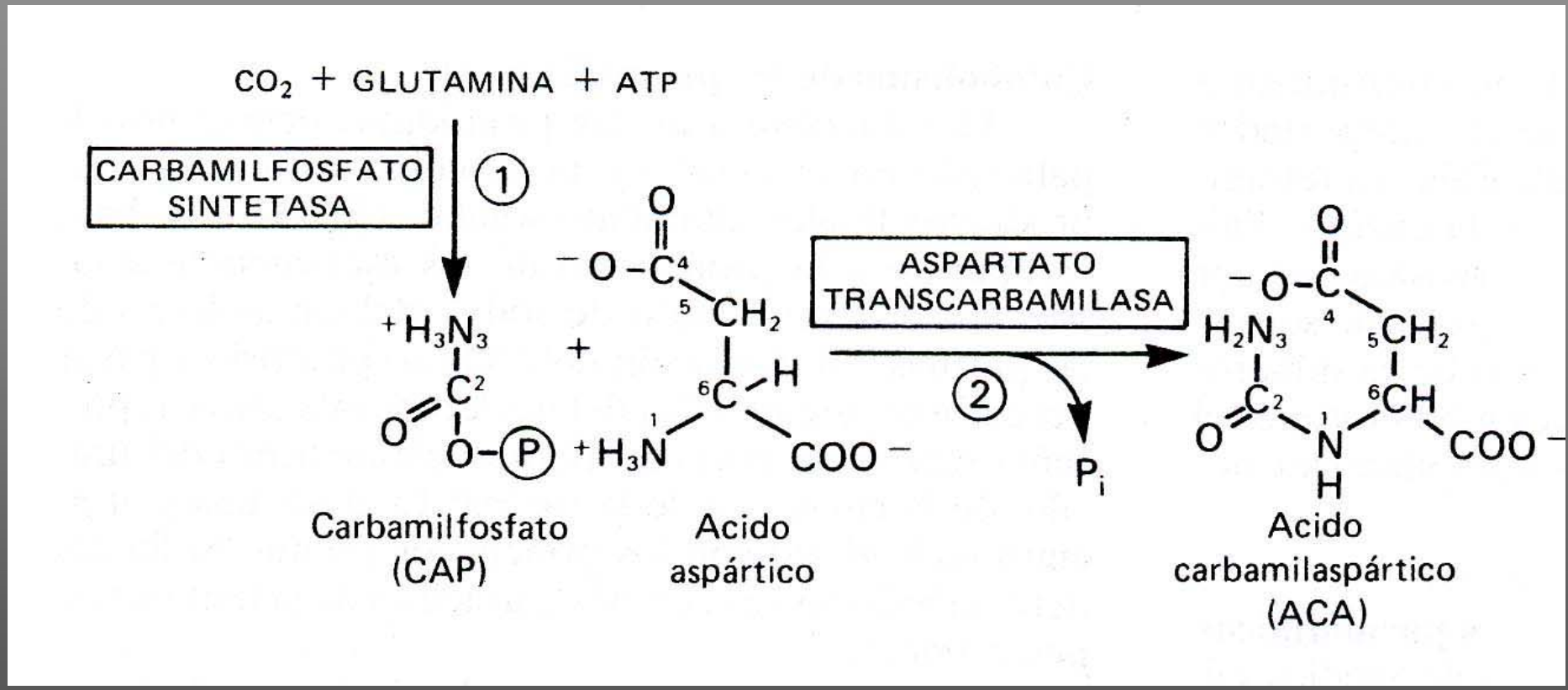

Hipoxantina
PRPP
PPi
IMP
HIPOXANTIN-GUANIN-
FOSFORRIBOSIL TRANSFERASA
Guanina
PRPP
PPi
GMP

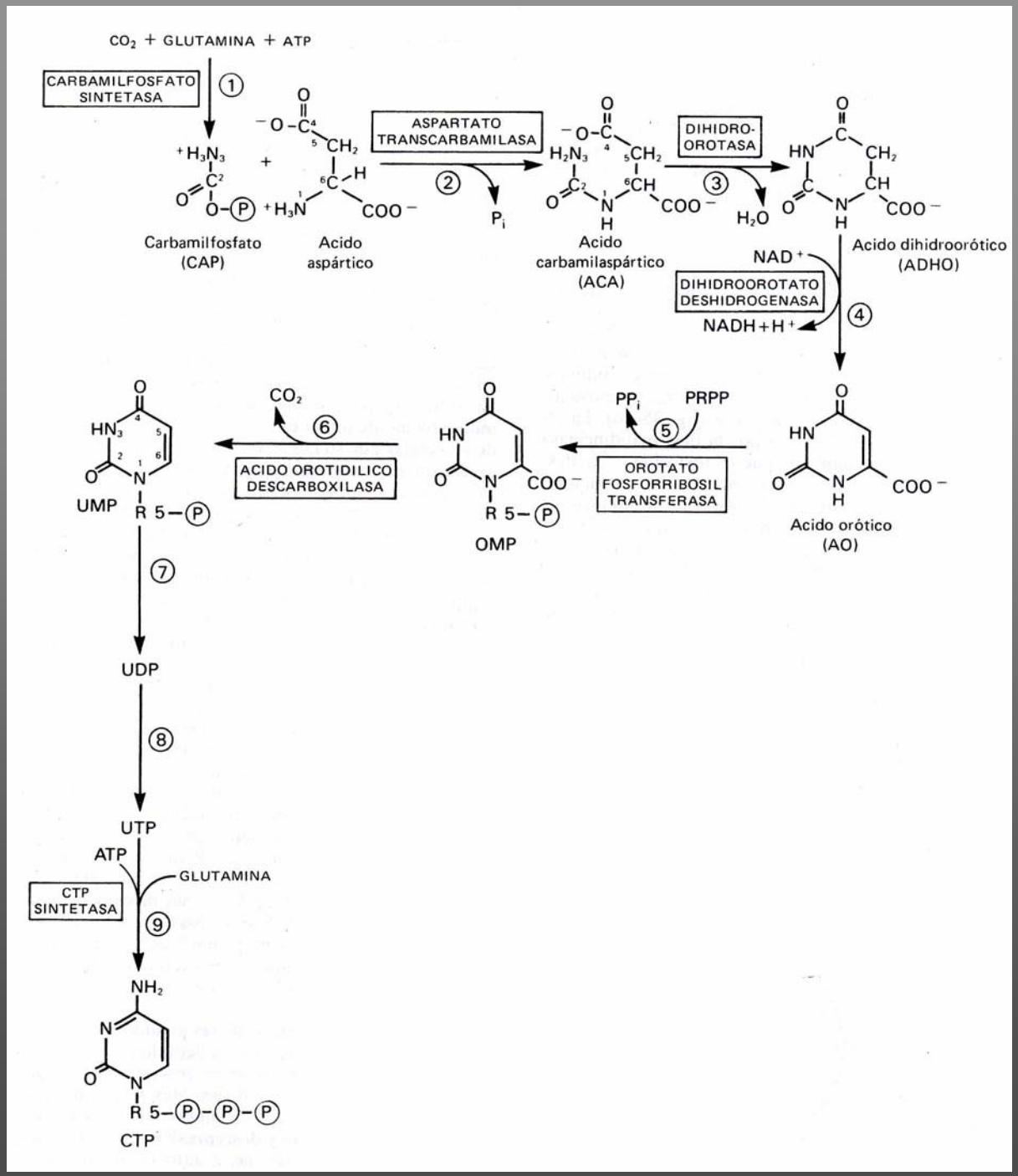

NH2
N
N
N
N
H
Adenine
PPriboseP
Adenine
phosphoribosyl transferase
PPi
NH2
N
N
N
N
O
CH2
HC
C
H
H
H
C
C
OH
OH
O
O
P
OH
O−
AMP

