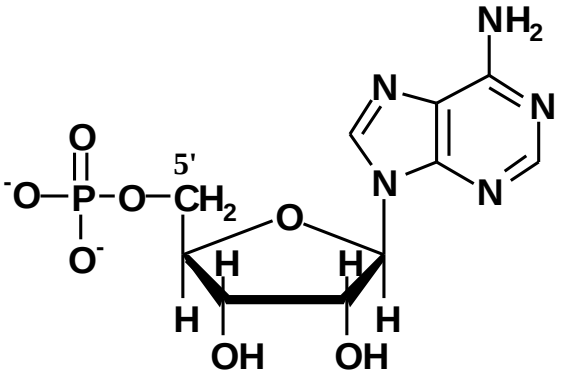
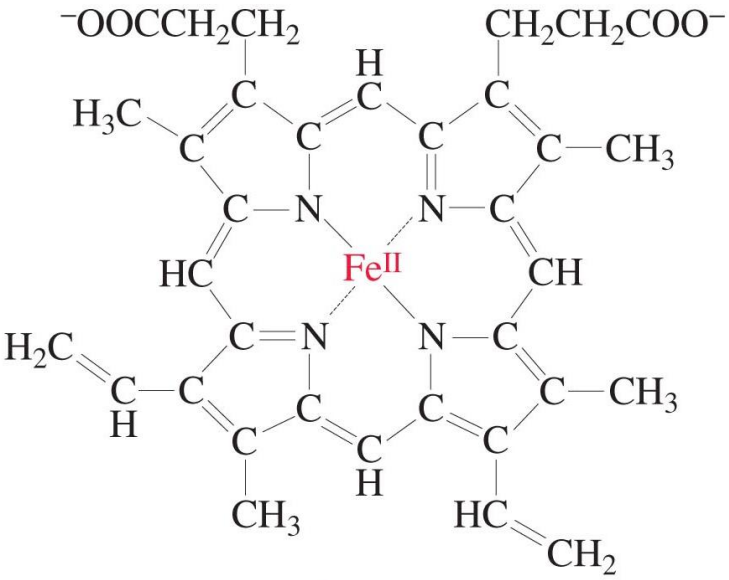


Lecture 6. Heterocyclic compounds. Nucleotides, nucleosides, nucleic acids.

Lecturer

Yanovska Anna Olexandrivna



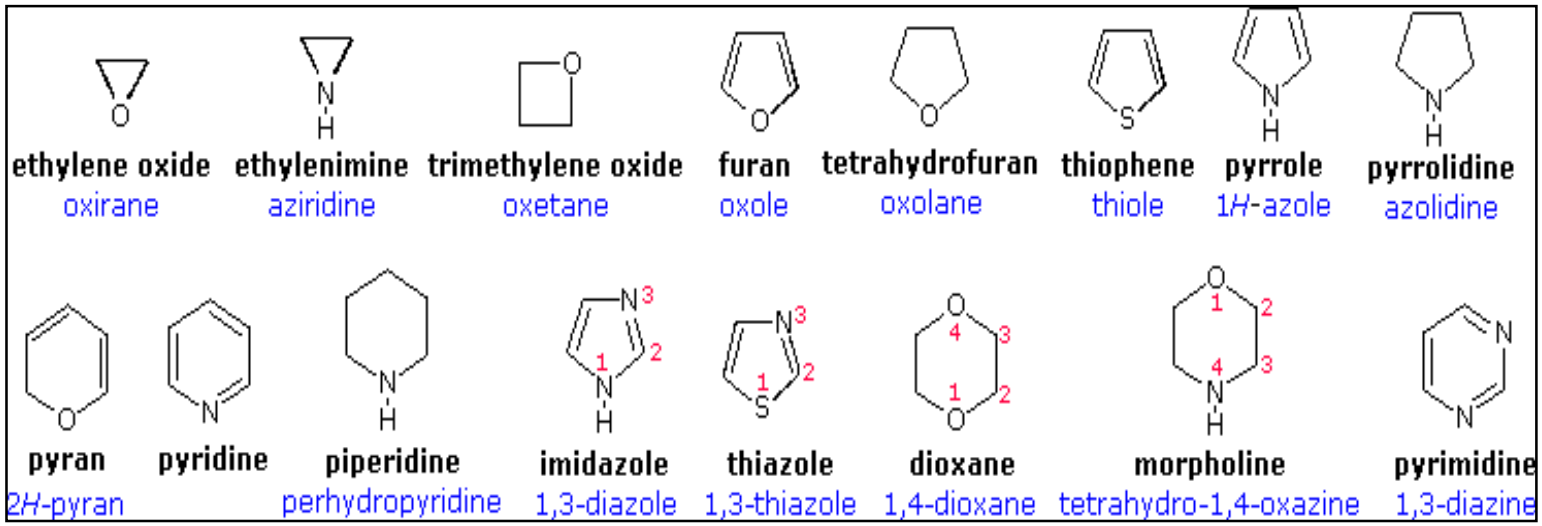
heme

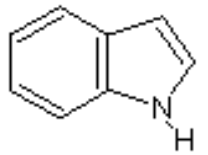
Heterocyclic compound

‘**Any of a class of organic compounds whose molecules contain one or more rings of atoms with at least one atom (the heteroatom) being an element other than carbon, most frequently oxygen, nitrogen, or sulfur**. Heterocyclic compounds include many of the biochemical material essential to life. For example, nucleic acids, the chemical substances that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together. Many naturally occurring pigments, vitamins, and antibiotics are heterocyclic compounds.

In general :

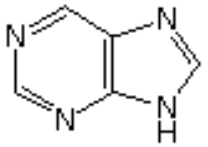
heterocyclic is the largest and most varied family of organic compounds, heterocyclic system can be 3, 4, 5, 6, 7 membered rings





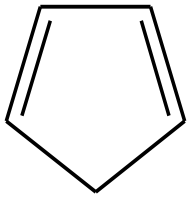
indole

2,3-benzopyrrole

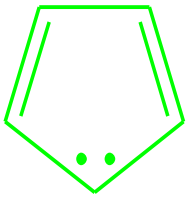


purine

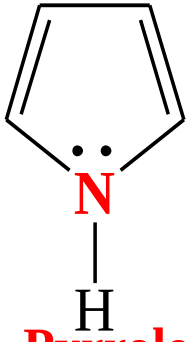
Heterocyclic compounds with one heteroatom
or
Five membered heterocycles



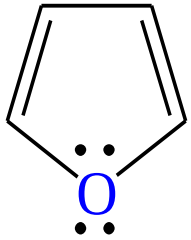
Cyclopentadiene



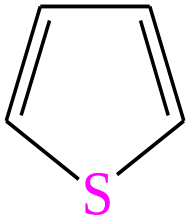
Cyclopentadiene anion



Pyrrole



Furan



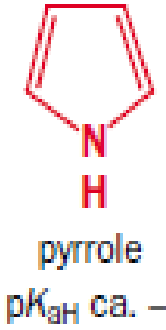
Thiophene

- Pyrrole, furan and thiophene are a five-membered heterocyclic compound, We might expect each of these compounds to have properties of conjugated diene of an amine , an ether or sulphide respectively.

- On this basis pyrrole , furan and thiophene must be considered to be aromatic, this is proved by NMR spectrum

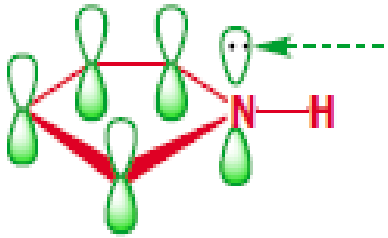
Pyrrole

The delocalization of the lone pair of Pyrrole pushes electrons from the nitrogen atom into the ring and we expect the ring to be electron-rich and become more nucleophile.
Thus, decreased basicity of the nitrogen atom and increased acidity of the NH group as a whole



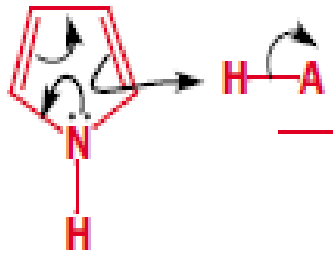
pyrrole

pK_{aH} ca. –4

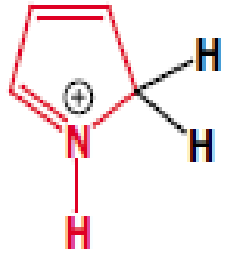


this lone pair is in a p orbital contributing to the 6π electrons in the aromatic ring

