BIOKIMIA
Metabolisme
Purin & Pirimidin

DOSEN PENGAMPU

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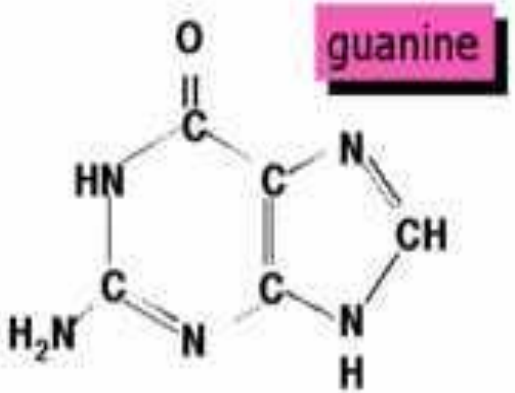
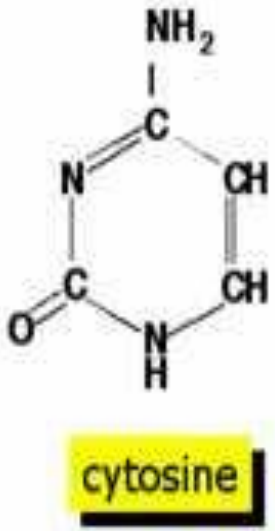
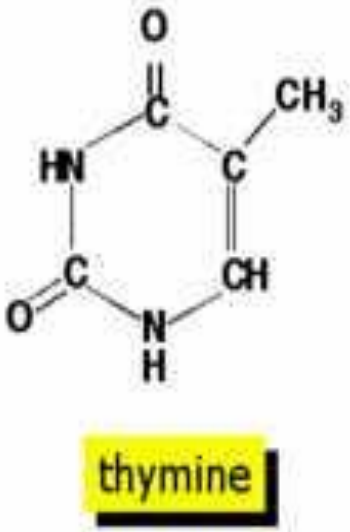
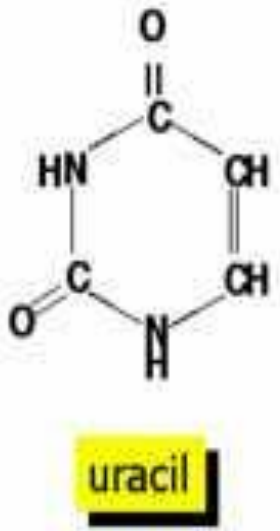
The nitrogenous bases

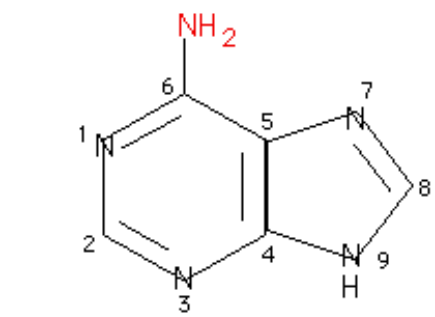




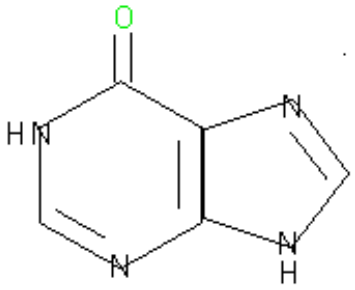




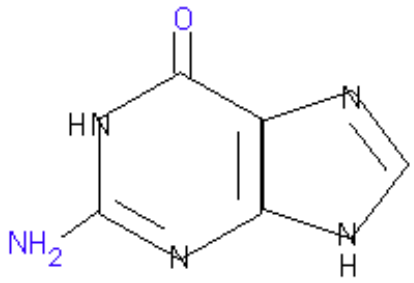
Basa-basa purin



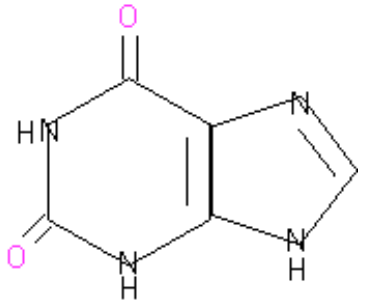
Adenine



Hypoxanthine



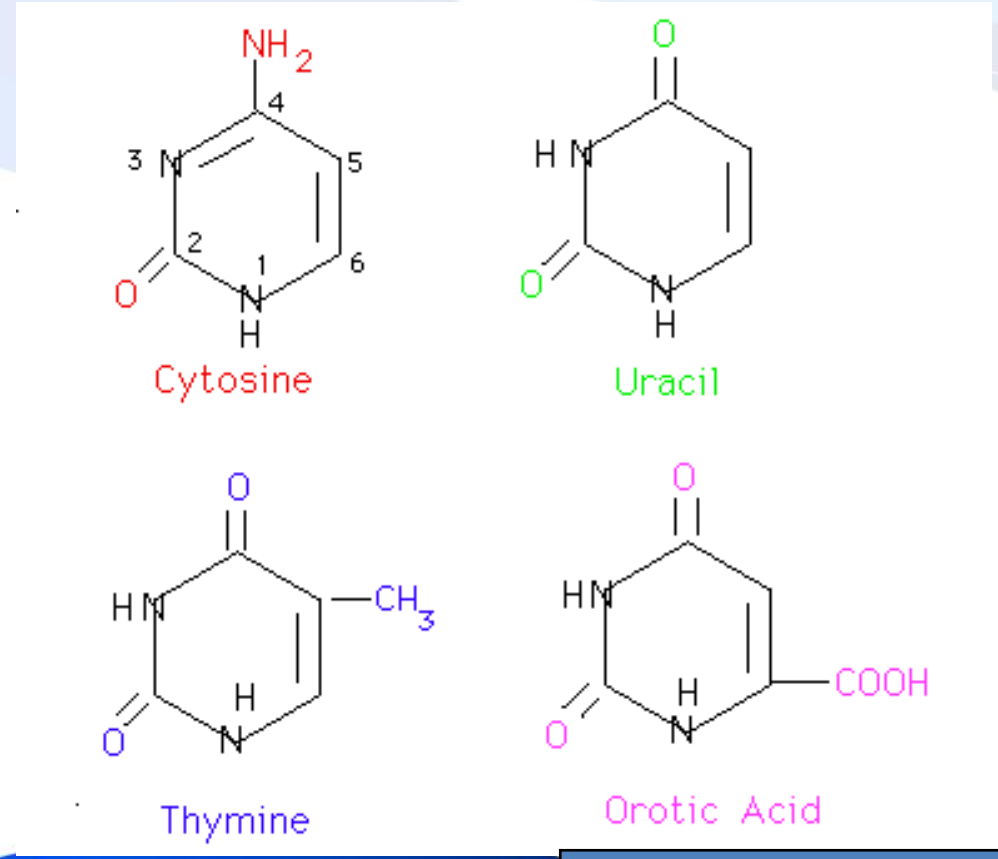
Guanine



Xanthine

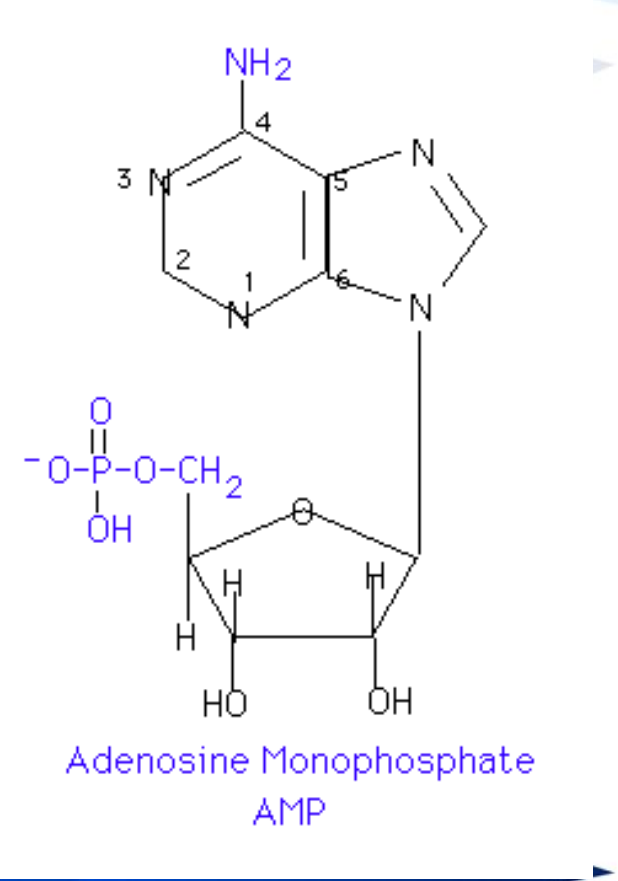
Adenin = 6-amino purin
Guanin = 2-amino-6-oksi purin
Hipoxanthin = 6-oksi purin
Xanthin = 2,6-dioksi purin

Basa-basa pirimidin

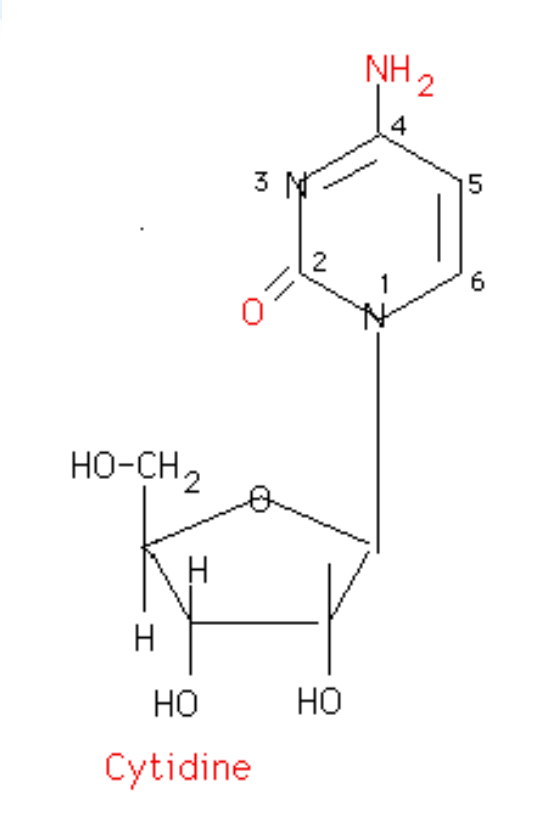


Uracil = 2,4-dioxy pyrimidine
Thymine = 2,4-dioxy-5-methyl pyrimidine
Cytosine = 2-oxy-4-amino pyrimidine
Orotic acid = 2,4-dioxy-6-carboxy pyrimidine

