- Nucleotides are organic compounds made up of a PO4 group, nitrogenous base & a sugar molecule.
- These are the building blocks of nucleic acids (DNA and RNA).
- They serve as sources of chemical energy (ATP, GTP), participate in cellular signalling (cAMP, cGMP) and function as important cofactors of enzymatic reactions (CoA, FAD, FMN, NAD^+).

Functions of nucleotide

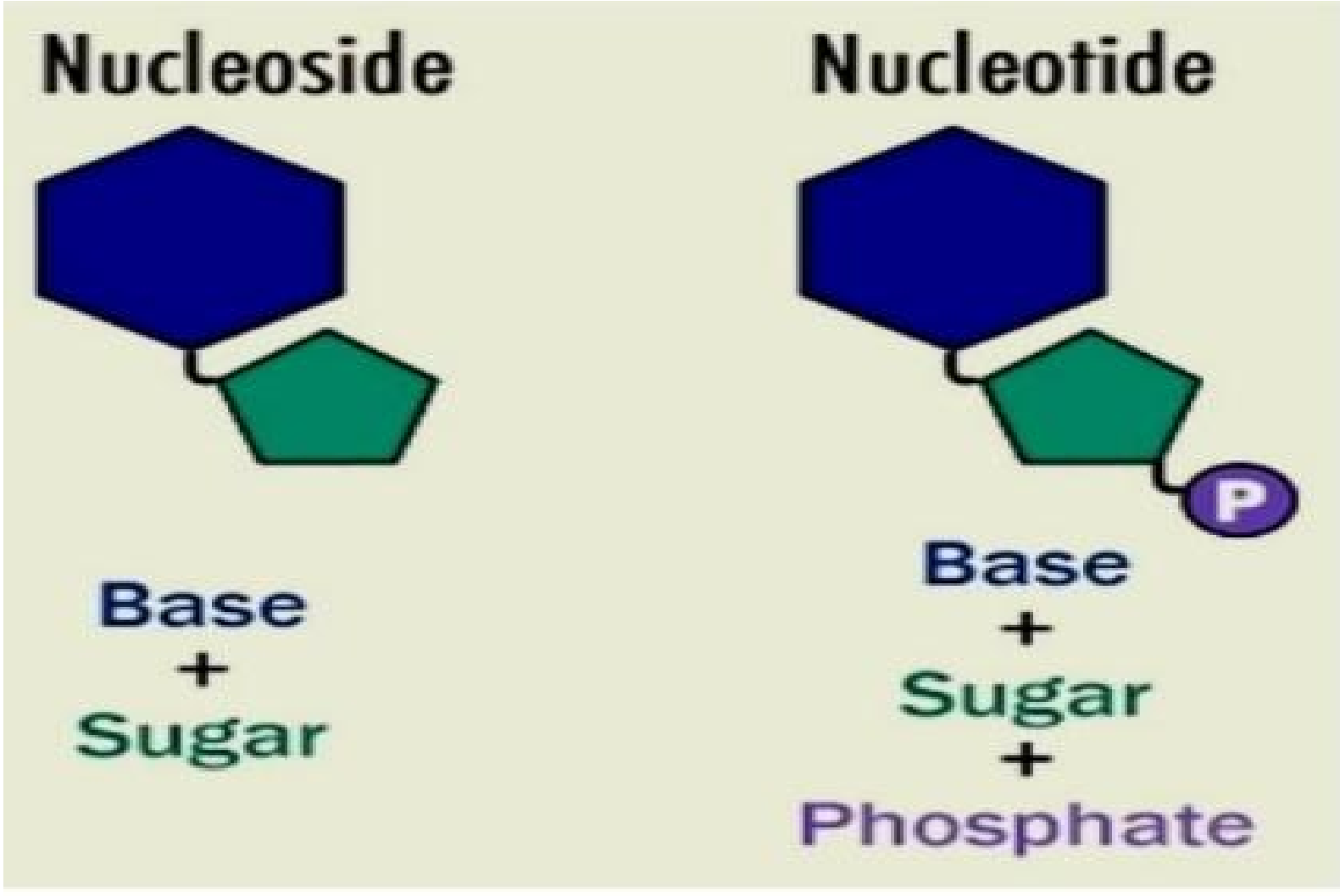
1. As Nucleic Acid:- being the monomeric units they carry the genetic code as DNA and RNA
2. In Biosynthesis of sugar:- UDP-Galactose is used in synthesis of lactose, UDP-Glucose in synthesis of Glycogen.
3. As components of coenzyme:- NAD, FAD, CoA.
4. As biological regulators:- as second messenger cAMP. participate in cellular signalling

5. As an energy source:-ATP as universal currency of energy in biological system.
6. Conjugation reaction:- UDP-Glucuronic acid forms the urinary glucuronide conjugate of bilirubin and of many drug including aspirin.
7. In biosynthesis of lipids:- CDP-Choline, CDP-Glycerol, CDP-ethonalamine are involved in phospholipid synthesis.
8. As active donor molecule:- S-adenosyl methionine as methyl donor, PAPS as sulfate donor, ATP as phosphate donor.

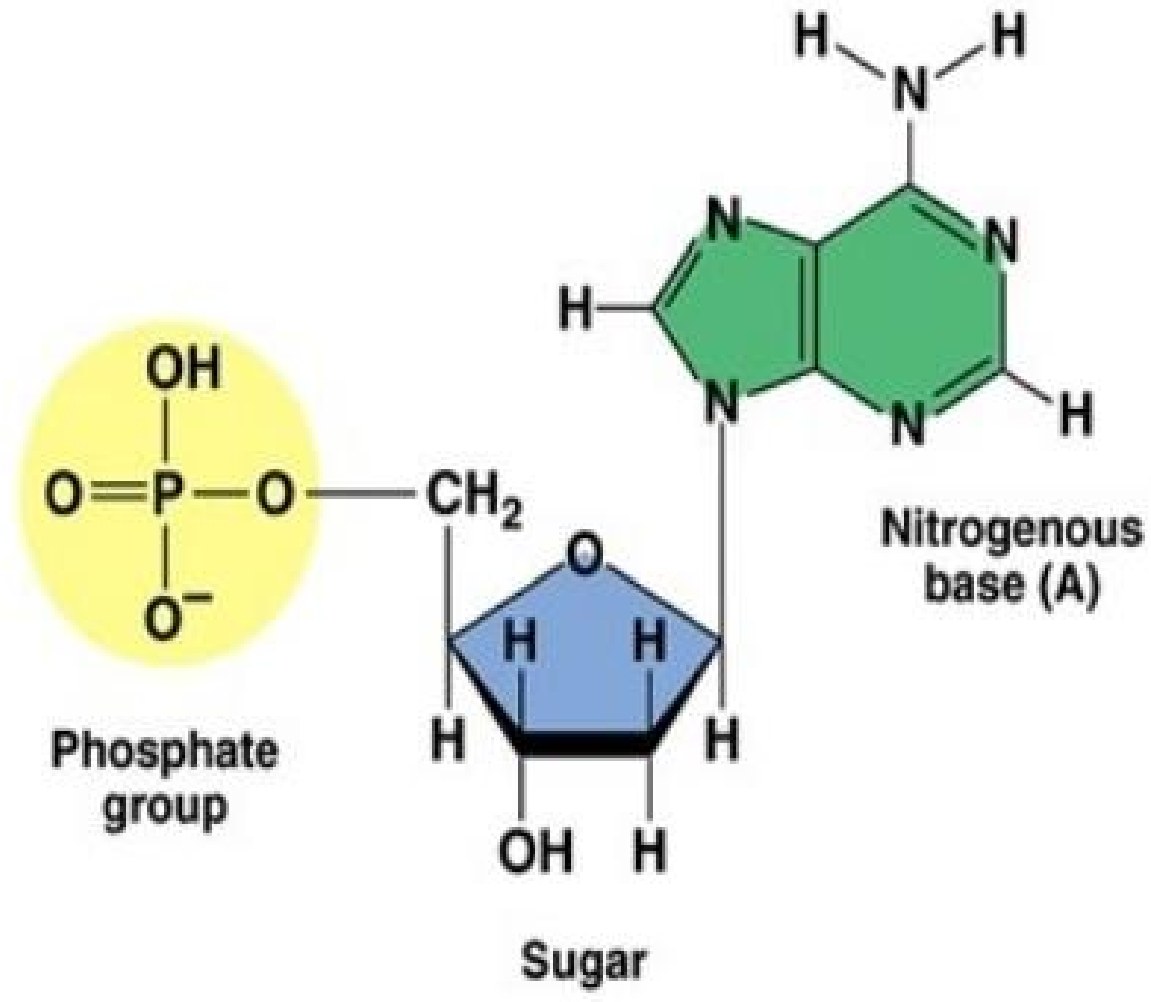
9. As an allosteric regulator:- GTP in protein synthesis.
10. In treatment of diseases:-