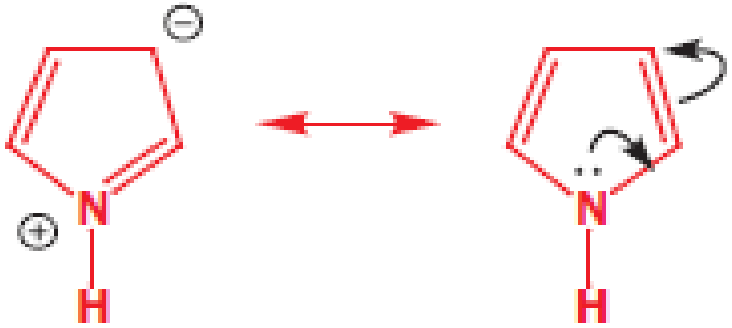
the aromaticity of pyrrole

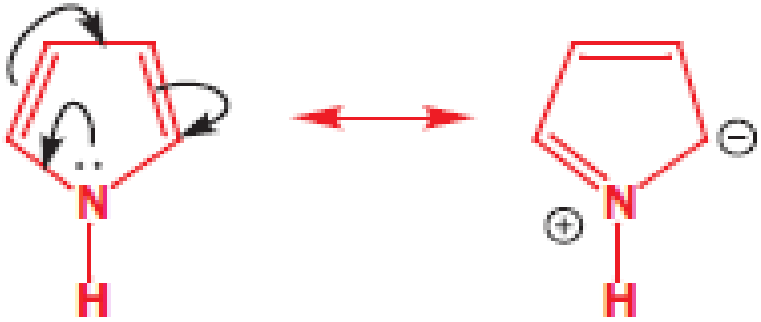


aromatic pyrrole

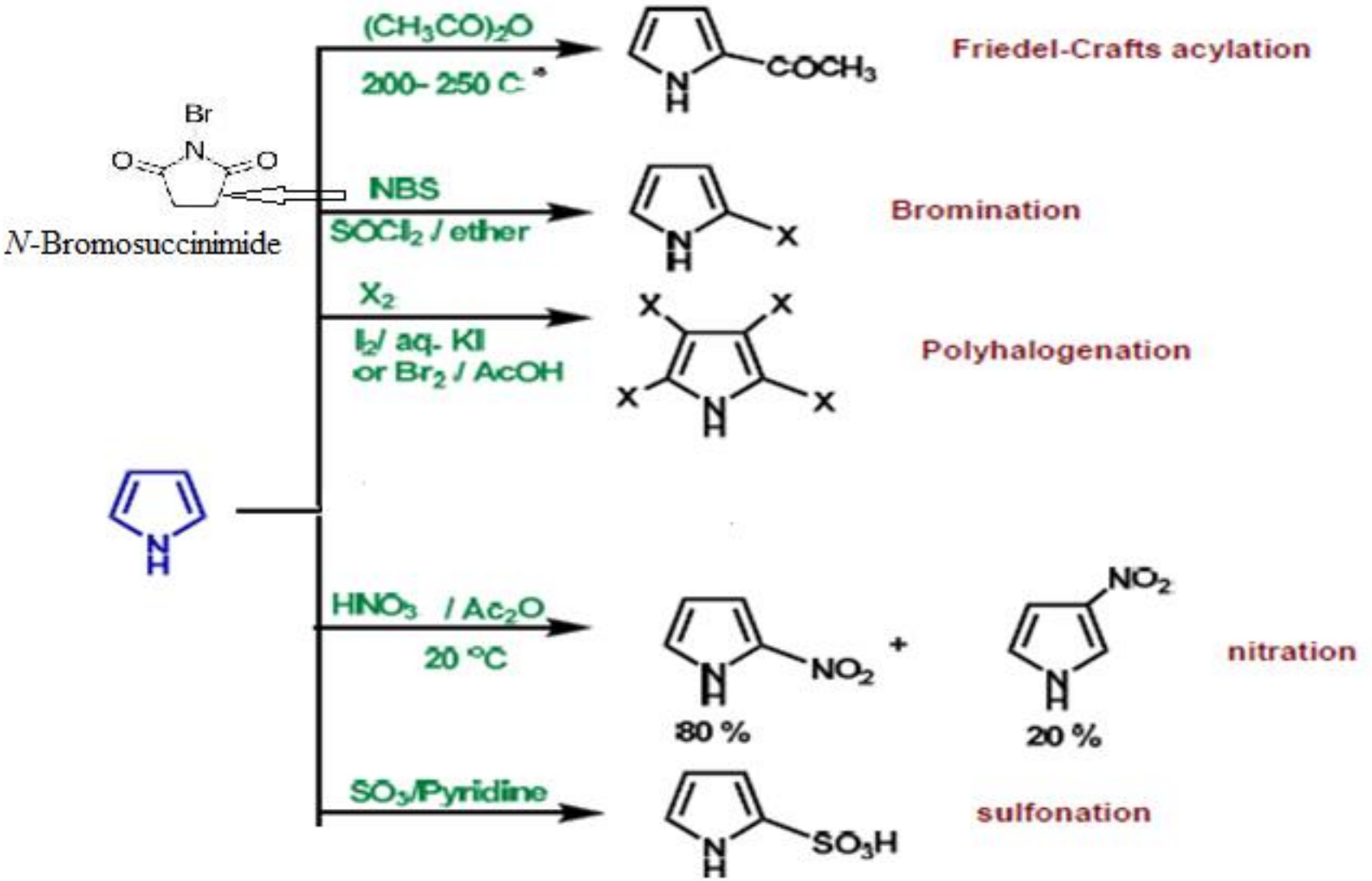


nonaromatic cation

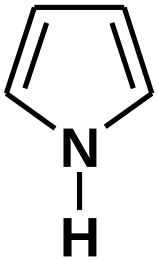




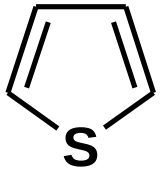
All these aromatic heterocycles react vigorously with chlorine and bromine, often forming polyhalogenated products reaction 3. while reagent *N*-bromosuxcinamide (NBS) give monosubstituted bromine



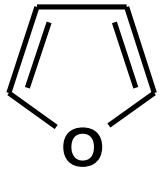
Other Five Membered Heterocycles



Pyrrole



Thiophene



Furan

Least reactive

More aromatic than Furan

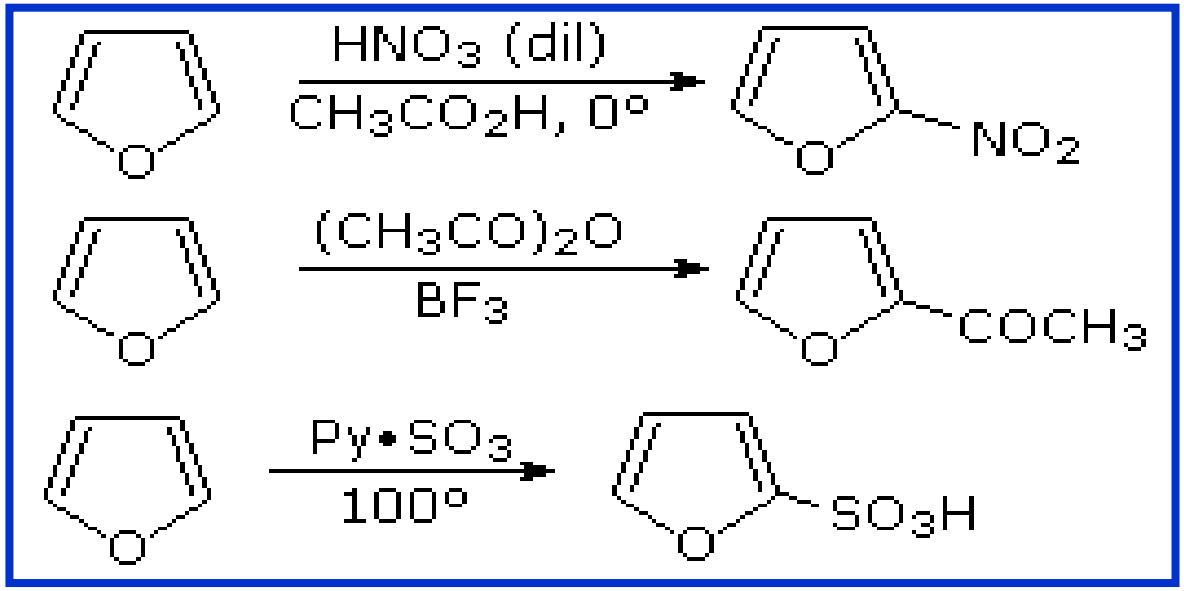
Electrophilic Substitution, not addition

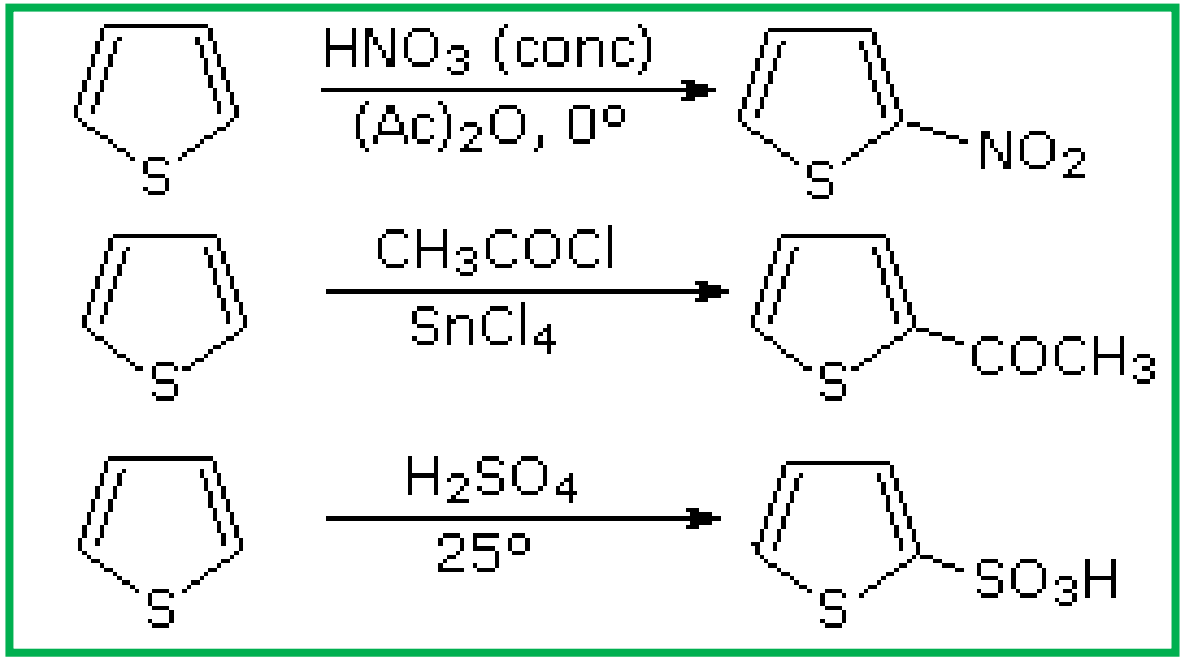
Thiophene has similar reactivity to benzene

The least aromatic:
The O atom is too electronegative

Less reactive than pyrrole, but substitution always at 2-position

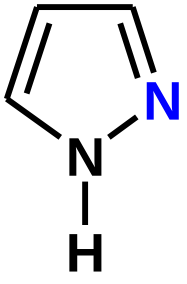
Can give addition, as well as substitution products when reacted with E^+