Nukleotida & Nukleosida

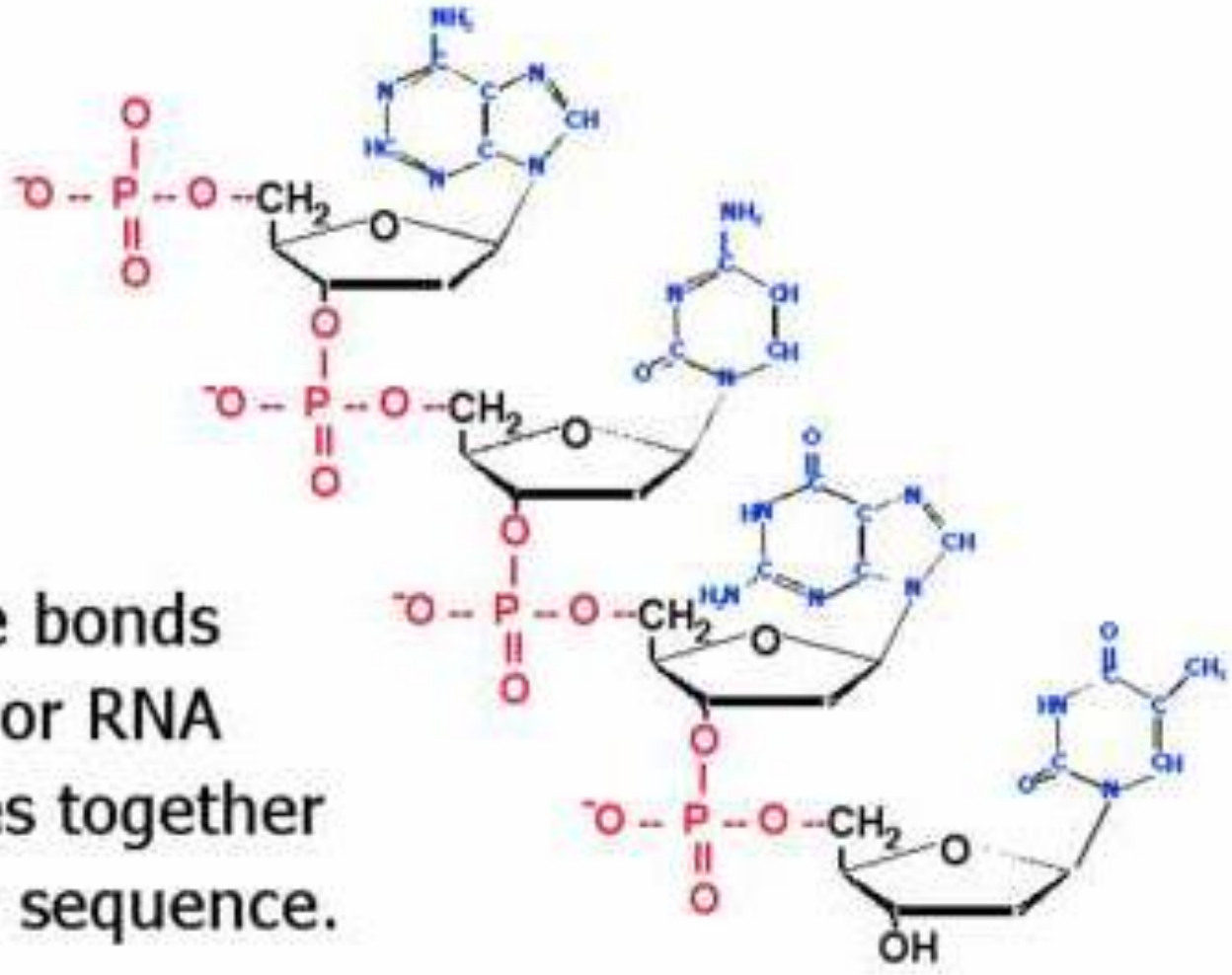


Adenosine Monophosphate
AMP

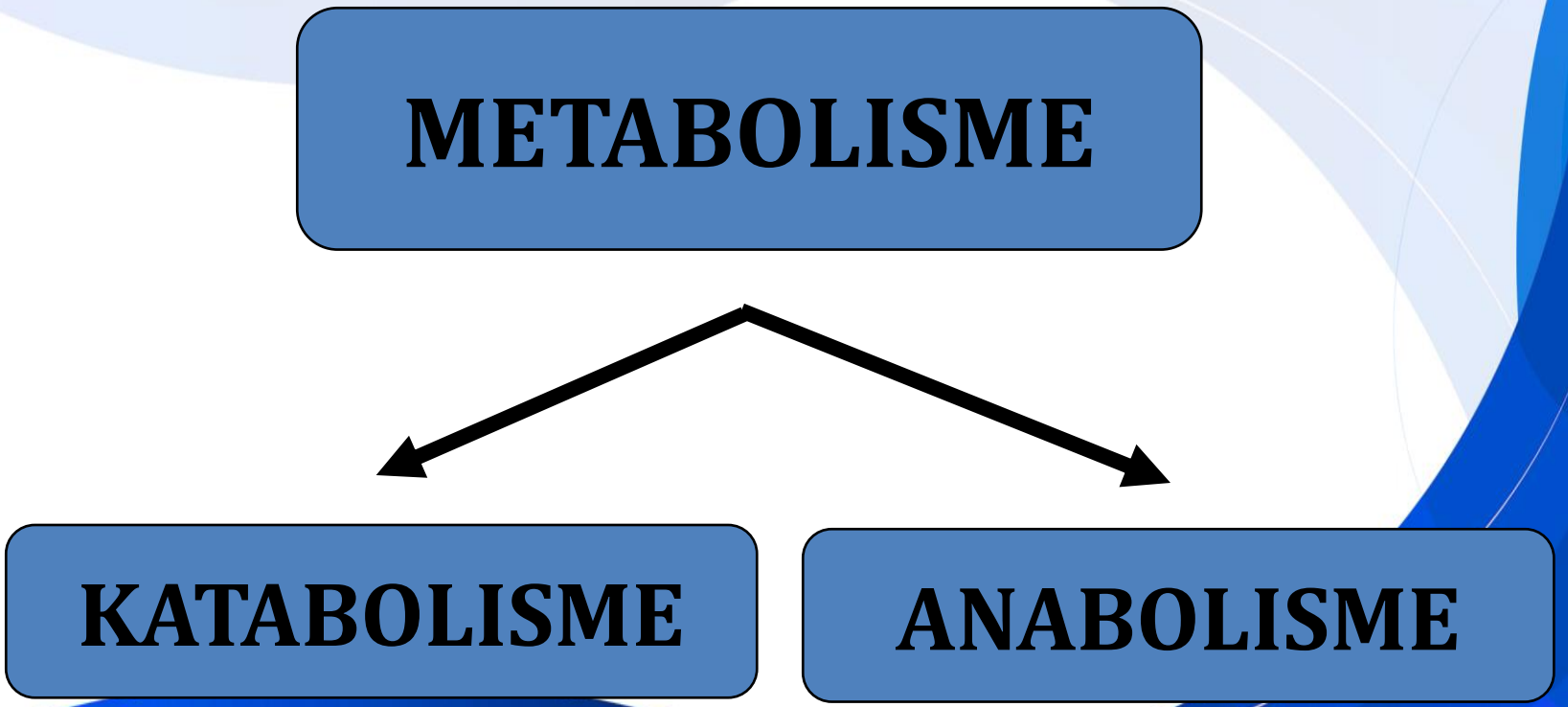


Cytidine

Oligonukleotida (potongan asam nukleat)



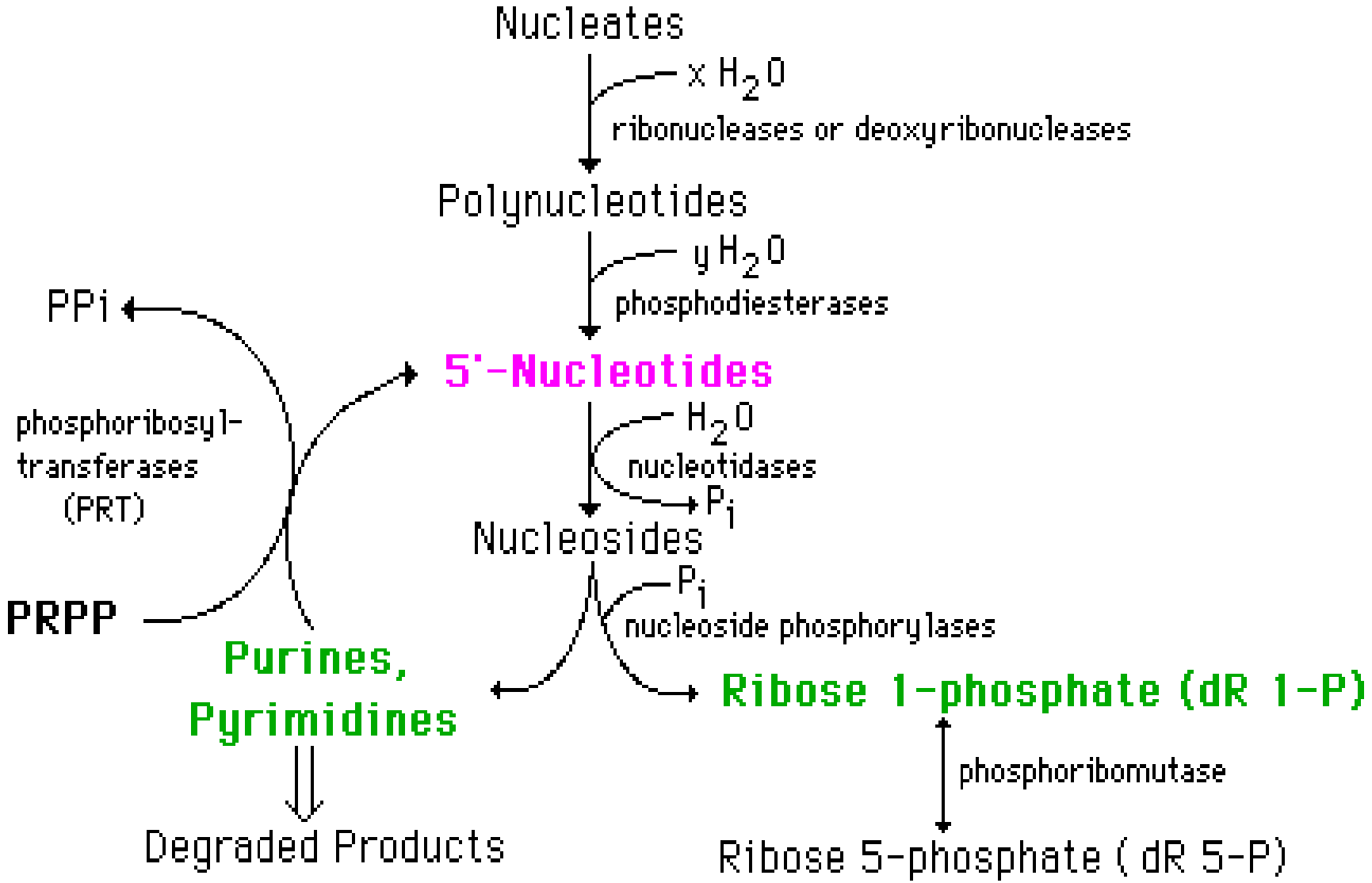
Phosphate bonds link DNA or RNA nucleotides together in a linear sequence.


METABOLISME
KATABOLISME
ANABOLISME

Katabolisme
Purin & Pirimidin

Hidrolisis Asam Nukleat

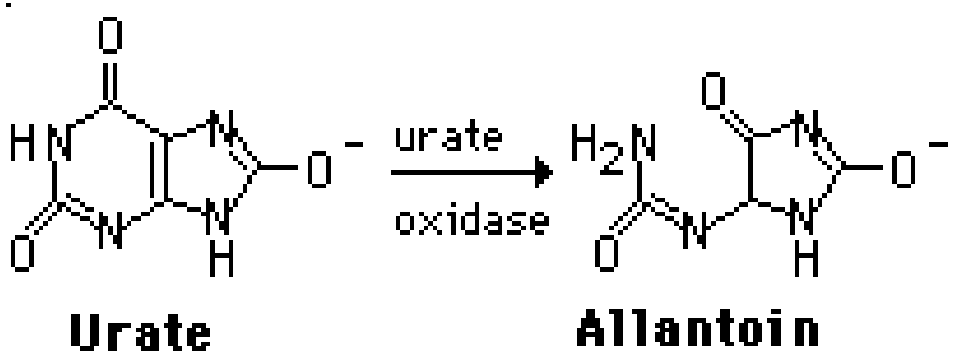
- Endonuklease: asam nukleat → oligonukleotida
- Eksonuklease/Fosfodiesterase: oligonukleotida → nukleotida
- Nukleotidase: nukleotida → nukleosida
- Nukleosidase/nukleosida fosforilase: nukleosida →basa purin/basa pirimidin + pentosa


Nucleates
x H_2O
ribonucleases or deoxyribonucleases
Polynucleotides
y H_2O
phosphodiesterases
5'-Nucleotides
H_2O
nucleotidases
P_i
Nucleosides
P_i
nucleoside phosphorylases
Ribose 1-phosphate (dR 1-P)
phosphoribomutase
Ribose 5-phosphate (dR 5-P)
PPi
phosphoribosyl-
transferases
(PRT)
PRPP
Purines,
Pyrimidines
Degraded Products

Produk akhir Katabolisme Purin-Pirimidin

- Basa purin ⟶ asam urat
- Basa pirimidin ⟶ β-alanin dan β-aminoisobutirat, NH_3 dan CO_2.

- Pada beberapa mamalia (sapi, kerbau, kambing, dll) asam urat diubah menjadi allantoin yang lebih mudah larut (enzim urat oksidase/uricase/ uratase)
- Amfibi, burung dan reptil sama dengan manusia mengekskresikan asam urat sebagai produk katabolisme purin

