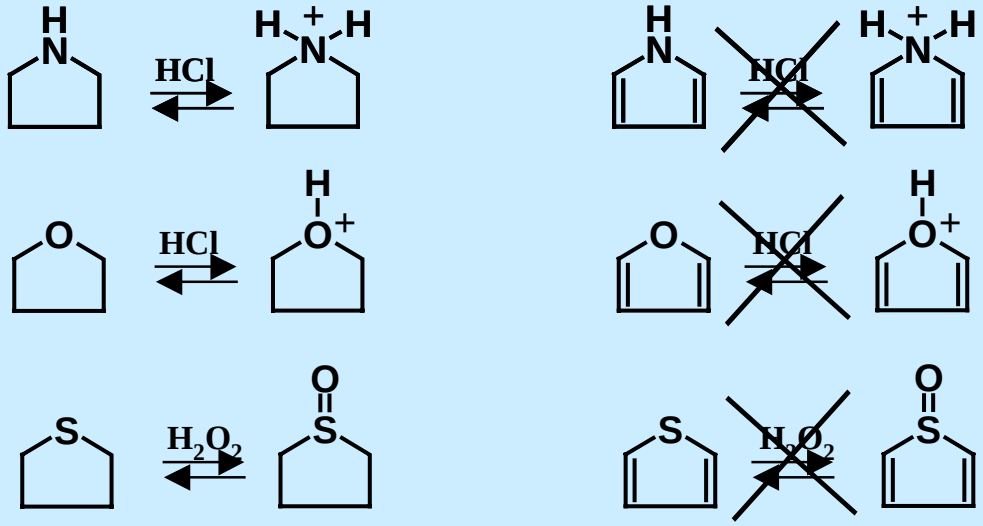
Heterocycles

Hückel's Rule for Aromaticity
- **4n+2 π-electrons**
- **planarity of the structure**

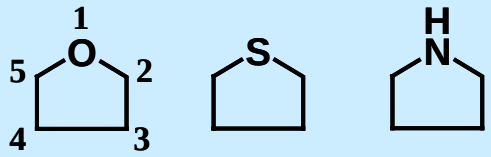
Aromatic?	**Y**	**Y**	**N**	**N**

✓ **Difference between reactions of aromatic and non-aromatic heterocycles**

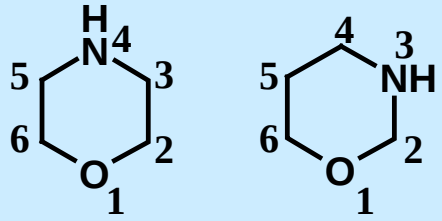


Nomenclature of Heterocyclic Compounds

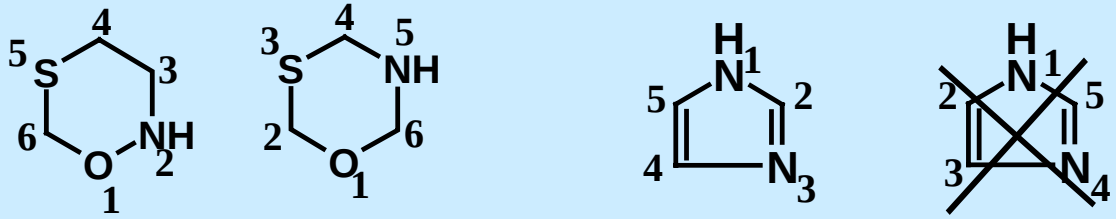
1. Heteroatom is to be counted as 1 or as low as possible



2. When there is more than one heteroatom, preference is given to O, then S, then N, then C. Also N-H presides over –N=. [Mnemonic: Old Soldiers Never Cry]

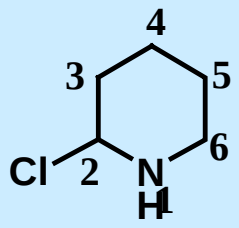


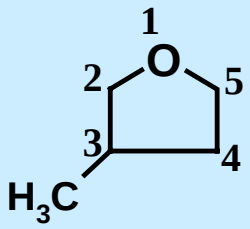
3. When there is more than one heteroatom, numbering should be as direct as possible from one to the other