HNO3 (dil)
CH3CO2H, 0°
NO2
(CH3CO)2O
BF3
COCH3
Py•SO3
100°
SO3H

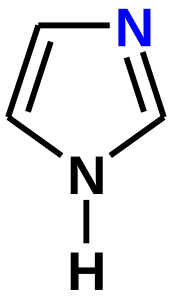

HNO3 (conc)
(Ac)2O, 0°
NO2
CH3COCl
SnCl4
COCH3
H2SO4
25°
SO3H

Five-membered Rings with Two or More Nitrogens

Diazoles



Pyrazole



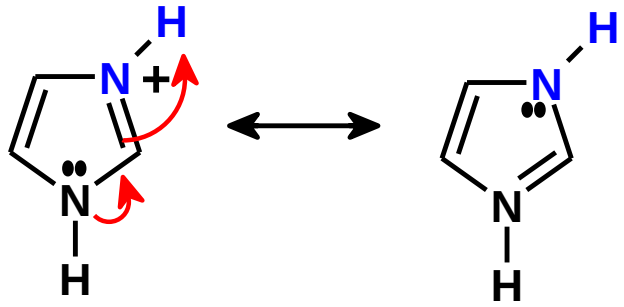
Imidazole

p*K*a = 14.5 (imidazole)

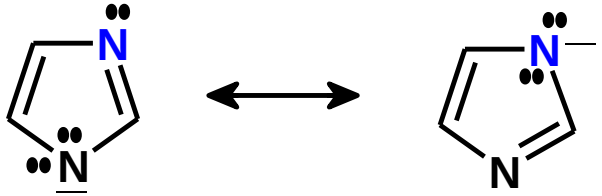
p*K*a = 16.5 (pyrrole)

Imidazole is more basic than pyridine, but more acidic than pyrrole

Imidazole + H^+ ⟶

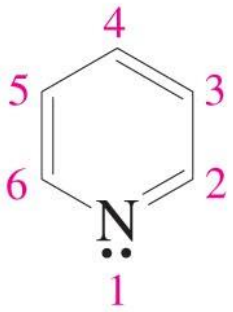


Imidazole - H^+ $\xrightarrow[-\ H_2O]{NaOH}$

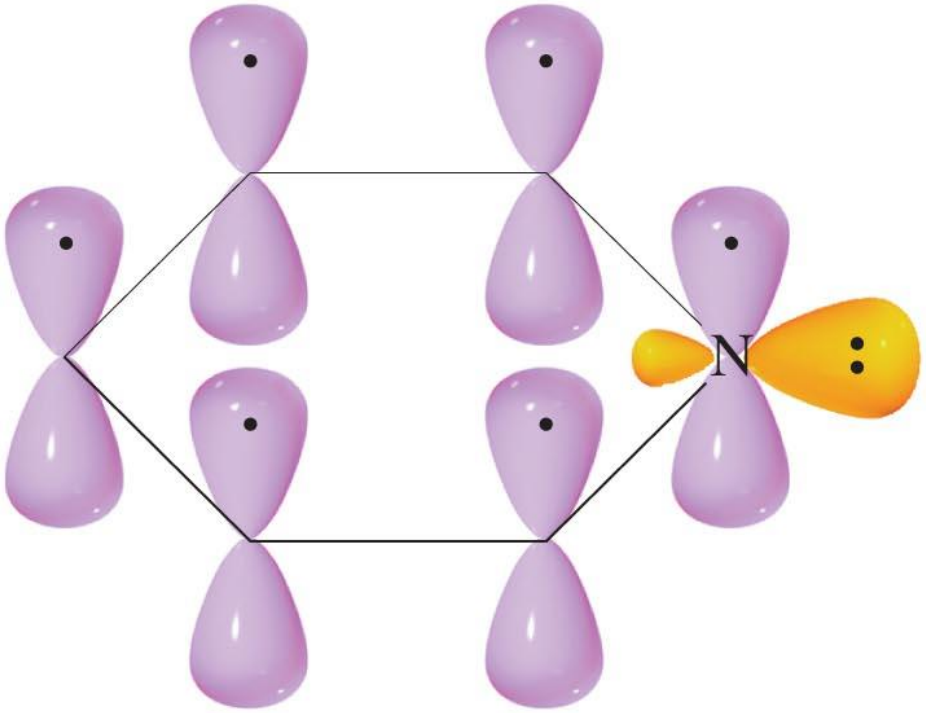


Properties: ***Very stable cation and anion of imidazole is formed***

Aromatic Six-Membered-Ring Heterocycles



pyridine

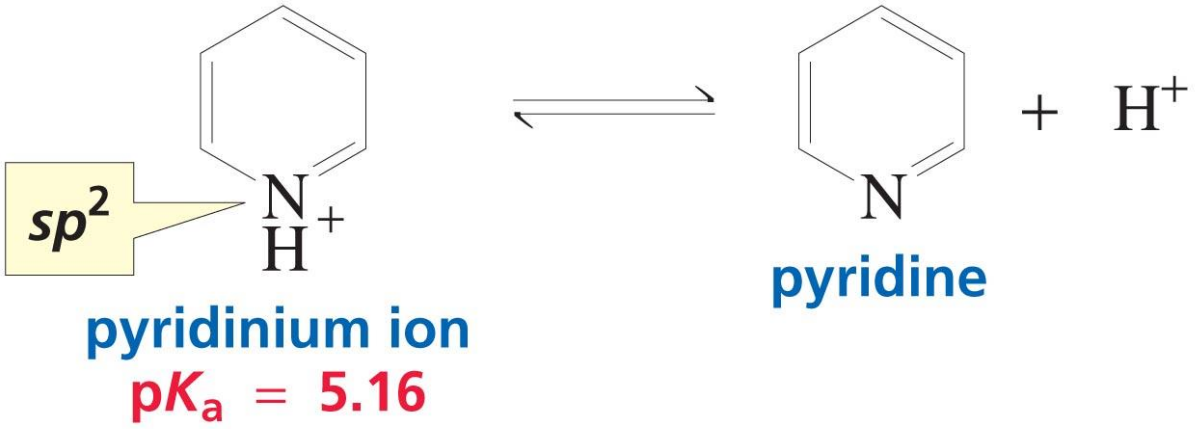


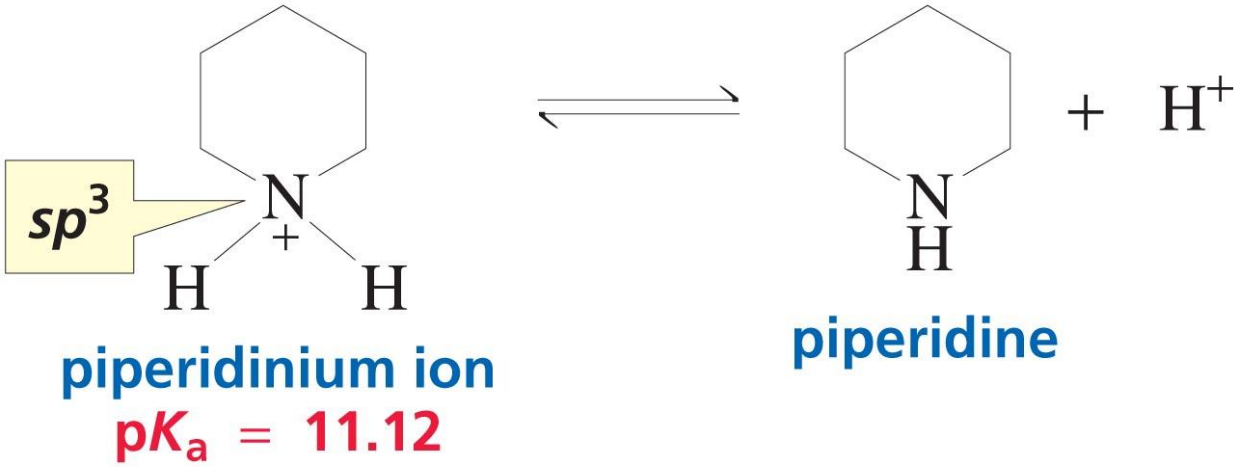
orbital structure of pyridine

these electrons are in an sp^2 orbital perpendicular to the *p* orbitals

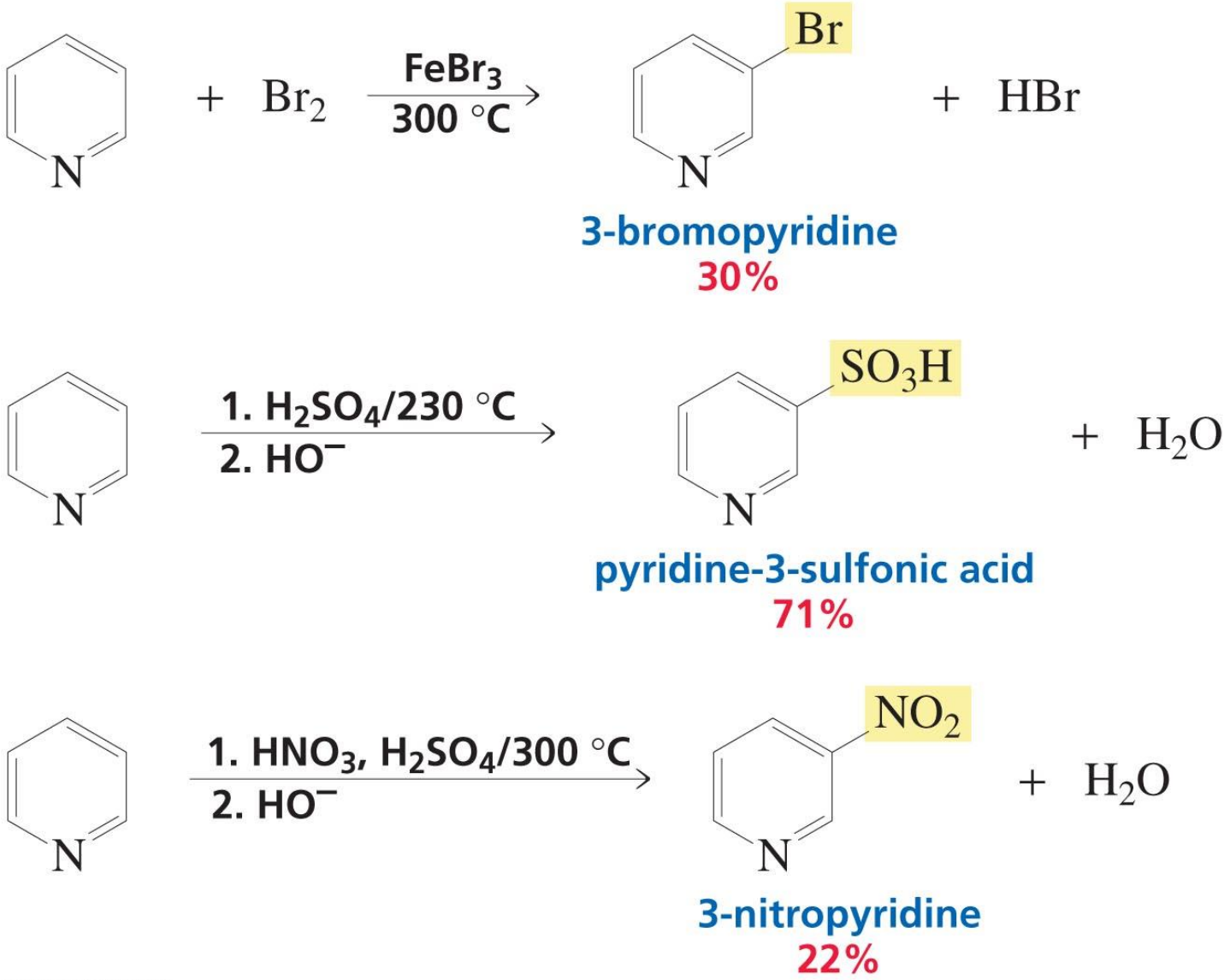
The pyridinium ion is a stronger acid than a typical ammonium ion