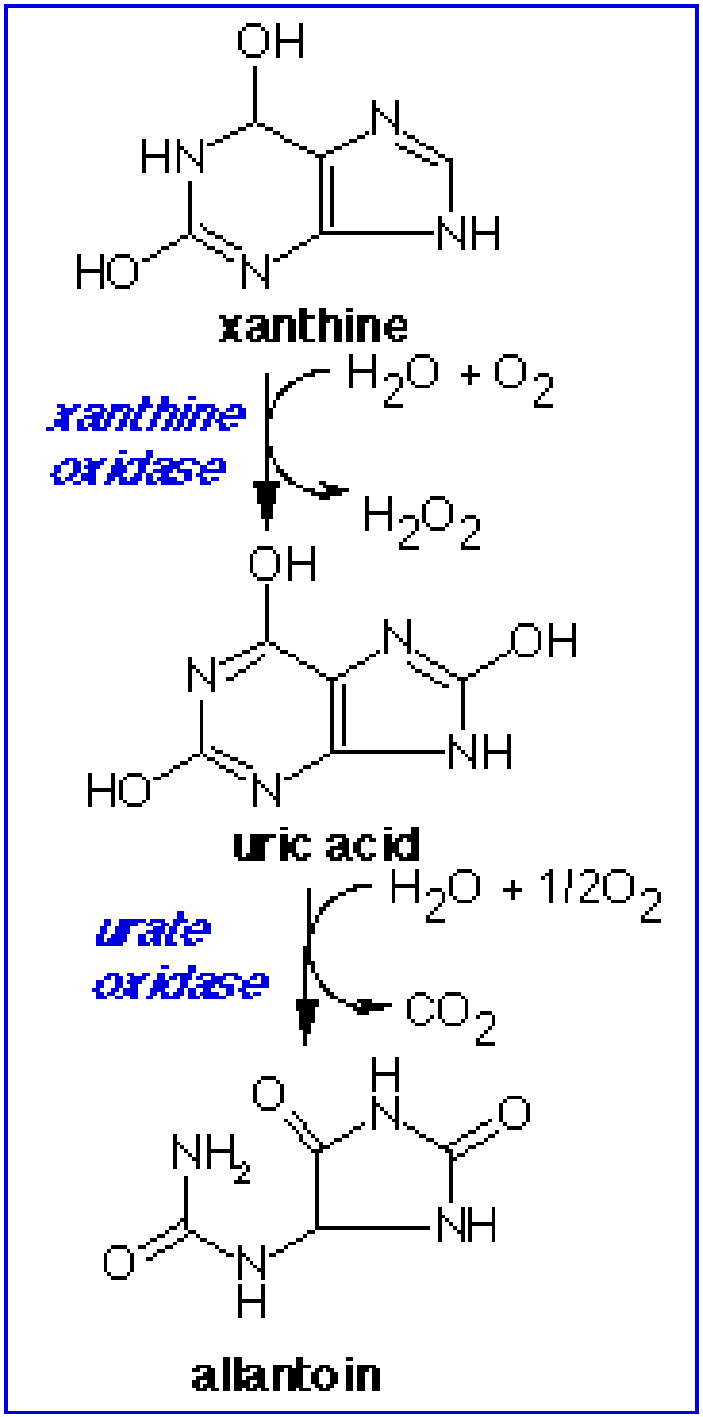


Oksidasi

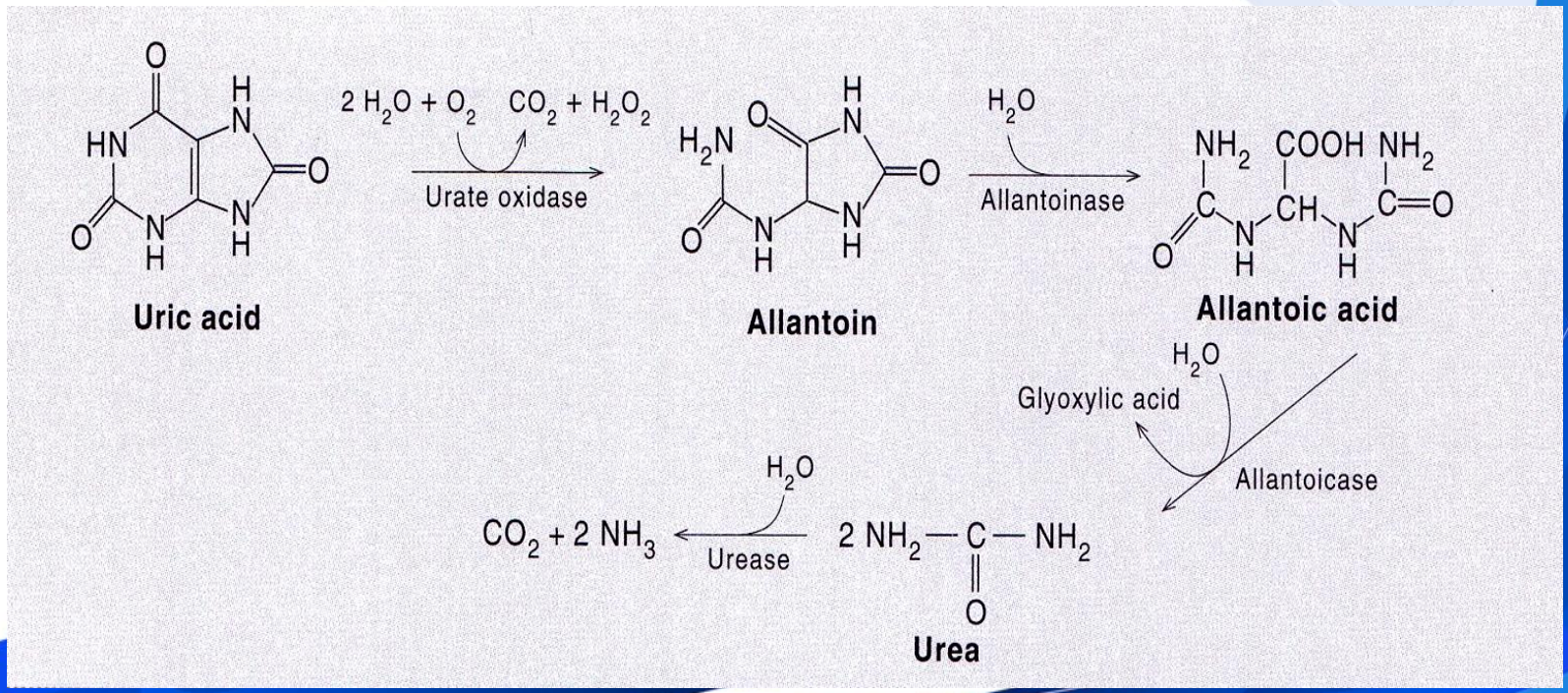
Asam Urat

↓

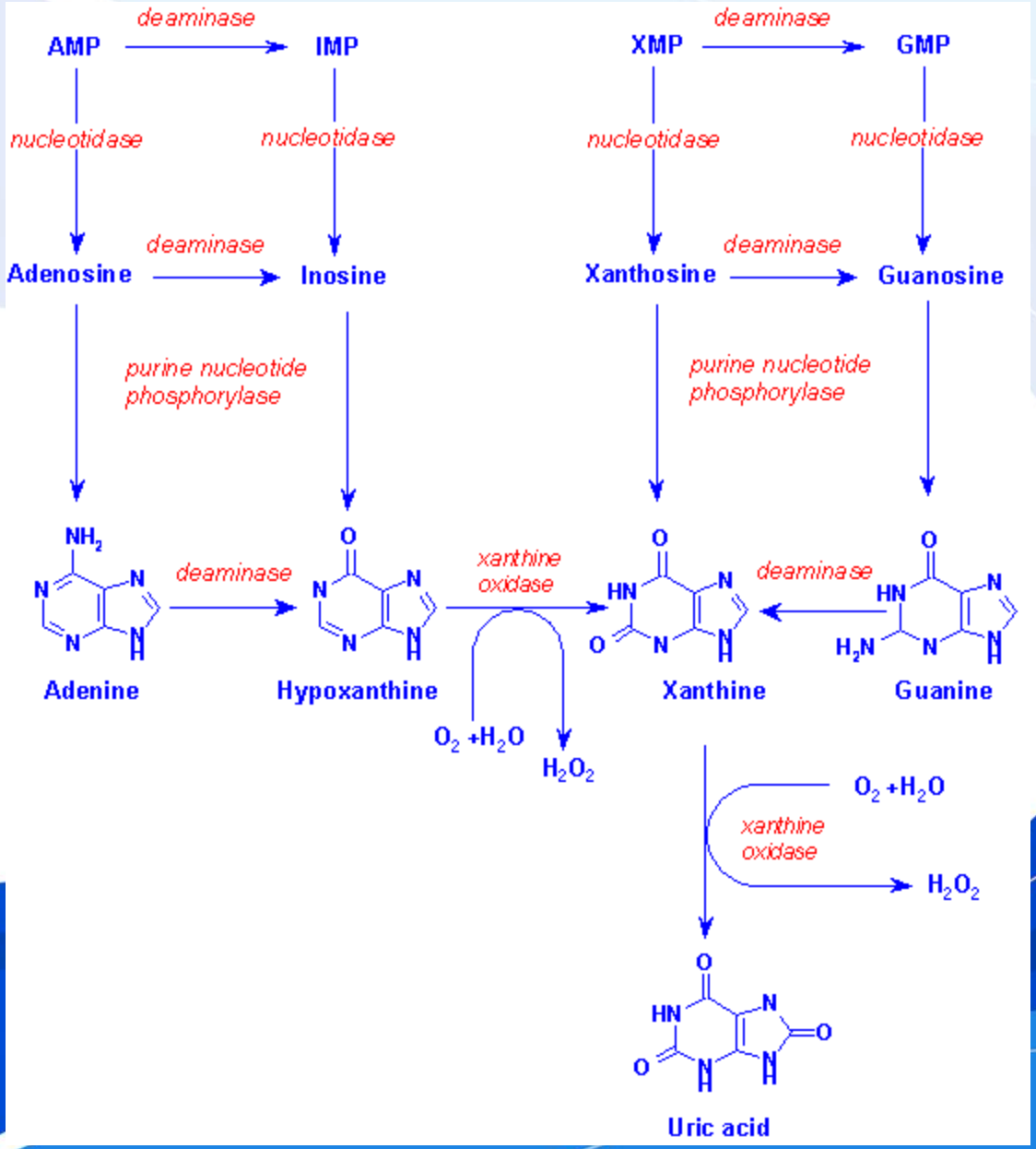
Alantoin



Pada beberapa hewan lain, asam urat dapat diubah lebih lanjut menjadi urea atau amonia + CO_2

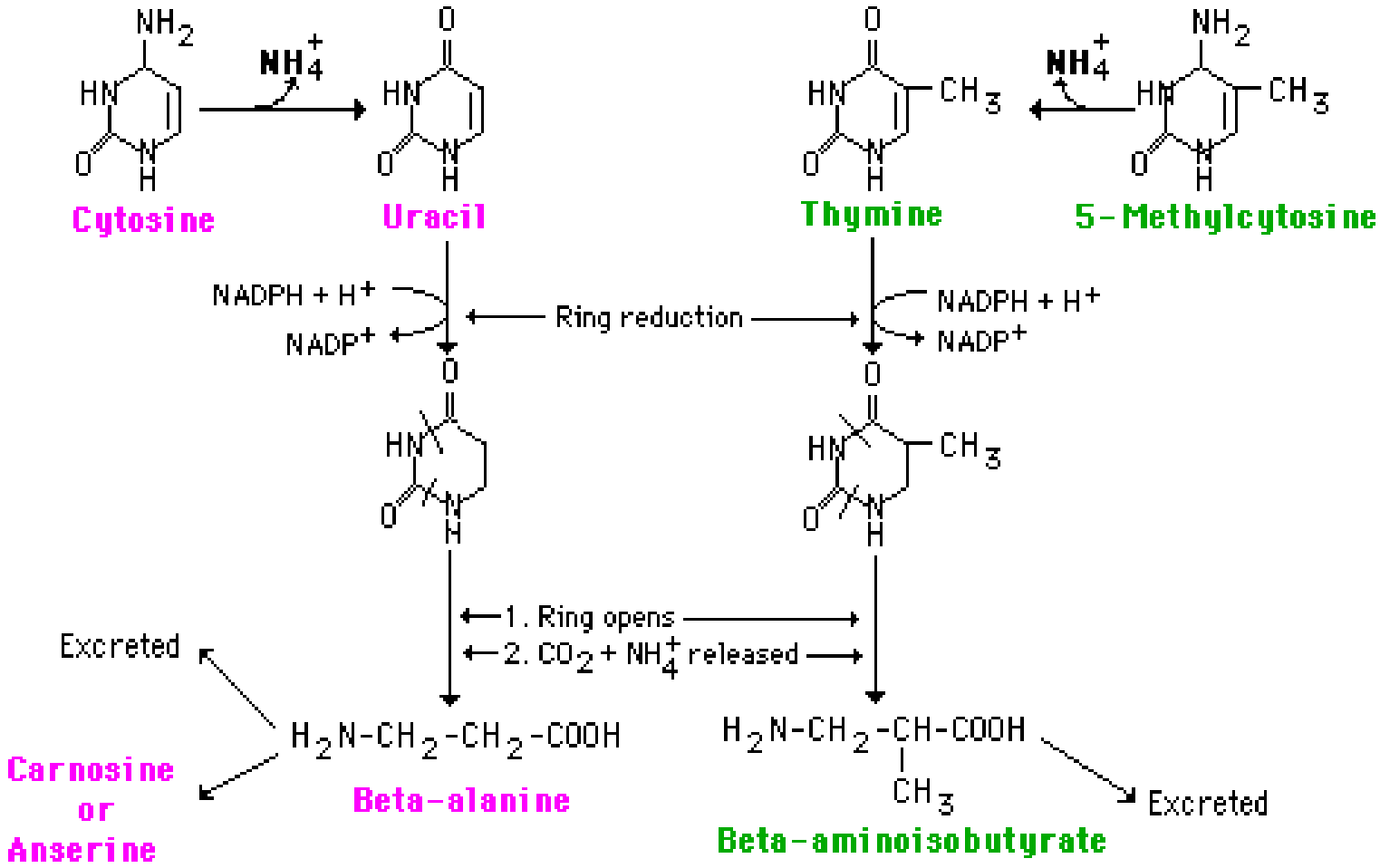


Katabolisme Nukleotida Purin



- Dalam cairan tubuh, asam urat berada dalam bentuk asam dan garam natrium.
- Na urat lebih mudah larut daripada bentuk asamnya.
- pH urin normal 5,8, pada pH ini urat yang dapat larut hanya 15 mg/dL.
- Kristal Na urat pada saluran kemih dapat ditingkatkan kelarutannya dengan cara alkalinisasi urin.