    5- flurouracil – Cancer

    Allopurinol - Gout



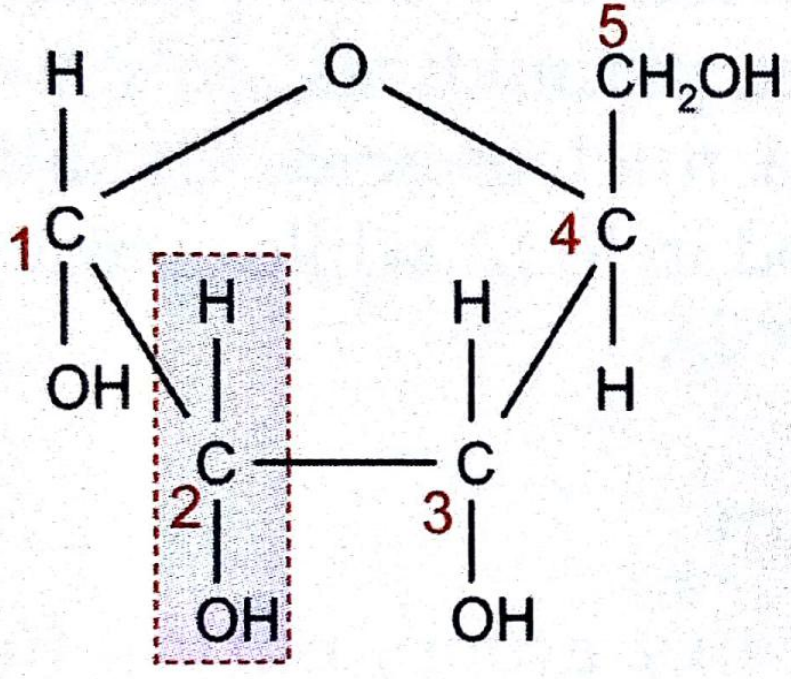
Structure



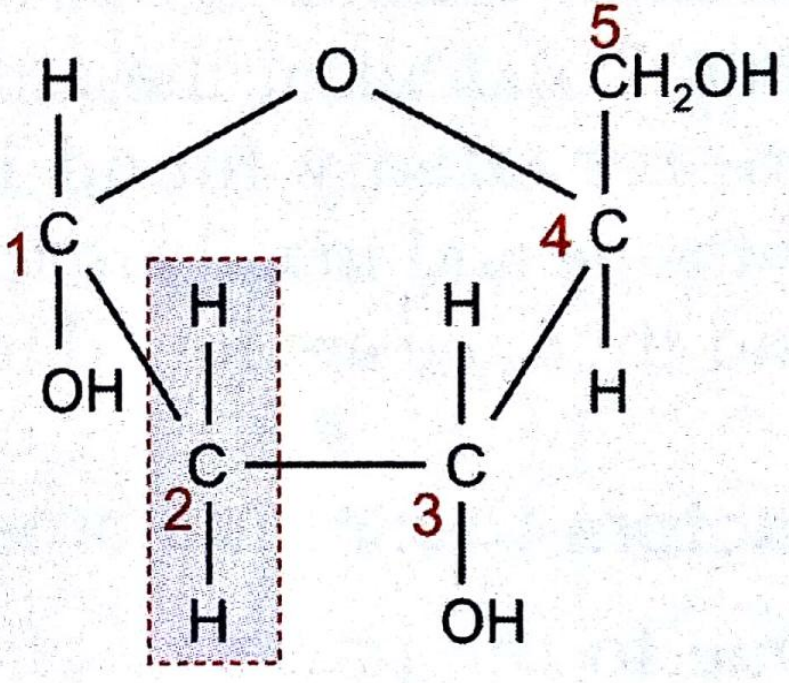
SUGARS

- Two main sugars

- Present in furanose form

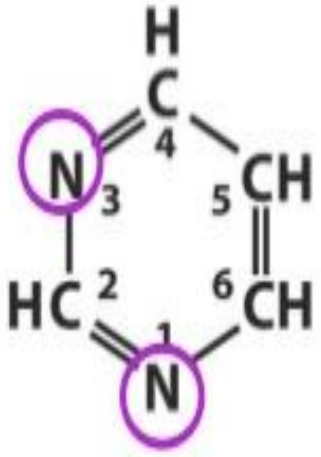


Ribose

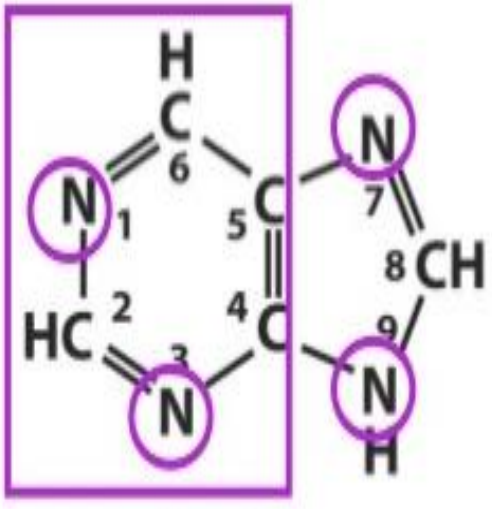


2-Deoxyribose

Bases



Pyrimidine



Purine

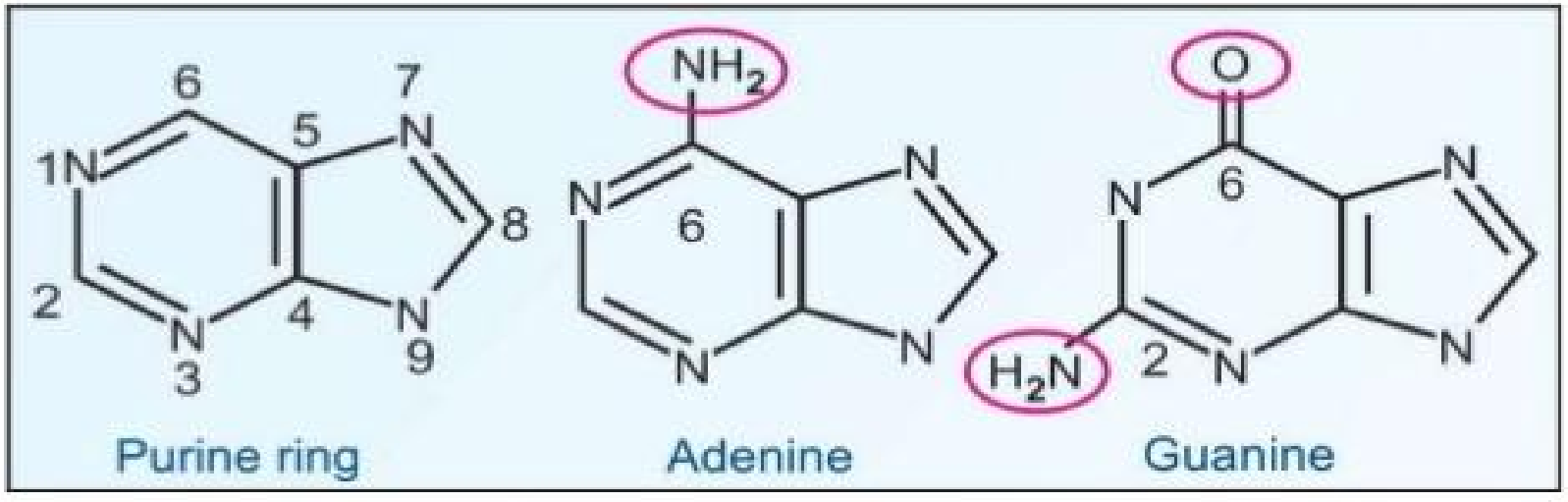
Nucleotide bases in nucleic acids are pyrimidines or purines. nitrogen-containing heterocycles, structures that contain, in addition to carbon, other (hetero) atoms such as nitrogen

The purine bases present in RNA and DNA are the same; - adenine and guanine.

Adenine is 6-amino purine and

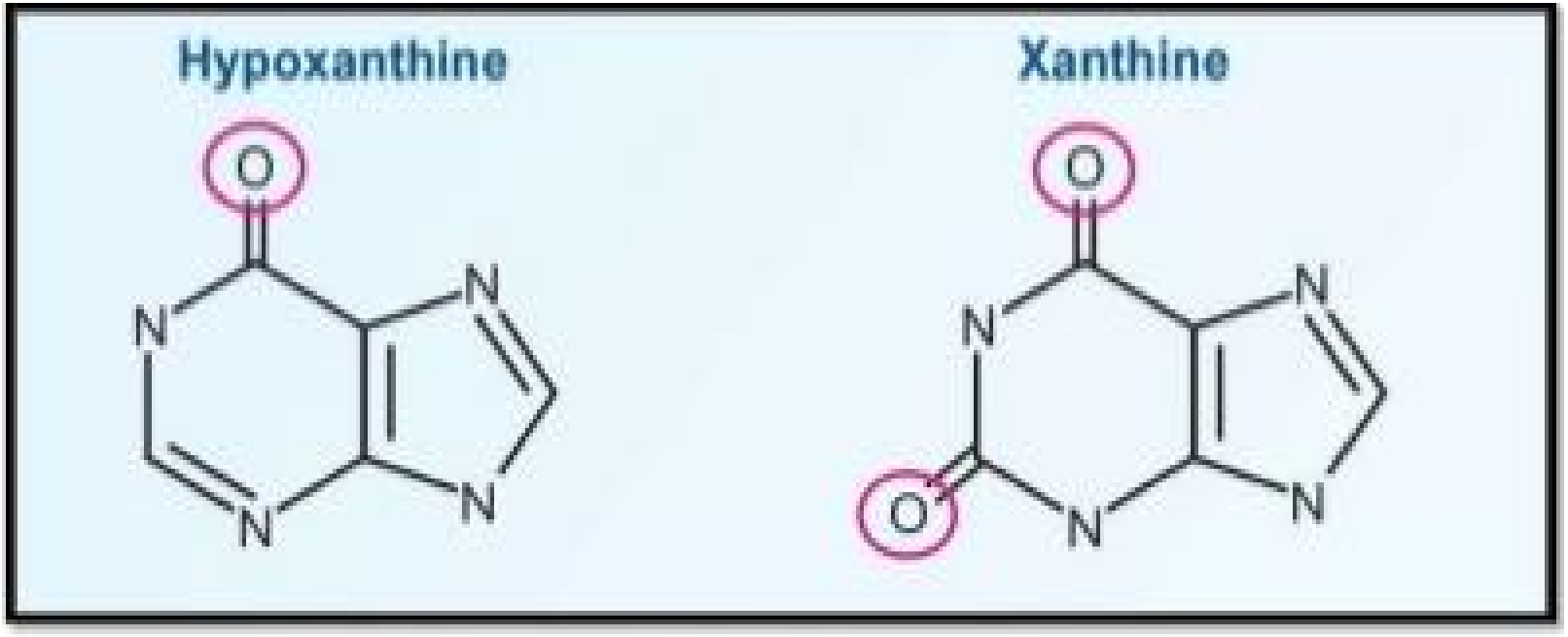
Guanine is 2-amino, 6-oxopurine.

