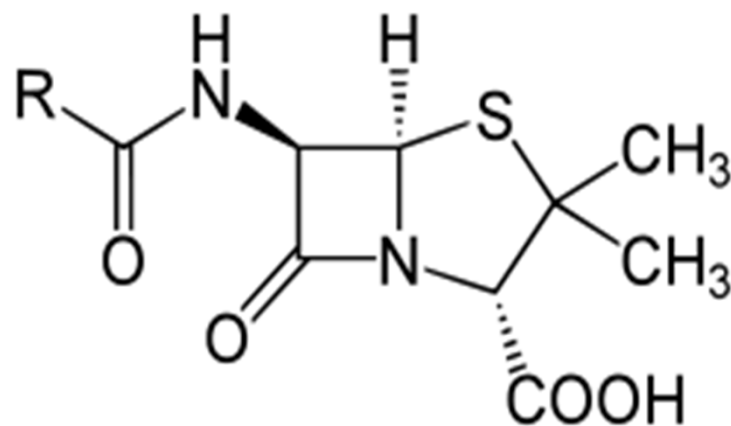


ORGANIC CHEMISTRY III

HETEROCYCLIC COMPOUNDS

BY: DR. MUNTHER A.M.ALI

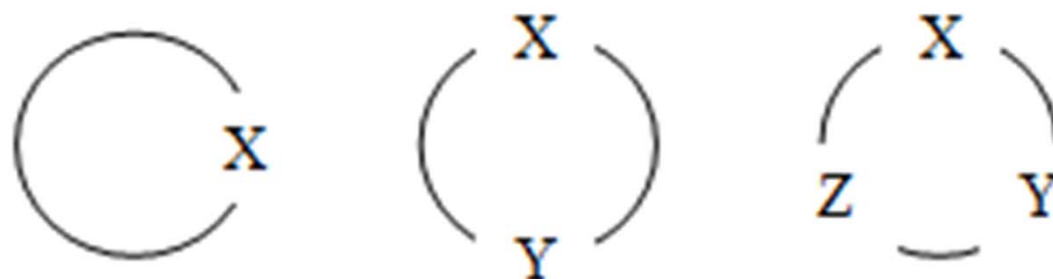


A CYCLIC ORGANIC COMPOUNDS

- **Carbocyclic compounds**, made up by carbon atoms.
- **Heterocyclic compounds**, at least one other atom which usually **N**, **O** or **S**.
- Heterocyclic compounds (H.Cs.) can be classified into: **Saturated**, **unsaturated** and **aromatic** compounds.
- Saturated cyclic analogues of amine, ethers, thioethers, amides, ..etc.
- Aromatic cyclic behave similar to benzene (aromaticity).
- H.Cs. ring may contain more than one hetero atom.
- H.Cs. occur widely in nature and non-naturally occurring compounds. For examples: alkaloids, antibiotics, essential amino acids, the vitamins, hemoglobin, the hormones, and large number of synthetic drugs.



THE GENERAL STRUCTURE:

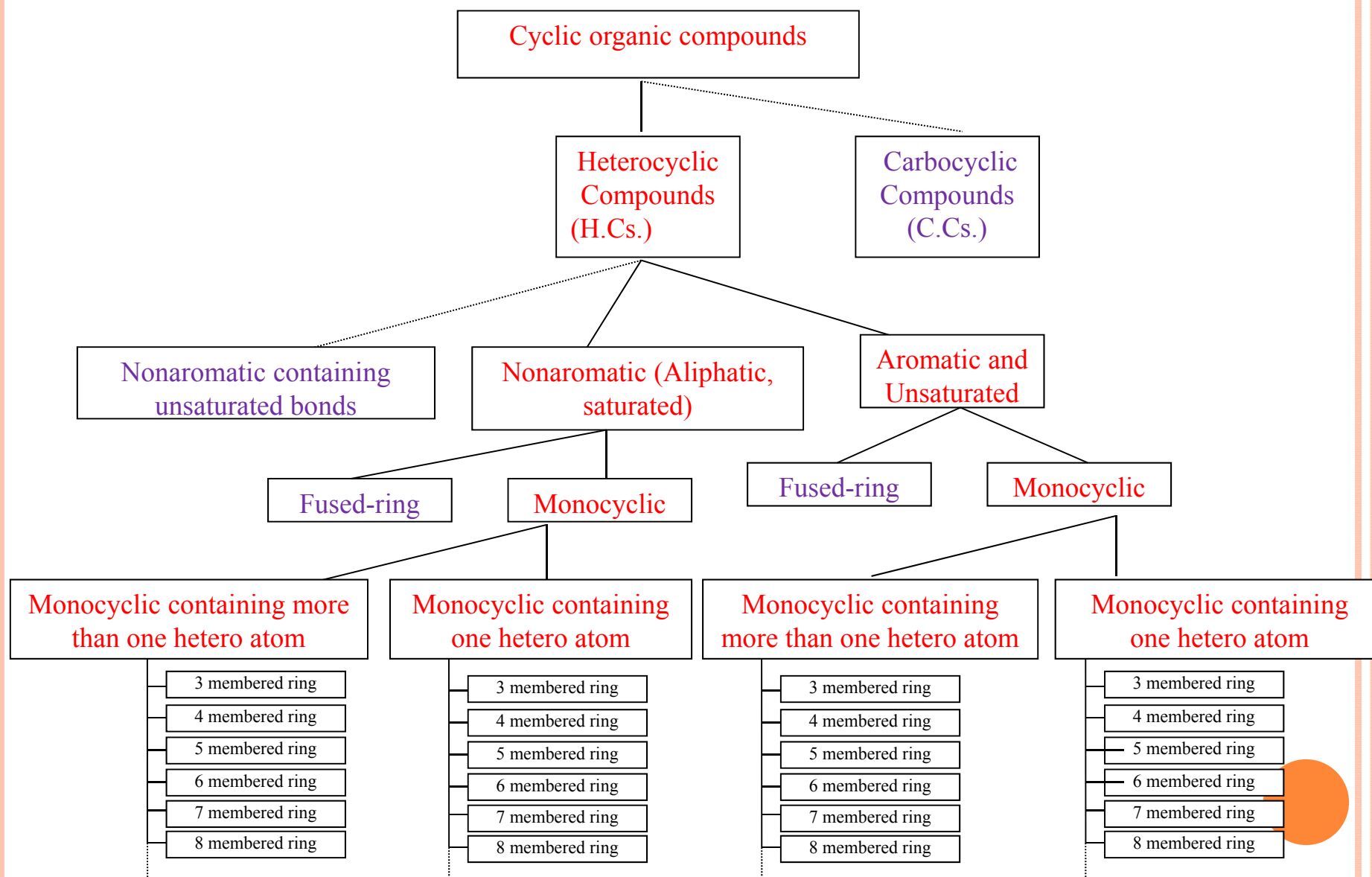


Where, X, Y and Z are usually N, O or S.

If X, Y and Z are C, the compounds called
Carbocyclic compounds (C.Cs.)

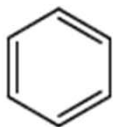


CLASSIFICATION OF H.Cs.

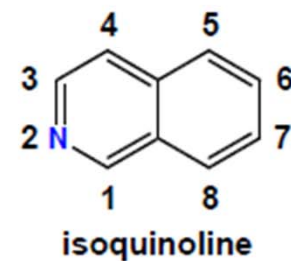
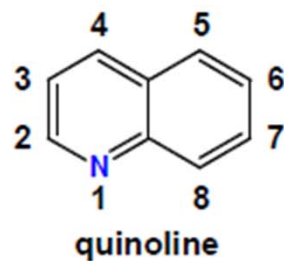
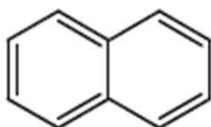
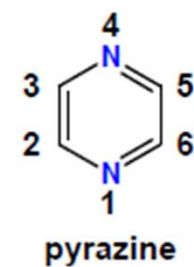
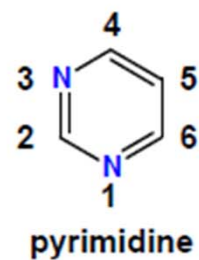
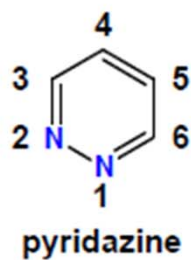
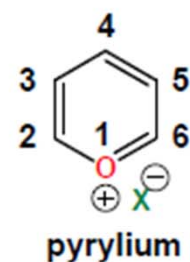
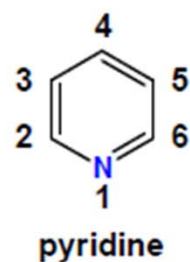


Classification – Aromatic Six-Membered

Isoelectronic carbocycle

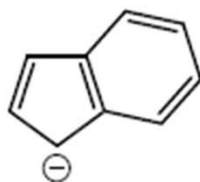


Heterocycles

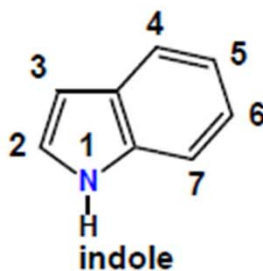
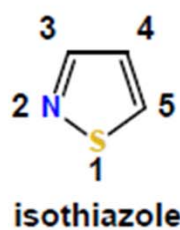
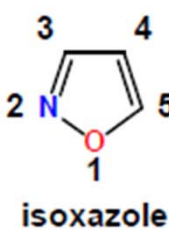
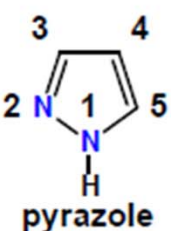
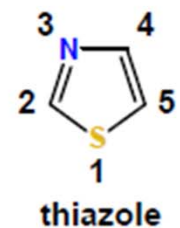
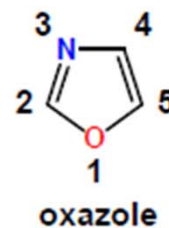
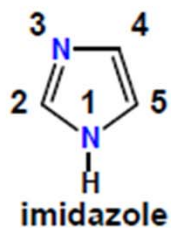
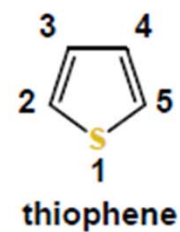
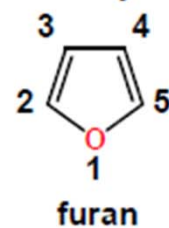
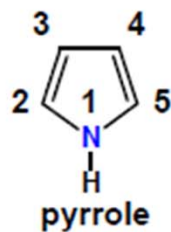