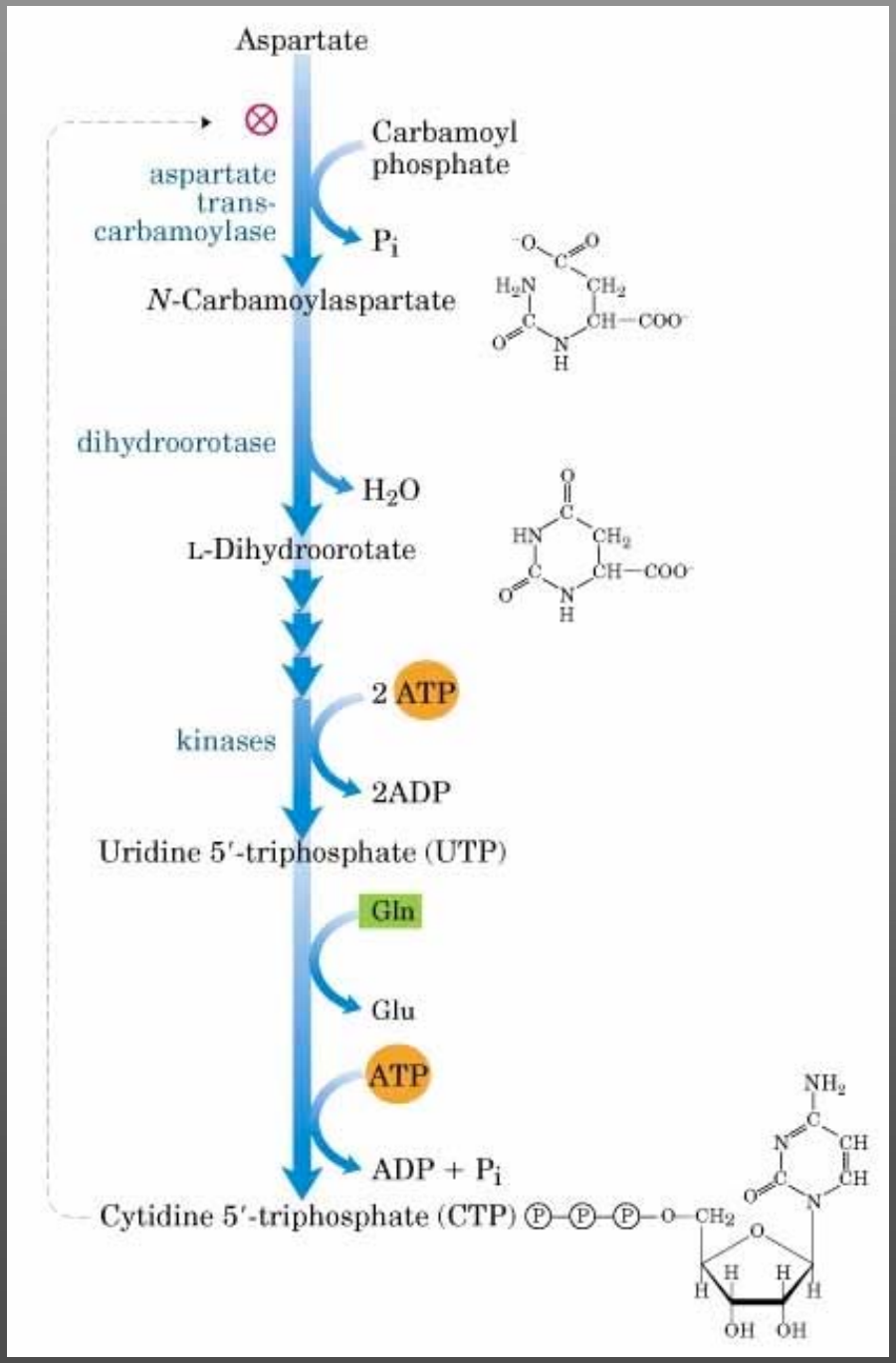

ATP
ADP
ADENOSINE KINASE

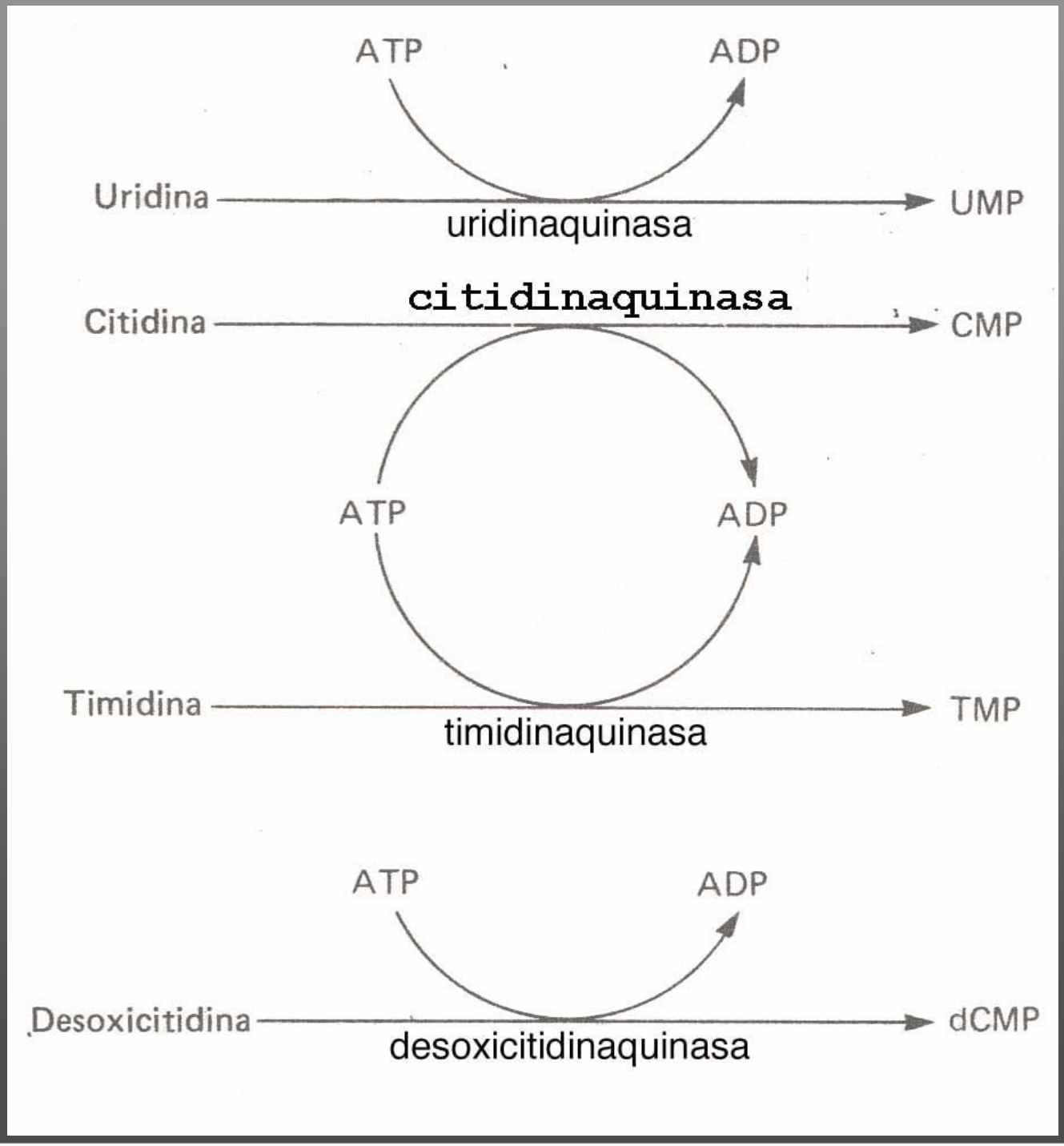

Glutamina
O
C
N
C
C
C
N
Aspártico
CO_2

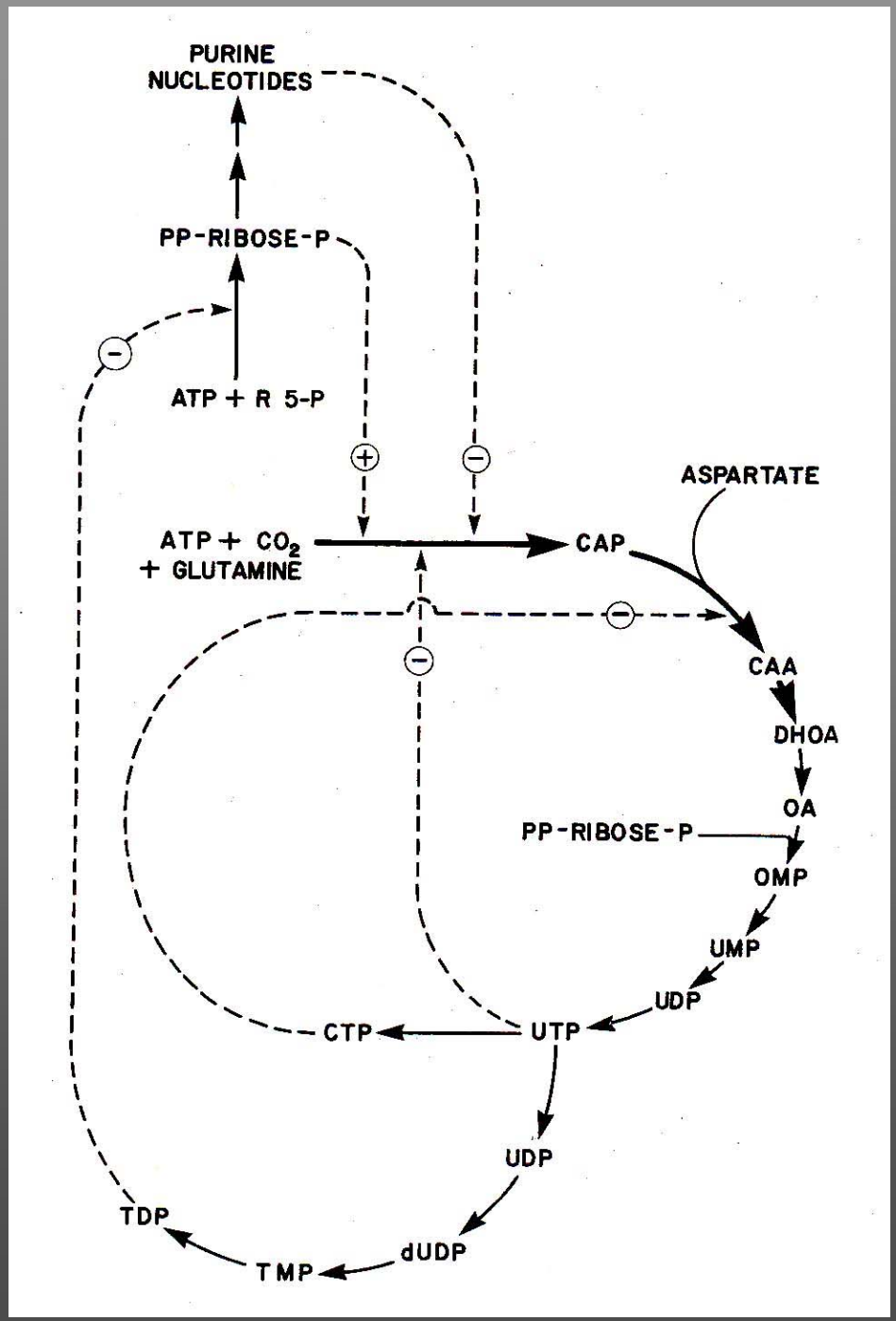

Bicarbonate
ATP
ADP
Carbonic-phosphoric acid anhydride
NH_4^+
P_i
Carbamate
ATP
ADP
Carbamoyl phosphate

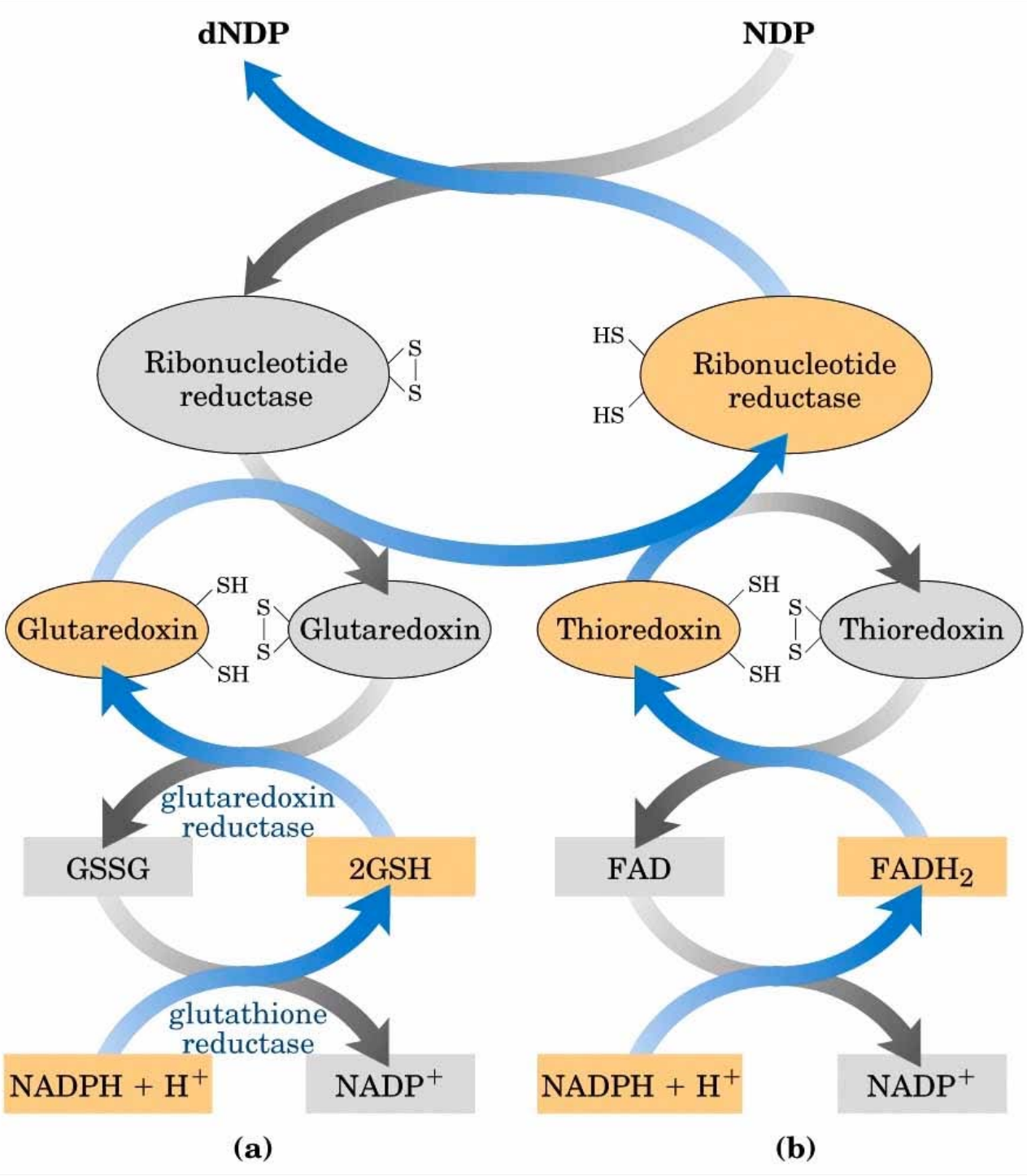

CO2 + GLUTAMINA + ATP
CARBAMILFOSFATO SINTETASA
1
ASPARTATO TRANSCARBAMILASA
2
Pi
Carbamilfosfato (CAP)
Acido aspártico
Acido carbamilaspártico (ACA)