Katabolisme pirimidin



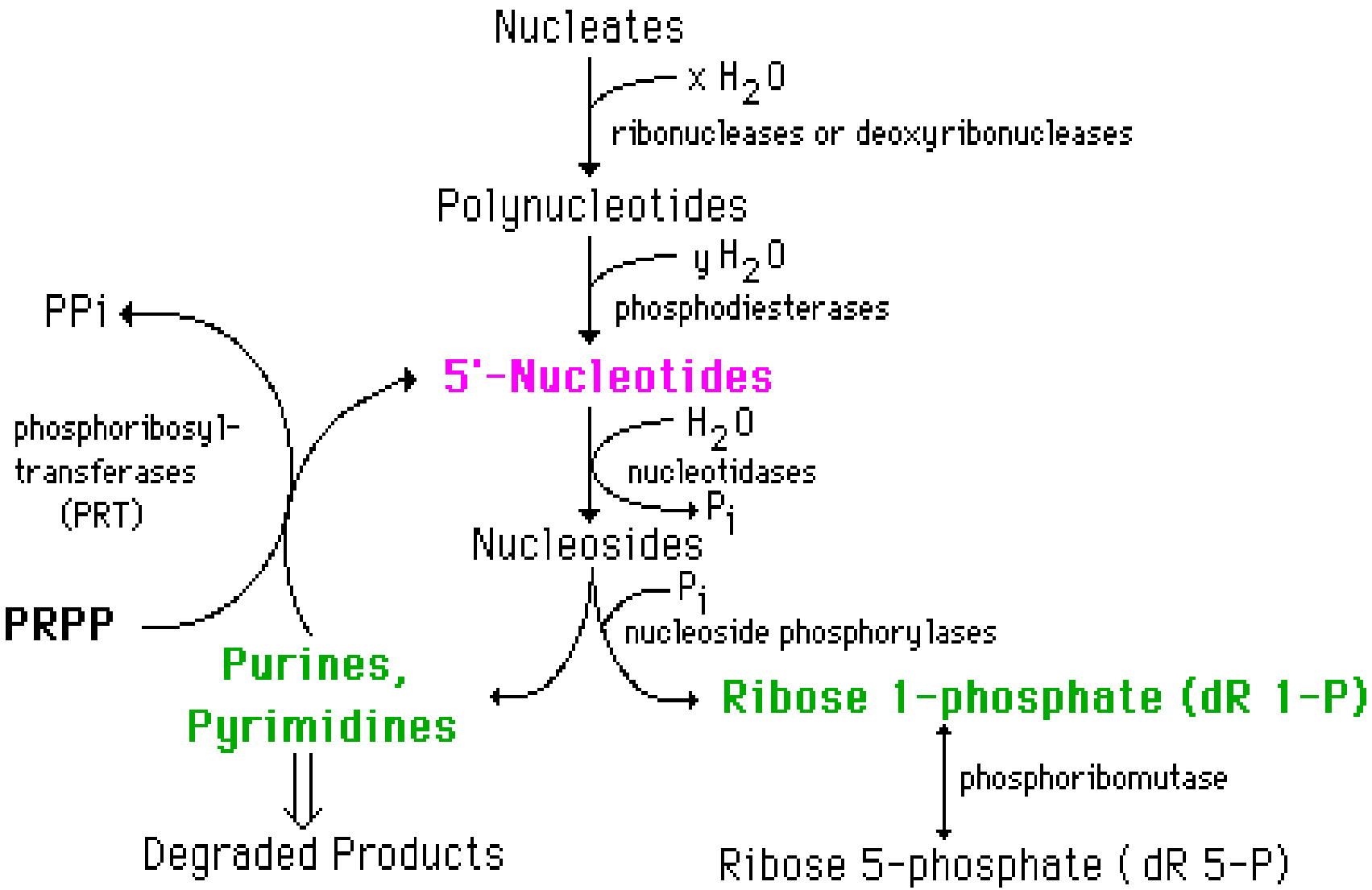
Anabolisme
Purin & Pirimidin

Sumber nukleotida

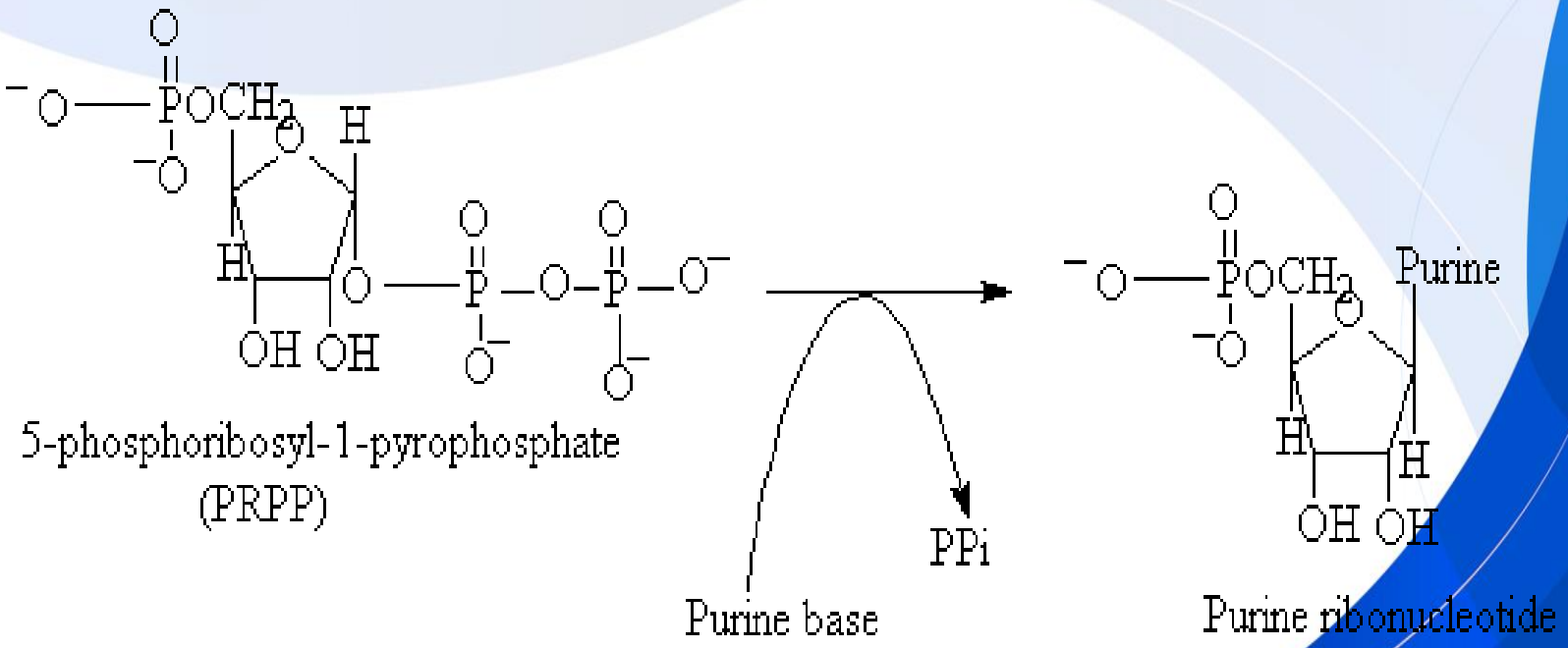
- Makanan
- Salvage pathway
- Biosintesis de novo

Hidrolisis Asam Nukleat

- Endonuklease: asam nukleat → oligonukleotida
- Fosfodiesterase/eksonuklease: oligonukleotida → nukleotida


Nucleates
x H_2O
ribonucleases or deoxyribonucleases
Polynucleotides
y H_2O
phosphodiesterases
5'-Nucleotides
H_2O
nucleotidases
P_i
Nucleosides
P_i
nucleoside phosphorylases
Ribose 1-phosphate (dR 1-P)
phosphoribomutase
Ribose 5-phosphate (dR 5-P)
PPi
phosphoribosyl-
transferases
(PRT)
PRPP
Purines,
Pyrimidines
Degraded Products

Salvage pathway of Purin nucleotides



Ada 2 enzim yang berperan dalam transfer residu ribosa dari PRPP ke basa purin (disertai dengan pelepasan PPi)

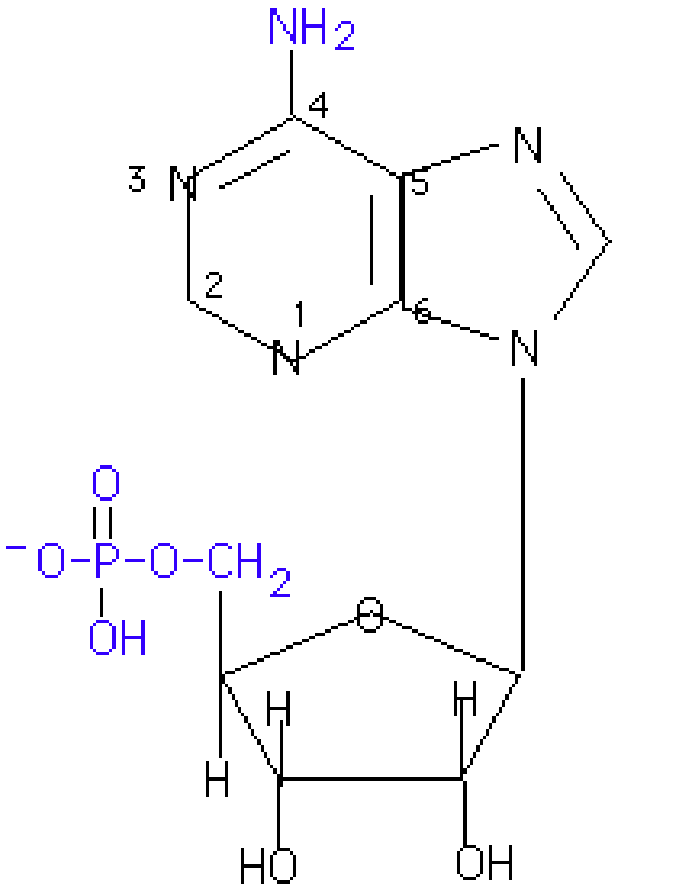
- Adenine phosphoribosyl transferase:

  Adenine + PRPP → adenylate + PPi

- Hypoxanthine-guanine phosphoribosyl transferase (HGPRT; defective in Lesch-Nyhan disease)

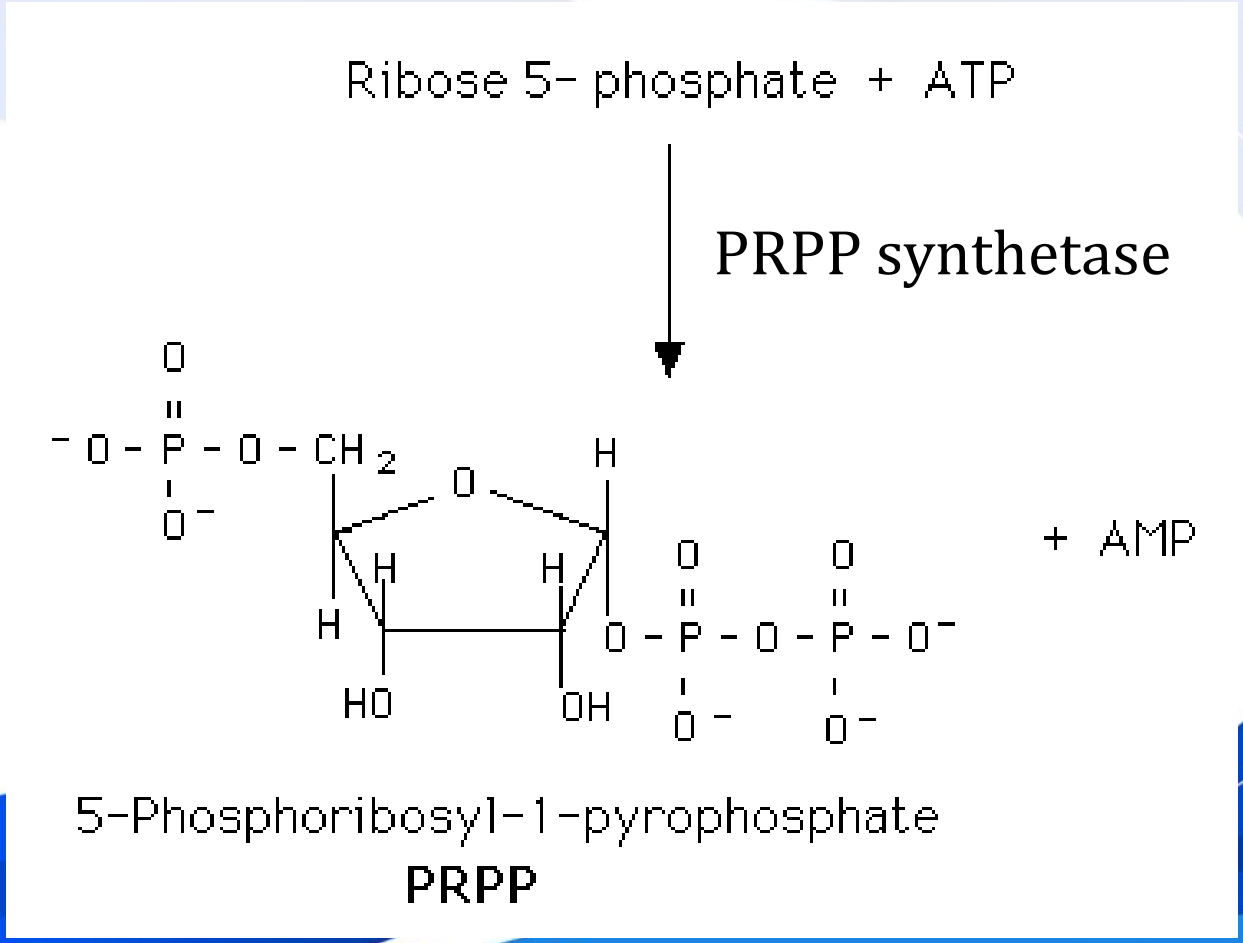
  Hypoxanthine + PRPP → inosinate + PPi
  Guanine + PRPP → guanylate + PPi