Classification – Aromatic Five-Membered

Isoelectronic carbocycle

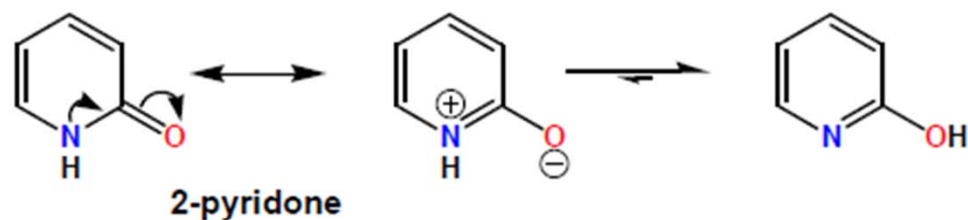
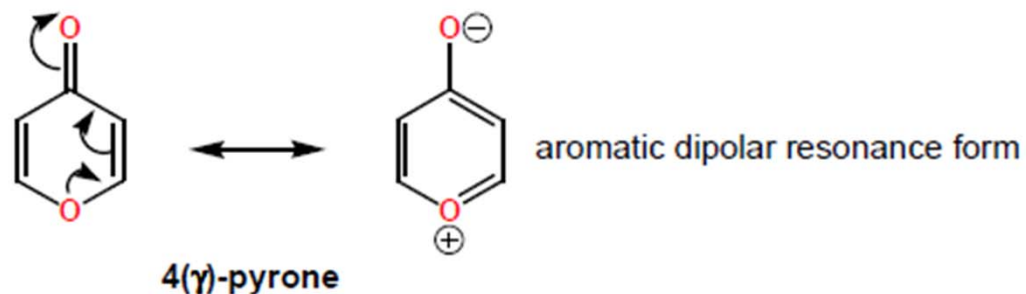


Heterocycles

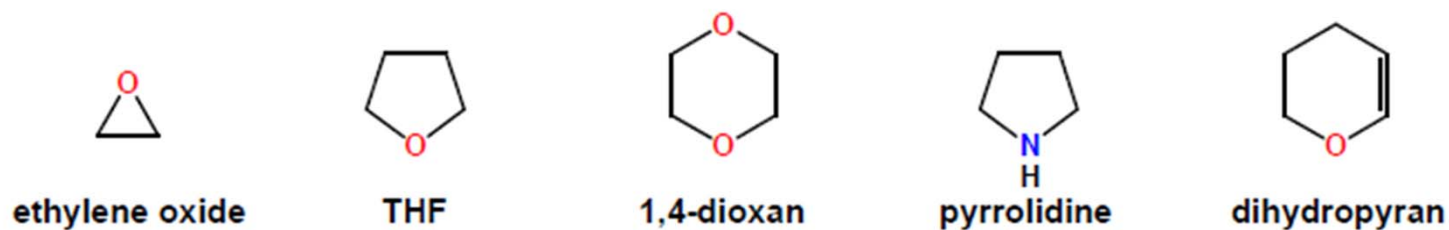


Classification – Unsaturated / Saturated

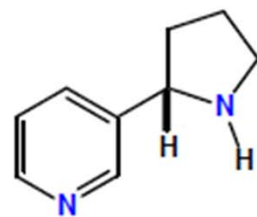
Unsaturated



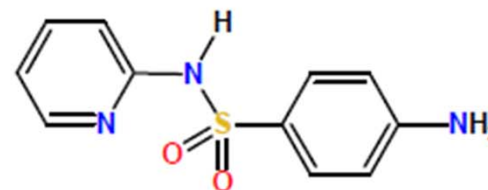
Saturated



Bioactive Pyridines

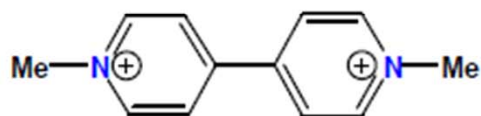


nicotine

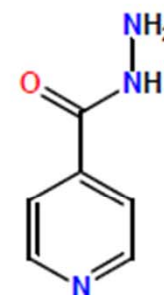


sulphapyridine

- Nicotine is pharmacologically active constituent of tobacco – toxic and addictive
- Sulphapyridine is a sulfonamide anti-bacterial agent – one of the oldest antibiotics



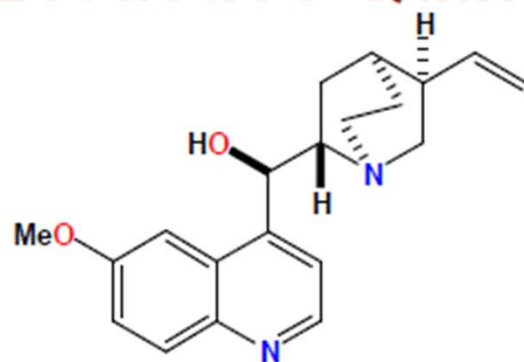
paraquat



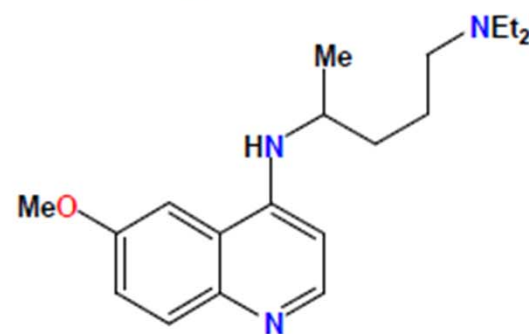
isoniazide

- Paraquat is one of the oldest herbicides – toxic and non-selective
- Isoniazide has been an important agent to treat tuberculosis – still used, but resistance is a significant and growing problem

Bioactive Quinolines/Isoquinolines

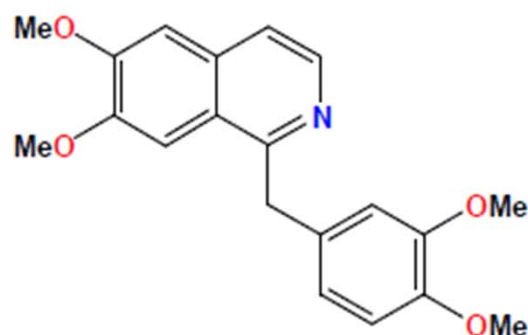


quinine



chloroquine

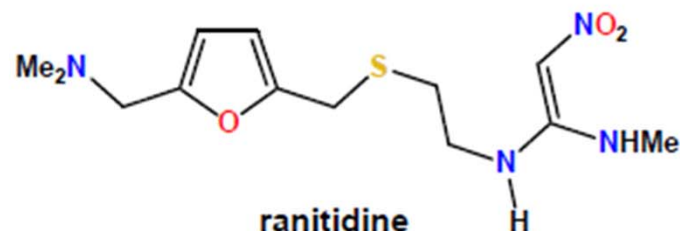
- Quinine is an anti-malarial natural product isolated from the bark of the *Cinchona* tree
- Chloroquine is a completely synthetic anti-malarial drug that has the quinoline system found in quinine – parasite resistance is now a problem



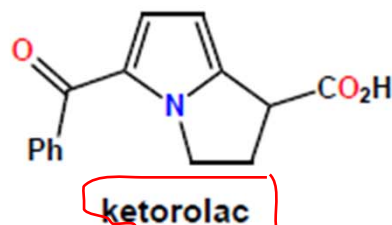
papaverine

- Papaverine is an alkaloid isolated from the opium poppy and is a smooth muscle₄₅ relaxant and a coronary vasodilator

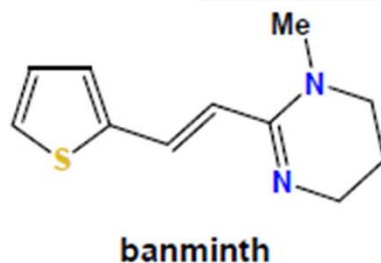
Bioactive Furans, Pyrroles and Thiophenes



- Ranitidine (Zantac®, GSK) is one of the biggest selling drugs in history. It is an H₂-receptor antagonist and lowers stomach acid levels – used to treat stomach ulcers