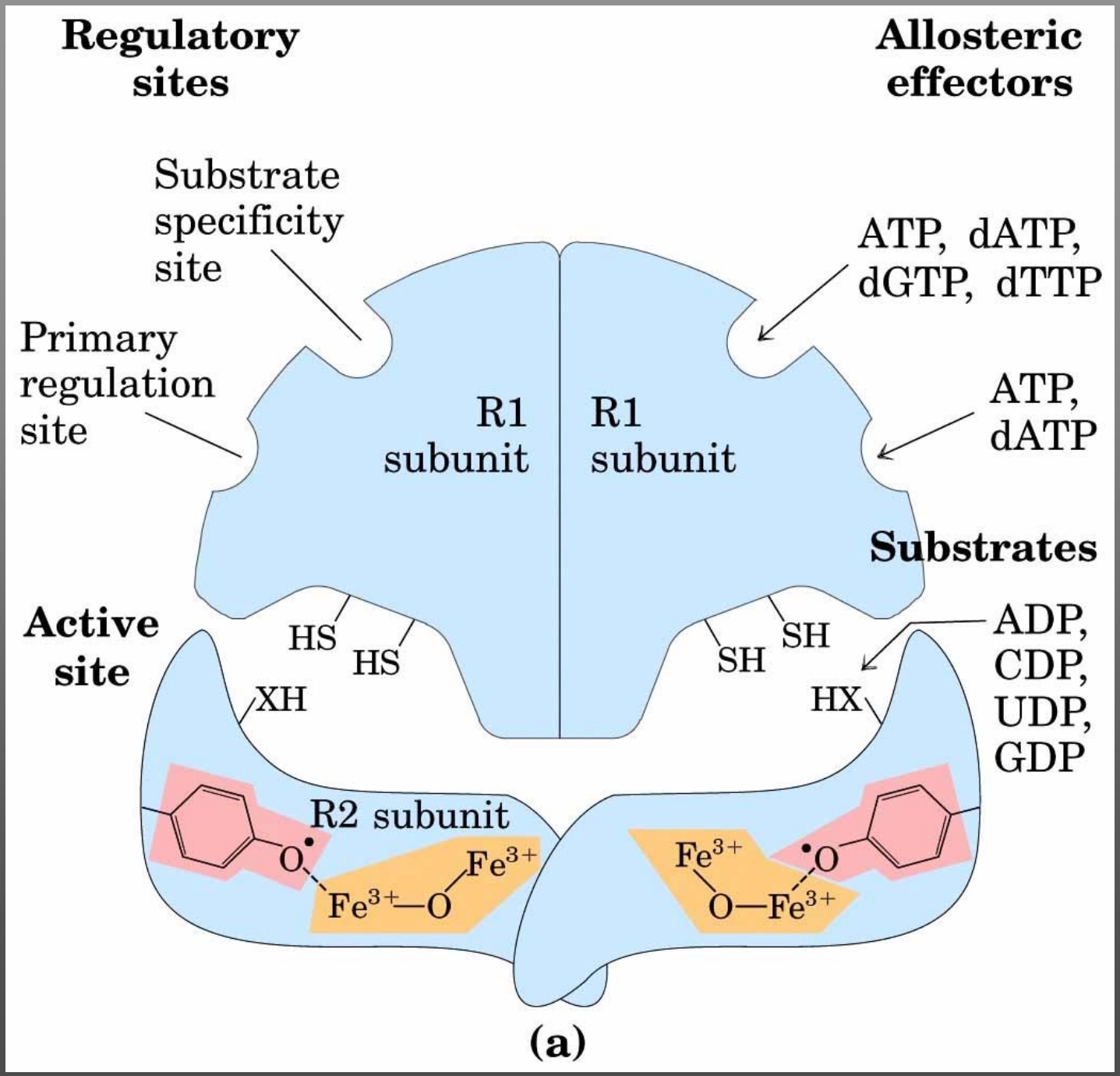

CO_2 + GLUTAMINA + ATP
CARBAMILFOSFATO SINTETASA
①
Carbamilfosfato (CAP)
Acido aspártico
ASPARTATO TRANSCARBAMILASA
②
P_i
Acido carbamilaspártico (ACA)
DIHIDRO-OROTASA
③
H_2O
Acido dihidroorótico (ADHO)
NAD^+
DIHIDROOROTATO DESHIDROGENASA
$NADH + H^+$
④
Acido orótico (AO)
PP_i
PRPP
⑤
OROTATO FOSFORRIBOSIL TRANSFERASA
OMP
CO_2
⑥
ACIDO OROTIDILICO DESCARBOXILASA
UMP
⑦
UDP
⑧
UTP
ATP
GLUTAMINA
CTP SINTETASA
⑨
CTP

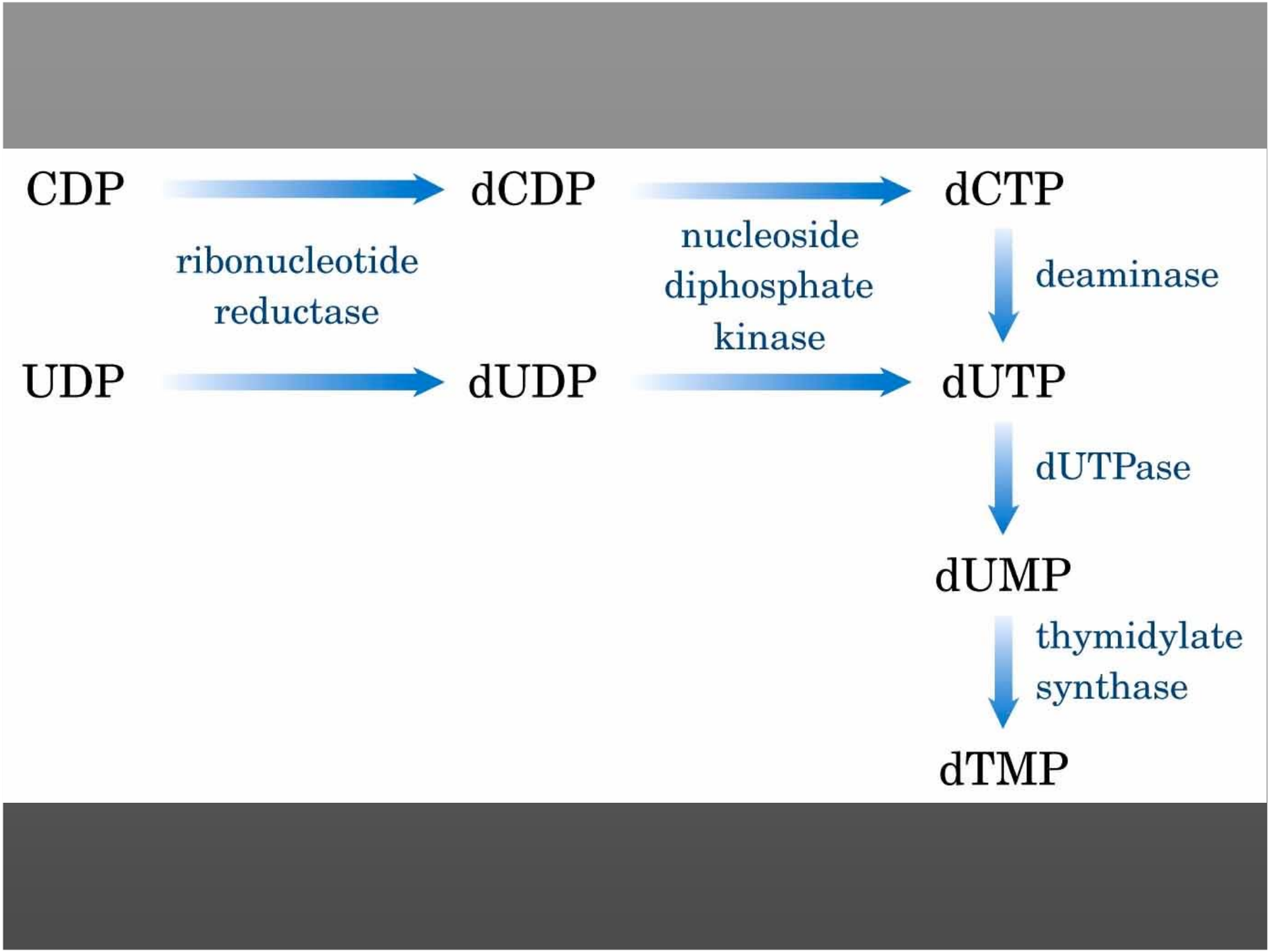

Aspartate
Carbamoyl phosphate
aspartate trans-carbamoylase
P_i
N-Carbamoylaspartate
dihydroorotase
H_2O
L-Dihydroorotate
2 ATP
kinases
2ADP
Uridine 5′-triphosphate (UTP)
Gln
Glu
ATP
ADP + P_i
Cytidine 5′-triphosphate (CTP)

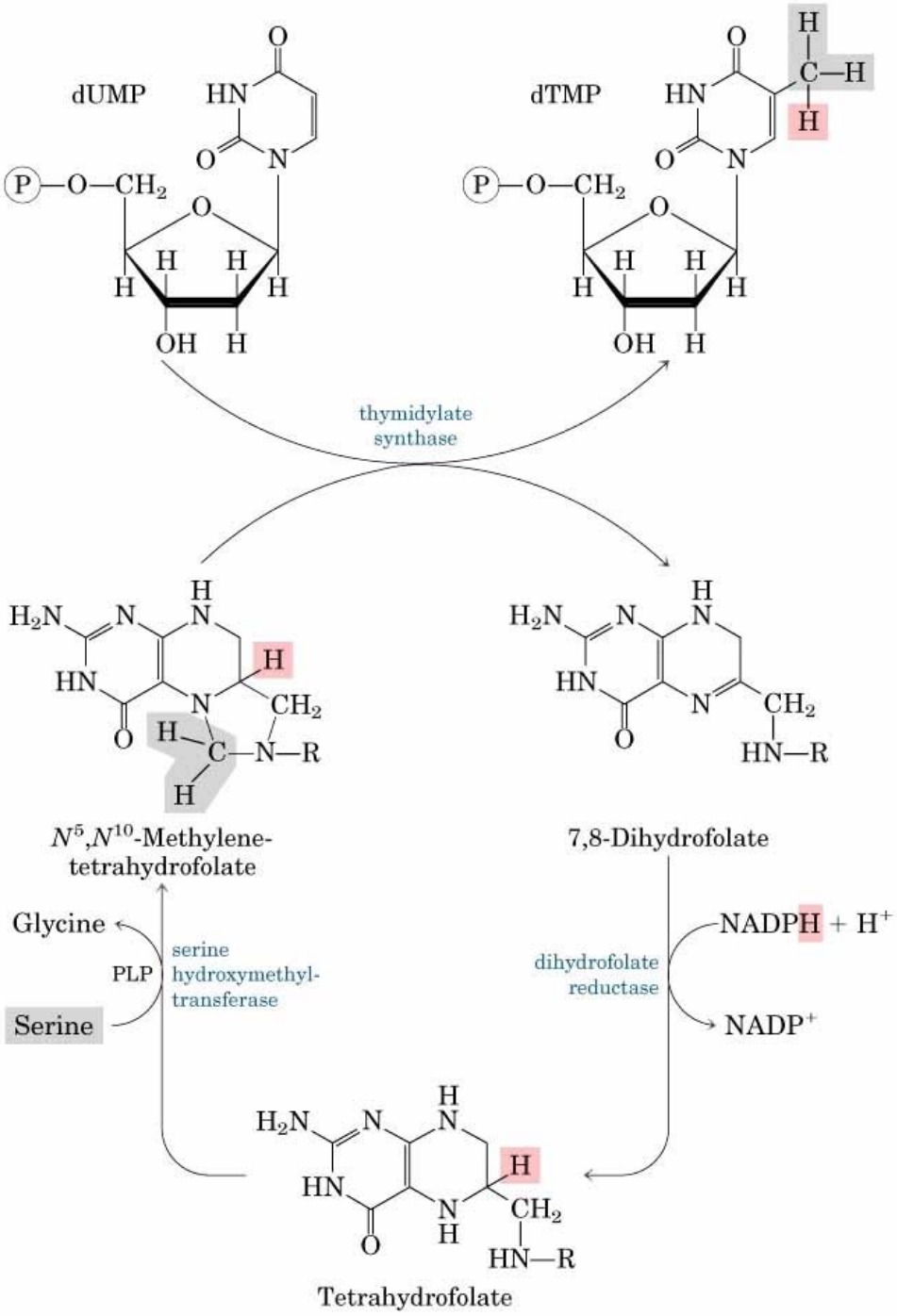

ATP
ADP
Uridina
UMP
uridinaquinasa
citidinaquinasa
Citidina
CMP
ATP
ADP
Timidina
TMP
timidinaquinasa
ATP
ADP
Desoxicitidina
dCMP
desoxicitidinaquinasa