The numbering of purine ring with structure of adenine and guanine are shown in Figure.



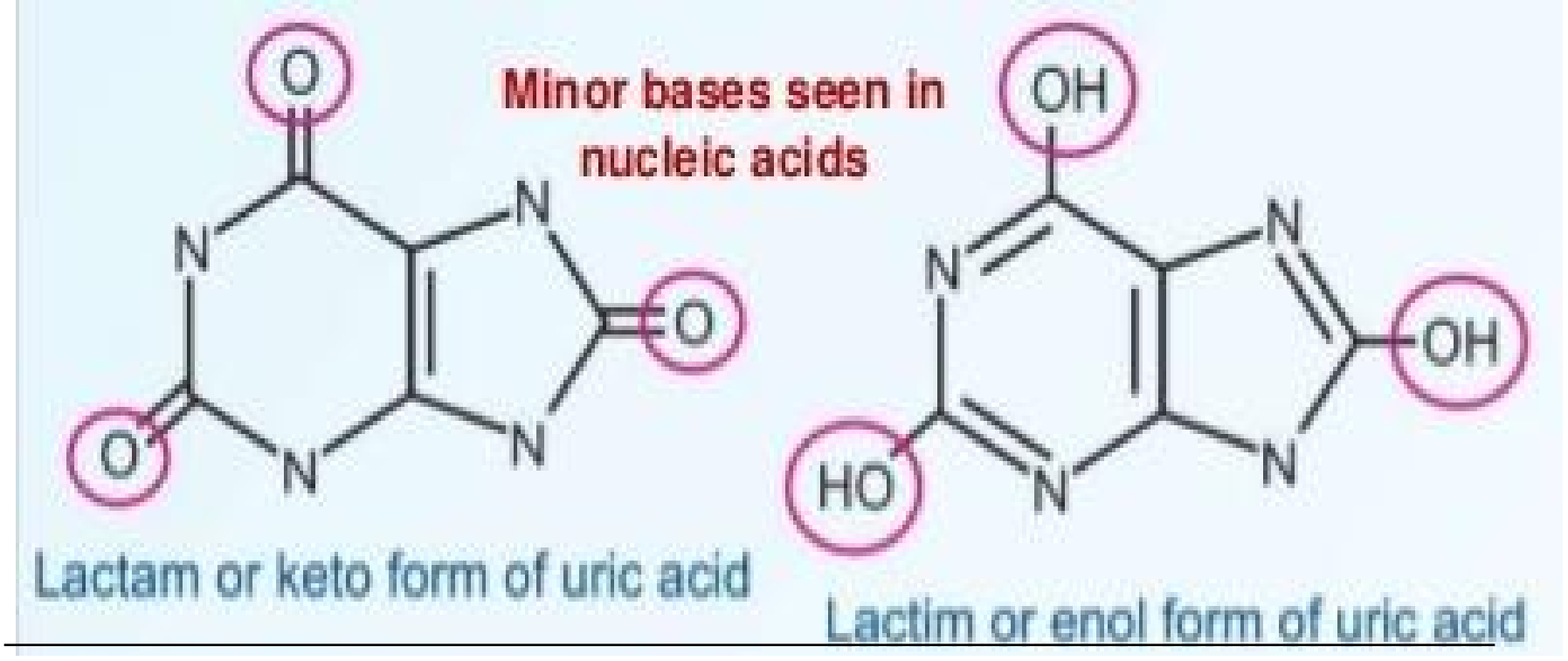
6-amino purine 2-amino, 6-oxopurine

- These bases may be found in small amounts in nucleic acids and hence called minor bases.
- These are hypoxanthine (6-oxopurine) and Xanthine (2, 6-di-oxopurine).



Minor bases seen in nucleic acids

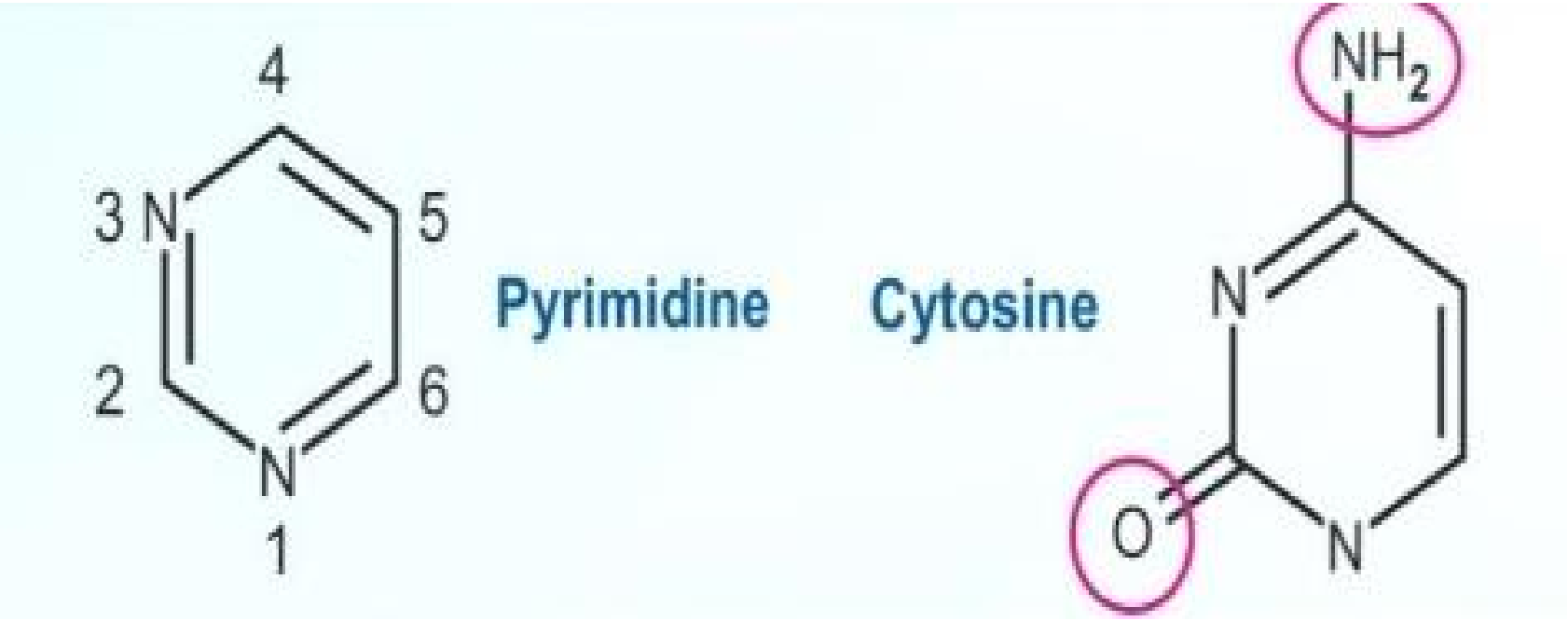
- Uric acid (2,6,8-tri-oxopurine) is formed as the end product of the catabolism of other purine bases.
- It can exist in the "enol" as well as "keto" forms (tautomeric forms).



PYRIMIDINE BASES

The pyrimidine bases present in nucleic acids are cytosine, thymine and uracil.