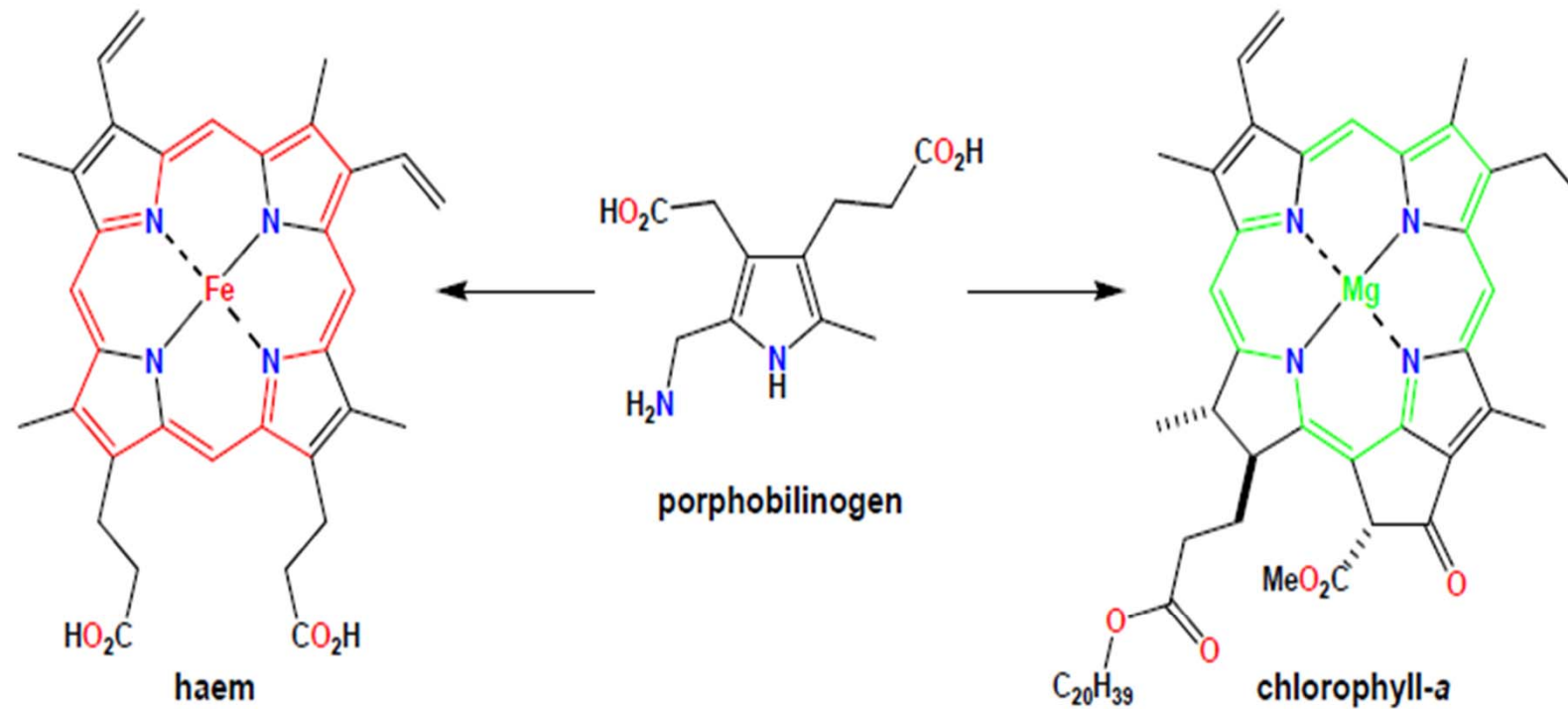


- Ketorolac (Toradol®, Roche) is an analgesic and anti-inflammatory drug



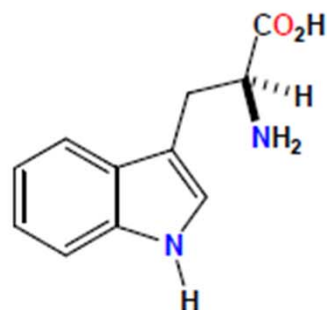
- Pyrantel (Banminth®, Phibro) is an anthelmintic agent and is used to treat worms in livestock

Porphyrin Natural Products

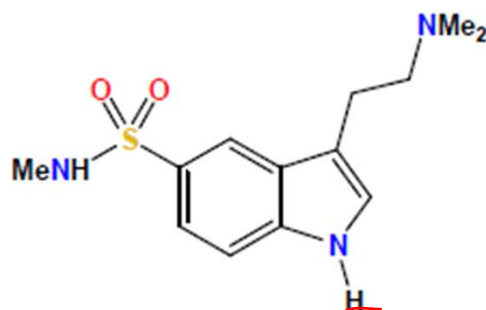


- The pigment haem is found in the oxygen carrier haemoglobin
- Chlorophyll-a is responsible for photosynthesis in plants
- Both haem and chlorophyll-a are synthesised in cells from porphobilinogen

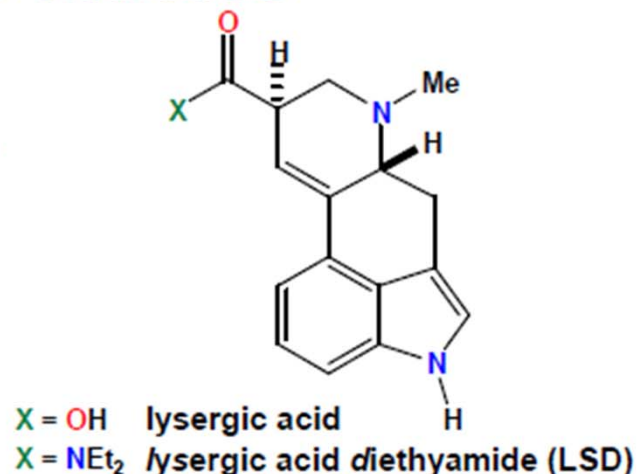
Indoles – Bioactive Indoles



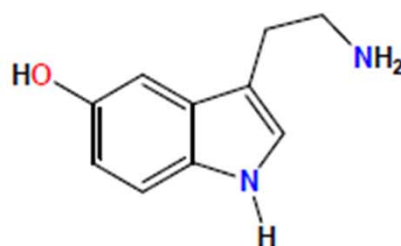
tryptophan



sumatriptan

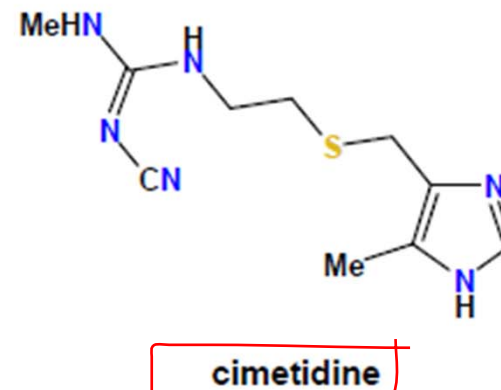
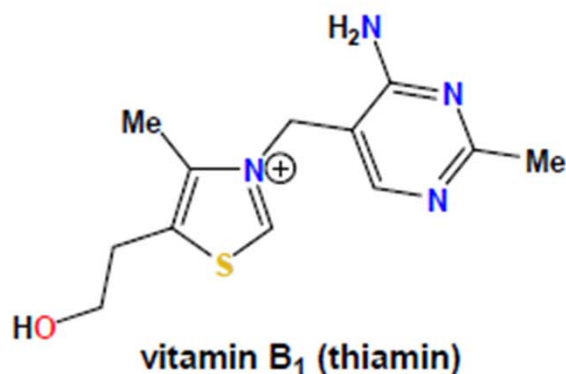
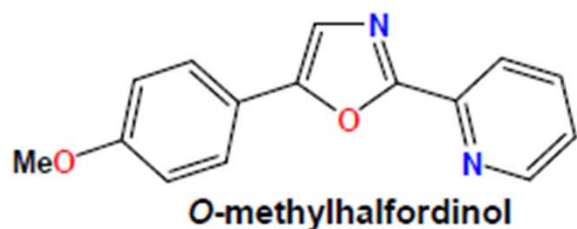


- Tryptophan is one of the essential amino acids and a constituent of most proteins
- Sumatriptan (Imigran®, GSK) is a drug used to treat migraine and works as an agonist for 5-HT receptors for in the CNS
- LSD is a potent psychoactive compound which is prepared from lysergic acid, an alkaloid natural product of the ergot fungus



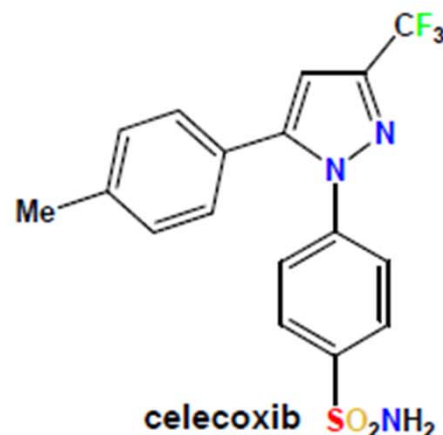
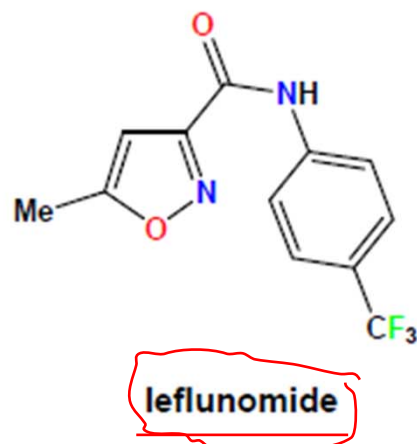
5-hydroxytryptamine (serotonin)

1,3-Azoles – Bioactive 1,3-Azoles



- O-Methylhalfordinol is a plant-derived alkaloid
- Vitamin B₁ (thiamin) is essential for carbohydrate metabolism. Deficiency leads to beriberi, a disease which is characterised by nerve, heart and brain abnormalities
- Cimetidine (Tagamet®, GSK) is an H₂-receptor antagonist which reduces acid secretion in the stomach and is used to treat peptic ulcers and heartburn

1,2-Azoles – Bioactive 1,2-Azoles



- Leflunomide (Arava®, Sanofi-Aventis) inhibits pyrimidine synthesis in the body and is used for the treatment of rheumatoid arthritis and psoriatic arthritis
- Celecoxib (Celebrex®, Pfizer) is a non-steroidal anti-inflammatory (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms
- Celecoxib is a COX-2 inhibitor, blocking the cyclooxygenase-2 enzyme responsible for the production of prostaglandins. It is supposed to avoid gastrointestinal problems associated with other NSAIDs, but side effects (heart attack, stroke) have emerged

NOMENCLATURE

- There are two types, Special name or called **Trivial** name, as pyrrole, thiophene, furan.
- Systematic name or **IUPAC**. According to this system, monocyclic 3-8 membered rings are named by combining **prefix** in Table 1 with a **suffix** in Table 2, and “a” from end of *prefix* has been omitted.

Table 1

O = Oxa	N = Aza	S = Thia
----------------	----------------	-----------------

Table 2

Ring size	Unsaturated compounds		Saturated compounds	
	With N	Without N	With N	Without N
3	-irine	-irene	-iridine	-irane
4	-ete	-ete	-etidine	-etane
5	-ole	-ole	-olidine	-olane
6	-ine	-in	-ane	-ane
7	-epine	-epin	-epane	-epane
8	-ocine	-ocine	-ocin	-ocane



EXAMPLES



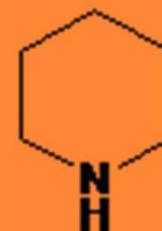
Azirine



Oxetane



Thiophene

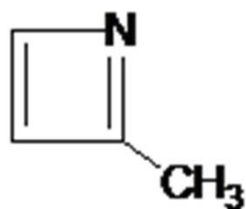


Azane

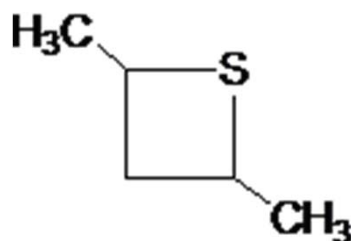


DERIVATIVES OF MONOCYCLIC COMPOUNDS CONTAINING **ONE** HETEROATOM IS:

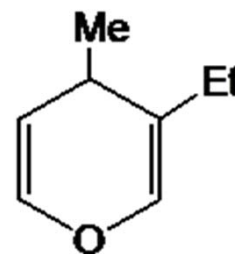
- The number of heteroatom is always 1, the substituted group is in the sequence



2-Methyl**azete**



2,4-Dimethyl**thietane**

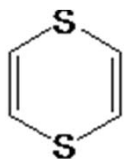


3-Ethyl-4-methyl**oxin**

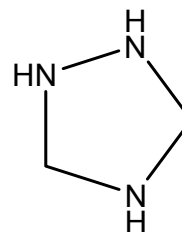


HETEROCYCLIC COMPOUNDS CONTAINING MORE THAN ONE HETEROATOM:

Two or more **similar atoms** are indicated by *prefixes* *di-*, *tri-*, etc. placed before the name and after the number of position.