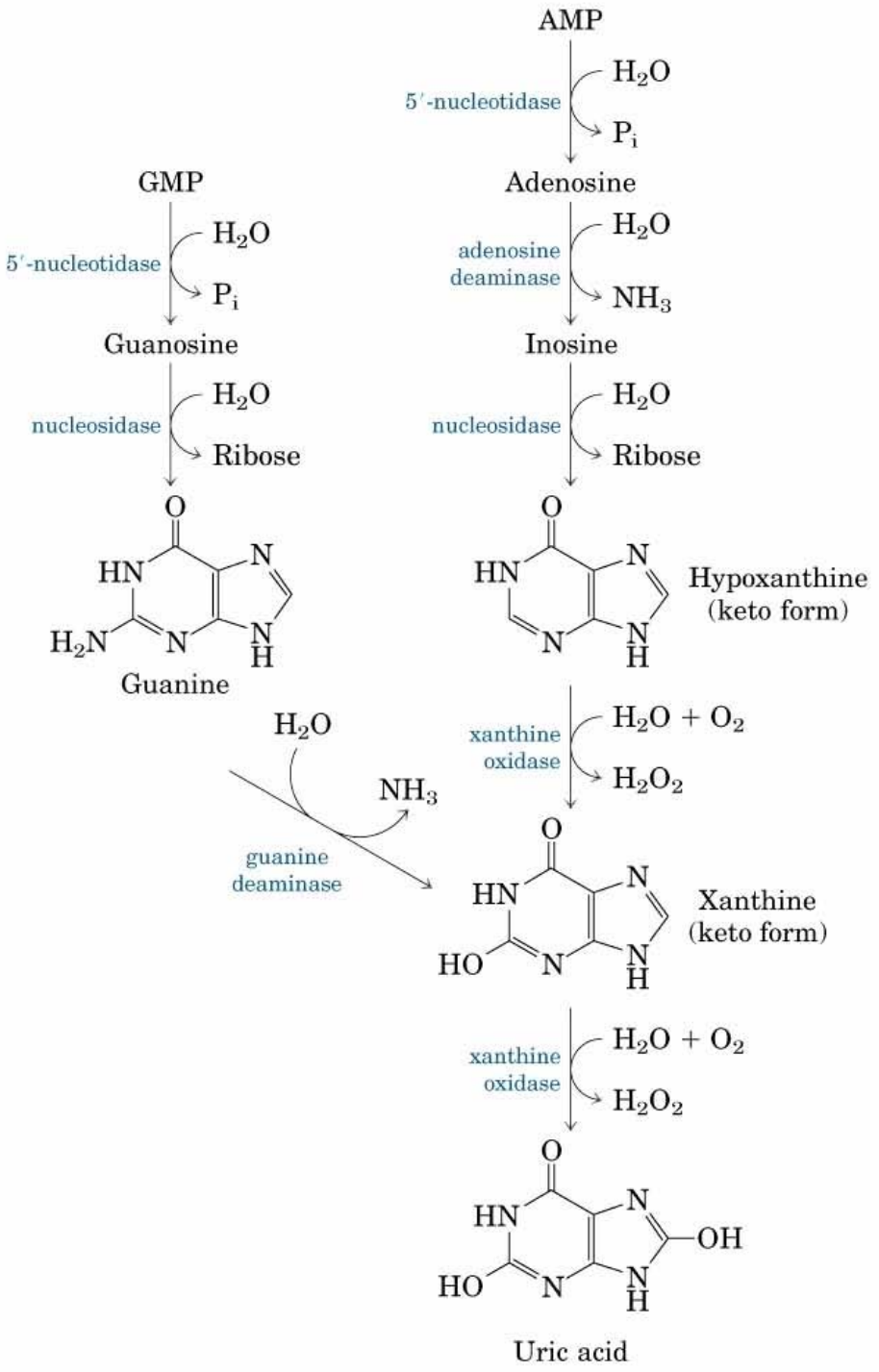

PURINE
NUCLEOTIDES
PP-RIBOSE-P
ATP + R 5-P
ATP + CO_2
+ GLUTAMINE
CAP
ASPARTATE
CAA
DHOA
OA
PP-RIBOSE-P
OMP
UMP
UDP
CTP
UTP
UDP
TDP
dUDP
TMP

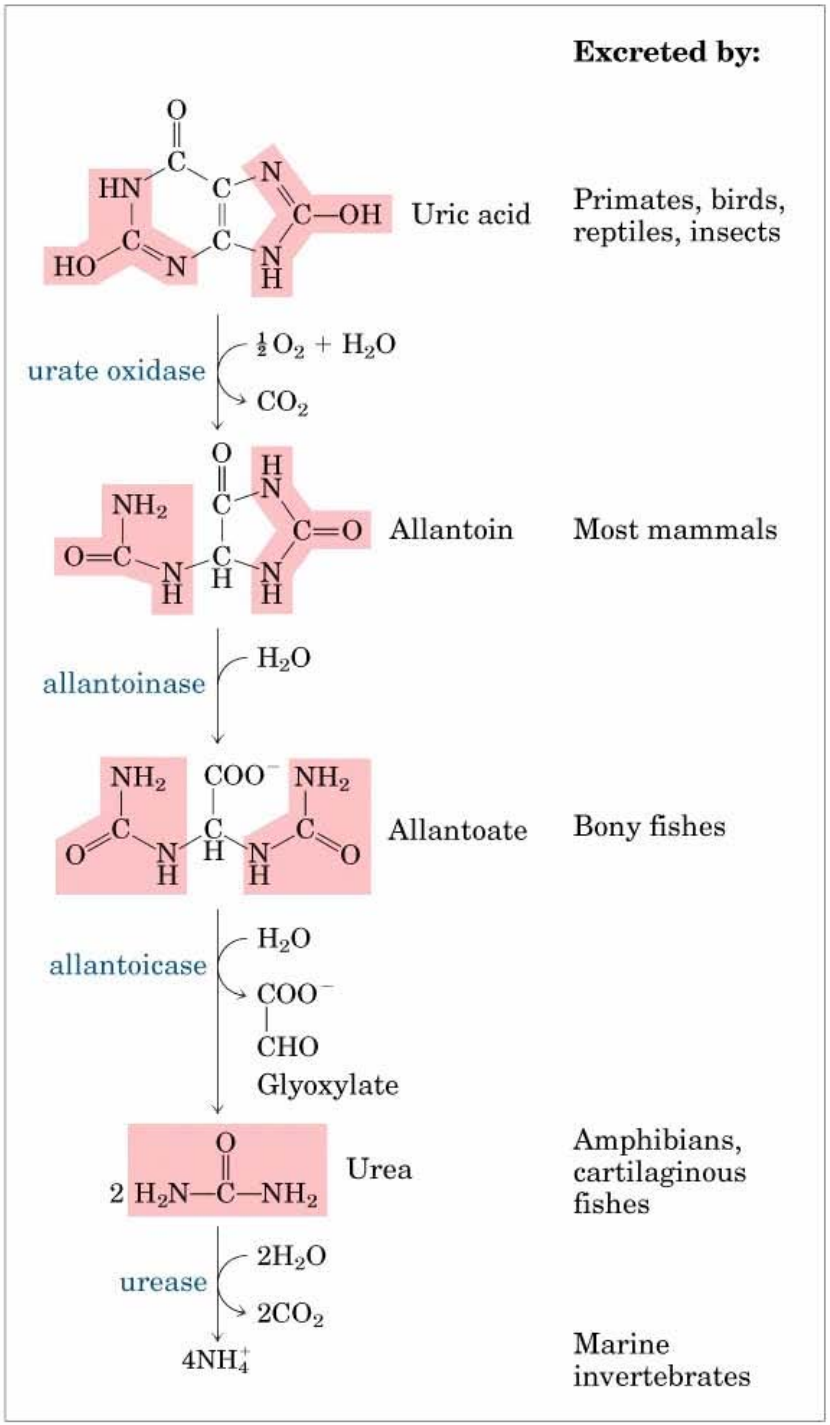

dNDP
NDP
Ribonucleotide reductase
S
S
HS
HS
Ribonucleotide reductase
Glutaredoxin
SH
SH
S
S
Glutaredoxin
Thioredoxin
SH
SH
S
S
Thioredoxin
glutaredoxin reductase
GSSG
2GSH
FAD
FADH2
glutathione reductase
NADPH + H+
NADP+
NADPH + H+
NADP+
(a)
(b)


Regulatory sites
Allosteric effectors
Substrate specificity site
ATP, dATP, dGTP, dTTP
Primary regulation site
ATP, dATP
R1 subunit
R1 subunit
Substrates
Active site
HS
HS
SH
SH
ADP, CDP, UDP, GDP
XH
HX
R2 subunit
O•
Fe3+
Fe3+—O
Fe3+
•O
O—Fe3+
(a)


CDP
dCDP
dCTP
ribonucleotide reductase
nucleoside diphosphate kinase
deaminase
UDP
dUDP
dUTP
dUTPase
dUMP
thymidylate synthase
dTMP


dUMP
dTMP
thymidylate synthase
N^5,N^{10}-Methylene-tetrahydrofolate
7,8-Dihydrofolate
Glycine
PLP
Serine
serine hydroxymethyl-transferase
dihydrofolate reductase
NADPH + H+
NADP+
Tetrahydrofolate


AMP
H_2O
5′-nucleotidase
P_i
GMP
Adenosine
H_2O
5′-nucleotidase
P_i
H_2O
adenosine deaminase
NH_3
Guanosine
Inosine
H_2O
nucleosidase
Ribose
H_2O
nucleosidase
Ribose
Hypoxanthine (keto form)
Guanine
H_2O
NH_3
guanine deaminase
$H_2O + O_2$
xanthine oxidase
H_2O_2
Xanthine (keto form)
$H_2O + O_2$
xanthine oxidase
H_2O_2
OH
Uric acid


Excreted by:
Uric acid
Primates, birds, reptiles, insects
urate oxidase
½ O2 + H2O
CO2
Allantoin
Most mammals
allantoinase
H2O
Allantoate
Bony fishes
allantoicase
H2O
COO⁻
CHO
Glyoxylate
Urea
Amphibians, cartilaginous fishes
urease
2H2O
2CO2
4NH4+
Marine invertebrates