1. Cytosine (2 deoxy,4 amino pyrimidine) is present in both DNA and RNA.



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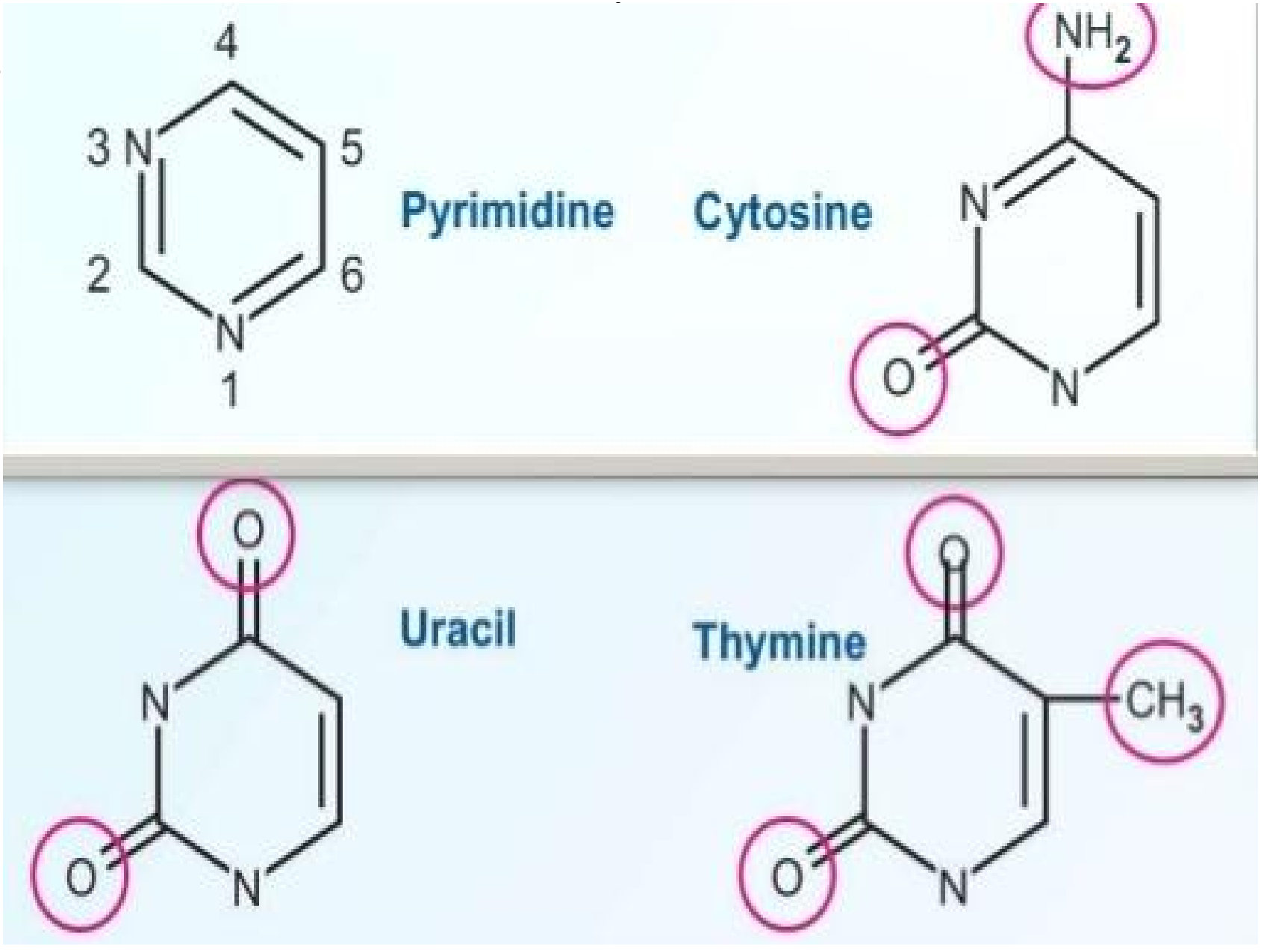

MODIFIED PYRIMIDINE BASES

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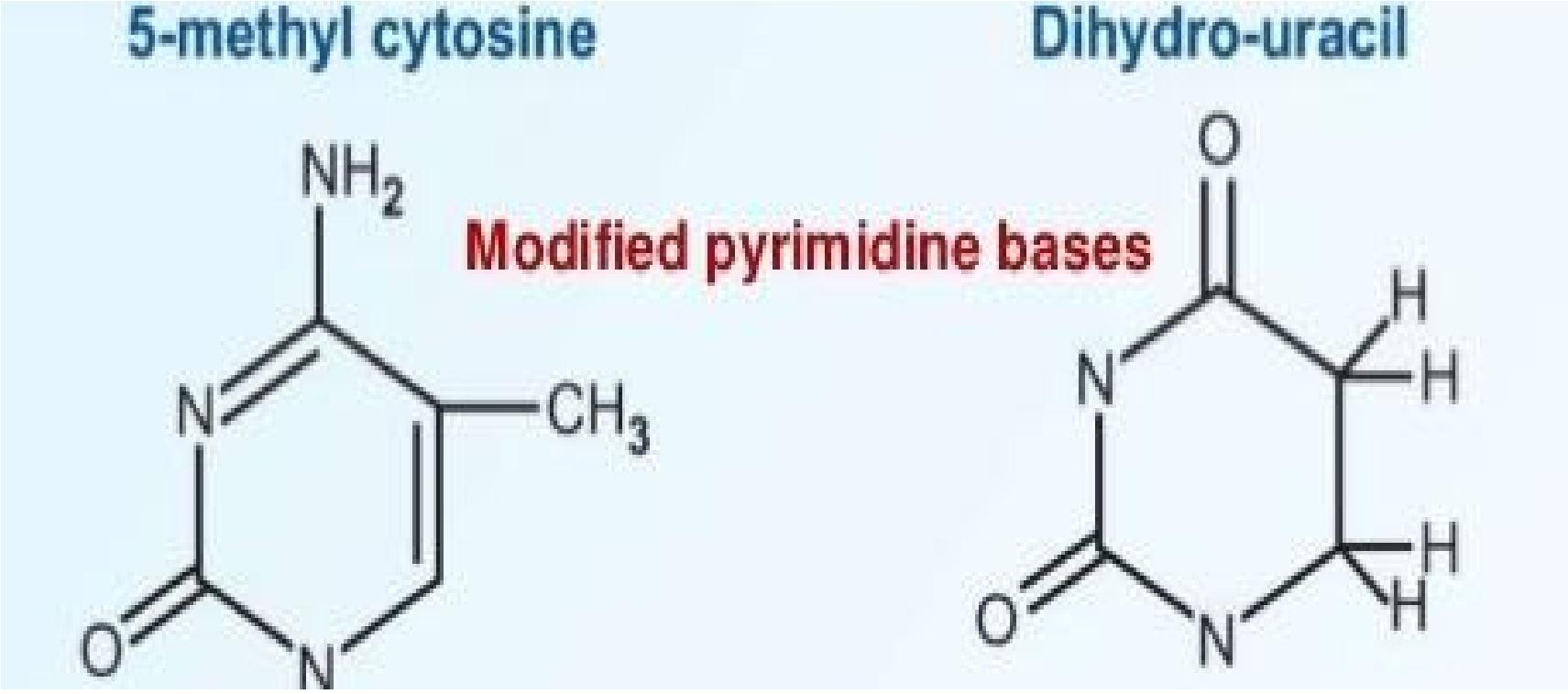
- A few other modified pyrimidine bases like dihydrouracil and 5-methyl cytosine are also found rarely in some types of RNA.