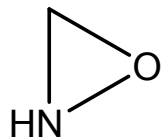


1,4-Di**thi**in

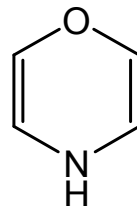


1,2,4-Tri**az**olidine

Two or more **different hetero atoms** named by combining the prefixes in Table 1 with suffix in Table 2 in order of O, S and N.



Oxaziridine

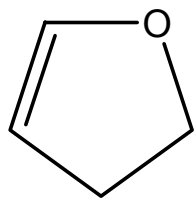


1,4-**Ox**azine

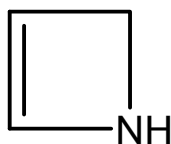


Partially saturated H.Cs.

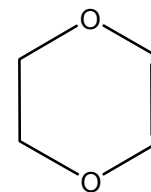
Partly saturated rings are denoted by the suffixes according to Table 2, and the prefixes dihydro-, tetrahydro-, etc. should be used. **The numbering is started from the heterocyclic atom toward the saturated carbon atom.**



2,3-Dihydro-oxole



1,2-Dihydro-azete

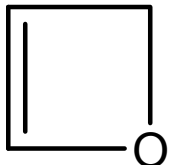


2,3-Dihydro-[1,4]dioxine

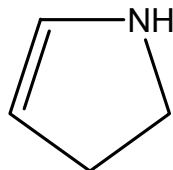


Indicated hydrogen

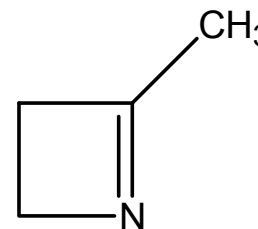
In some cases, heterocyclic systems occur as one or more structural isomers which **differ only in the position of an H-atom**. These isomers are designated by indicating the **number corresponding to the position of the hydrogen atom in front of the name**, followed by an ***italic capital H***. Such a prominent **H-atom** is called an **indicated hydrogen** and must be assigned the **lowest possible location**.



2*H*-Oxete

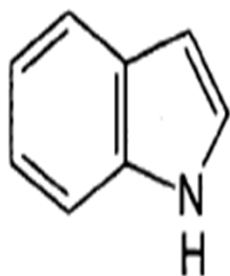


2,3-Dihydro-1*H*-pyrrole
2,3-Dihydro-1*H*-azole

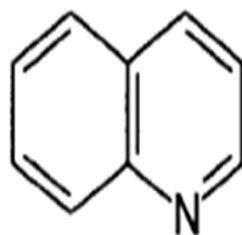


Bicyclic systems with one benzene ring and one heteroatom

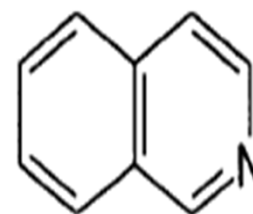
Systems in which at least two neighboring atoms are common to two or more rings are known as fused systems. For several bicyclic benzo-fused heterocycles, trivial names are permitted, e.g.:



indole

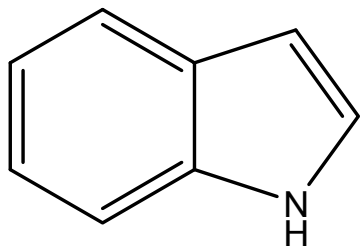


quinoline

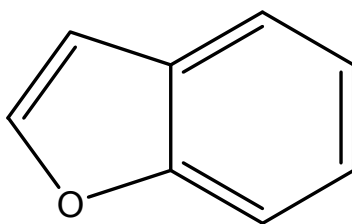


isoquinoline

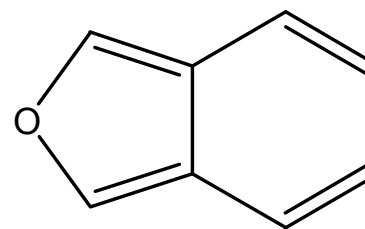
Use the **prefix benzo-** and the **trivial name of the heterocyclic component** as follows:



Indole
Benzo[b]pyrrole



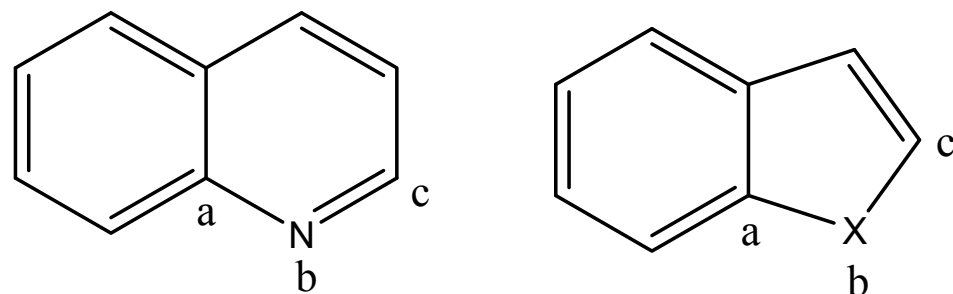
Benzo[b]furan



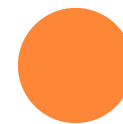
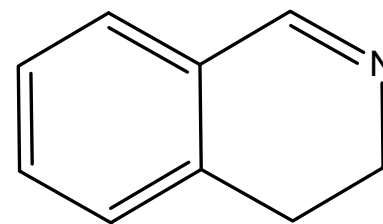
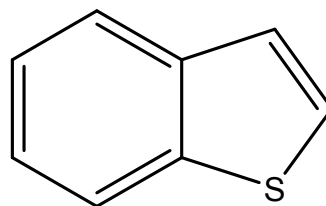
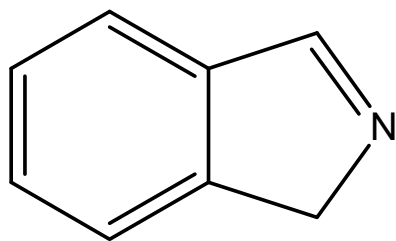
Benzo[c]furan



The letters *a*, *b*, *c* indicated to site of heteroatom

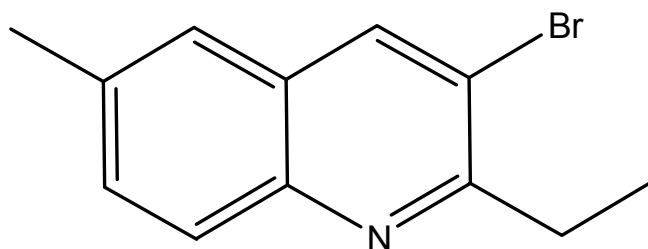
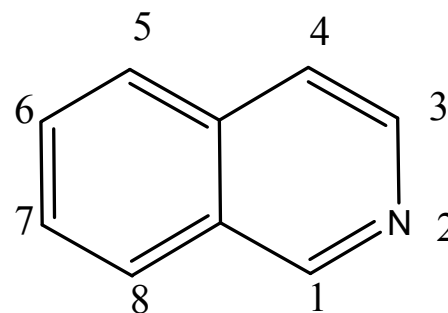
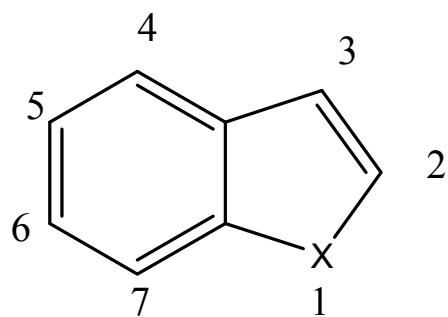


Give the name of the following:

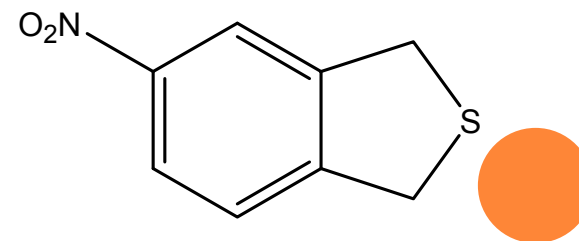
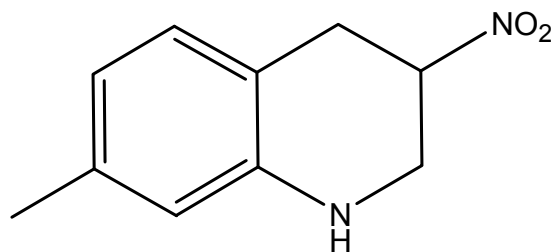
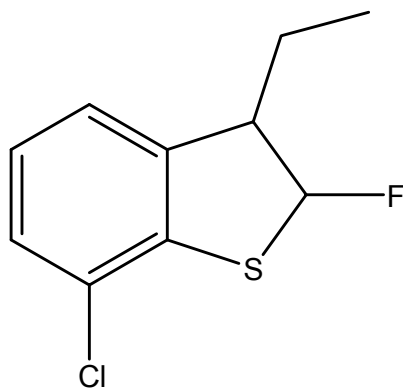


Substituted Bicyclic systems

The numbering of atom in bicyclic system is the following direction:

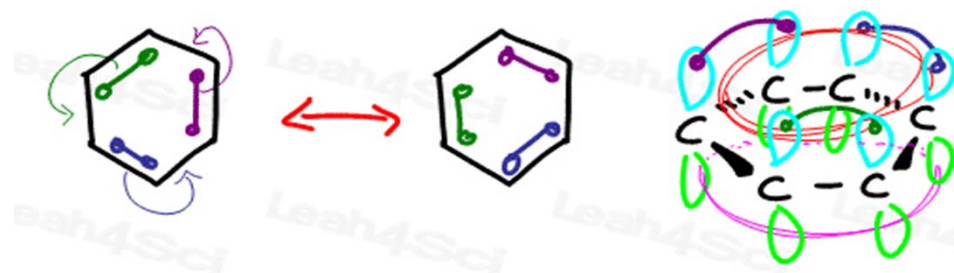


3-Bromo-2-ethyl-6-methyl-quinoline



Aromaticity of heterocyclic compounds

Aromatic compounds are very stable due to resonance stability of the conjugated electrons and overlapping π bonds.