Biosintesis de novo Nukleotida Purin

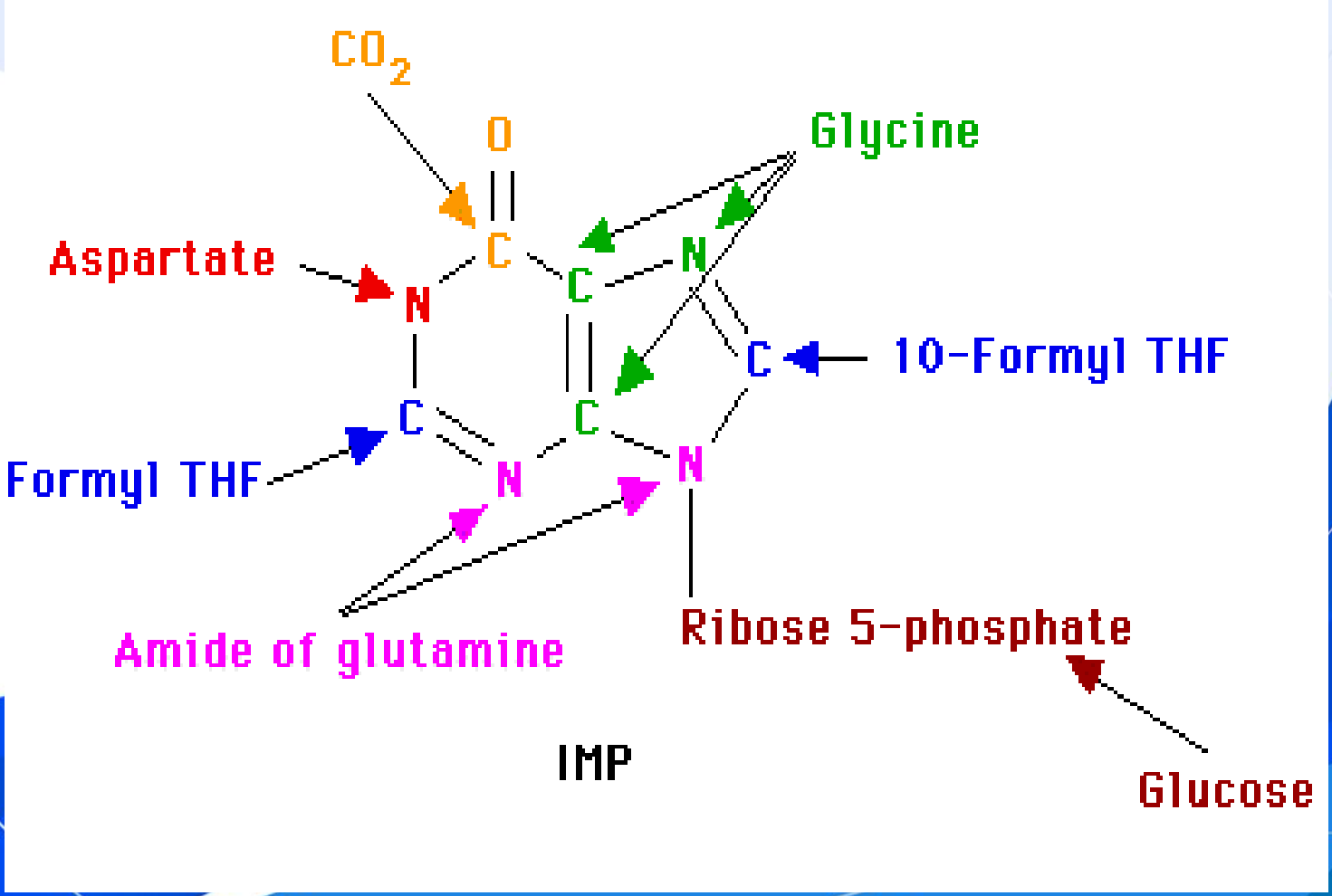


Adenosine Monophosphate
AMP

Biosintesis PRPP



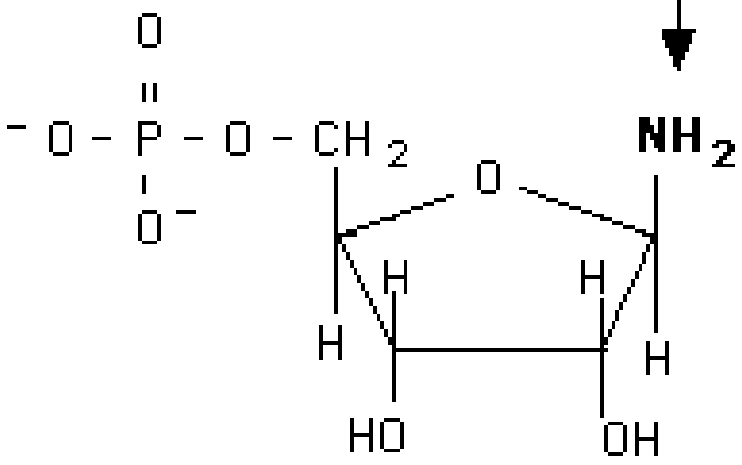
Asal atom C & N pada biosintesis purin



Amide nitrogen of glutamine becomes N-9 of purine

PRPP + Glutamine

Gln-PRPP amidotransferase

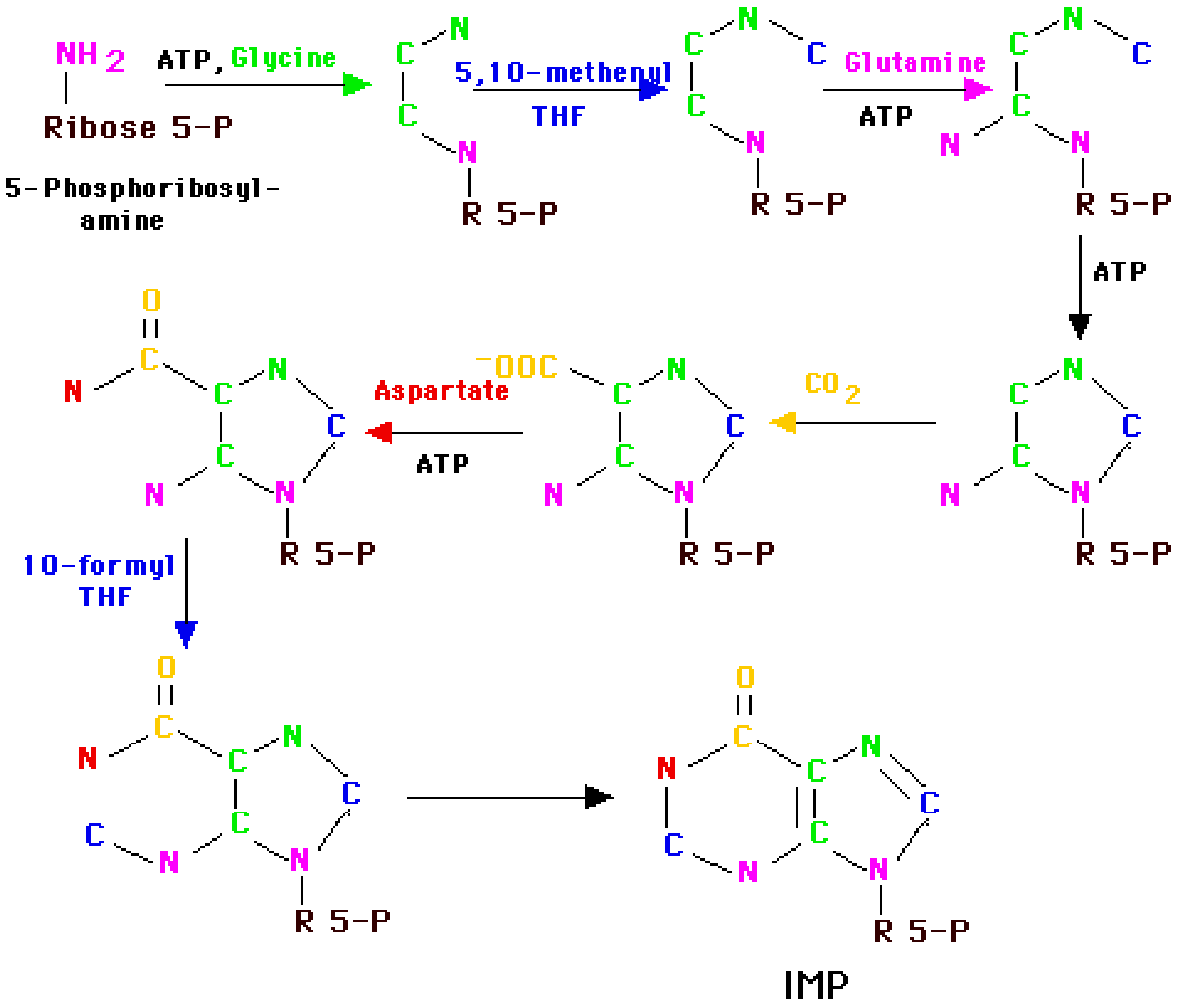


5-Phosphoribosylamine

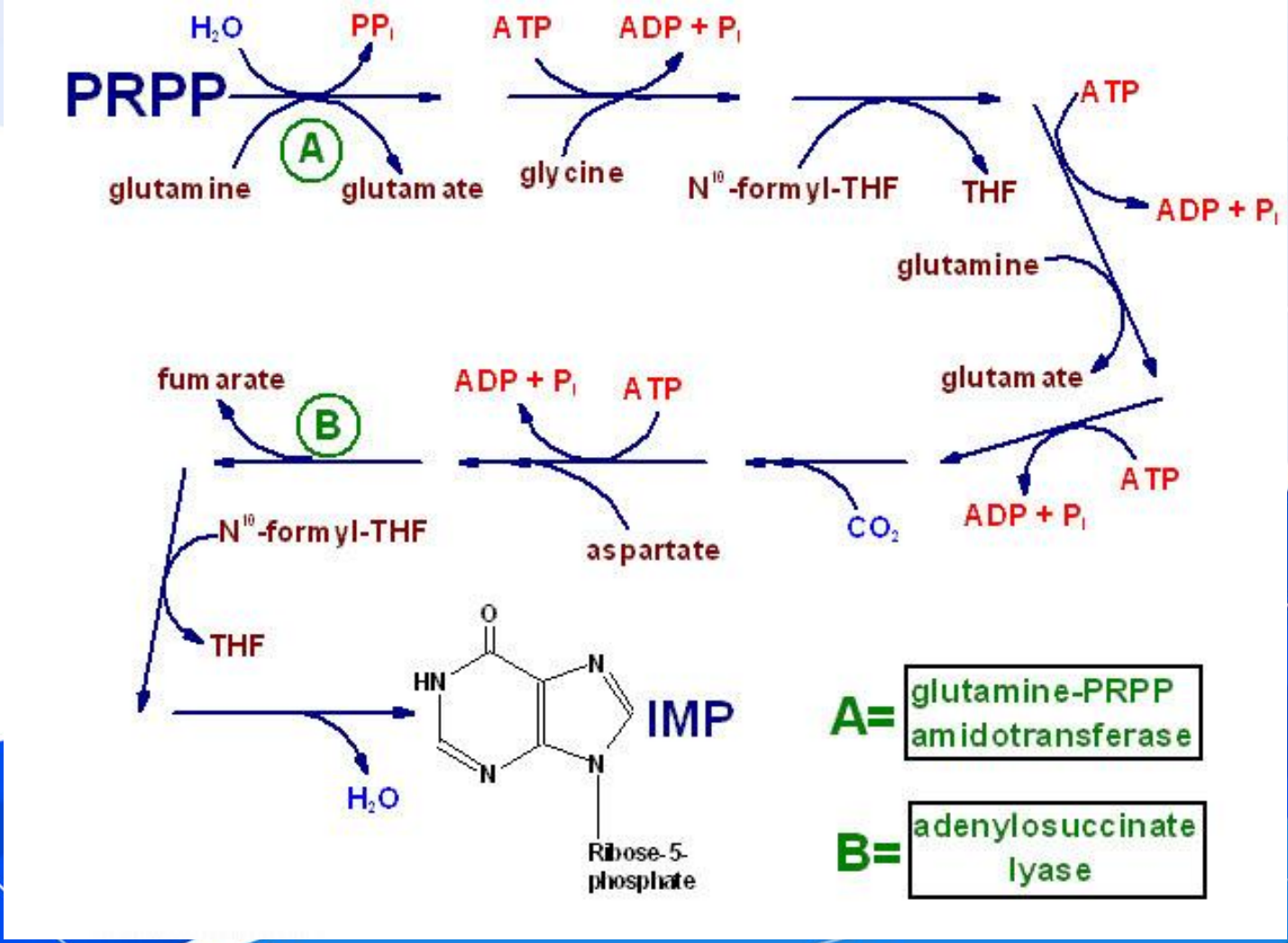
+ Glutamate + PPi

2 Pi

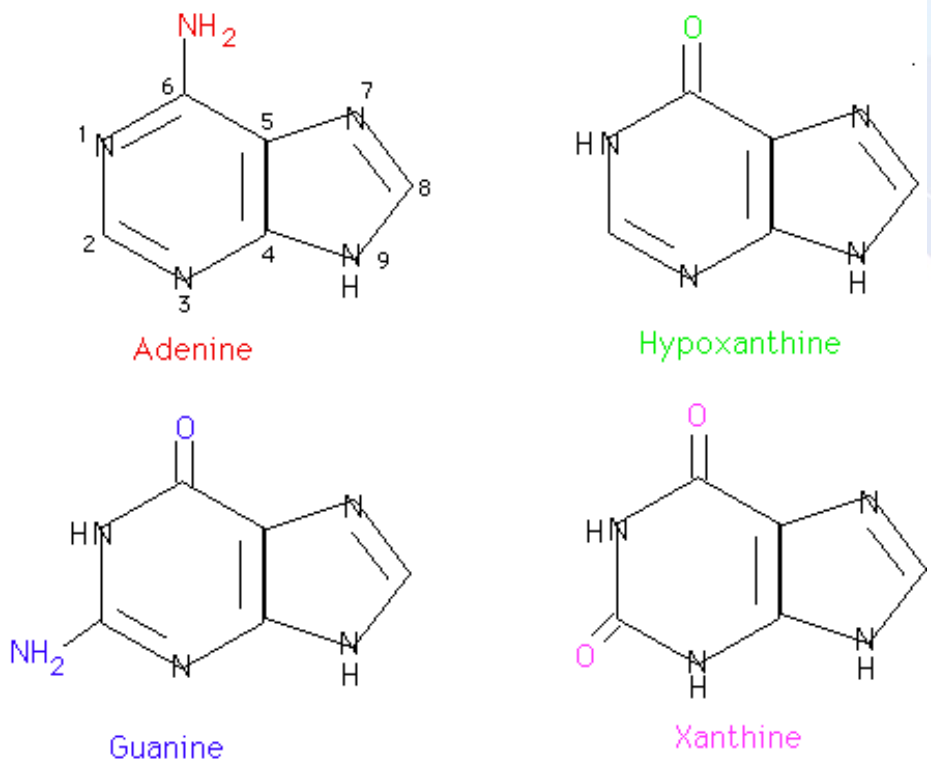
Schematic Representation of Purine Nucleotide Synthesis