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MODIFIED BASES

5 hydroxy methyl cytosine – bacteriophages, viral nucleic acids

5-methyl cytosine – bacteria and human DNA

Dimethylated adenine & 7- methyl guanine – m RNAs

Theophylline – 1,3 dimethyl xanthine

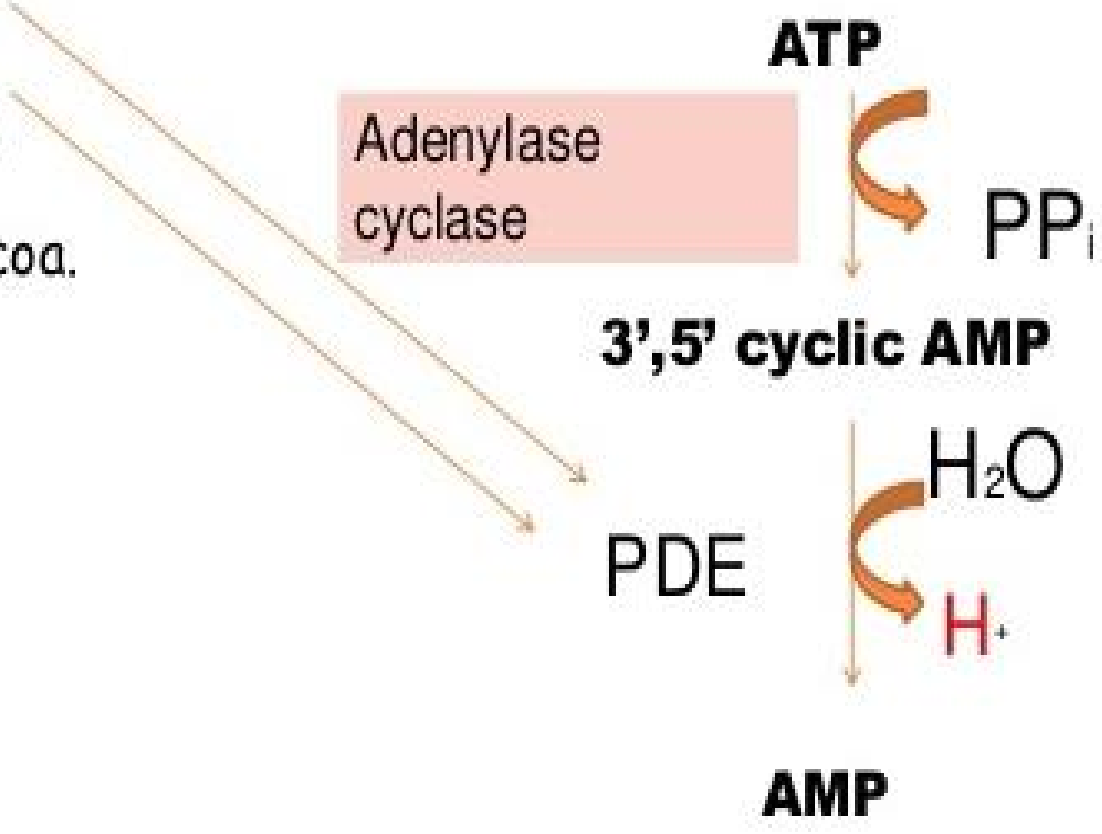
Theobromine – 3,7 dimethyl xanthine

Caffeine- 1,3,7 trimethyl xanthine

METHYLATED HETEROCYCLIC PLANT DERIVATIVES

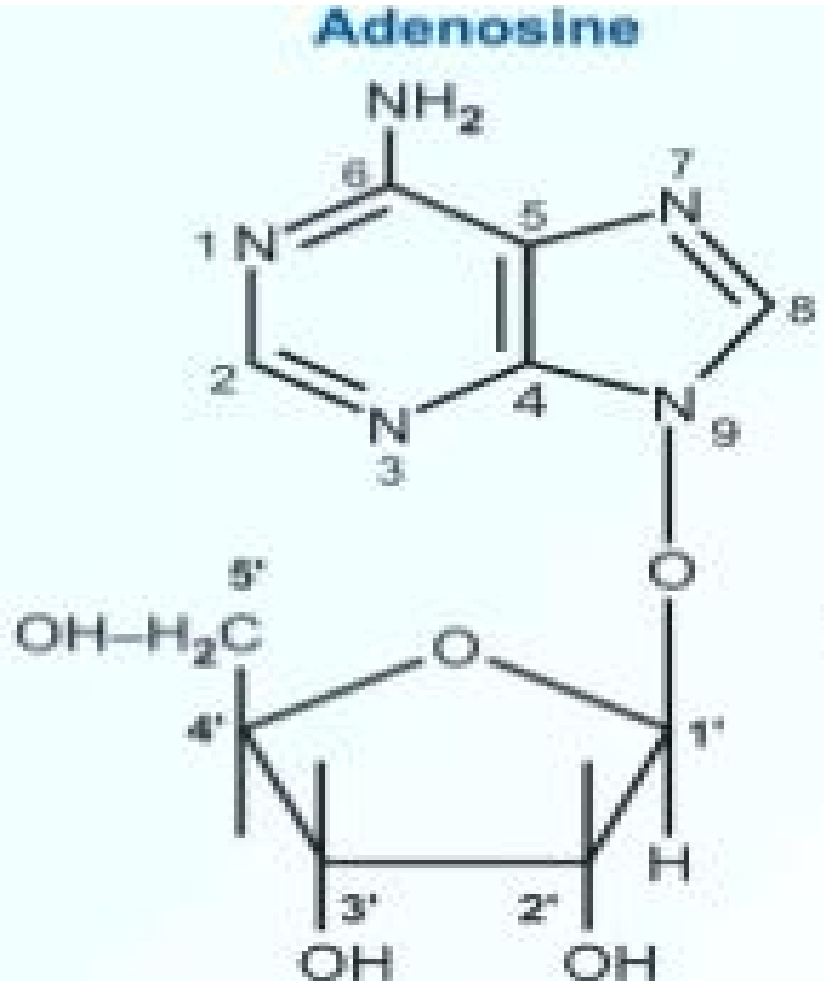
Methylated heterocycles of plants include the xanthine derivatives

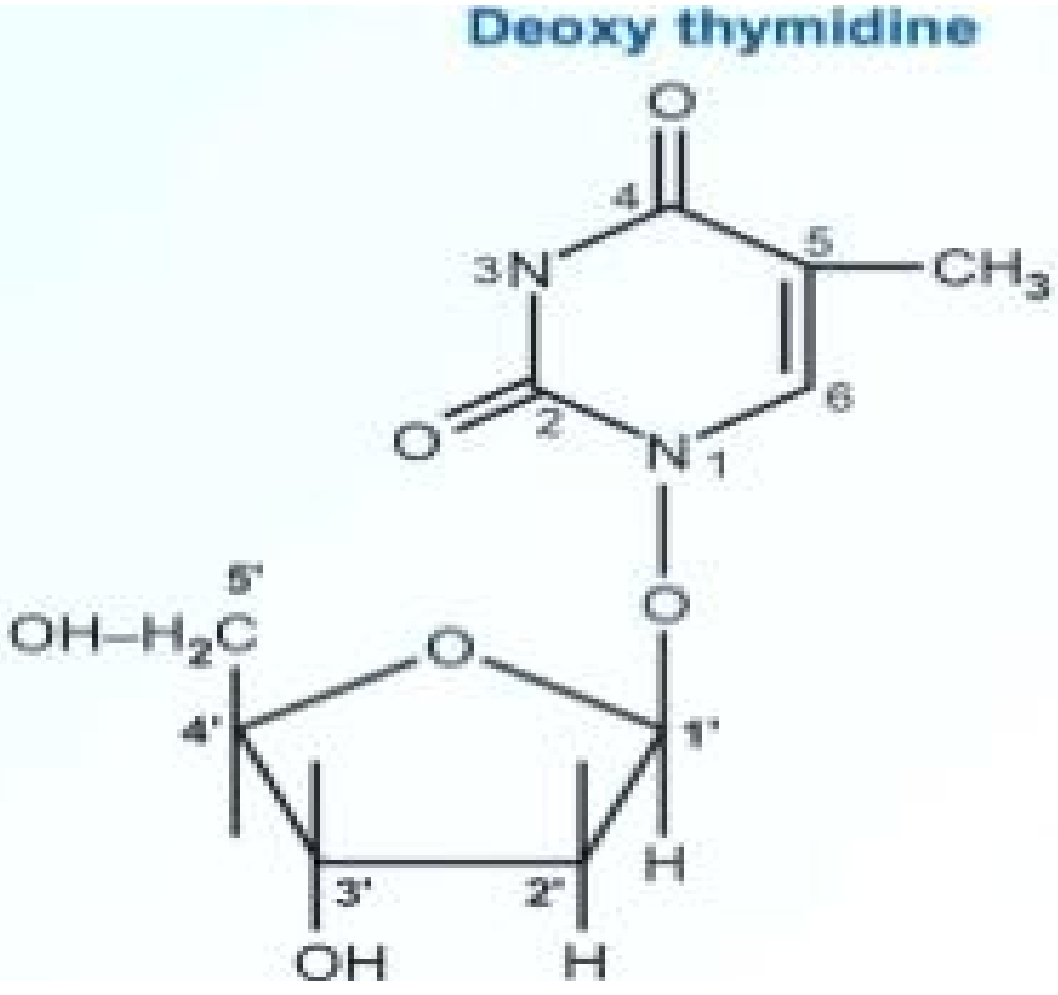
- Caffeine of coffee
- Theophylline of tea
- Theobromine of cocoa.



NUCLEOSIDES

- Nucleosides are formed when bases are attached to the pentose sugar, D-ribose or 2-deoxy-D-ribose.
- The carbon atoms of the pentose sugar are denoted by using a prime number to avoid confusion with the carbon atoms of the purine or pyrimidine ring





- All the bases are attached to the corresponding pentose sugar by a beta-N-glycosidic bond between the 1st carbon of the pentose sugar and N9 of a purine or N1 of a pyrimidine

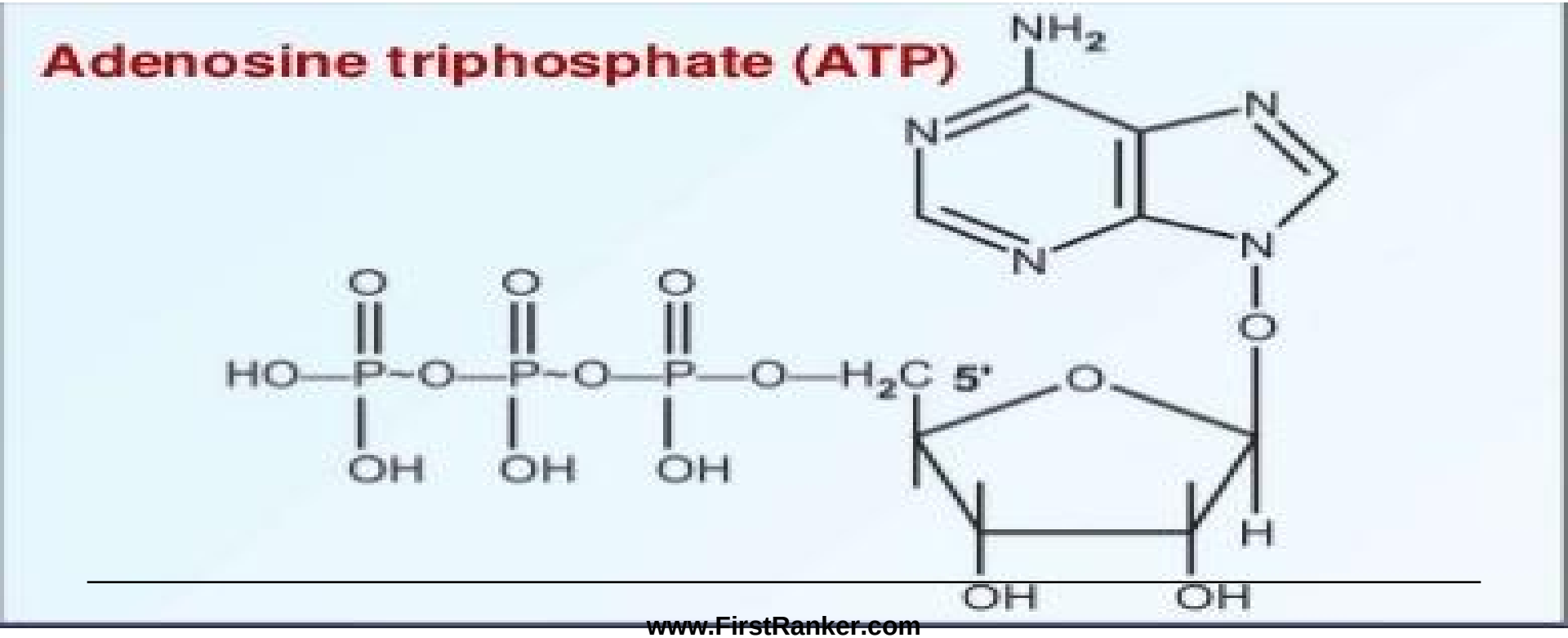
Ribonucleosides		
Adenine + Ribose	→	Adenosine
Guanine + Ribose	→	Guanosine
Uracil + Ribose	→	Uridine
Cytosine + Ribose	→	Cytidine
Hypoxanthine + Ribose	⊢→	Inosine
Xanthine + Ribose	→	Xanthosine
Deoxyribonucleosides		
Adenine + Deoxy ribose	→	Deoxy adenosine (d-adenosine)
Guanine + Deoxy ribose	→	d-guanosine
Cytosine + Deoxy ribose	→	d-cytidine
Thymine + Deoxy ribose	→	d-thymidine