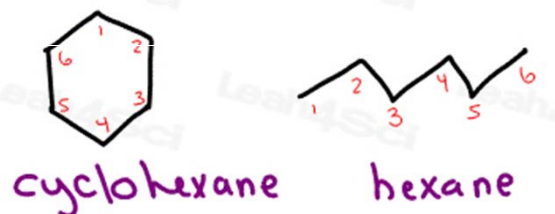
Look for the following 4 criteria to identify aromatic compounds

- ✓ cyclic
- ✓ planar
- ✓ conjugated
- ✓ Huckel's Rule



- **Cyclic,**

Cycle or cyclic implies a ring

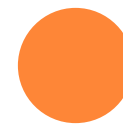
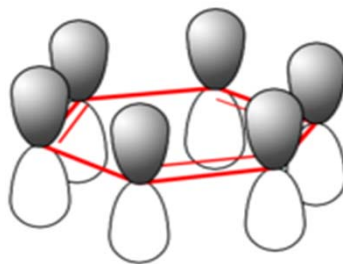


- **Planar,**

Since aromaticity relies on the ability of orbitals to overlap, the ring must have its atoms in the same plane.

The molecule must be **flat**.

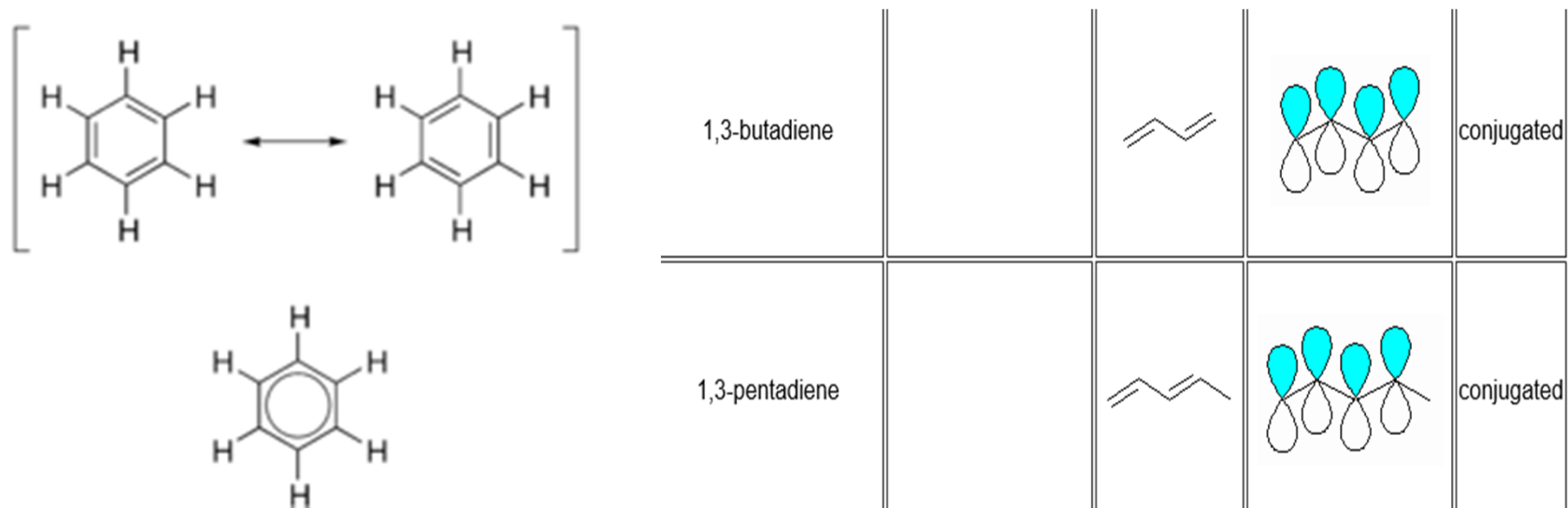
sp^2 carbons are trigonal planar or simply 'flat'



Conjugated,

You may have memorized that conjugated systems **have alternating single and double bonds**.


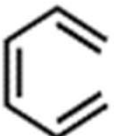
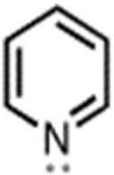


sp² atoms capable of resonance



Huckel's Rule

Huckel's Rule: $4n+2$ = Number of Resonating Electrons

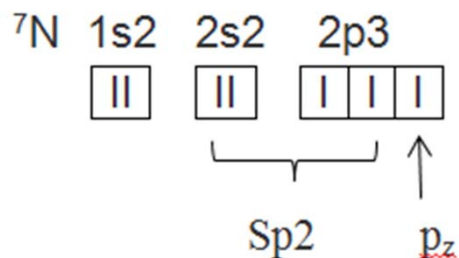
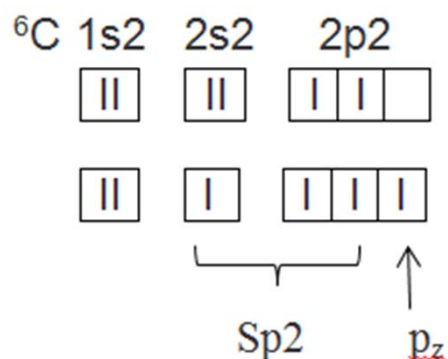


Molecule	Cyclic?	Conjugated?	π bonds	Lone Pairs	π electrons	Aromatic?
	Y	Y	3	–	6	Y
	N					N
	Y	Y	3	0**	6	Y
	Y	N				N
	Y	Y	1	1	4	N

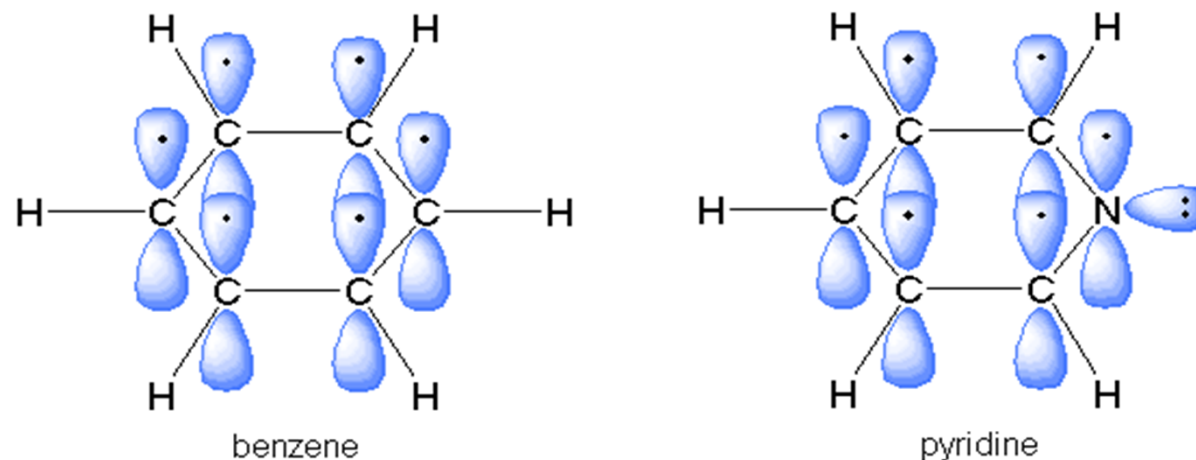
** the orientation of the lone pair is not aligned with the pi system.

Pyridine: An Aromatic Six-Membered Heterocyclic Compound

The structure of pyridine considerably resembles that of benzene. It may be formally derived from the structure of benzene through the exchange of one ring carbon for a nitrogen. However, is pyridine, which is structurally and electronically allied to benzene, also aromatic?.



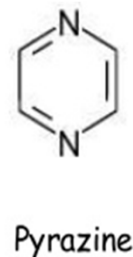
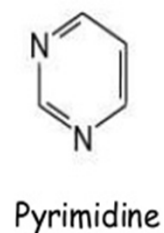
The nitrogen of pyridine is sp^2 -hybridized and possesses one lone electron pair. This electron pair is located in an sp^2 orbital that is parallel to the ring plane. The nitrogen's lone electron pair of pyridine does not participate in the aromatic π electron system.



Huckel's Rule: $4n+2 = \text{Number of Resonating Electrons}$
 $= 6$

$n = 1$ aromatic

Similar for all six membered ring containing more than one N atom

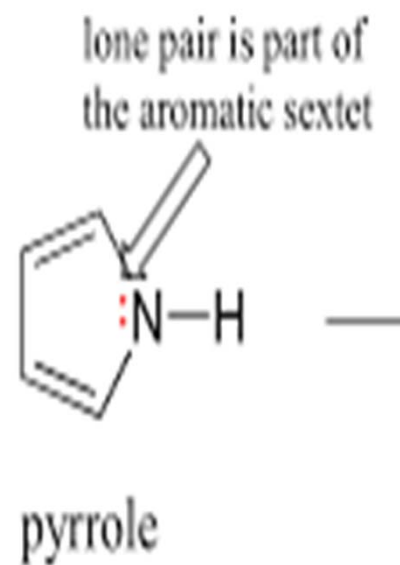
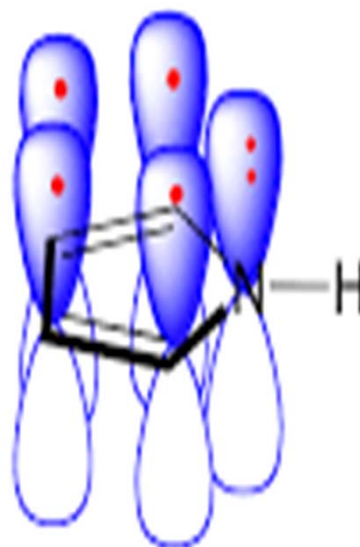
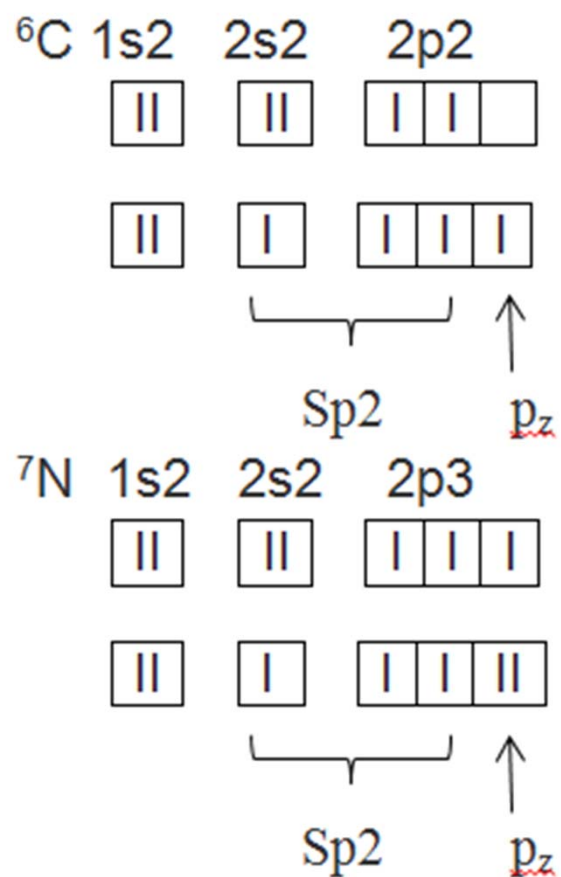
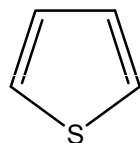
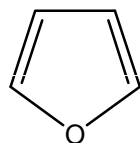
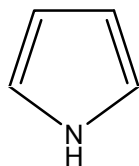