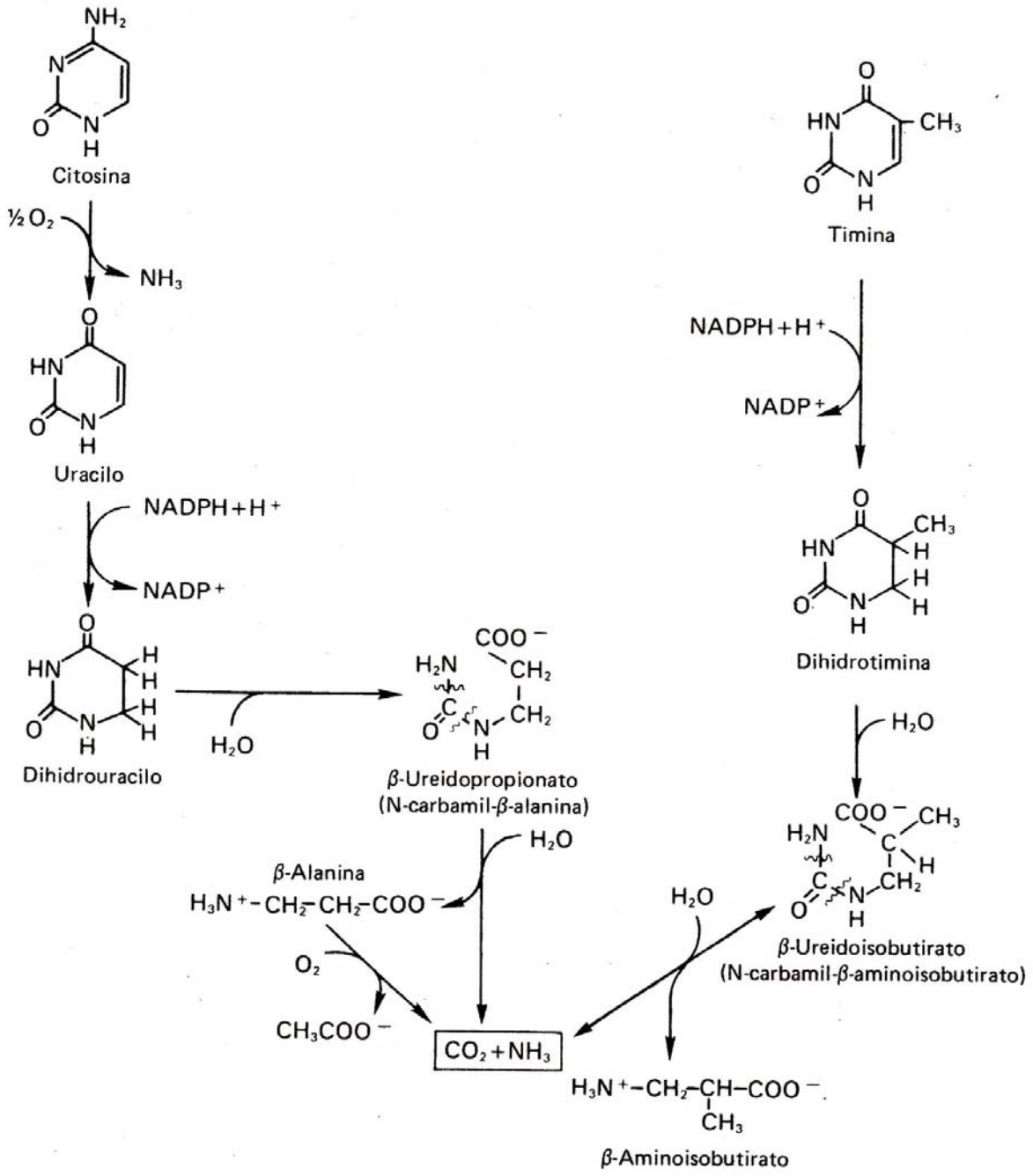


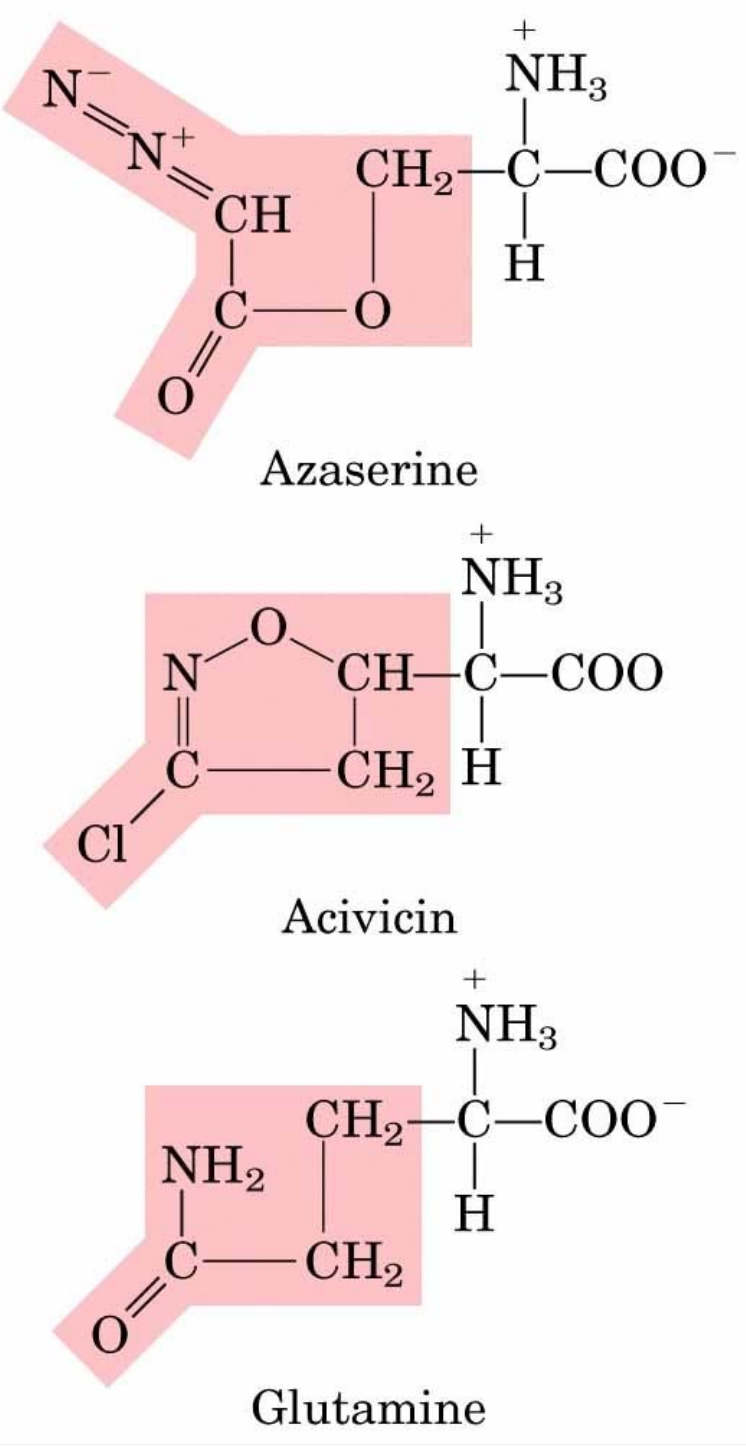
Fig. 35–17. Catabolismo de las pirimidinas.