Biosintesis Nukleotida Purin

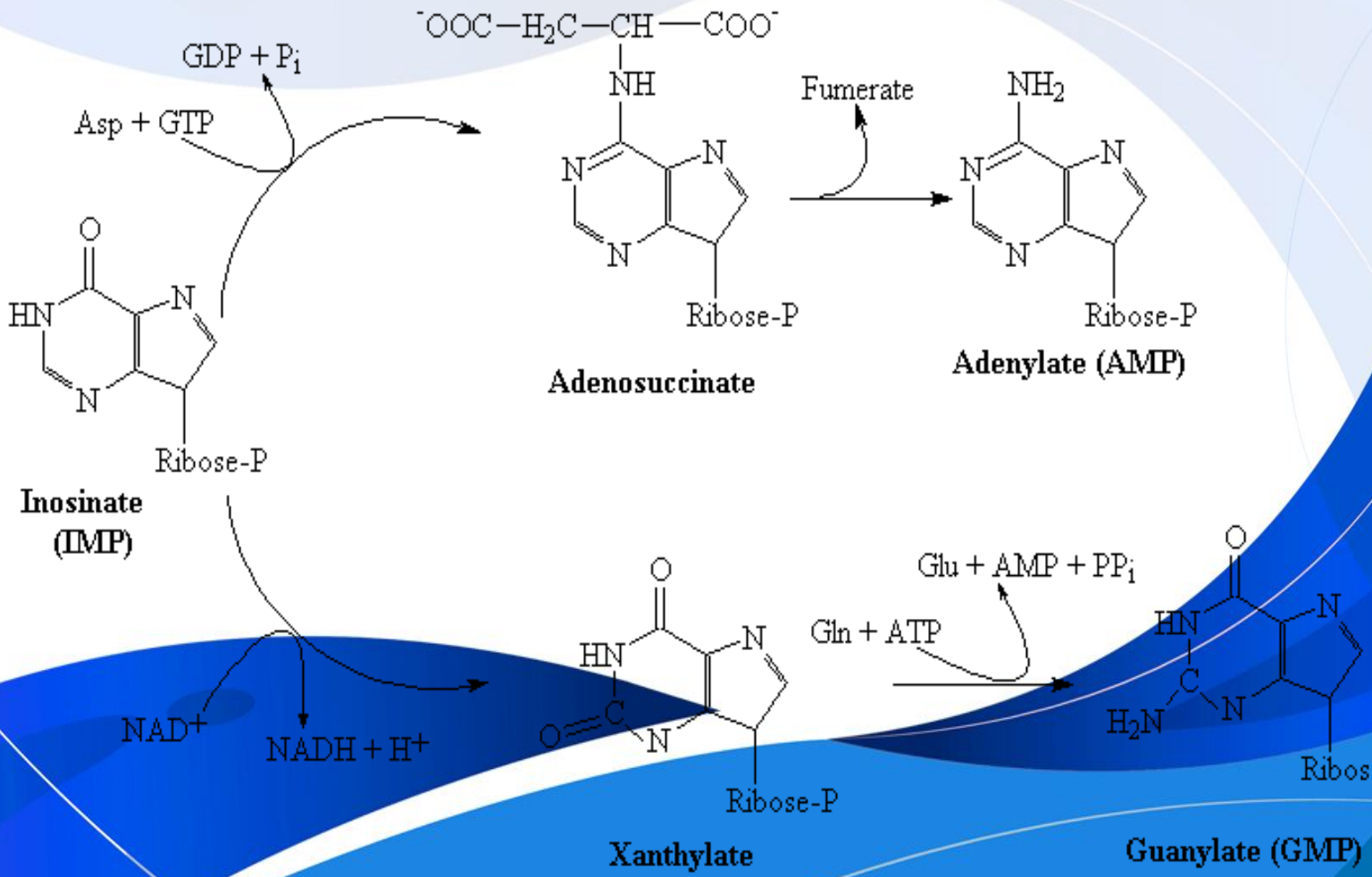


Basa-basa purin

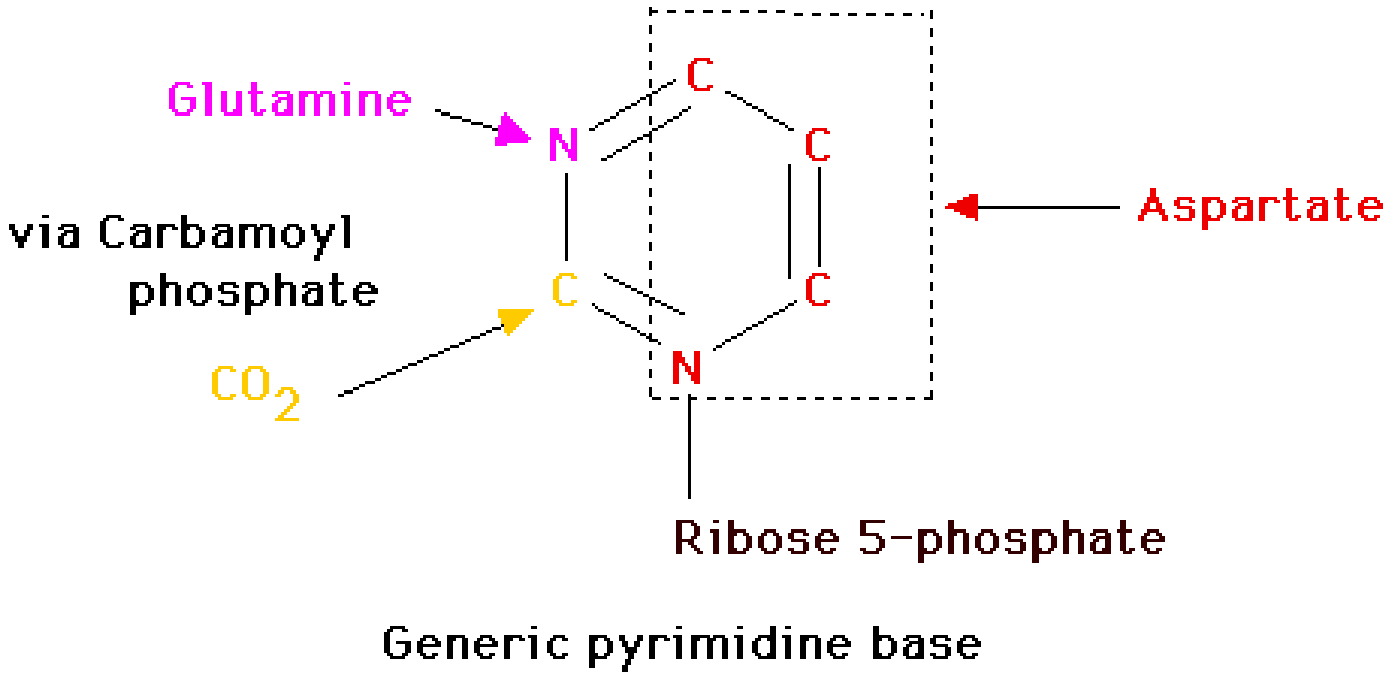


Adenin = 6-amino purin
Guanin = 2-amino-6-oksi purin
Hipoxanthin = 6-oksi purin
Xanthin = 2,6-dioksi purin