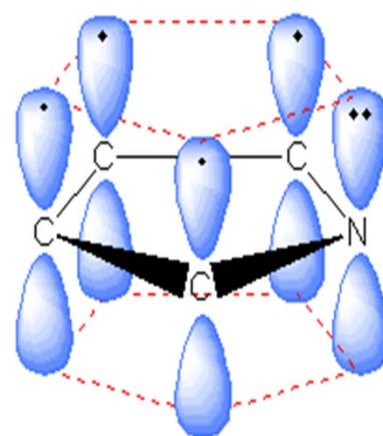
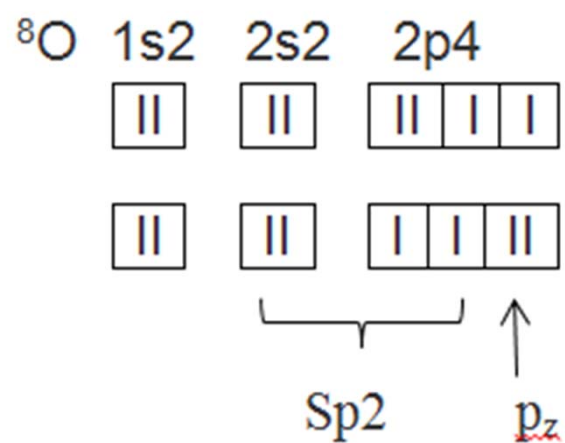
Aromatic Five-Membered Heterocyclic Compound

Pyrrole

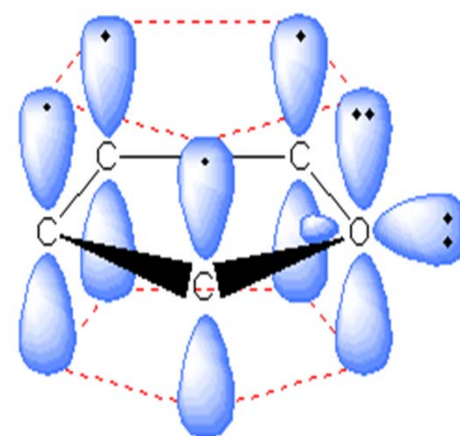
furan

thiophene

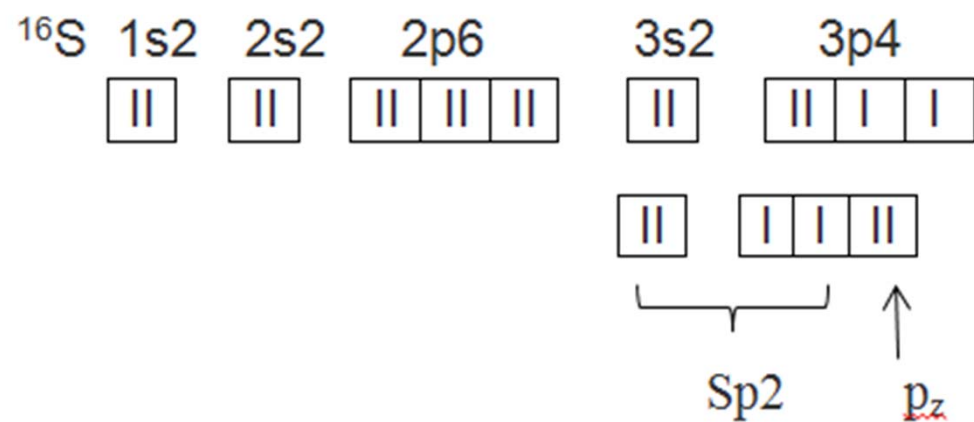


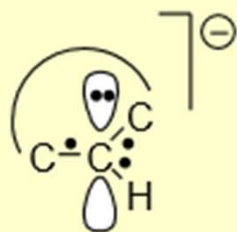
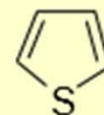
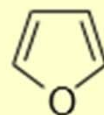
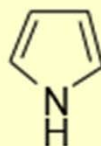
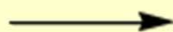


pyrrole

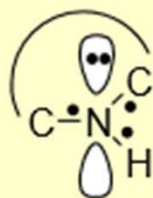


furan





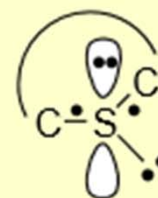
sp^2 hybrid **CH**[⊖]



sp^2 hybrid **NH**

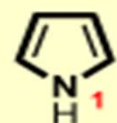


sp^2 hybrid **O**

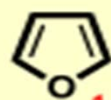


sp^2 hybrid **S**

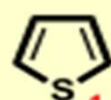




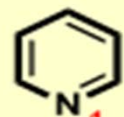
pyrrole



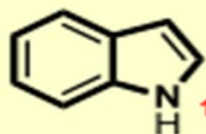
furan



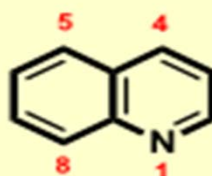
thiophene



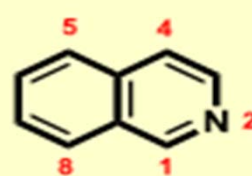
pyridine



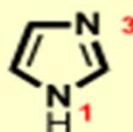
indole



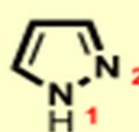
quinoline



isoquinoline

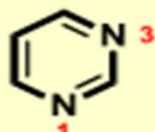


imidazole

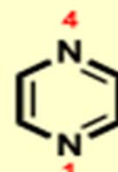


pyrazole

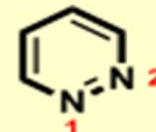
diazoles



pyrimidine



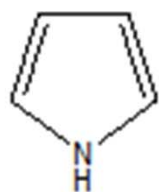
pyrazine



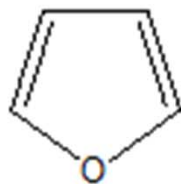
pyridazine

diazines

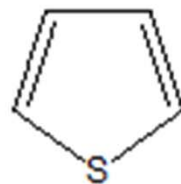
TRIVIAL NAME OF SOME H.Cs.



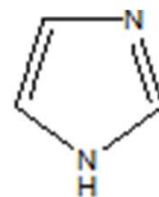
Pyrrole



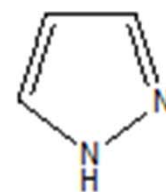
Furan



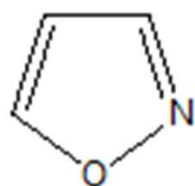
Thiophene



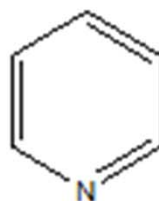
Imidazole



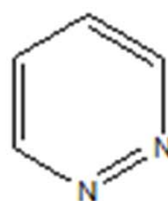
Pyrazole



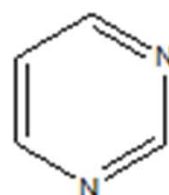
Isoxazole



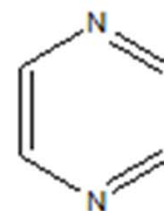
Pyridine



Pyridazine



Pyrimidine

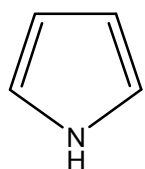


Pyrazine

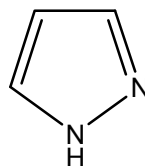


AZOLE AND AZINE

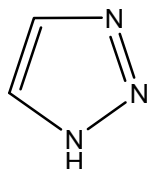
- The H.Cs. containing one or more nitrogen atoms may have various structures with **5** and **6** membered aromatic monocyclic ring, as shown:



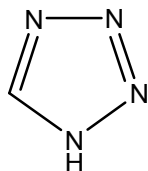
Azole



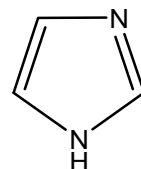
1,2-Diazole



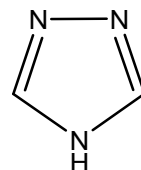
1,2,3-Triazole



1,2,3,4-Tetrazole

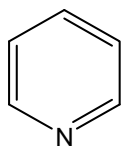


1,3-Diazole

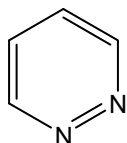


1,2,4-Triazole

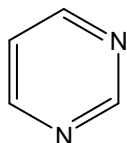




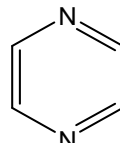
Azine



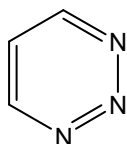
1,2-Diazine



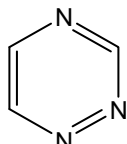
1,3-Diazine



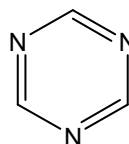
1,4-Diazine



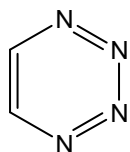
1,2,3-Triazine



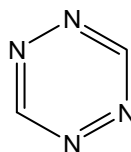
1,2,4-Triazine



1,3,5-Triazine



1,2,3,4-Tetrazine



1,2,4,5-Tetrazine



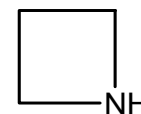
MEDICINAL USES OF HETEROCYCLIC COMPOUNDS:

(1) Antibiotics

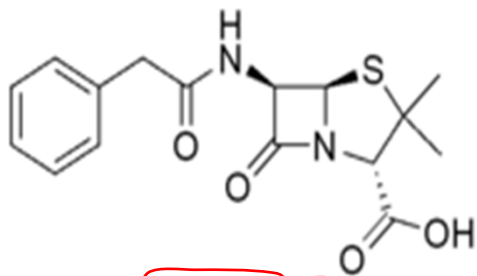
comes from Greek anti (against) and bios (life), are drugs can destroy bacteria or prevent their reproduction.