NUCLEOTIDES

- These are phosphate esters of nucleosides.
- Base plus pentose sugar plus phosphoric acid is a nucleotide
- Nucleotides are Polyfunctional Acids
- The phosphoryl groups of nucleosides have pKa - 1.0.
- Bear significant negative charge at physiologic pH
- pKa values of the secondary phosphoryl groups - 6.2
- serve as proton donors or acceptors at pH values approximately two or more units above or below neutrality.

NUCLEOTIDES

- The esterification occurs at the 5th or 3rd hydroxyl group of the pentose sugar.
- Most of the nucleoside phosphates involved in biological function are 5'-phosphates.
- Figure : Structure of ATP



Ribonucleotides		
Adenosine	+ Pi	→Adenosine monophosphate (AMP) (Adenylic acid)
Guanosine	+ Pi	→Guanosine monophosphate (GMP) (Guanylic acid)
Cytidine	+ Pi	→Cytidine monophosphate (CMP) (Cytidylic acid)
Uridine	+ Pi	→Uridine monophosphate (UMP) (Uridylic acid)
Inosine	+ Pi	→Inosine monophosphate (IMP) (Inosinic acid)
Deoxyribonucleotides		
d-adenosine	+ Pi	→d-AMP (d-adenylic acid)
d-guanosine	+ Pi	→d-GMP (d-guanylic acid)
d-cytidine	+ Pi	→d-CMP (d-cytidylic acid)
d-thymidine	+ Pi	→d-TMP (d-thymidylic acid)

NUCLEOTIDES

- Since 5'-nucleotides are more often seen, they are simply written without any prefix.
- For example, 5'-AMP is abbreviated as AMP; but 3' variety is always written as 3'-AMP.
- Many co-enzymes are derivatives of adenosine monophosphate.
- Examples are NAD+, NADP, FAD and Co-enzyme A.

Table Nucleotide and Nucleic Acid Nomenclature

Base	*Nucleoside*	*Nucleotide*	*Nucleic acid*
Purines			
Adenine	Adenosine	Adenylate	RNA
	Deoxyadenosine	Deoxyadenylate	DNA
Guanine	Guanosine	Guanylate	RNA
	Deoxyguanosine	Deoxyguanylate	DNA
Pyrimidines			
Cytosine	Cytidine	Cytidylate	RNA
	Deoxycytidine	Deoxycytidylate	DNA
Thymine	Thymidine or deoxythymidine	Thymidylate or deoxythymidylate	DNA
Uracil	Uridine	Uridylate	RNA

ATP (ADENOSINE TRIPHOSPHATE)

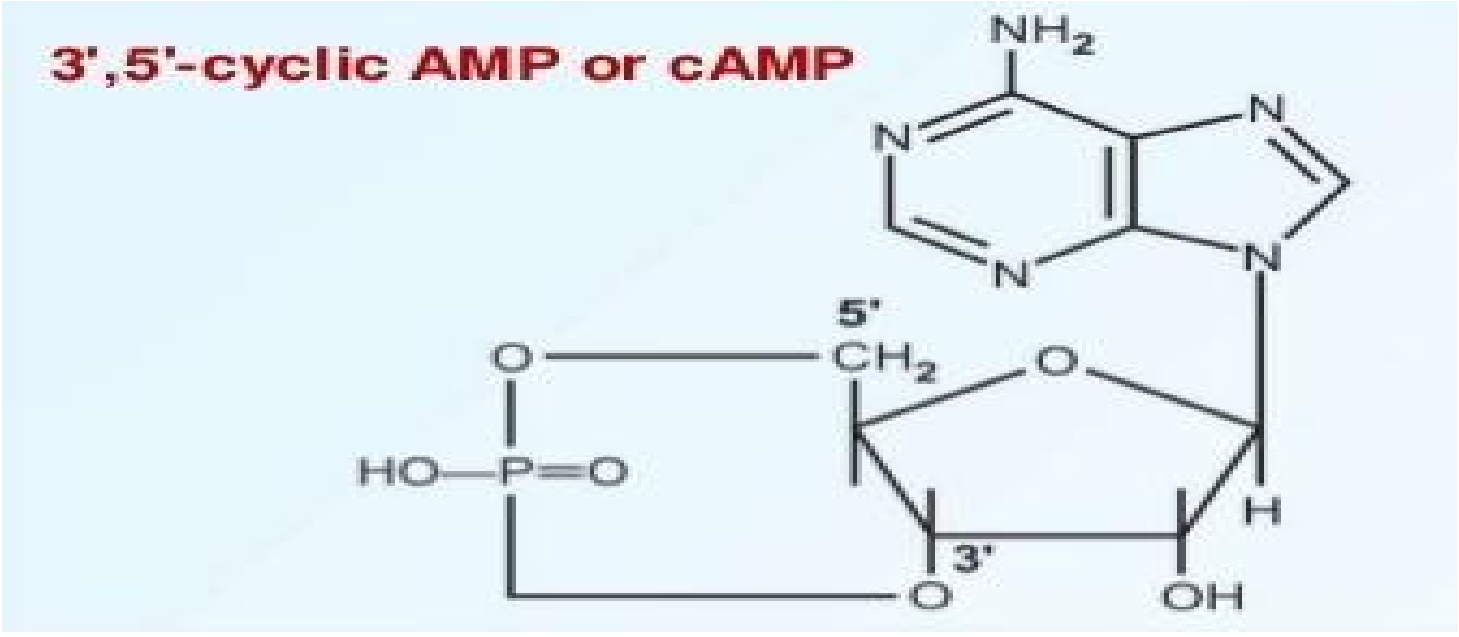
- Many synthetic reactions requires energy, e.g. arginosuccinate synthetase reaction in urea cycle.
- ATP is required for the synthesis of Phospho creatine from creatine, synthesis of FA from acetyl CoA, formation of glucose from pyruvic acid, etc.
- ATP is an important source of energy for muscle contraction, transmission of nerve impulses, transport of nutrients across cell membrane, motility of spermatozoa.
- ATP is required for the formation of active methionine, which is required for methylation reaction
- ATP donates phosphate for a variety of phosphotransferase reactions e.g., hexokinase reaction.

ADENOSINE DI PHOSPHATE (ADP)

- ADP plays an important role as a primary PO4 acceptor in oxidative phosphorylation and muscle contraction, etc
- ADP is also important as an activator of the enzyme glutamate dehydrogenase.

ADENOSINE MONO PHOSPHATE (AMP)

- In the glycolytic pathway, the enzyme phosphofructokinase is inhibited by ATP but the inhibition is reversed byAMP.
- AMP can also act as an inhibitor of certain enzymes like fructose-1-6- bisphosphatase and adenylosuccinate synthetase.
- In resting muscles, AMP is formed from ADP, by adenylate kinase, the AMP produced activates the phosphorylase b enzyme of muscle and increase breakdown of glycogen.