Pyridine reacts like a tertiary amine:



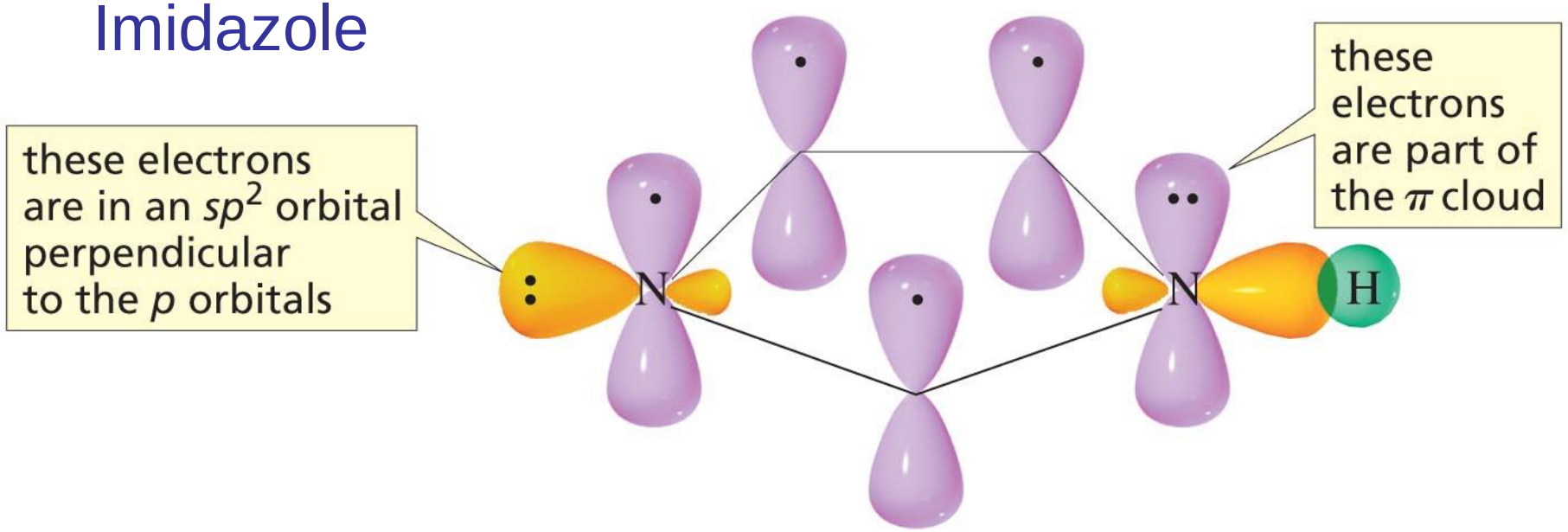


The pyridine nitrogen is a meta director:



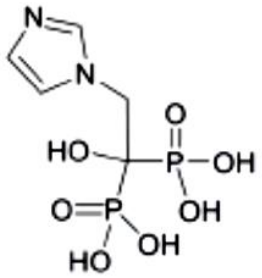
Some Biologically Important Heterocycles

Imidazole



orbital structure of imidazole

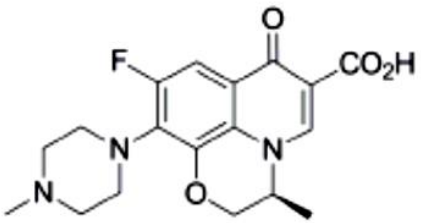
57 **Zometa**
(Zoledronate)



NOVARTIS

$1811 Million
Bone Calcium Regulators

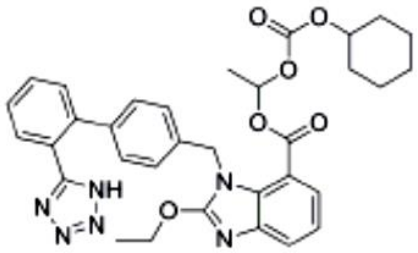
58 **Levaquin**
(Levofloxacin)



Johnson & Johnson

$1743 Million
Fluoro-Quinolones

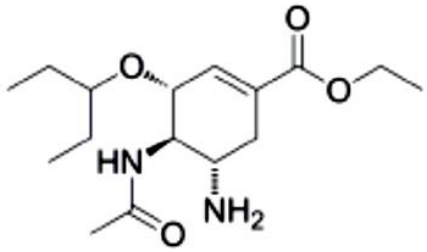
59 **Blopress**
(Candesartan)



Takeda

$1705 Million
Angioten-II Antag, Plain

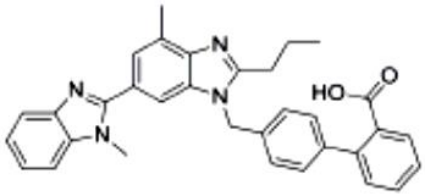
60 **Tamiflu**
(Oseltamivir)



Roche

$1606 Million
Antivirals Excl Anti-HIV

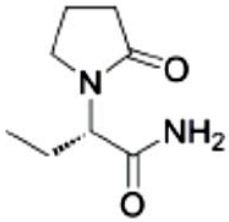
77 **Micardis**
(Telmisartan)



Boehringer Ingelheim

$1422 Million
Angioten-II Antag, Plain

78 **Keppra**
(Levetiracetam)



ucb

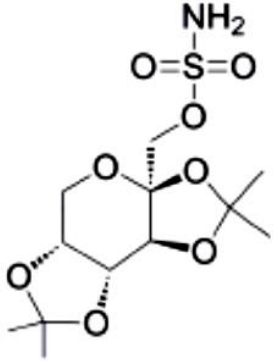
$1406 Million
Anti-Epileptics

79 **Erbitux**
(Cetuximab)

Lilly

$1398 Million
All Oth. Antineoplastics

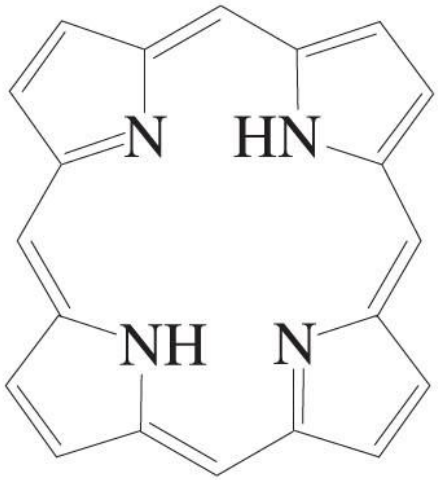
80 **Topamax**
(Topiramate)