(1) β -Lactam antibiotics

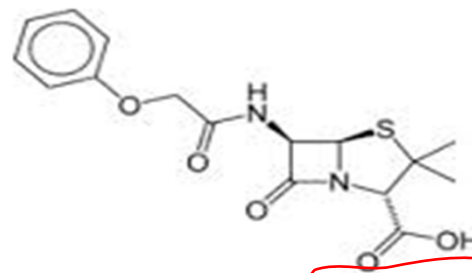
Which containing the azetidine group



(A) Penicillin analogous



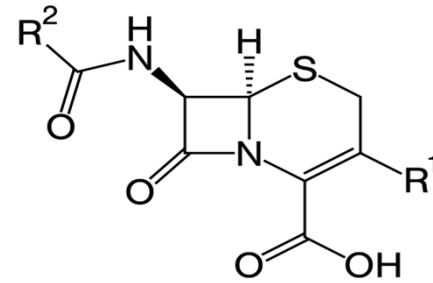
Penicillin G



Penicillin V

Another examples, **Nafcillin**, **Cloxacillin**, **Amoxicillin**

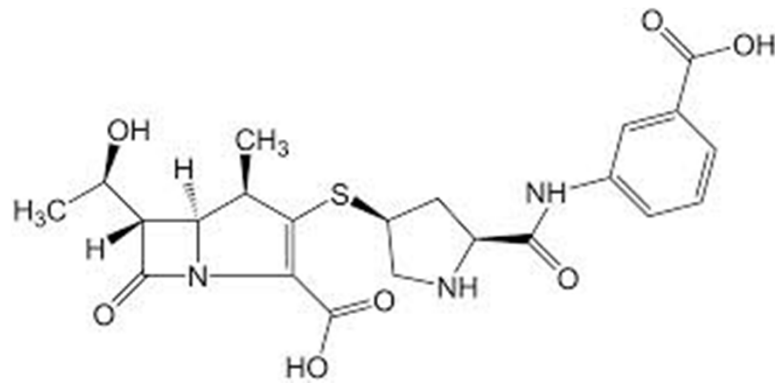
(B) Cephalosporin



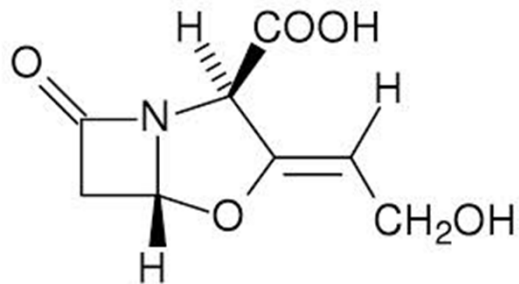
Drug	R1	R2
Cefradine	-CH ₃	 <chem>CC(C)Nc1ccccc1</chem>
Ceftrizoxime	-H	 <chem>CN1C(=N1C(=O)C(=N)OC)S</chem>
Ceftriaxone	 <chem>CN1C=NC(=O)NC1=O</chem>	 <chem>CN1C(=N1C(=O)C(=N)OC)S</chem>



(C) Other β -Lactam



Ertapenem



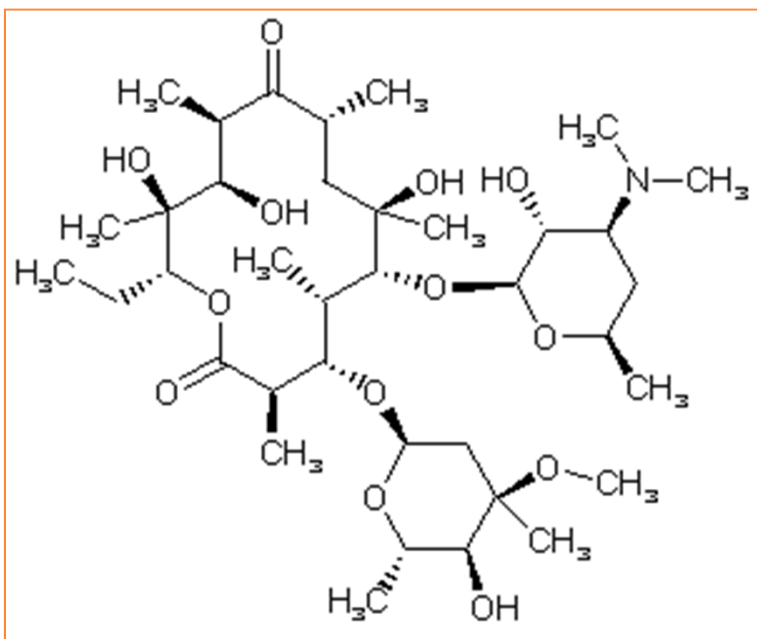
Clavulanic acid

Augmentin drug
(amoxicillin and clavulanic acid)

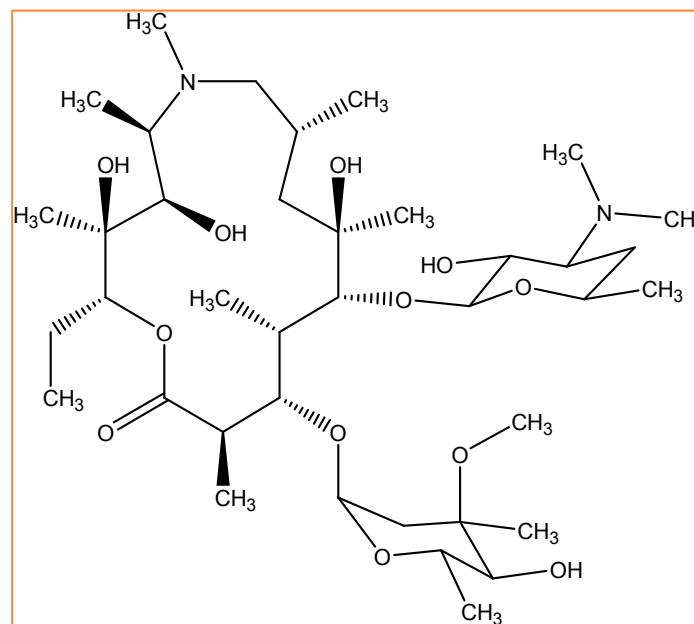


(2) Macrolide antibiotic

Large drugs containing **macrocylic lactone** ring (macrolide ring). The lactone rings are usually 14, 15 and 16membered.



Erythromycin

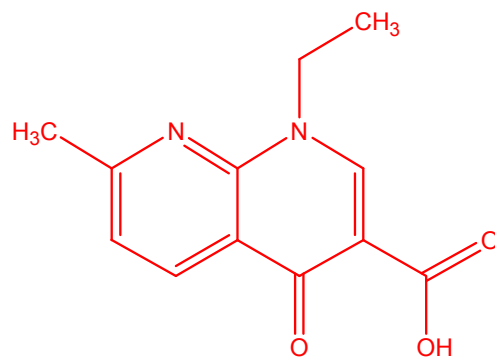


Azithromycin

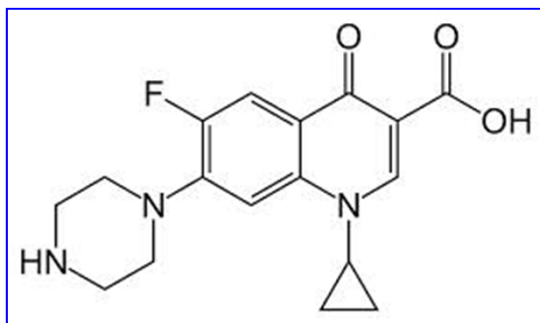


(3) Quinolone antibiotics

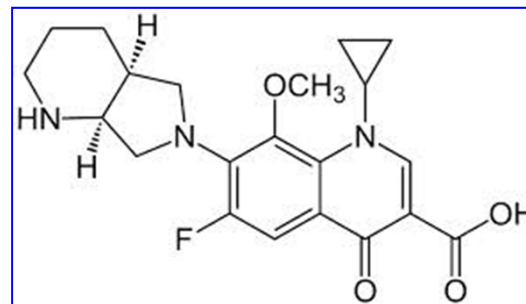
Nalidixic acid is first generation of quinolone used in 1962 for treatment of urinary tract infections (UTI) in human



Nalidixic acid



Ciprofloxacin

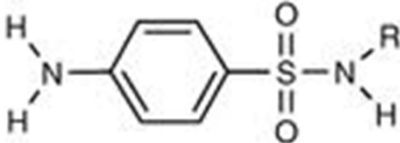
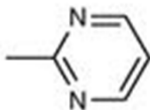
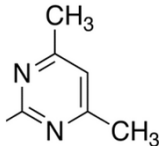
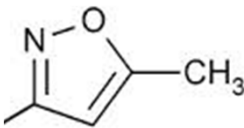


Moxifloxacin



(4) Sulfonamide antibiotics

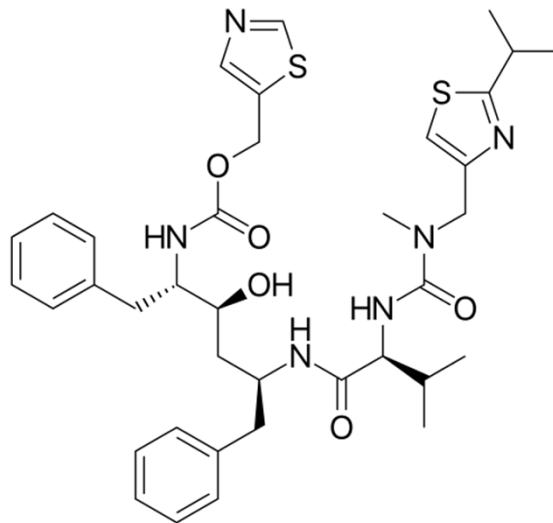
Containing **p-aminobenzoic sulfonamide**, called **sulfa drugs**, for examples for these types of drugs:

		
Name of drug	R	Name of heterocyclic ring
Sulfadiazine		Pyrimidine
Sulfamethazine		Methazine
Sulfamethoxazole		Methoxazole



(2) Antiviral Drugs

Treatment viral infections, for example, **Ritonavir** is antiretroviral drug used to treat HIV (Human Immunodeficiency virus) and AIDS (Acquired Immunodeficiency Syndrome).