- cAMP act as second messenger for calcitonin, corticotrophin, epinephrine, FSH TSH,LH,MSH etc.
- It enhances glycogenolysis and lipolysis
- Increases acid secretion from gastric mucosa
- Dispersion of melanin pigment
- Aggregation of platelets

ADENOSINE 3'-PHOSPHATE-5'-PHOSPHOSULFATE (PAPS)

- sulfate donor for sulfated proteoglycans and for sulfate conjugates of drugs;

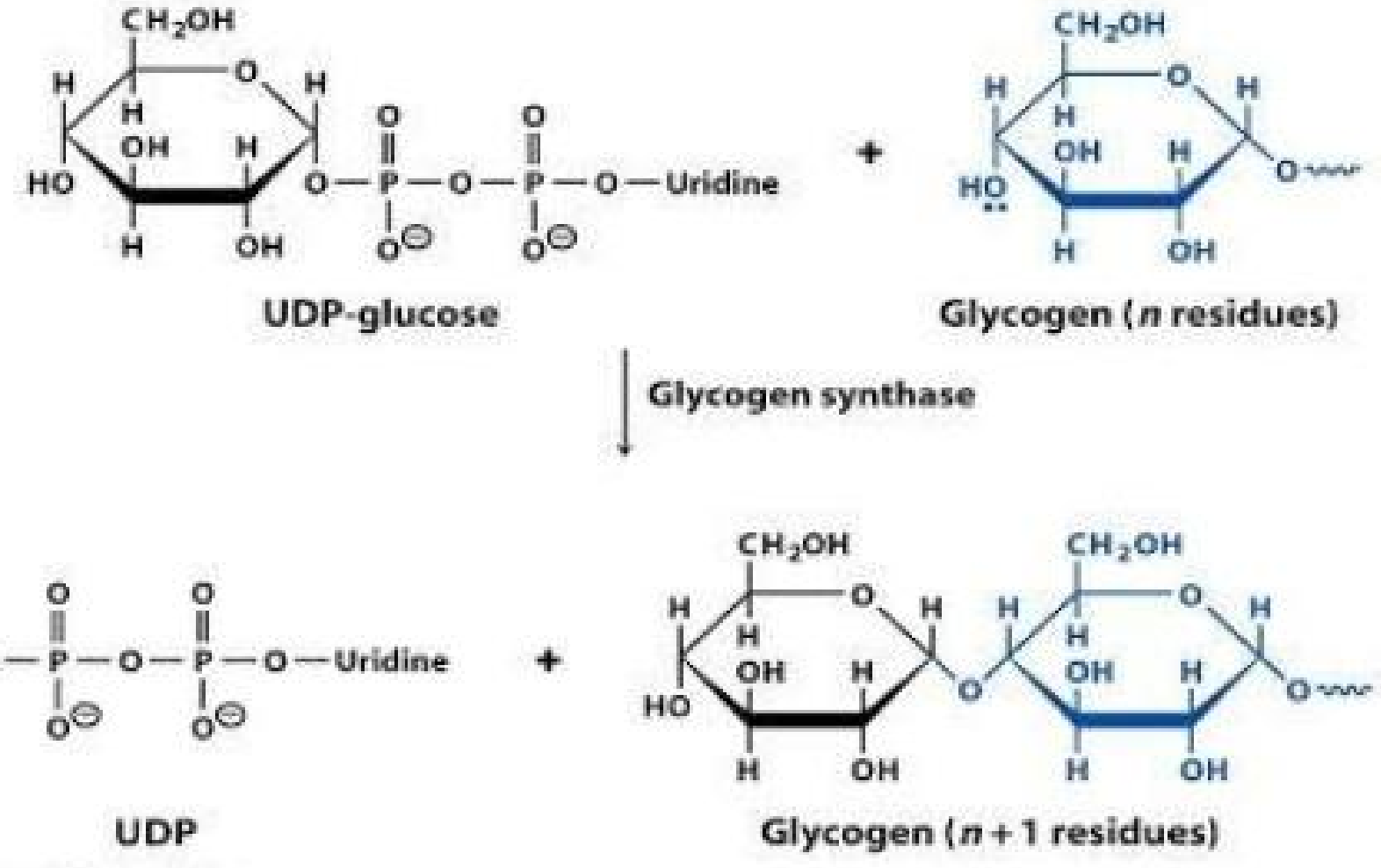
S- ADENOSYLMETHIONINE (SAM)–

METHYL DONAR

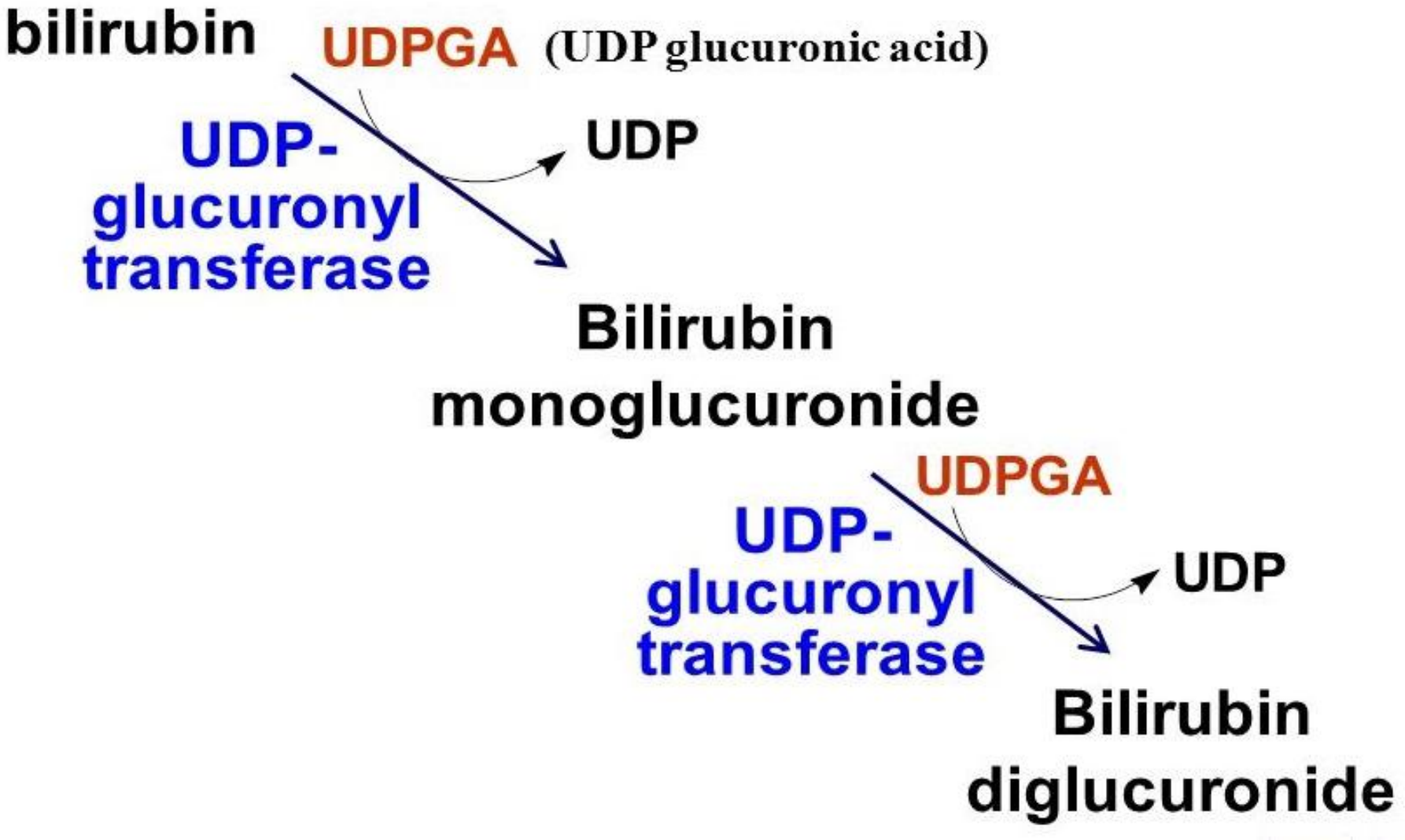
URIDINE NUCLEOTIDES

- UTP also has the role of a source of energy or an activator of substrates in metabolic reactions, like that of ATP, but more specific.
- When UTP activates a substrate, UDP-substrate is usually formed and inorganic phosphate is released. UDP-glucose enters the synthesis of glycogen.
- UTP is used in the metabolism of galactose, where the activated form UDP-galactose is converted to UDP-glucose
- UDP-glucuronate is used to conjugate bilirubin to a more water-soluble bilirubin diglucuronide

UDP ROLE IN GLYCOGEN SYNTHESIS



CONJUGATION OF BILIRUBIN



CYTIDINE NUCLEOTIDES

- CDP- choline, CDP-glycerol and CDP ethanolamine are involved in the biosynthesis of phospholipids
- CMP-acetyl neuraminic acid is an important precursor of cell-wall polysaccharides in bacteria.

C GMP

- c-GMP is second messenger in photo transduction in the eyes.
- It has been claimed that c-GMP as second messengers regulate the closing and opening of **Na+ channels**. In the dark there are high levels of c-GMP which bind to Na+ channels causing them to open. Reverse occur in light.
- cGMP serves as a second messenger in response to nitric oxide (NO) during relaxation of smooth muscle

INOSINE MONOPHOPHATE

- Hypoxanthine ribonulcleotide, usually called IMP is a precursor of all purine nucleotide synthesized de-novo
- Inosinate can also be formed by deamination of AMP, a reaction which occurs particularly in muscles as a part of purine nucleotide cycle.

SYNTHETIC ANALOGUES OF BIOMEDICAL IMPORTANCE

- Synthetic analogues of nucleobases, nucleosides and nucleotides are recently of wide use in medical sciences and clinical medicine.
- The heterocyclic ring structure or the sugar moiety is altered in such a way as to induce toxic effects when the analogues get incorporated into cellular constituents of the body.