Drogas usadas en el tratamiento del Cáncer

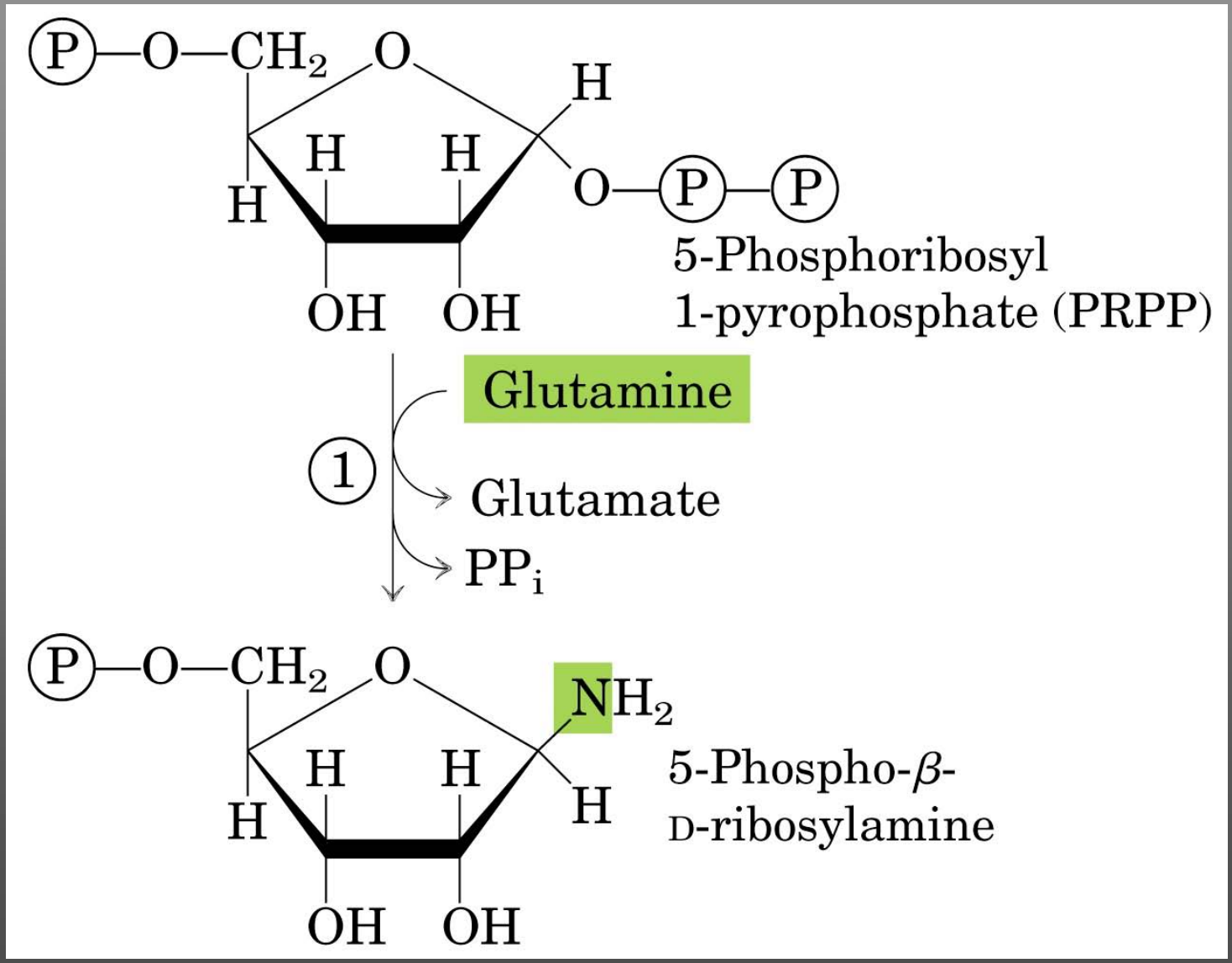
Mecanismos de Acción

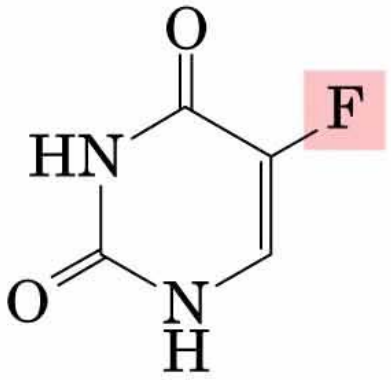
inhiben a las amido transferasas

análogos de la glutamina

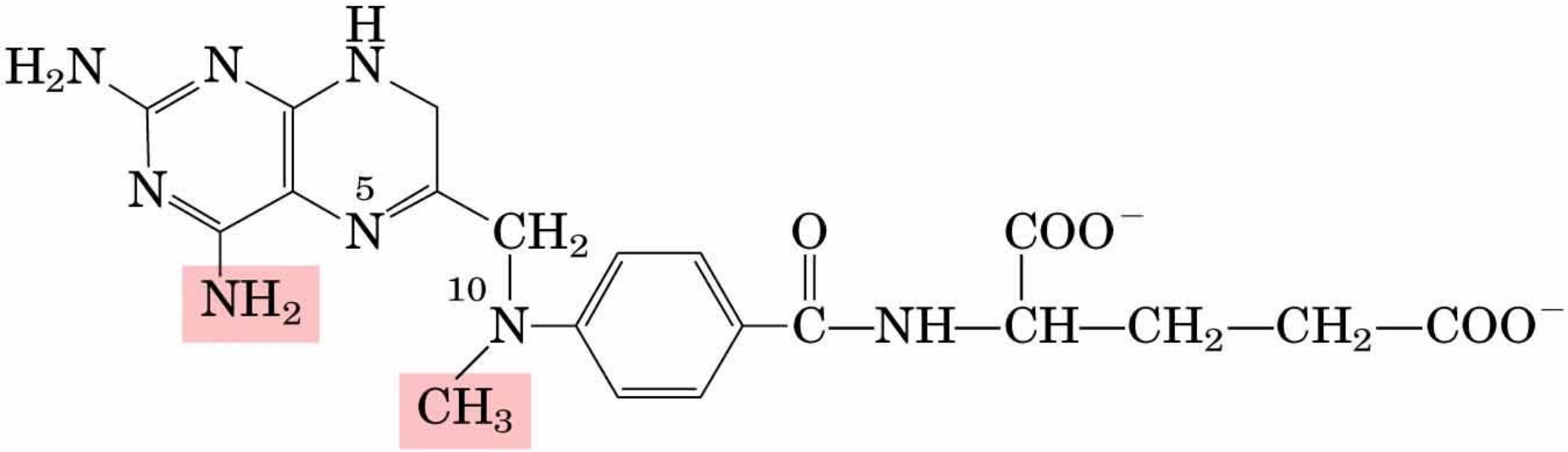


Ejemplo: PRPP-glutamina amido transferasa





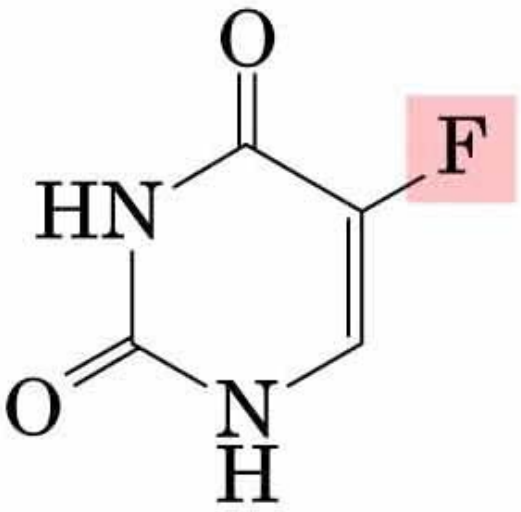
Fluorouracil



Methotrexate

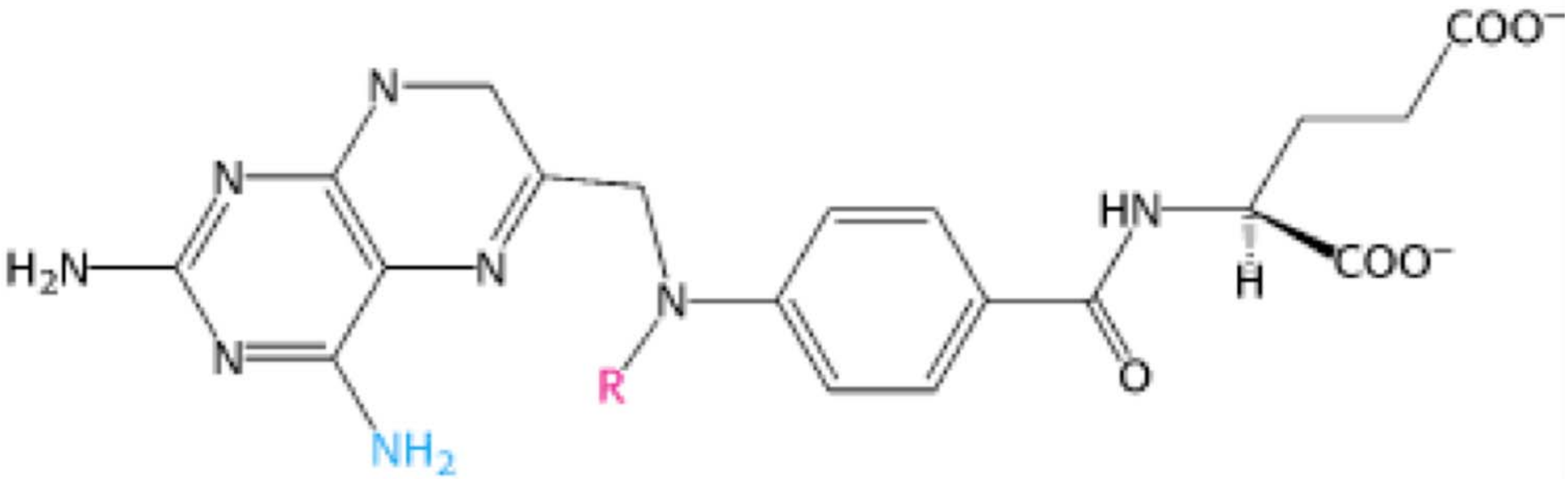
(b)

Inhibidor de la timidilato sintetasa

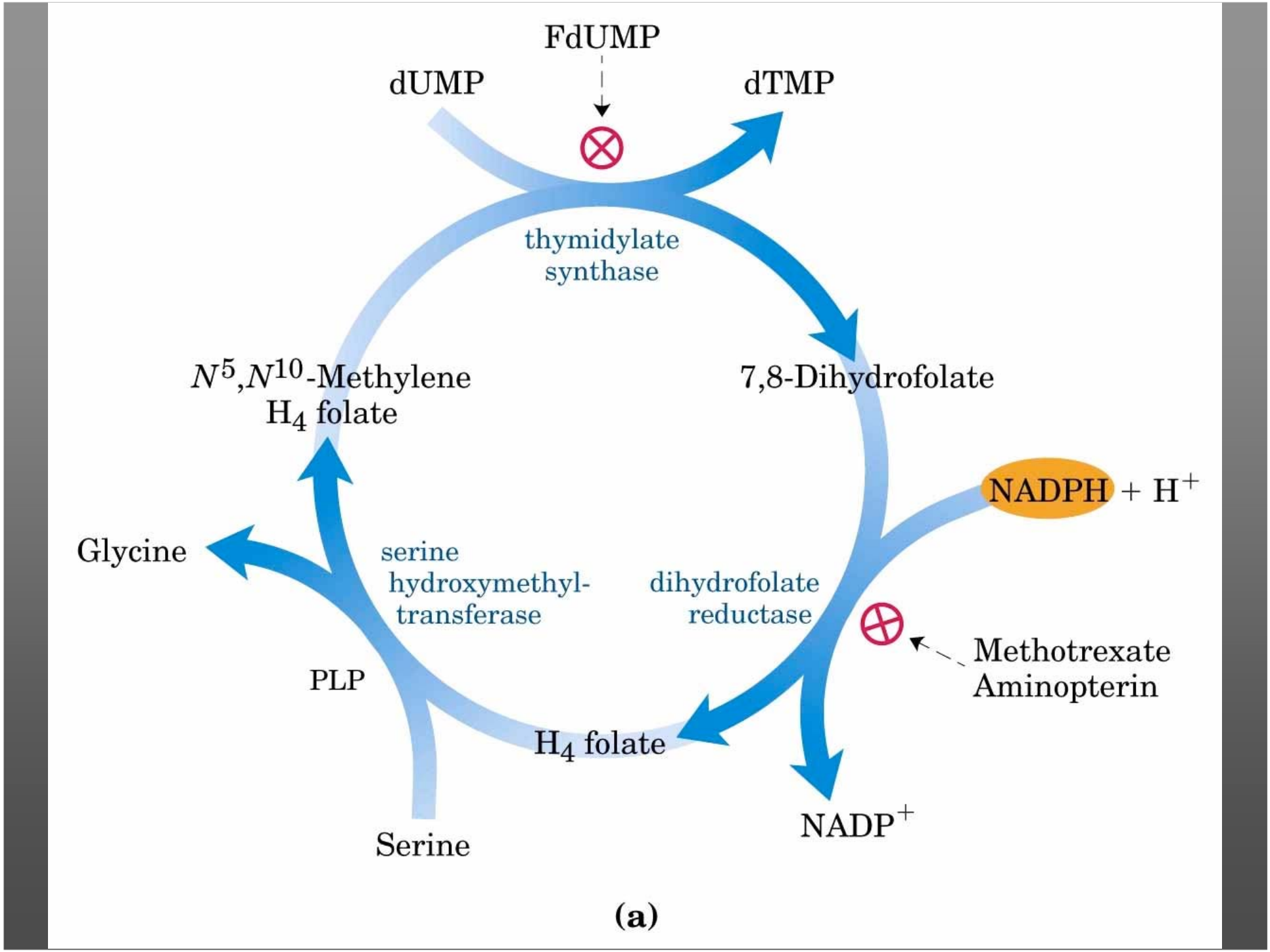


Fluorouracil

metotrexato y aminopterina:
inhibidores de la dihidrofolato reductasa



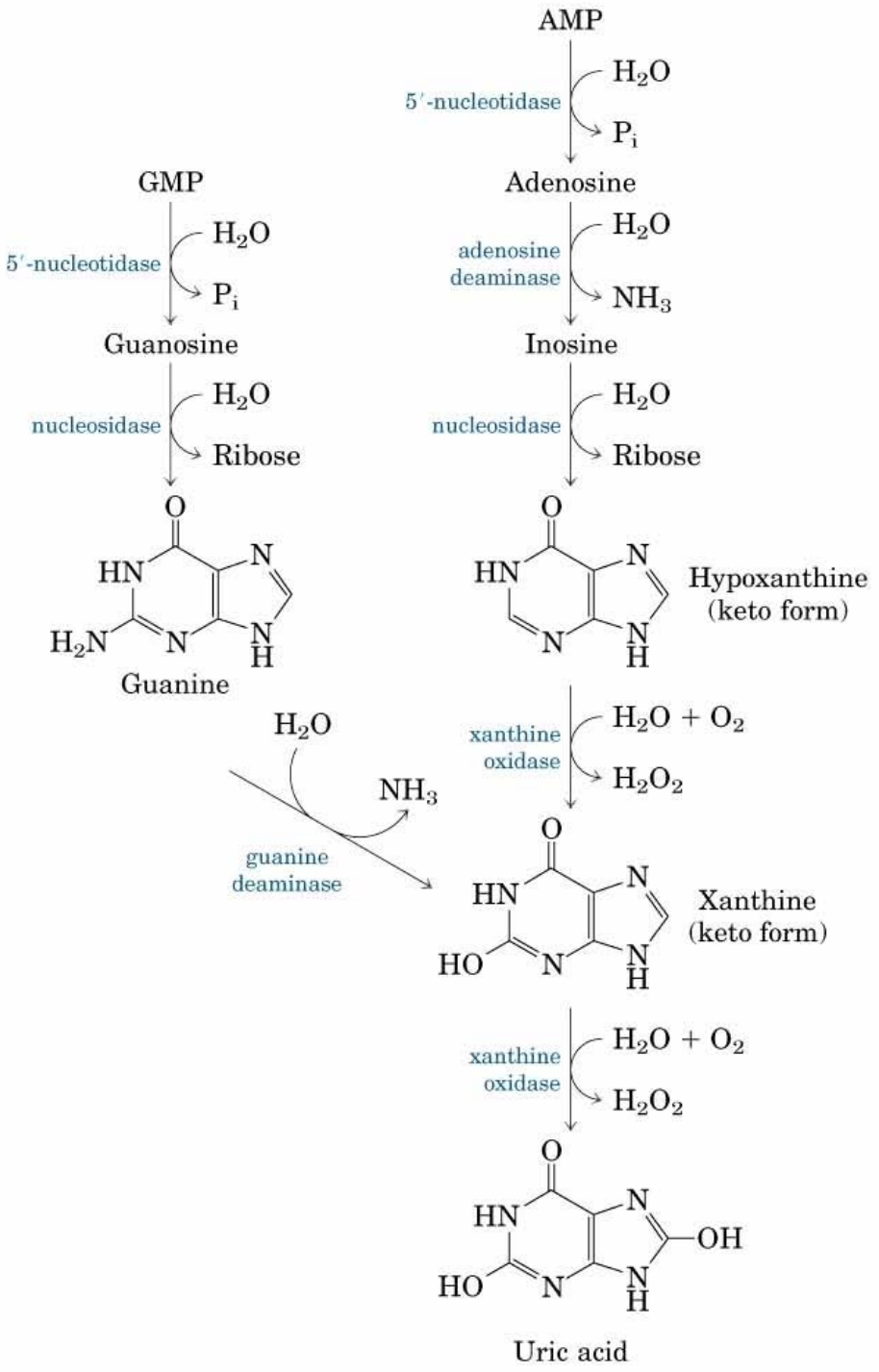
Aminopterin (R = H) or methotrexate (R = CH_3)