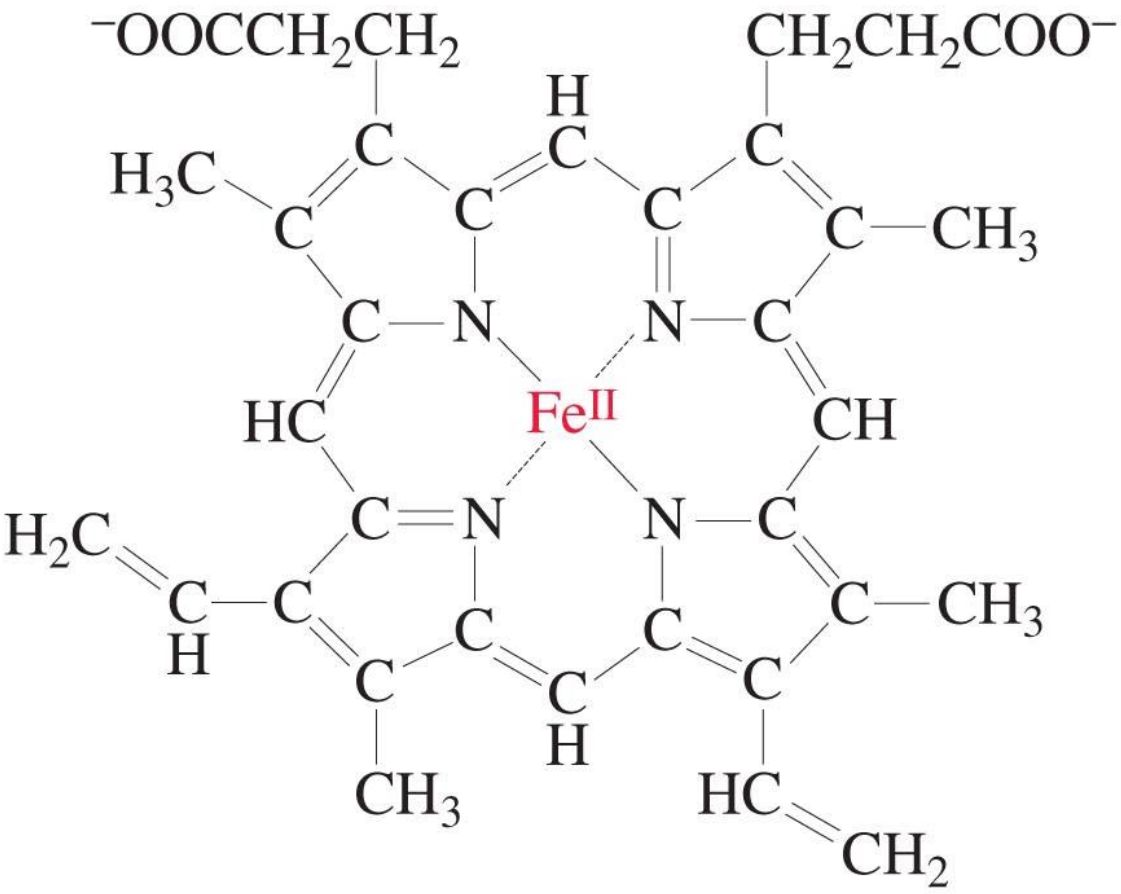
Johnson & Johnson

$1375 Million
Anti-Epileptics

Porphyrin

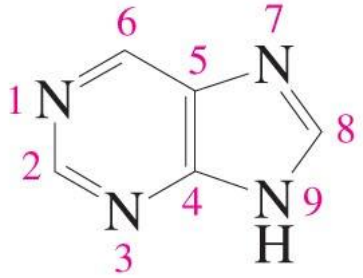


a porphyrin ring system

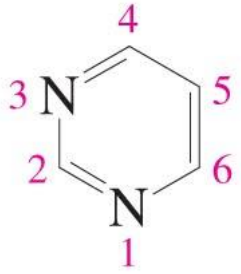


heme

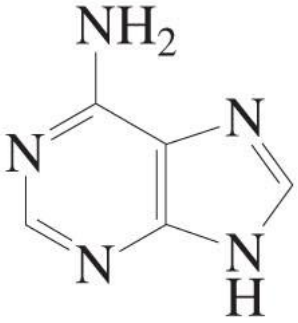
Purine and Pyrimidine



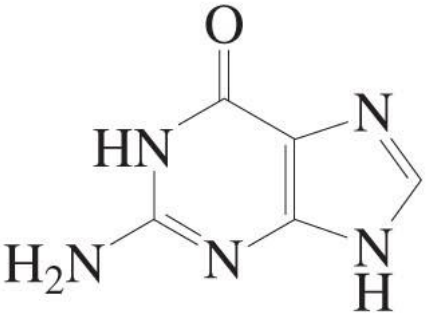
purine



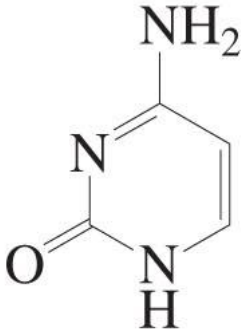
pyrimidine



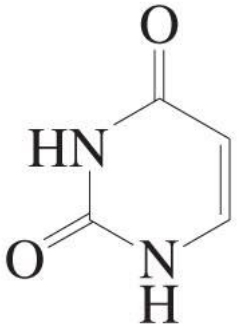
adenine



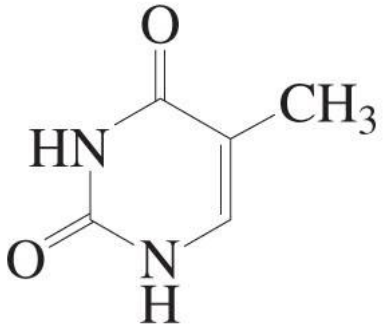
guanine



cytosine



uracil

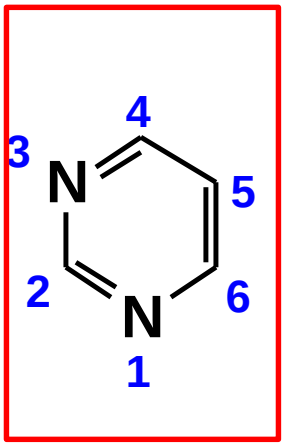


thymine

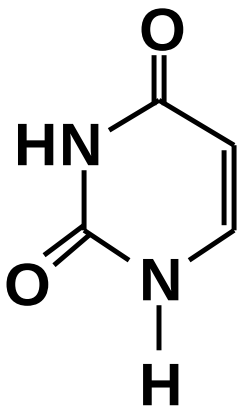
Nucleic Acids Components

- Nucleic acid: A biopolymer containing three types of monomer units.
  - Heterocyclic aromatic amine bases derived from purine and pyrimidine.
  - The monosaccharides D-ribose or 2-deoxy-D-ribose
  - Phosphoric acid.

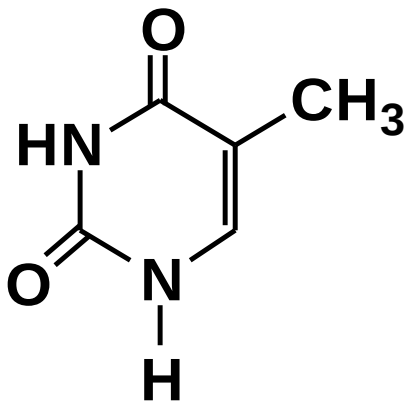
Purine/Pyrimidine Bases



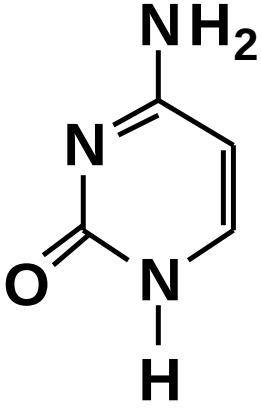
Pyrimidine



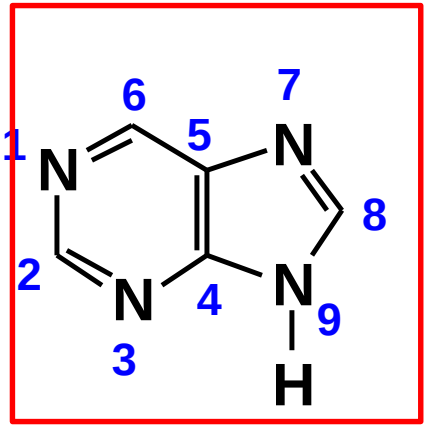
Uracil (U)



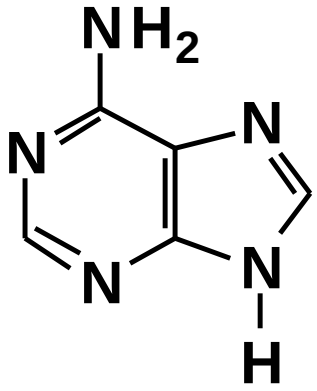
Thymine (T)



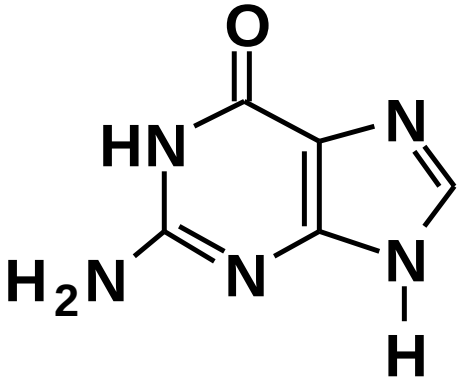
Cytosine (C)



Purine

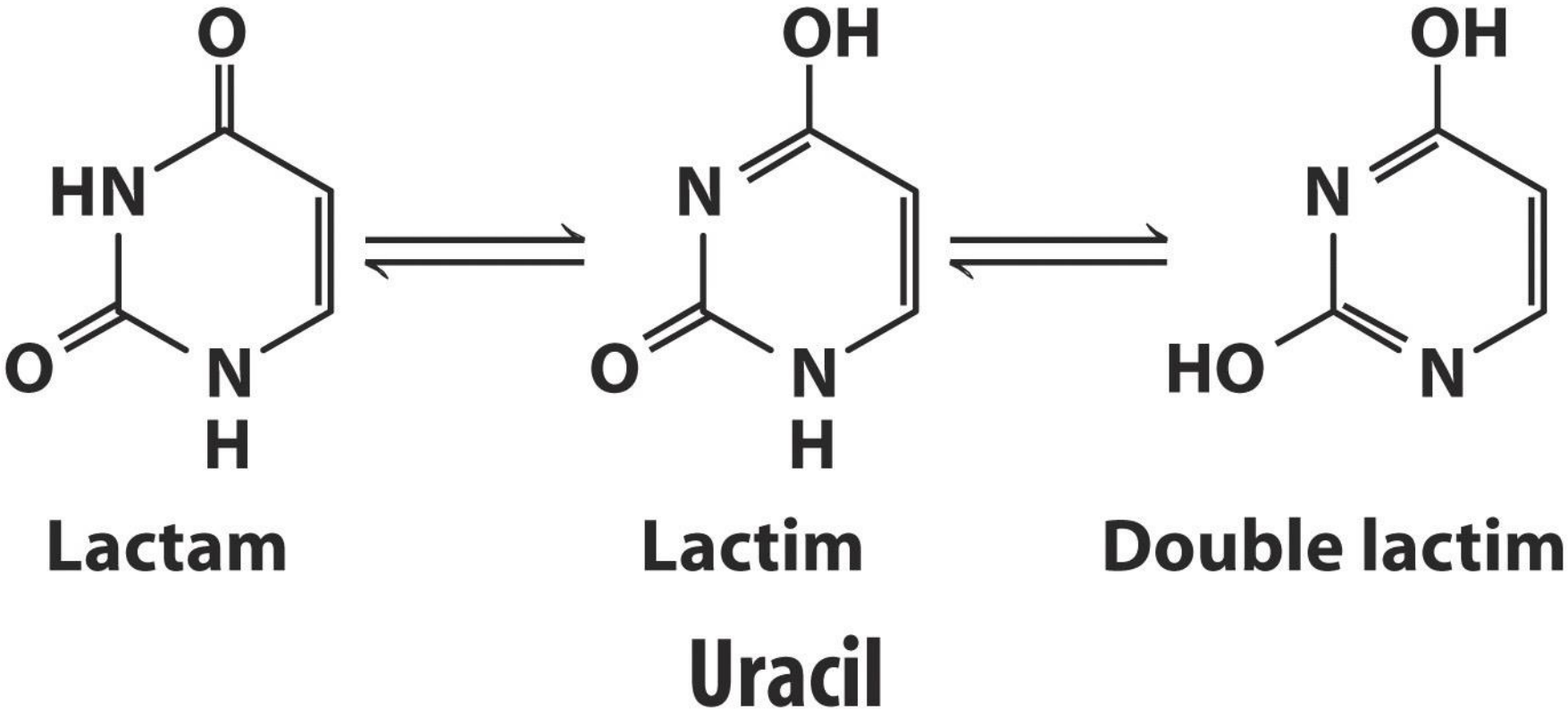


Adenine (A)