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- Toxic effects reflect either inhibition of enzymes essential for nucleic acid synthesis or their incorporation into nucleic acids with resulting disruption of base-pairing

APPLICATIONS

6- thio- guanine and 6 mercaptopurine ⟶ Structural analogues of inosine and guanine

5-FU and 5-Iodouracil ⟶ Thymine or thymidine analogues

used in cancer chemotherapy

Azapurine, Azacytidine, 8 Azaguanine – cancer chemothearpy

Allopurinol- inhibitor of xanthinine oxidase, used in hyperuricemia and gout

Cytarabine (Arabinose replaces ribose)

Vidarabine – nucleoside analogue

cancer chemothearpy and viral infection

Azathiopurine catabolized to 6-mercaptopurine ⟶ organ transplantation

5 iodo deoxy uridine ⟶ herpes keratitis

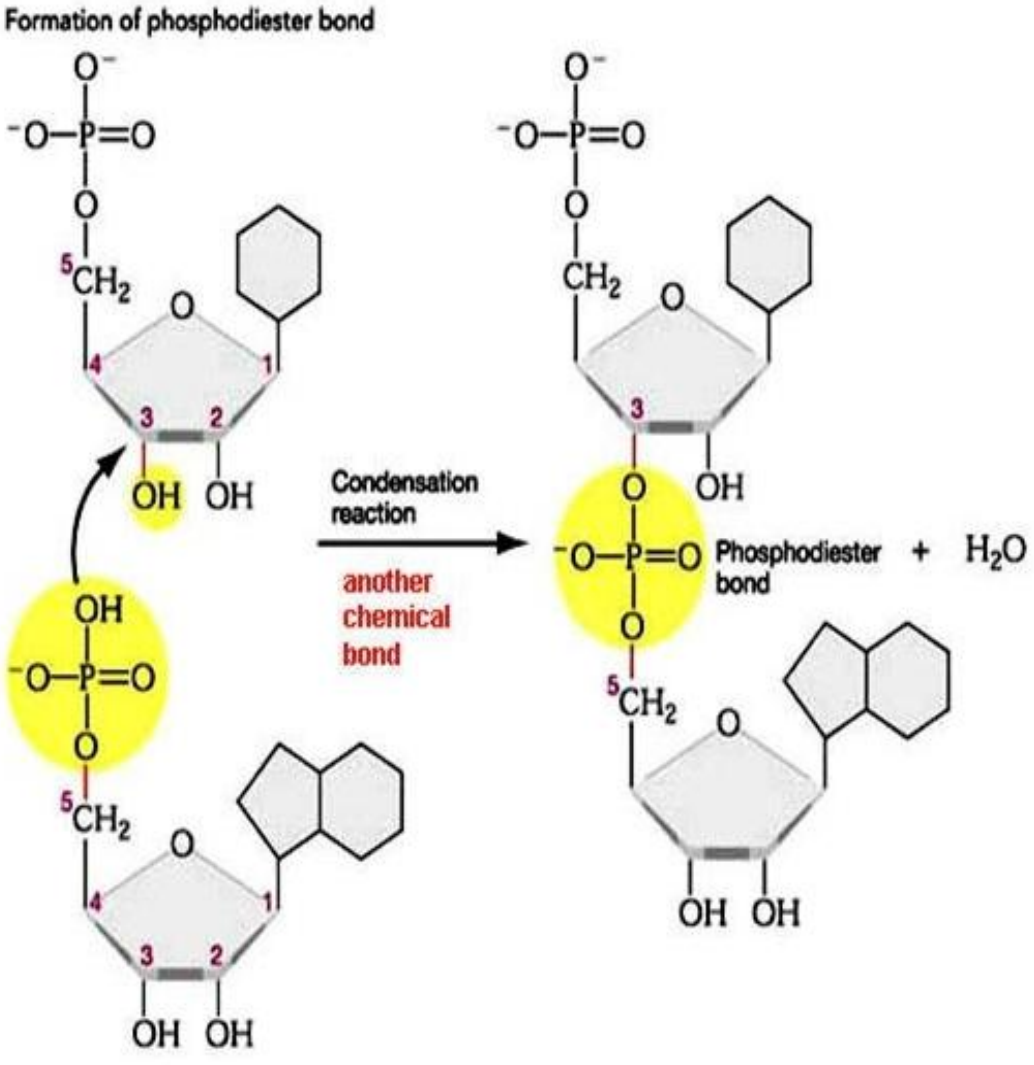
Aminophylline and theophylline- ⟶ ↑ CAMP levels, Used as bronchodilators

Acyclovir – guanosine attached to incomplete ribose ⟶ herpes simplex

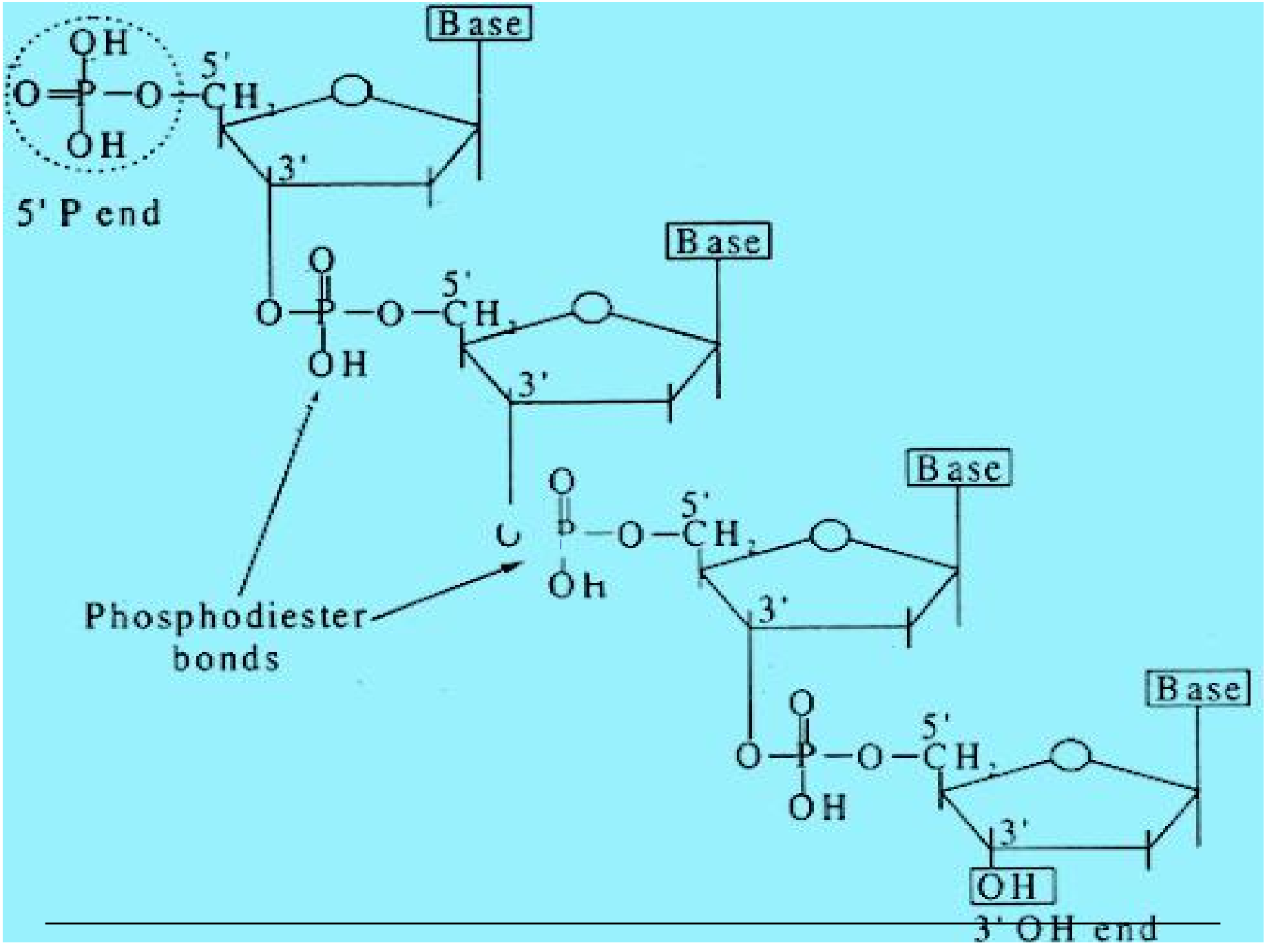
POLYNUCLEOTIDES

- The 5′-phosphoryl group of a mononucleotide can esterify a second -OH group, forming a phosphodiester.
- The second -OH group is the 3′-OH of the pentose of a second nucleotide.
- This forms a dinucleotide in which the pentose moieties are linked by a 3′ → 5′ phosphodiester bond to form the "backbone" of RNA and DNA.

Phosphodiester Bond



- Links nucleotides together
- Sugar and phosphate involved
- This example is a 3’-5’ bond
- Gives two distinct ends



- Phosphodiesterases rapidly catalyze the hydrolysis of phosphodiester bonds whose spontaneous hydrolysis is an extremely slow process. Consequently, DNA persists for considerable periods and has been detected even in fossils.

WHY UV RAYS ARE MUTAGENIC?

- Nucleotides and nucleic acids absorb light at a wavelength of 260 nm; this aspect is used to quantitate them.
- As nucleic acids absorb ultraviolet light, chemical modifications are produced leading to mutation and carcinogenesis.