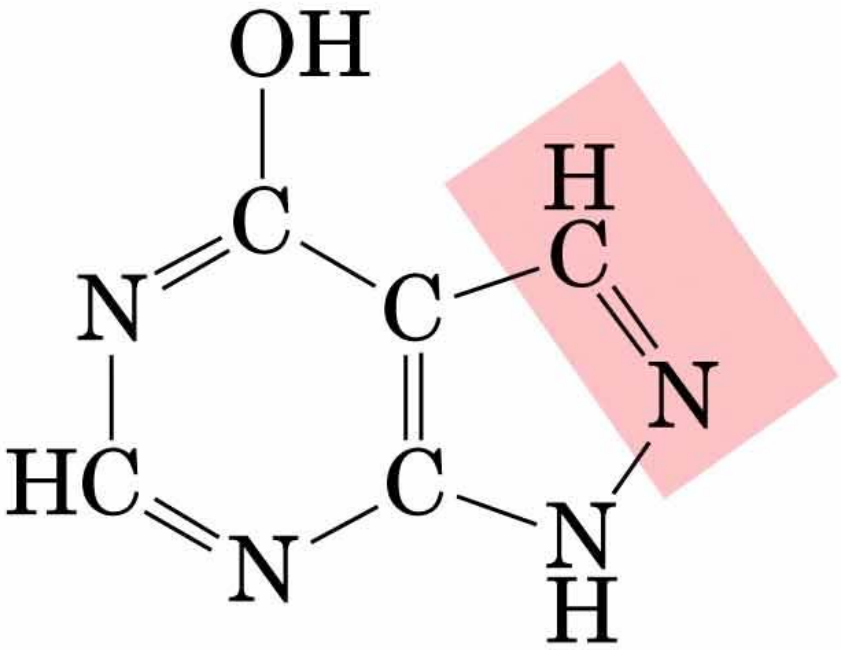

FdUMP
dUMP
dTMP
thymidylate synthase
7,8-Dihydrofolate
NADPH + H+
Methotrexate
Aminopterin
dihydrofolate reductase
NADP+
H4 folate
serine hydroxymethyl-transferase
PLP
Serine
Glycine
N5,N10-Methylene H4 folate

(a)

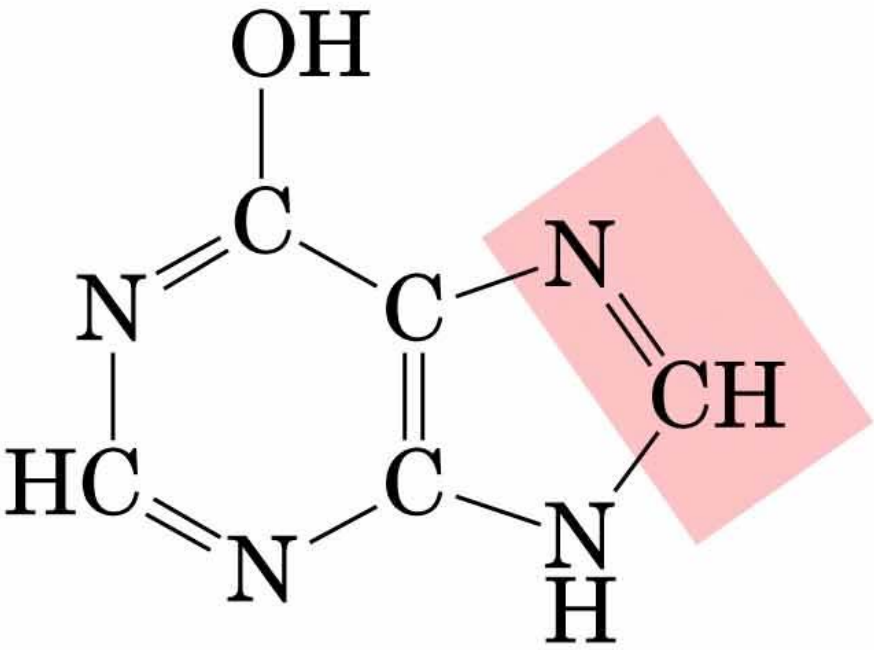
Tratamiento de la Gota:

alopurinol


AMP
H_2O
5′-nucleotidase
P_i
GMP
Adenosine
H_2O
5′-nucleotidase
P_i
H_2O
adenosine deaminase
NH_3
Guanosine
Inosine
H_2O
nucleosidase
Ribose
H_2O
nucleosidase
Ribose
Hypoxanthine (keto form)
Guanine
H_2O
NH_3
guanine deaminase
$H_2O + O_2$
xanthine oxidase
H_2O_2
Xanthine (keto form)
$H_2O + O_2$
xanthine oxidase
H_2O_2
OH
Uric acid



Allopurinol

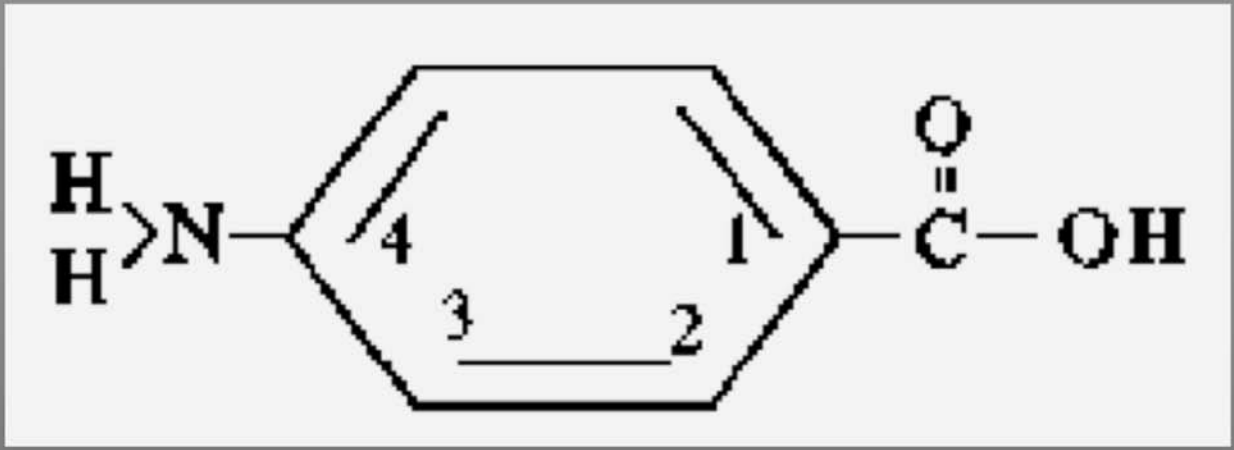


Hypoxanthine
(enol form)

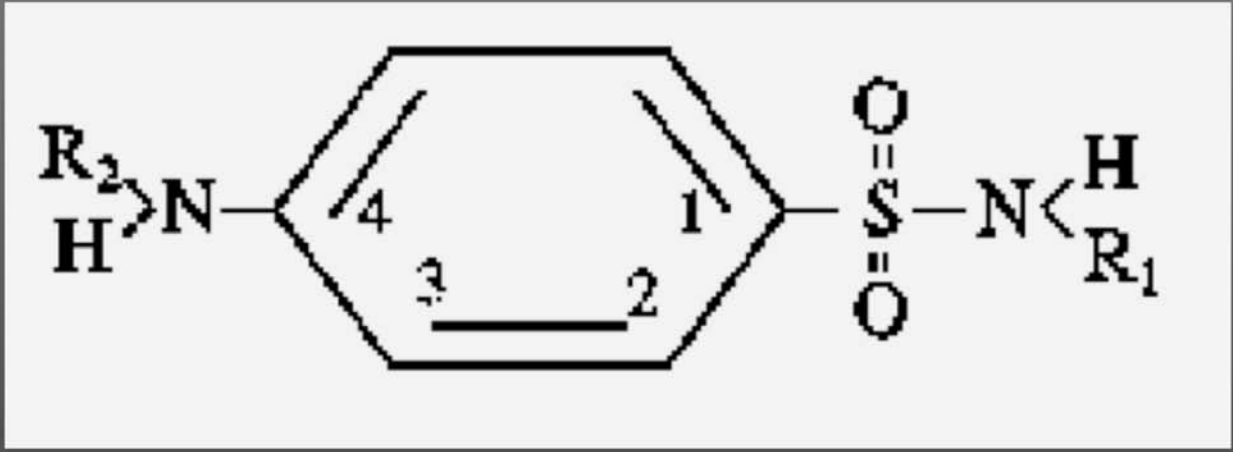
Sulfas y Trimethoprim

Acción Farmacológica

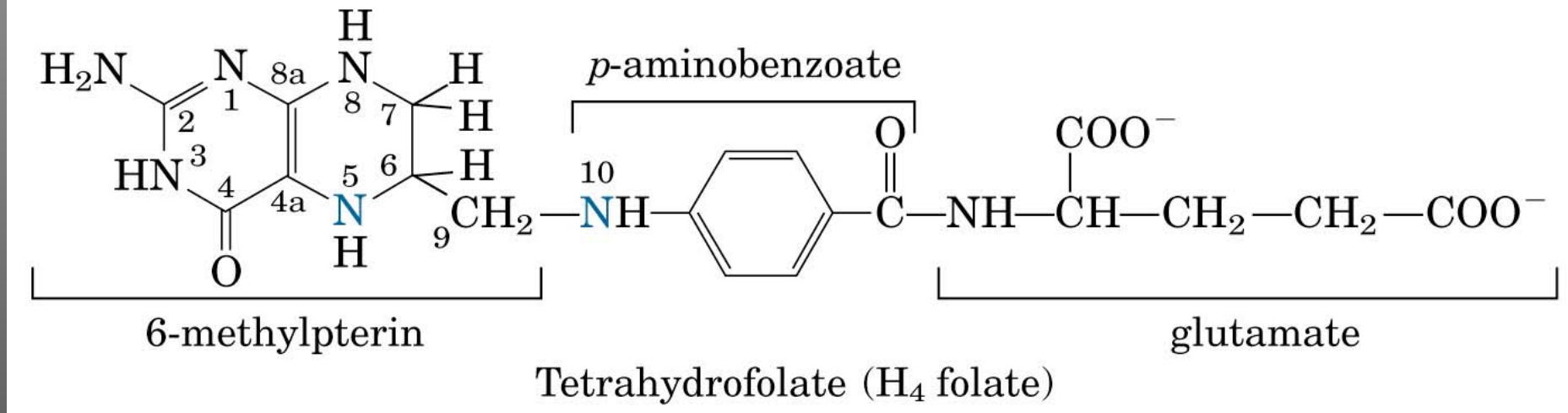
SULFAS



PABA (ácido p-aminobenzoico)