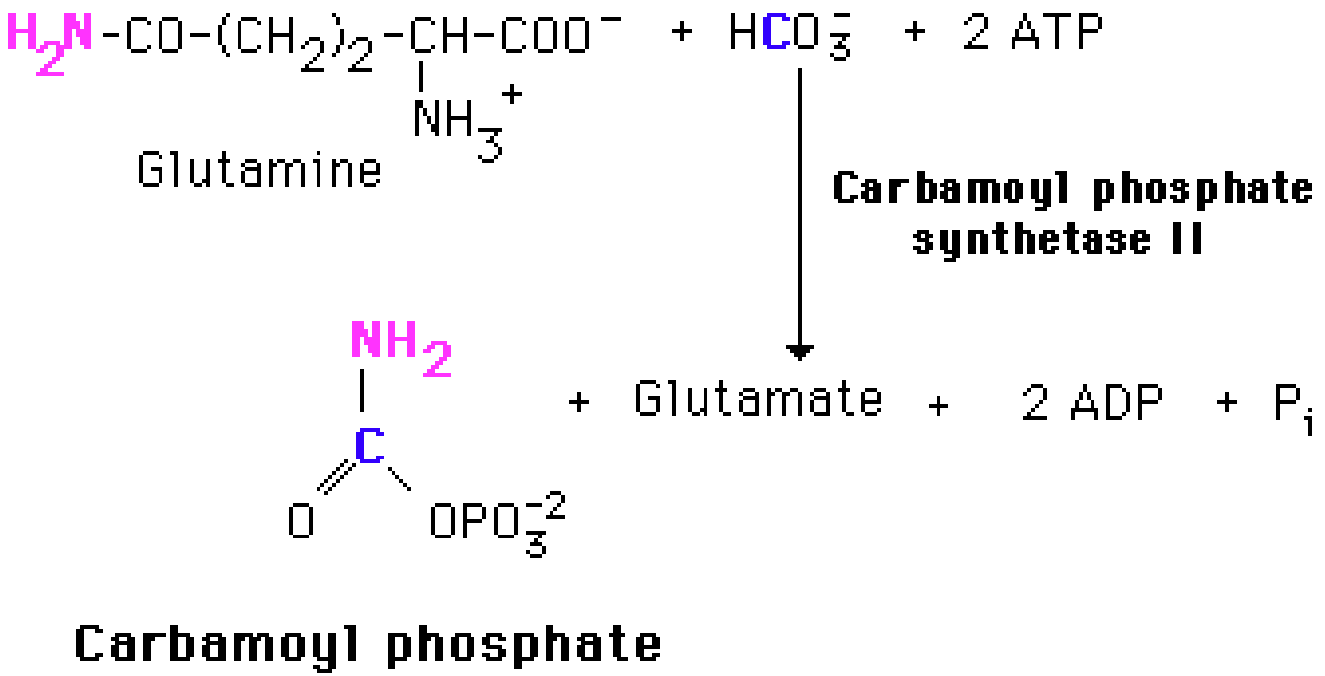
Konversi IMP → AMP & GMP



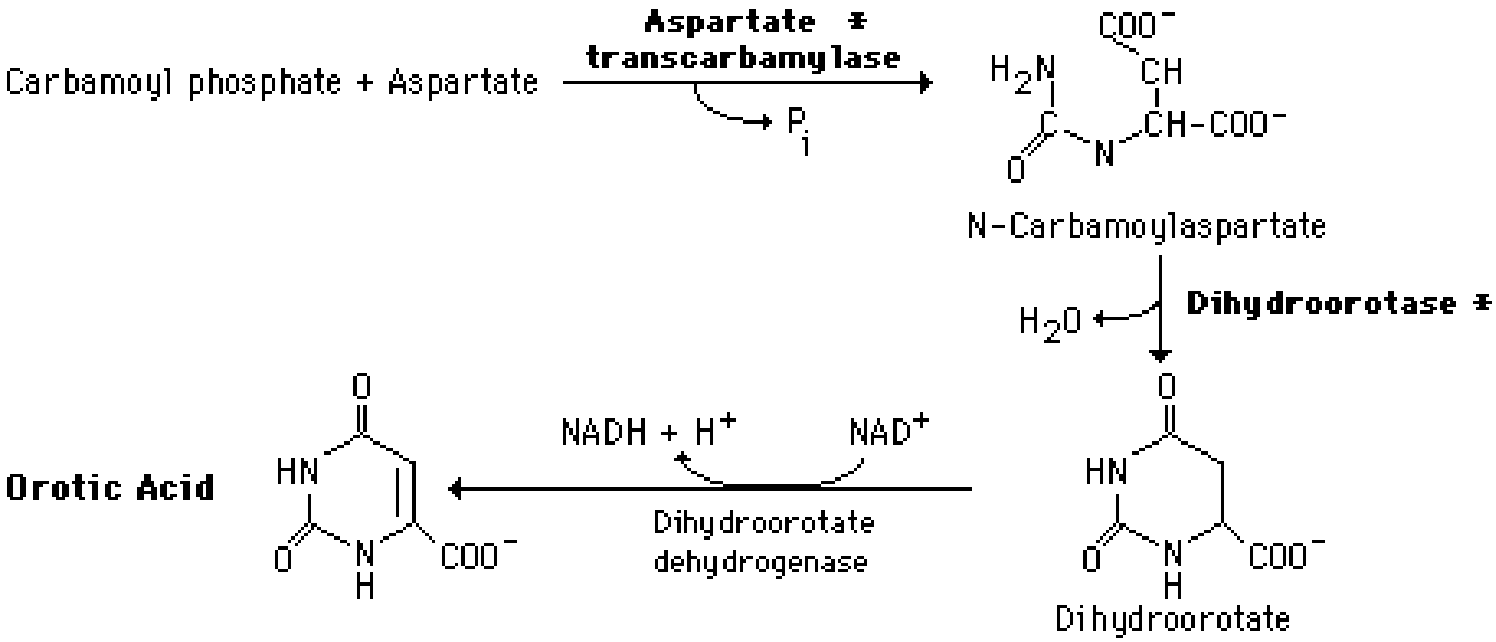
Biosintesis Pirimidin



Pembentukan Karbamoil Fosfat

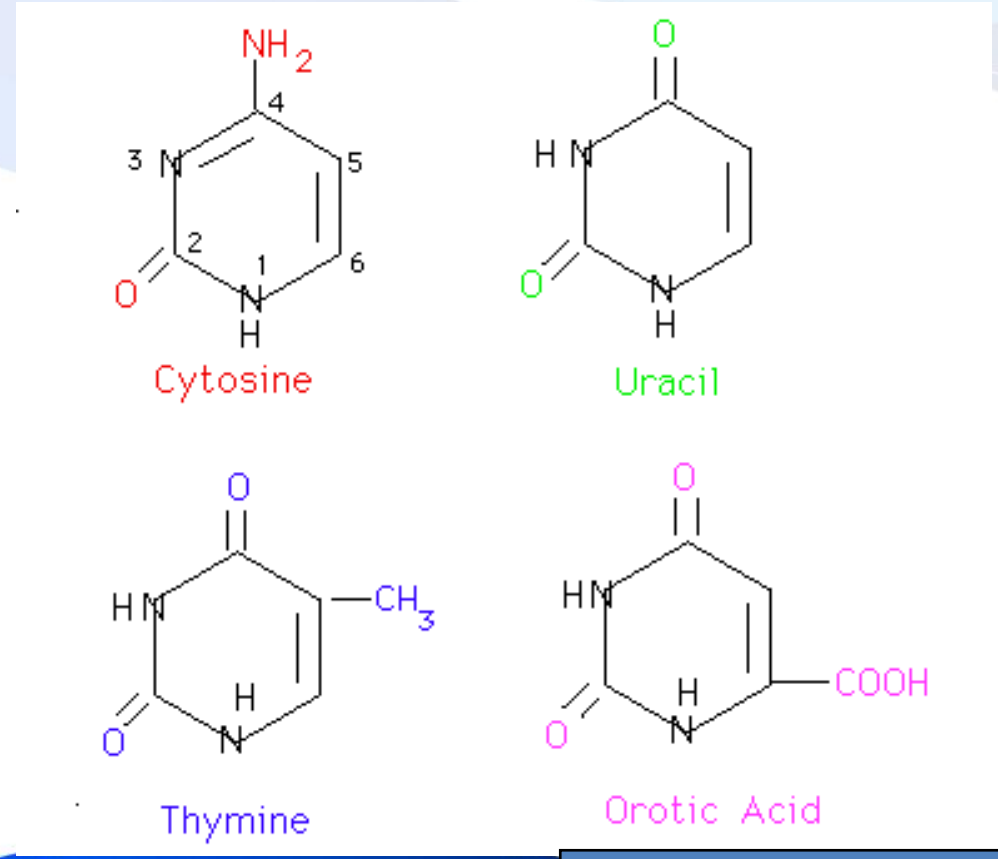


Pembentukan cincin pirimidin



ǂ Part of the same multi-functional protein

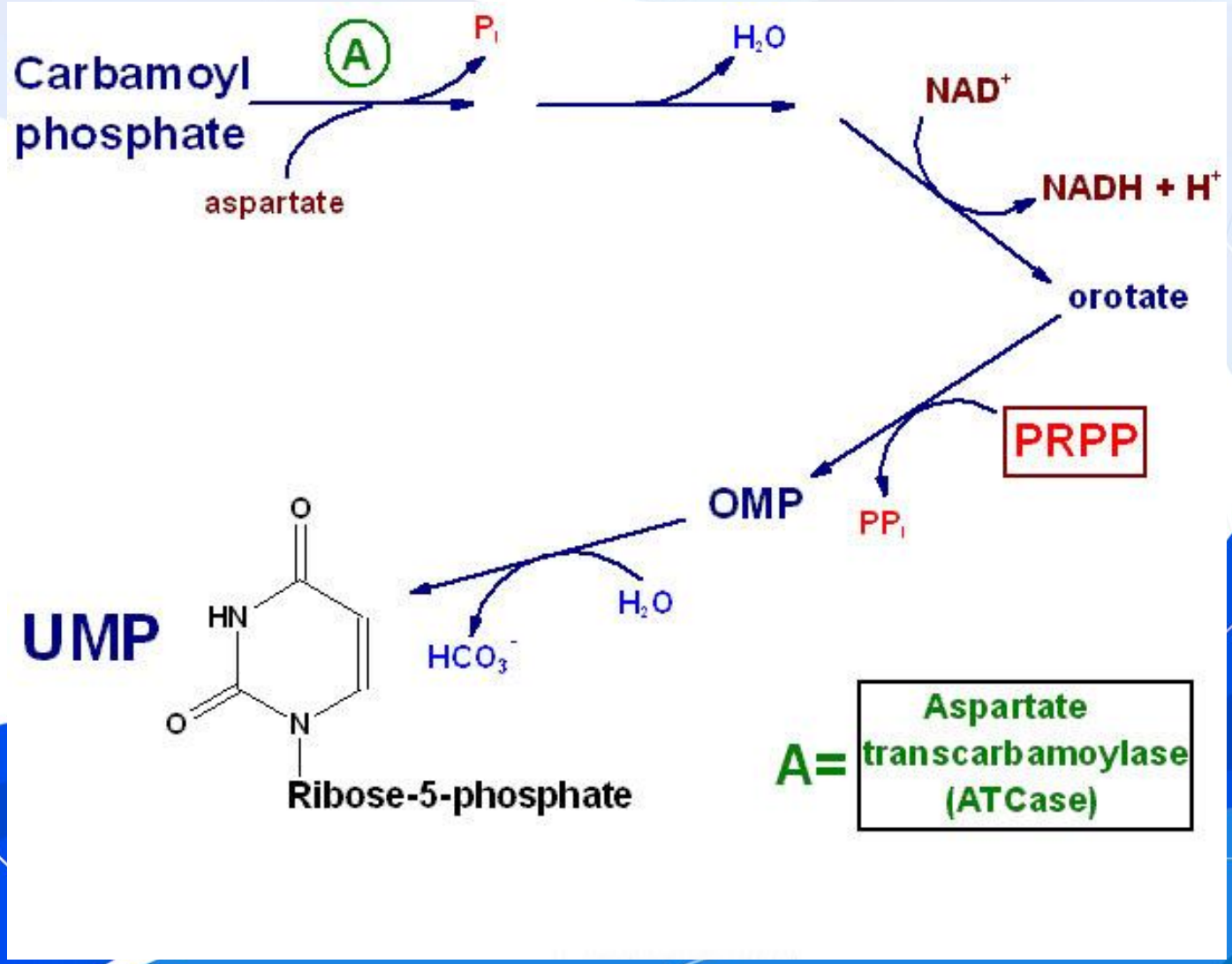
Basa-basa pirimidin



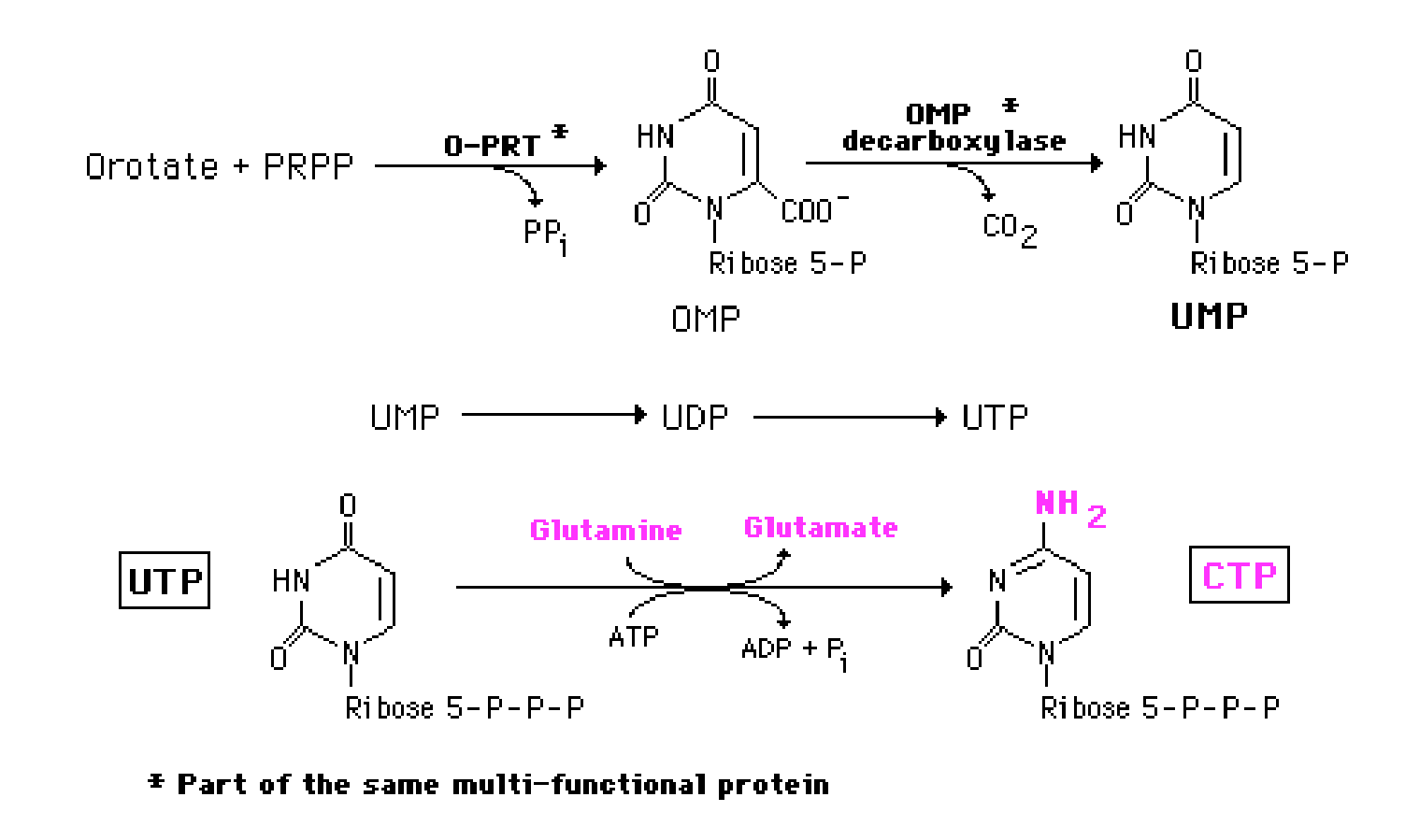
Uracil = 2,4-dioxy pyrimidine
Thymine = 2,4-dioxy-5-methyl pyrimidine
Cytosine = 2-oxy-4-amino pyrimidine