Guanine (G)

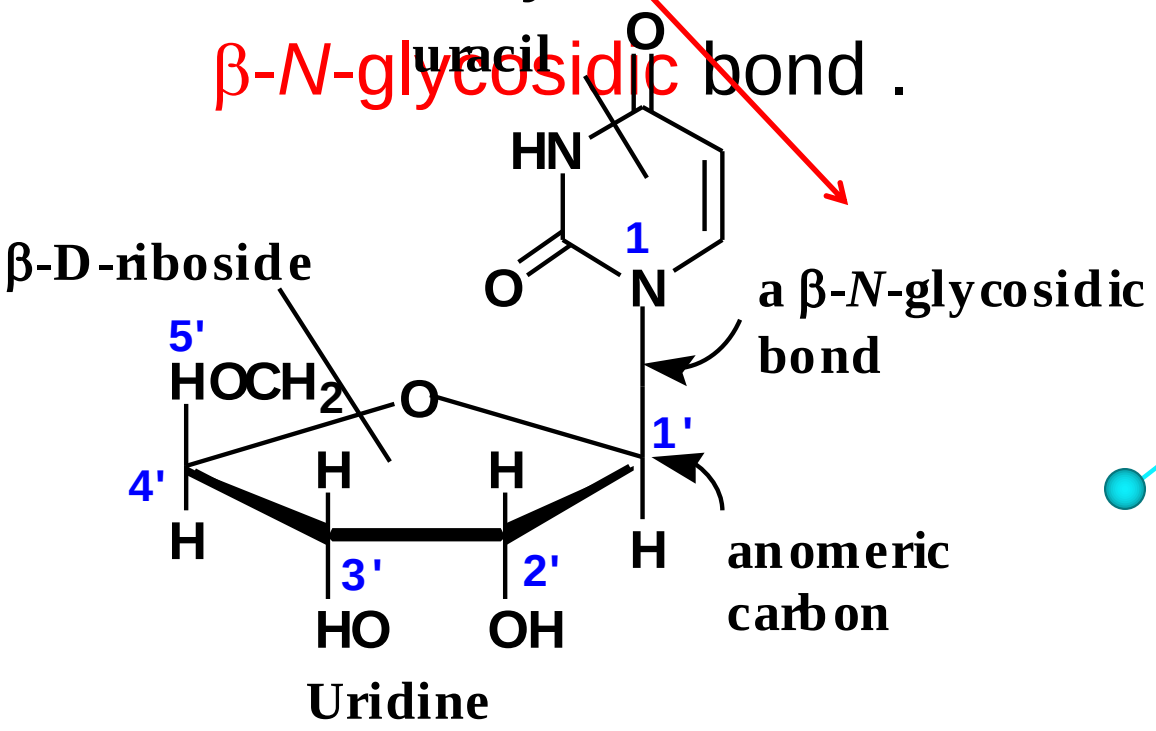
Tautomeric forms of uracil

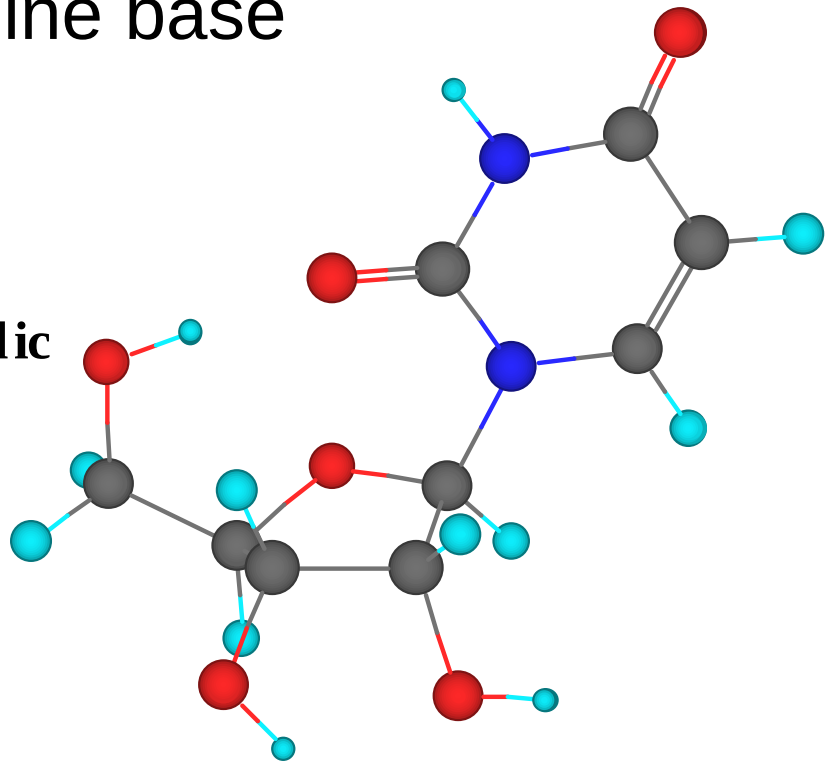


Nucleosides Definition

- Nucleoside: A building block consisting of
  - D-ribose or 2-deoxy-D-ribose
  - heterocyclic aromatic amine base

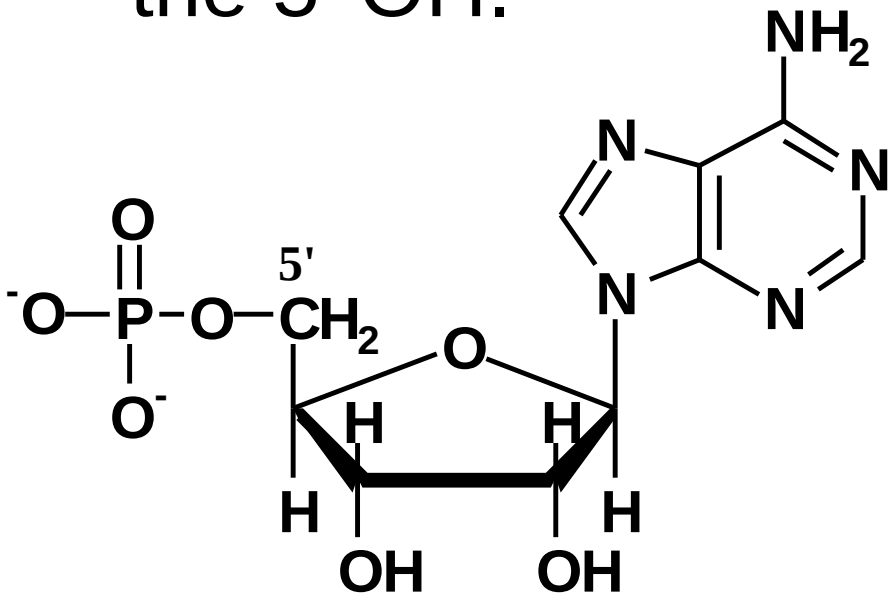
β-*N*-glycosidic bond .