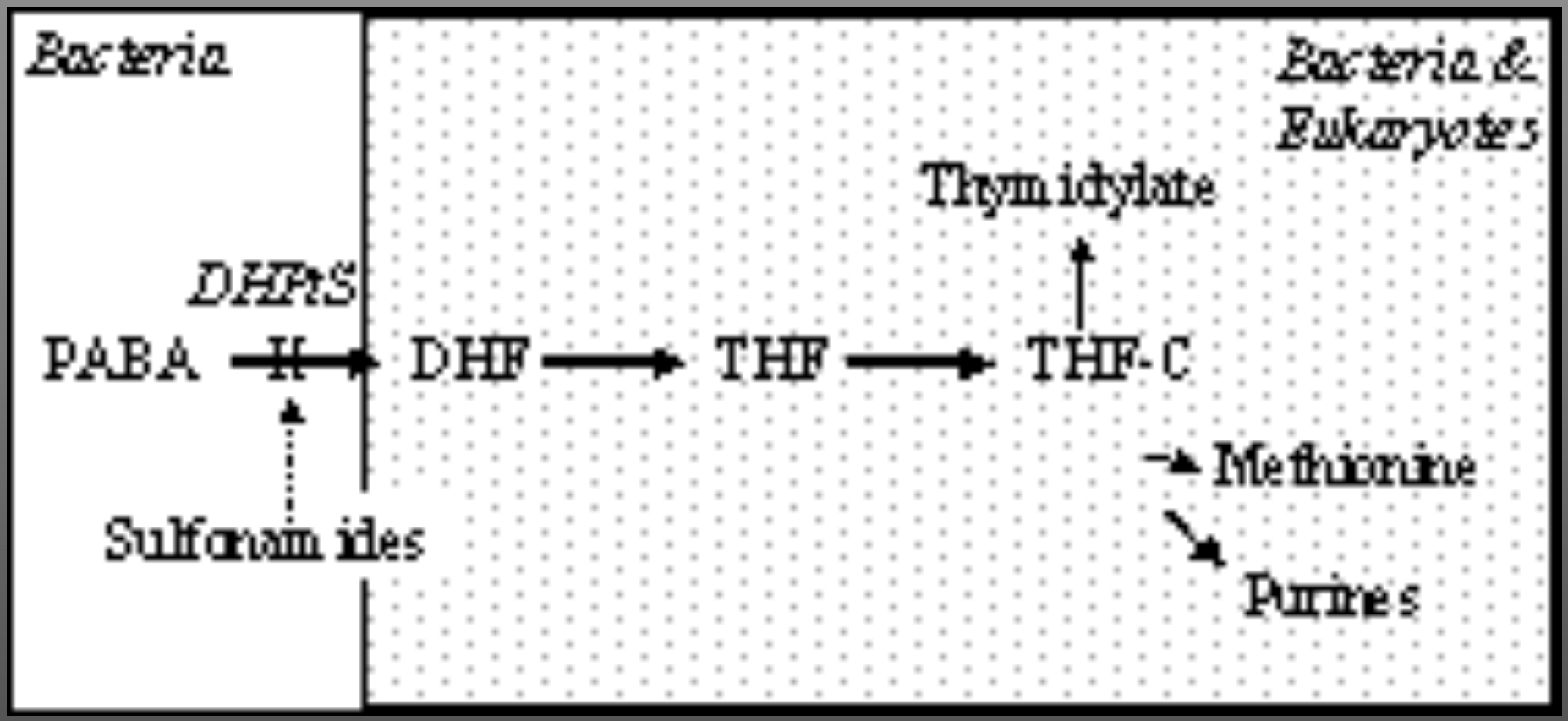


Sulfonamida: estructura madre

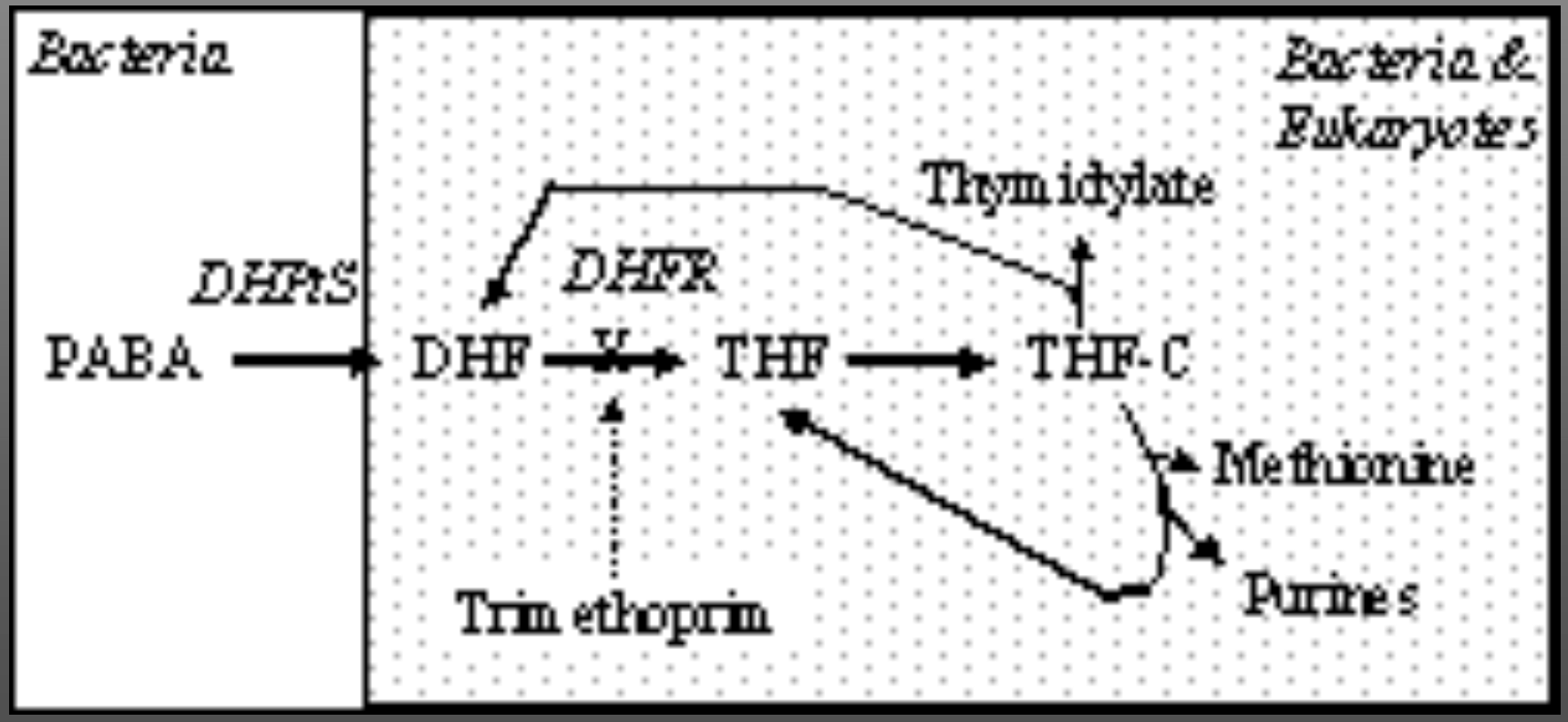


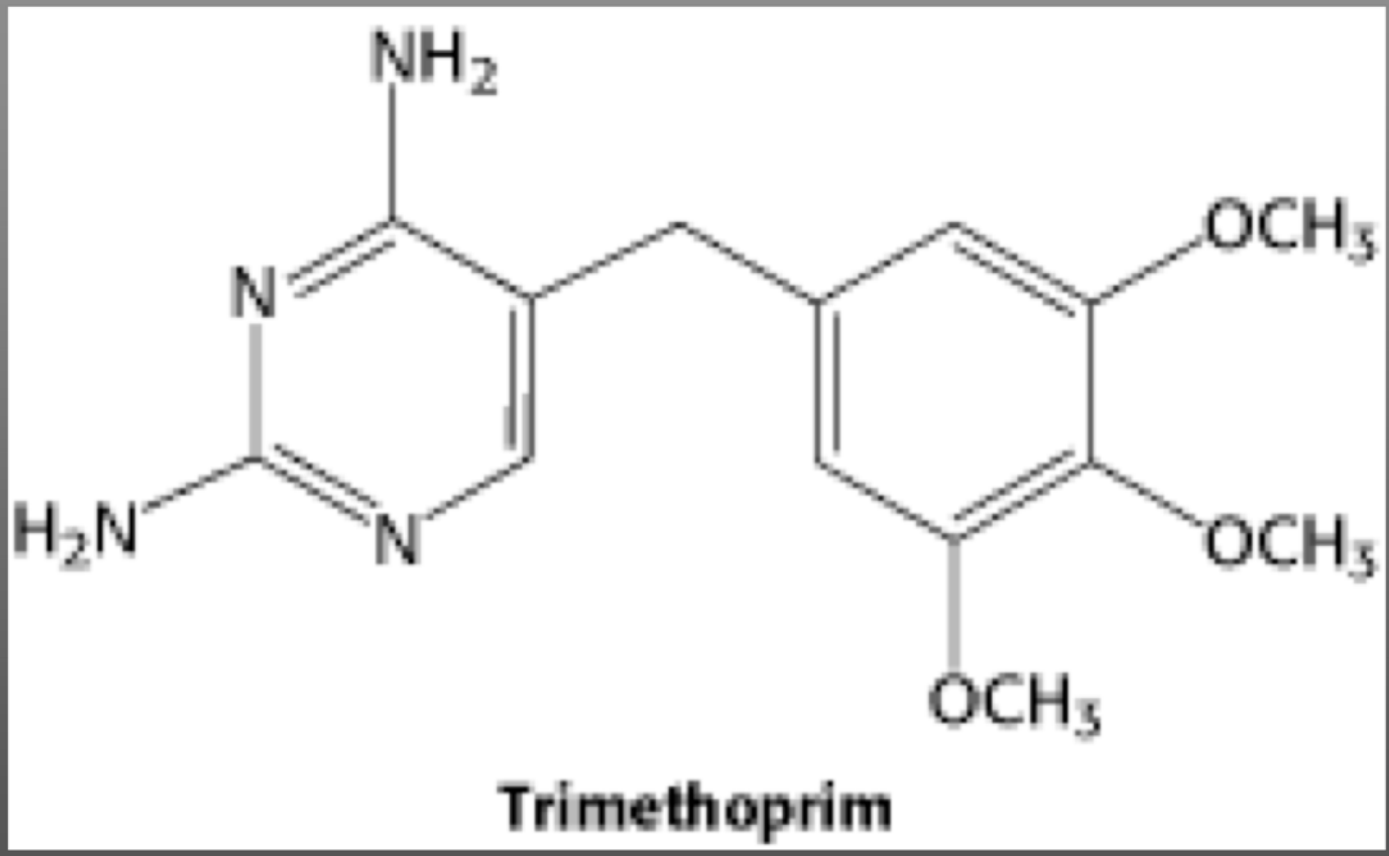
Tetrahydrofolate (H_4 folate)

Sulfas: Compiten con el PABA para inhibir la síntesis del DHF: Dihydropteroate synthase



Trimethoprim: inhibe a la DHFR





Trimethoprim

Concentración requerida para inhibir la DHFR en un 50%

DRUG	RAT LIVER	E. coli	P. berghei
	IC50 (nM)	IC50 (nM)	IC50 (nM)
Pyrimethamine	700	2,500	~0.5
Trimethoprim	260,000	5	70

GG 8th, p985. Original data from Ferone, Burchall & Hitchings, 1969

Combinación de ambas drogas