Ritonavir

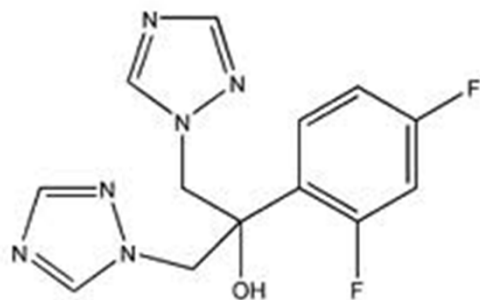
Another example: Nelfinavir



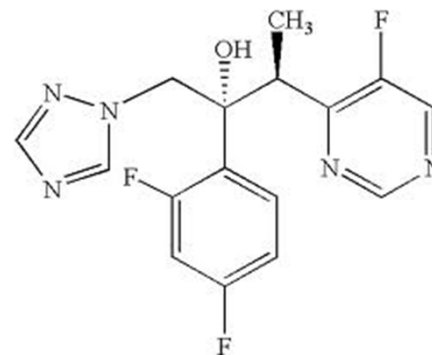
(3) Antifungal Drugs

Treatment fungal infections. The azole antifungal include two broad classes, Triazoles and Imidazoles

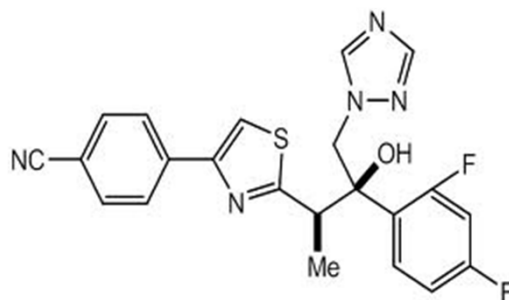
Triazole drugs



Fluconazole



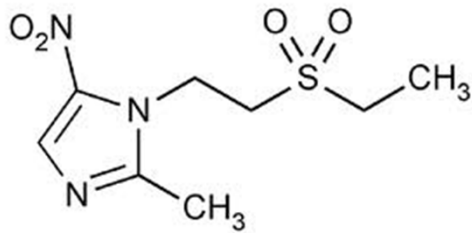
Voriconazole



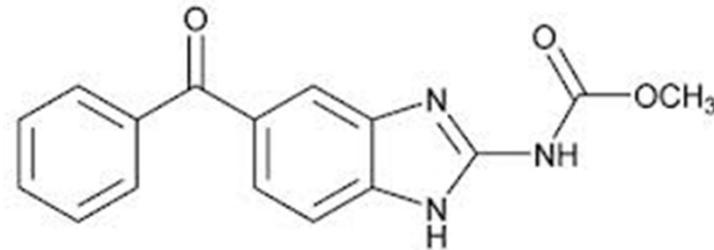
Ravuconazole

Imidazole Drugs

Antihelminthics or Anthelmintics drugs (anti-parasitic) expel parasitic worms (helminthes) from body.



Tinidazole

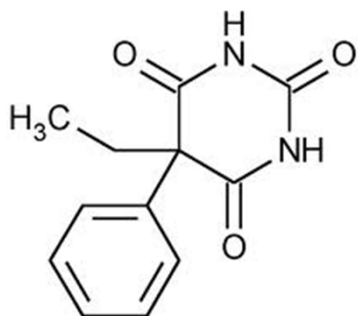


Mebendazole

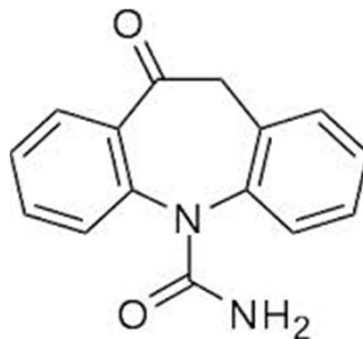


(4) Anticonvulsants Drugs (antiepileptic)

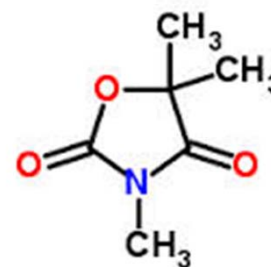
Treatment epileptic seizures.



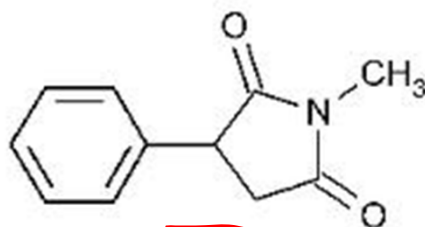
Phenobarbital
(diazane ring)



Oxcarbazepine
(azepine ring)



Troxidone
(oxazolidine ring)

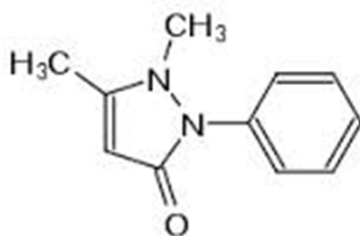


Phensuximide
(succinimide ring)

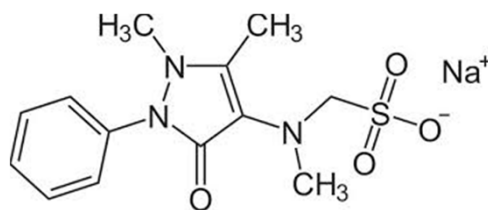


(5) Antipyretic and Non-steroidal anti-inflammatory Drugs

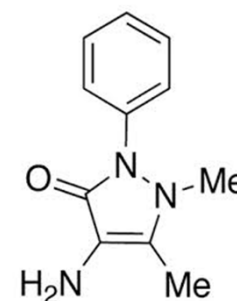
Pyrazolone derivatives



Phenazone



Metamizaole

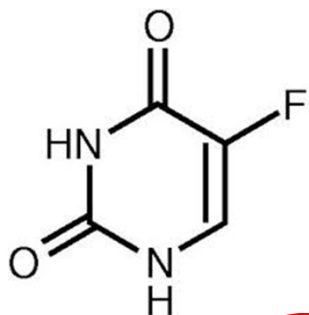


Aminophenazone

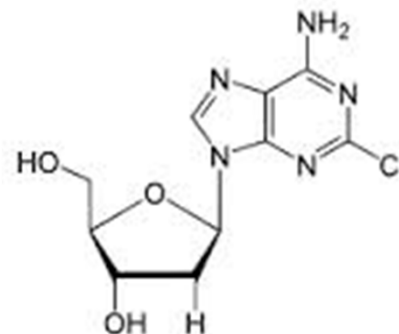


(6) Cytostatic Drugs

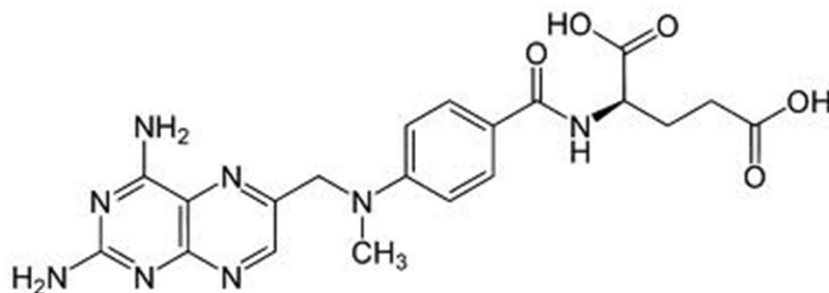
Antineoplastic agents used to treat various forms of cancer.



Fluorouracil
(pyrimidine ring)



Cladribine
(purine ring)

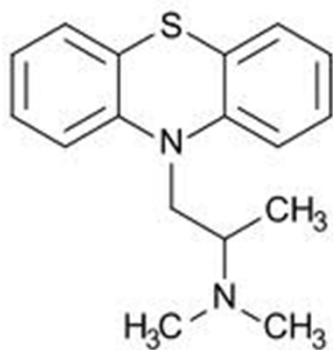


Methotrexate (antifolate)
(pteridine ring)



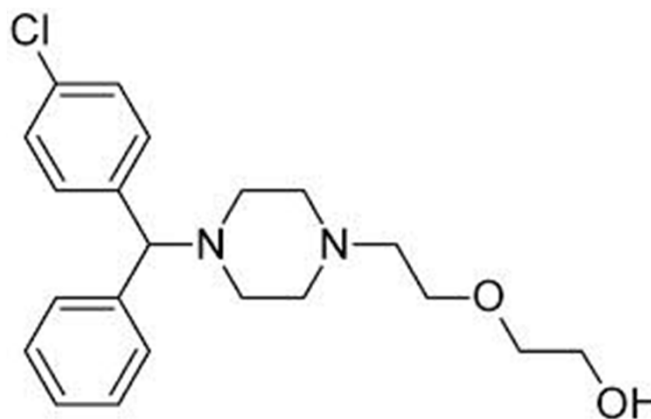
(7) Anti-Histamine Drugs

There are different H₁ receptors act as antihistamines



Promethazine

Phenothiazine derivatives



Hydroxyzine

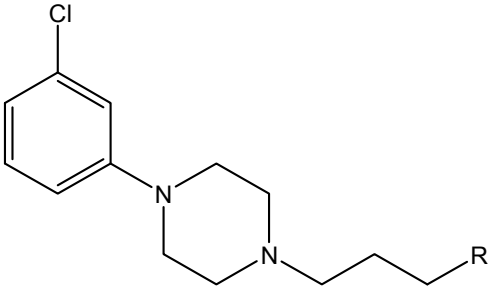
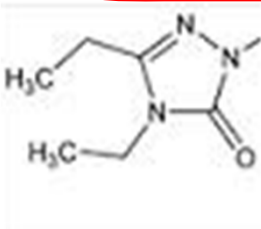
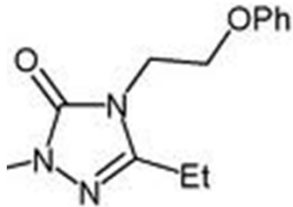
Piperazine analogues



(8) Psychoactive Drugs

Psychotropic substance is chemical substance that acts primarily upon the central nervous system (CNS) where it alters brain function.

Ex: m-Chlorophenylpiperazine derivatives

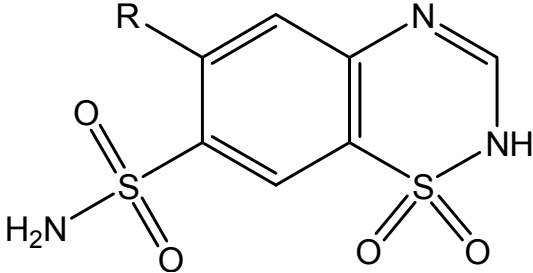
	
Etoperidone	Nefazodone
R = 	R = 

(9) Antihypertensive Drugs

Treatment of hypertension

Ex:

Benzothiadiazine derivatives

	
Chlorothiazide	Flumethiazide
R = Cl	R = CF ₃



Give the name and chemical structure presence in the following drugs