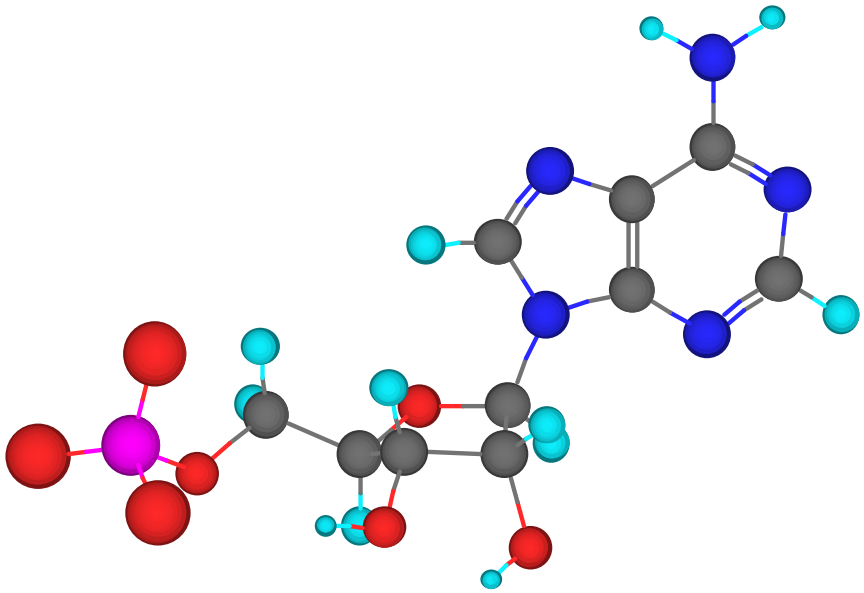


Nucleotides Definition

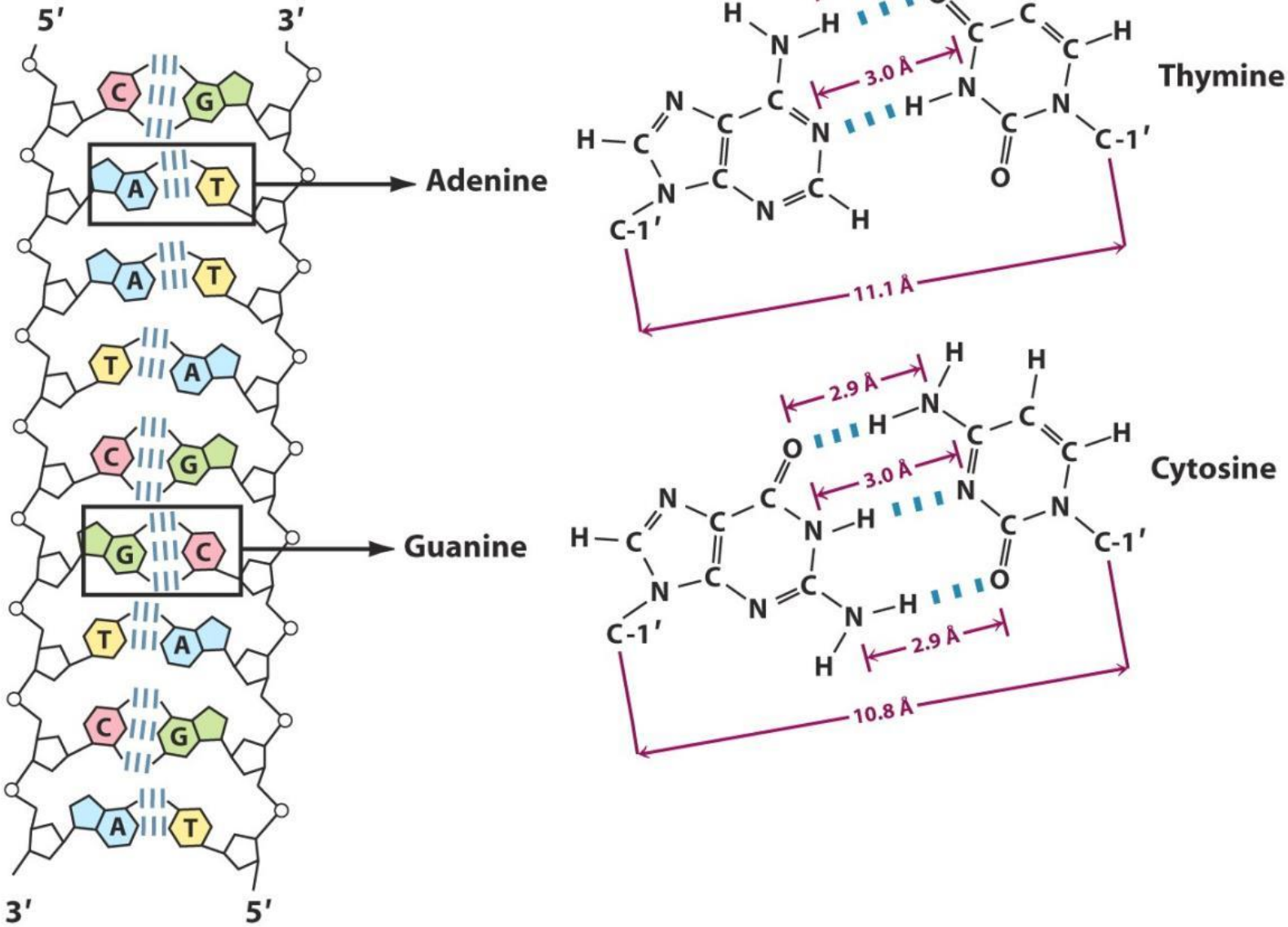
- Nucleotide: Phosphoric acid ester of a nucleoside, most commonly either the 3’ or the 5’ OH.



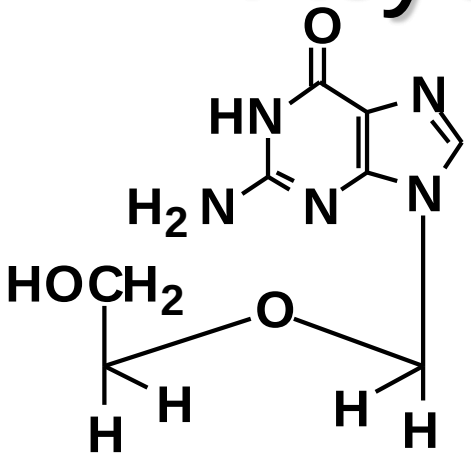
Adenosine 5'-monophosphate (AMP)



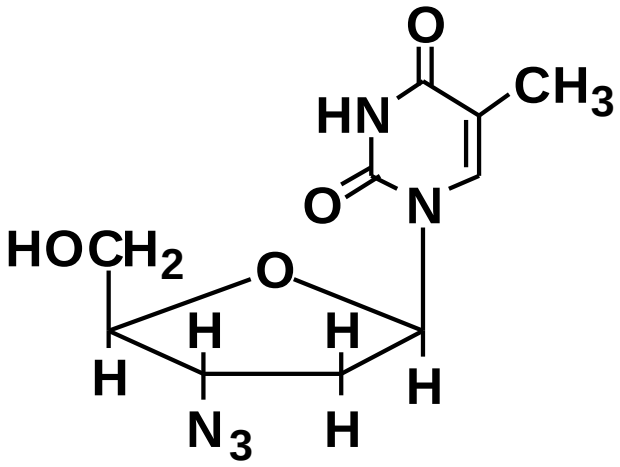
Hydrogen-bonding patterns in the base pairs defined by Watson and Crick



Acyclovir & AZT



Acyclovir
(drawn to show its structural relationship to 2-deoxyguanosine



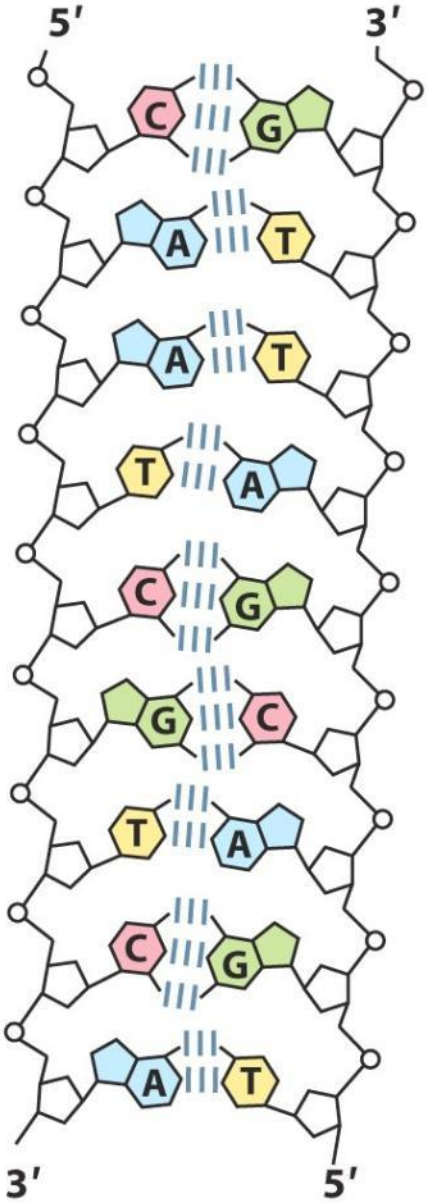
Azidothymidine (AZT)

Used to treat HIV

It is used to treat or prevent infections caused by certain kinds of viruses. Examples of these infections include herpes and shingles

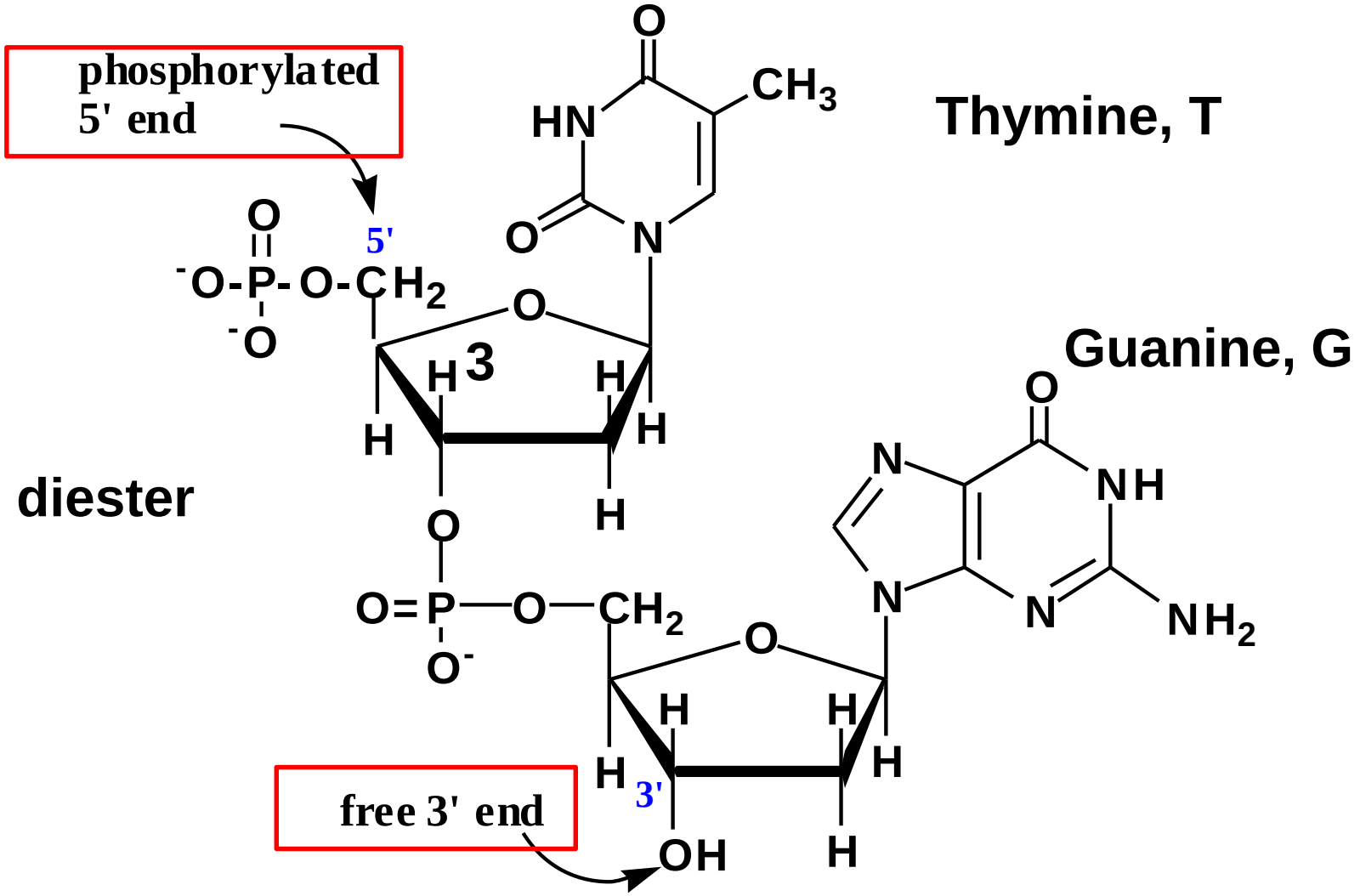
DNA - 1° Structure

- Deoxyribonucleic acids (DNA)
  - A backbone of alternating units of 2-
    ribose and phosphate in which the 3
    one 2-deoxy-D-ribose is joined by a
    phosphodiester bond to the 5'-OH of
    2-deoxy-D-ribose.
- Primary Structure: The sequence of ba
  the pentose-phosphodiester backbone
  molecule (or an RNA molecule).
  - Read from the 5' end to the 3' end.