Orotic acid = 2,4-dioxy-6-carboxy pyrimidine

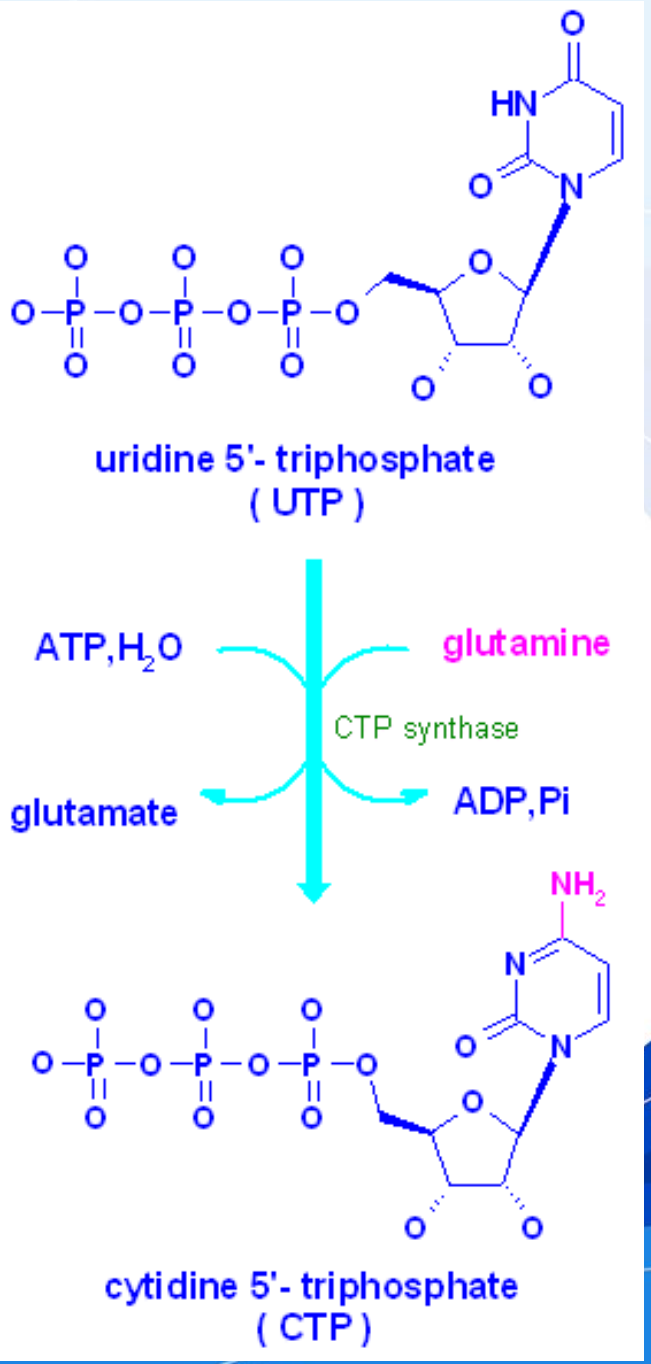
Biosintesis Nukleotida Pirimidin



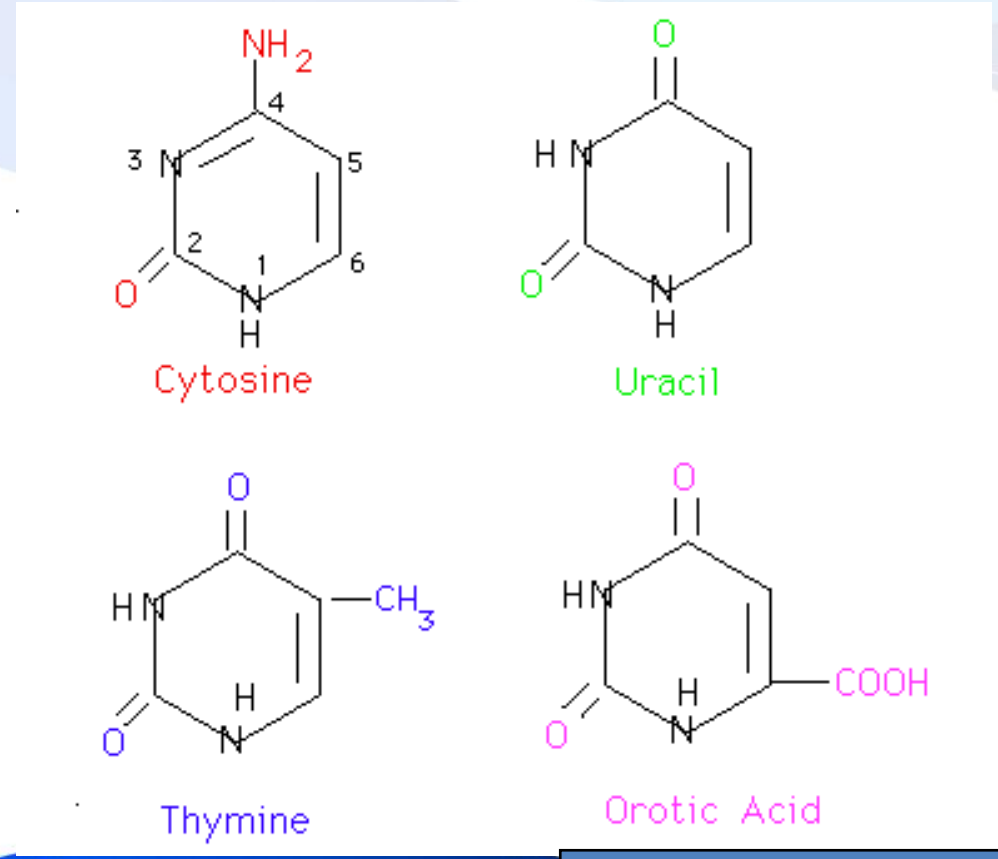
Biosintesis CTP (dari UMP)



Biosintesis CTP (dari UTP)



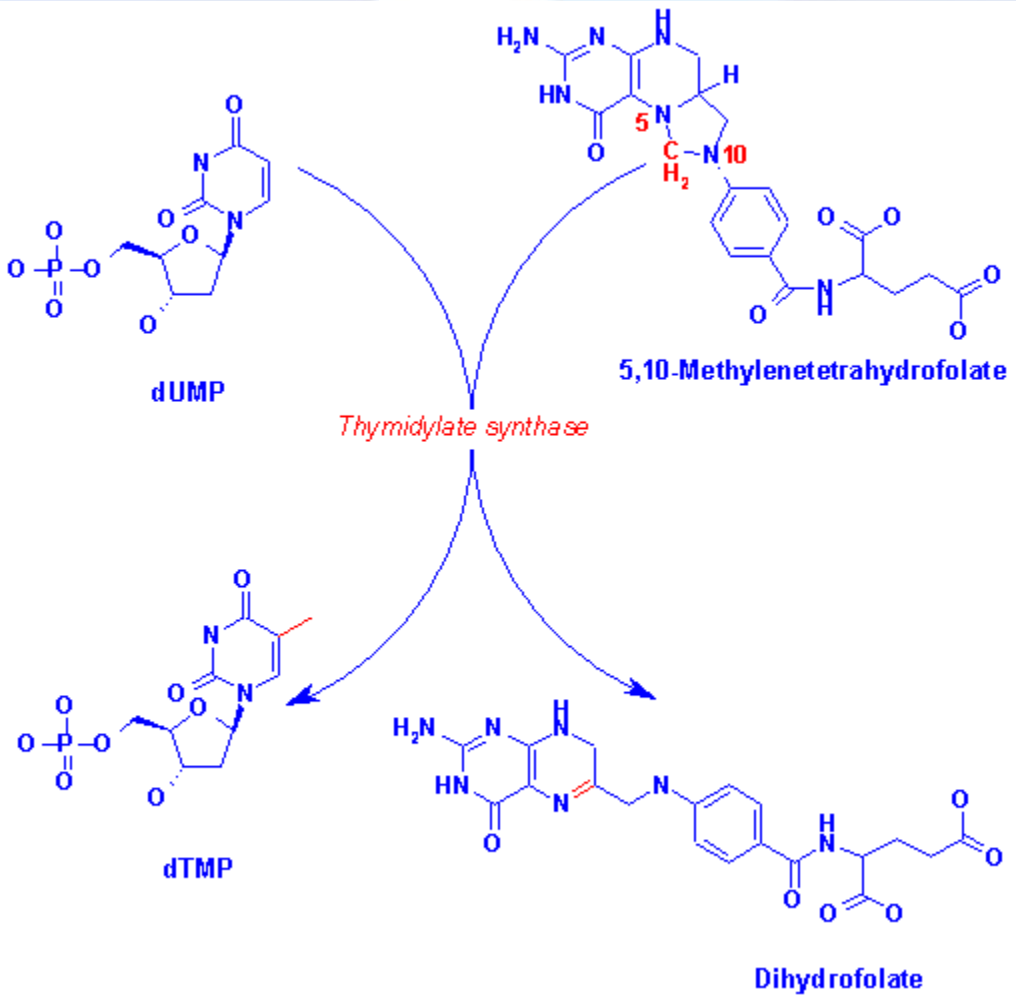
Basa-basa pirimidin



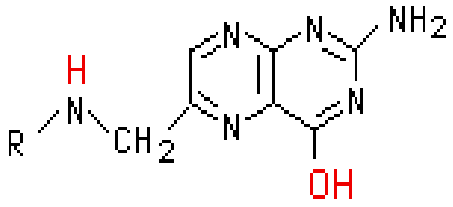
Uracil = 2,4-dioxy pyrimidine
Thymine = 2,4-dioxy-5-methyl pyrimidine
Cytosine = 2-oxy-4-amino pyrimidine

Orotic acid = 2,4-dioxy-6-carboxy pyrimidine

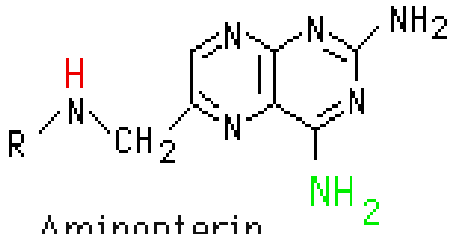
Biosintesis dTMP



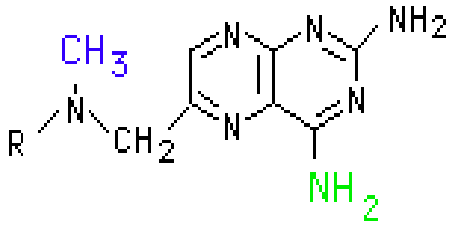
Metotreksat (4-amino-10-metil folat) dan Aminopterin (4-amino folat) sebagai Obat Kanker → Sitotoksik



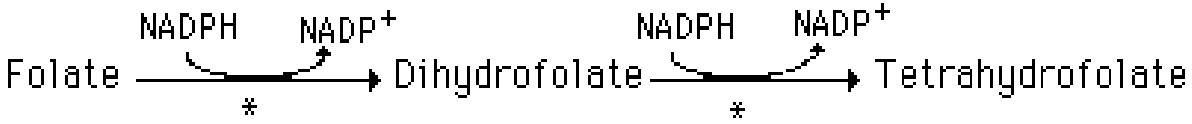
Folate



Aminopterin



Methotrexate

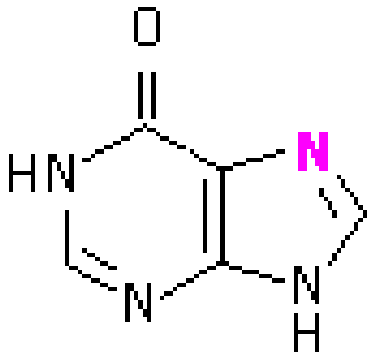


* Aminopterin and Methotrexate are inhibitors of dihydrofolate reductase

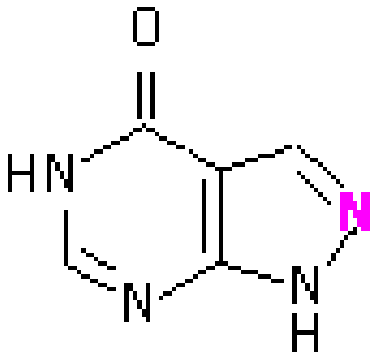
Disorders of Purine Metabolism

Disorder	Defect	Nature of Defect	Comments
Gout	PRPP synthetase	increased enzyme activity due to elevated Vmax	hyperuricemia
Gout	PRPP synthetase	enzyme is resistant to feed-back inhibition	hyperuricemia
Gout	PRPP synthetase	enzyme has increased affinity for ribose-5-phosphate (lowered Km)	hyperuricemia
Gout	PRPP amidotransferase	loss of feed-back inhibition of enzyme	hyperuricemia
Gout	HGPRTa	partially defective enzyme	hyperuricemia
Lesch-Nyhan syndrome	HGPRT	lack of enzyme	see above
SCID	ADAb	lack of enzyme	see above
Immunodeficiency	PNPc	lack of enzyme	see above
Renal lithiasis	APRTd	lack of enzyme	2,8-dihydroxyadenine renal lithiasis
Xanthinuria	Xanthine oxidase	lack of enzyme	hypouricemia and xanthine renal lithiasis
von Gierke's disease	Glucose-6-phosphatase	enzyme deficiency	see above

Allopurinol: Obat Gout



Hypoxanthine



Allopurinol

- Allopurinol is a substrate for xanthine oxidase, but the product binds so tightly that the enzyme is now unable to oxidized its normal substrate. Uric acid production is diminished and xanthine and hypoxanthine levels in the blood rise. These are more soluble than urate and are less likely to deposit as crystals in the joints.
- Another approach is to stimulate the secretion of urate in the urine.

Disorders of Pyrimidine Metabolism

Disorder	Defective Enzyme	Comments
Orotic aciduria, Type I	orotate phosphoribosyl transferase and OMP decarboxylase	see above
Orotic aciduria, Type II	OMP decarboxylase	see above
Orotic aciduria (mild, no hematologic component)	the urea cycle enzyme, ornithine transcarbamoylase, is deficient	increased mitochondrial carbamoyl phosphate exits and augments pyrimidine biosynthesis; hepatic encephalopathy
b-aminoisobutyric aciduria	Transaminase, affects urea cycle function during deamination of a-amino acids to of α-keto acids	benign, frequent in Orientals
Drug induced orotic aciduria	OMP decarboxylase	Allopurinol and 6-azauridine treatments cause orotic acidurias without a hematologic component; their catabolic by-products inhibit OMP decarboxylase

Soal Latihan:

- Jika sebuah molekul DNA dihidrolisis secara bertahap sampai menjadi basa purin/pirimidin, senyawa-senyawa apakah yang diperoleh pada setiap tahap hidrolisis ? Jelaskan.
- Apa perbedaan antara nukleotida dengan nukleosida ? Gambarkan struktur sebuah nukleotida dan sebuah nukleosida!
- Apa pula perbedaan antara basa purin dengan basa pirimidin ? Gambarlah sebuah basa purin dan sebuah basa pirimidin yang Saudara ketahui, dan sebutkan namanya.

PRPP adalah senyawa yang sangat penting dalam anabolisme atau biosintesis nukleotida

- Apa kepanjangan dari PRPP? Tuliskan nama kimianya dengan lengkap.
- Apa fungsi PRPP dalam biosintesis nukleotida?
- Tuliskan reaksi biosintesis PRPP dari prekursornya (ribose-5-fosfat), enzim apa yang mengkatalisis reaksi ini? Menurut Saudara, reaksi ini (reaksi biosintesis PRPP dari ribose-5-fosfat) merupakan reaksi yang menghasilkan energi atau justru membutuhkan energi ? Jelaskan alasan Saudara.

- Gambar secara skematis biosintesis de novo untuk nukleotida purin
- Apa senyawa prekursor awal dari rangkaian reaksi biosintesis de novo nukleotida purin
- Sebutkan nukleotida purin yang pertama kali terbentuk dalam rangkaian reaksi biosintesis de novo nukleotida purin, yang merupakan prekursor untuk pembentukan AMP dan GMP

- Gambar secara skematis biosintesis de novo untuk nukleotida pirimidin
- Apa senyawa prekursor awal dari rangkaian reaksi biosintesis de novo nukleotida pirimidin
- Sebutkan nukleotida pirimidin yang pertama kali terbentuk dalam rangkaian reaksi biosintesis de novo nukleotida pirimidin, yang merupakan prekursor untuk pembentukan nukleotida-nukleotida pirimidin yang lain

- Nukleotida untuk biosintesis DNA berbeda dengan nukleotida yang diperlukan untuk biosintesis RNA. Jelaskan dimana perbedaannya
- Bagaimana membentuk nukleotida-nukleotida untuk biosintesis DNA

- Susunlah jalur biosintesis nukleotida-nukleotida purin menggunakan senyawa-senyawa berikut ini: IMP, PRPP, AMP, GMP dan Ribosa-5-fosfat. Beri penjelasan secukupnya.

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