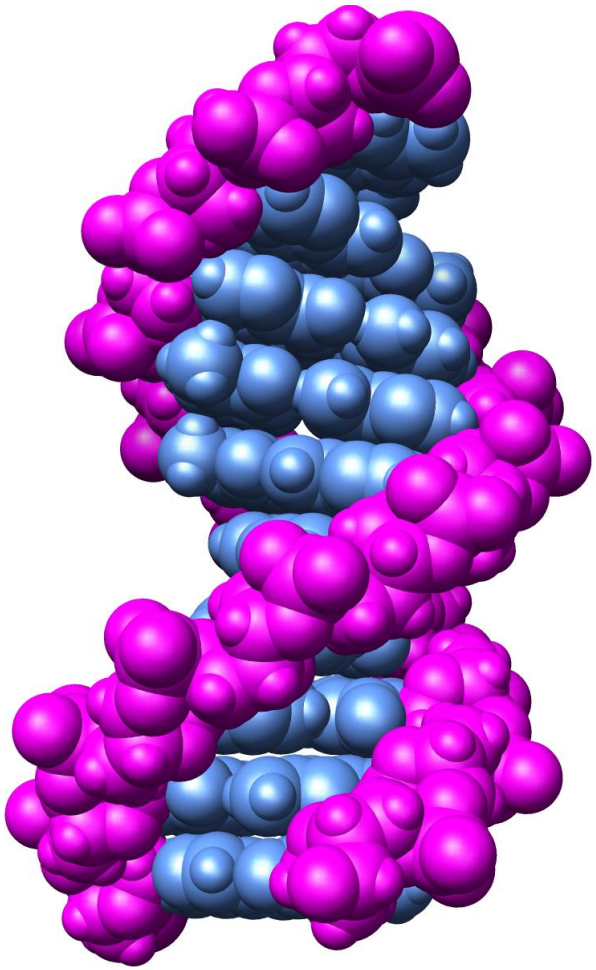
DNA - 1° Structure

– A structural formula for TG phosphorylated at the 5’ end.



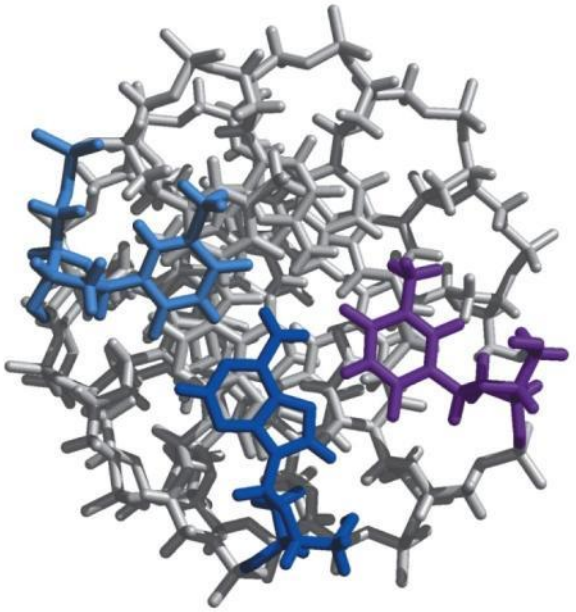
DNA - 2° Structure

- Secondary structure: The orde of nucleic acid strands.
- The double helix model of DNA proposed by James Watson ar 1953.
- Double helix: A type of 2° struc molecules in which two antipar polynucleotide strands are coil handed manner about the sam



DNA - 3° Structure

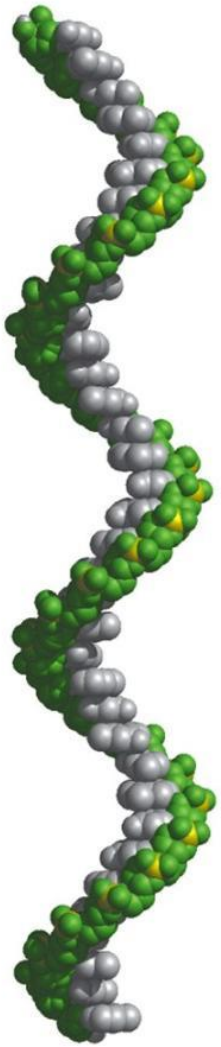
- Tertiary structure: The three-dimensional arrangement of all atoms of a do
DNA, commonly referred as supe
- Circular DNA: A type of double-s
which the 5’ and 3’ ends of each
by phosphodiester bonds.
- Histone: A protein, particularly ric
amino acids lysine and arginine,
associated with DNA molecules.



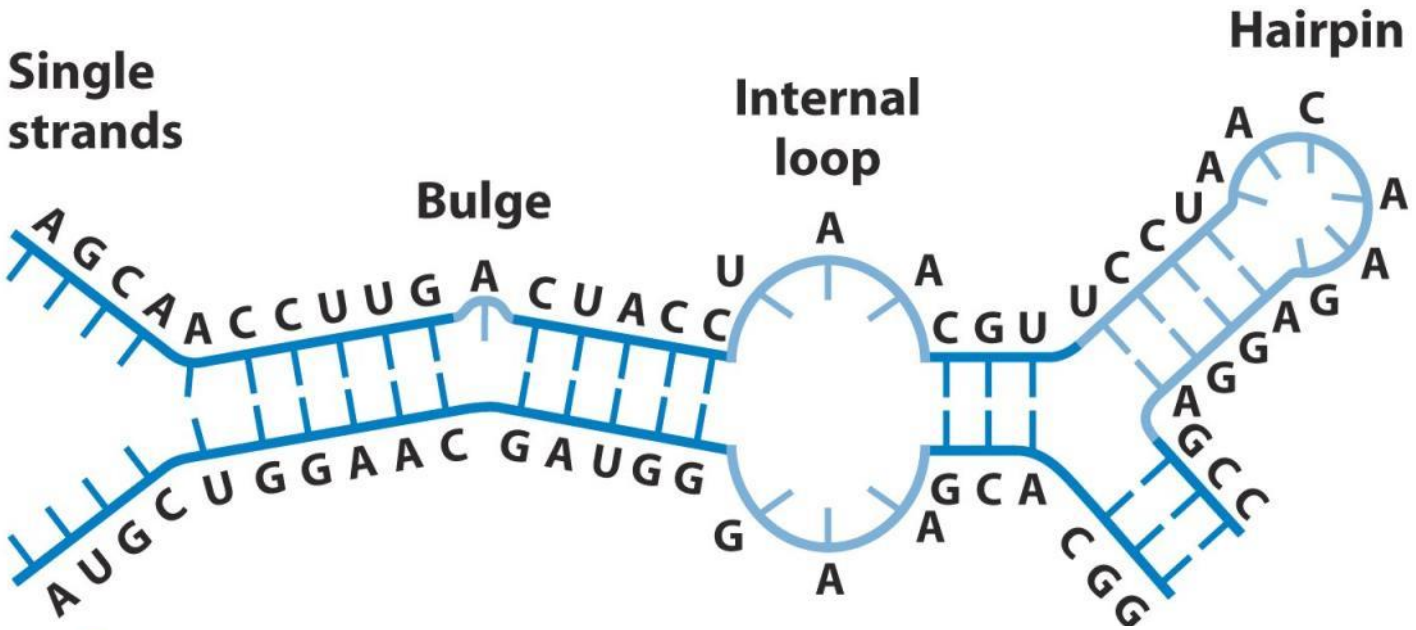
Ribonucleic Acids (R

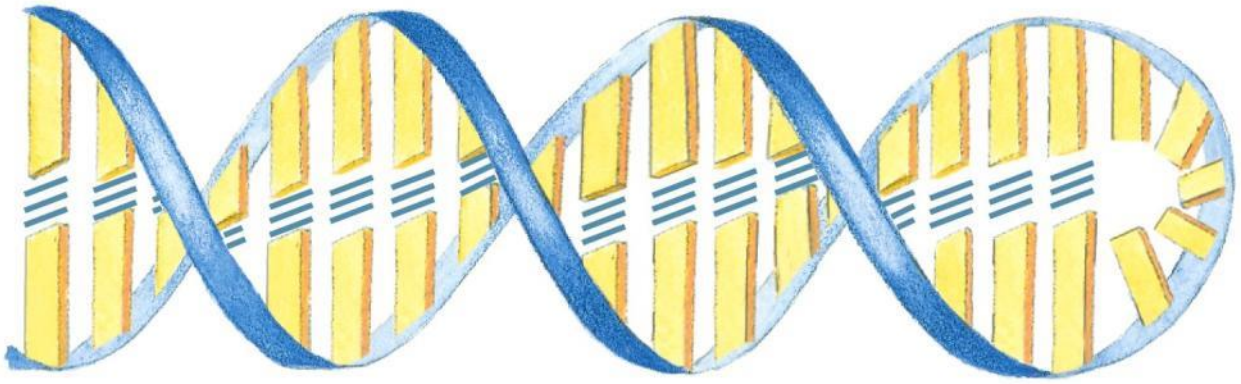
(RNA)
A –Uracil
C –Cytosine

- RNA
  - long, unbranched chains of nucleotides joined by phosphodiester groups between the 3’-OH of one pentose and the 5’-OH of the next;
  - Consists of A, U (Uracil), G, C.
  - the pentose unit in RNA is β-D-ribose rather than β-2-deoxy-D-ribose.
  - the pyrimidine bases in RNA are uracil and cytosine rather than thymine and cytosine.
  - RNA is single stranded rather than double stranded.



Secondary structure of RNAs





Hairpin double helix

Reversible denaturation and annealing (renaturation) of DNA