Nomenclature of Heterocyclic Compounds

4. Substituents are numbered as low as possible



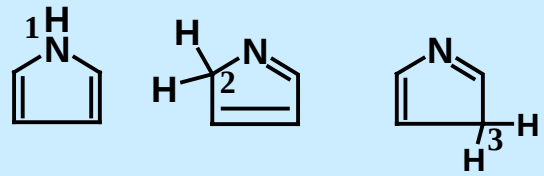


5. Acceptable prefixes for common heteroatoms: **O** = Oxa; **N** = Aza; **S** = Thia
6. Common suffixes for N- and non-N-heterocycles

Ring Size	***Saturated***	***Partly Saturated***	***Unsaturated***
*Rings with **N***			
3	-iridine		-irine
4	-etidine		-ete
5	-olidine	-oline	-ole
6	-ine	(di or tetrahydro)	-ine
7	(hexahydro)	(di or tetrahydro)	-epine
8	(octahydro)	(di, tetra, or hexahydro)	-ocine
*Rings without **N***			
3	-irane		-irene
4	-etane		-ete
5	-olane	-olene	-ole
6	-ane	(di or tetrahydro)	-ine
7	-epane	(di or tetrahydro)	-epine
8	-ocane	(di, tetra, or hexahydro)	-ocin

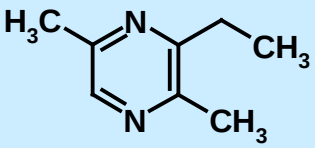
Nomenclature of Heterocyclic Compounds

7. For partially unsaturated systems, H is(are) are used to indicate the location of saturation

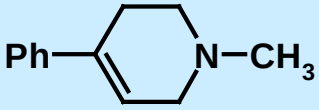


1H-azole *2H-azole* *3H-azole*

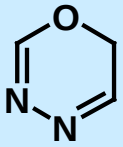
Examples:



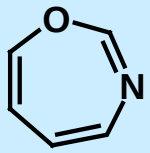
Common Name: 2-ethyl-3,6-dimethyl-pyrazine
IUPAC: 2-ethyl-3,6-dimethyl-1,4-diazine



Common Name: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine



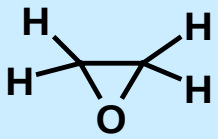
Common Name: 6H-diazapyran
IUPAC: 6H-1,3,4-oxadiazine



Common Name: 1,3-oxazepine

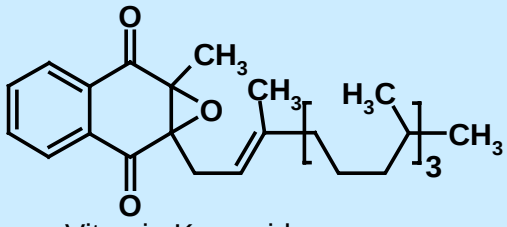
Oxygen Containing Heterocycles

✓ **3-Membered Ring ::** Ethylene Oxide or oxirane

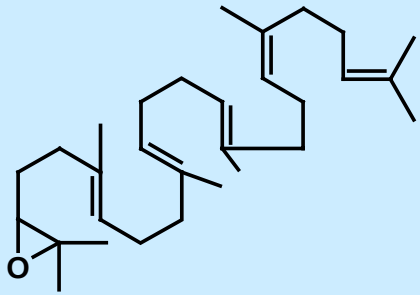


- Functional group is epoxide
- planar structure
- gas at room temperature
- used as sterilant for operating room equipment
- extremely toxic to living cell and is thought to be mutagen and probably a carcinogen

✓ **Examples of epoxides in our System**



Vitamin K epoxide

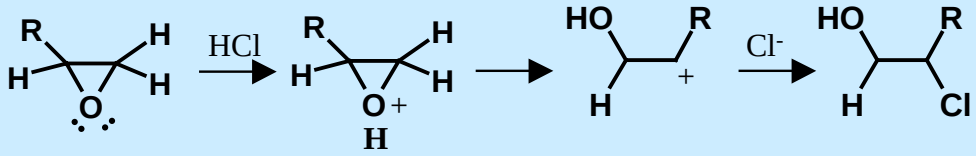


Squalene Epoxide

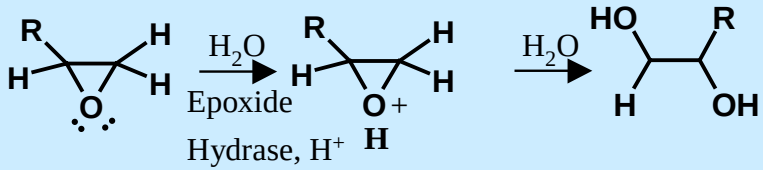
Oxygen Containing Heterocycles

✓ **Reactions of Epoxides**

Acid Opening of Epoxides



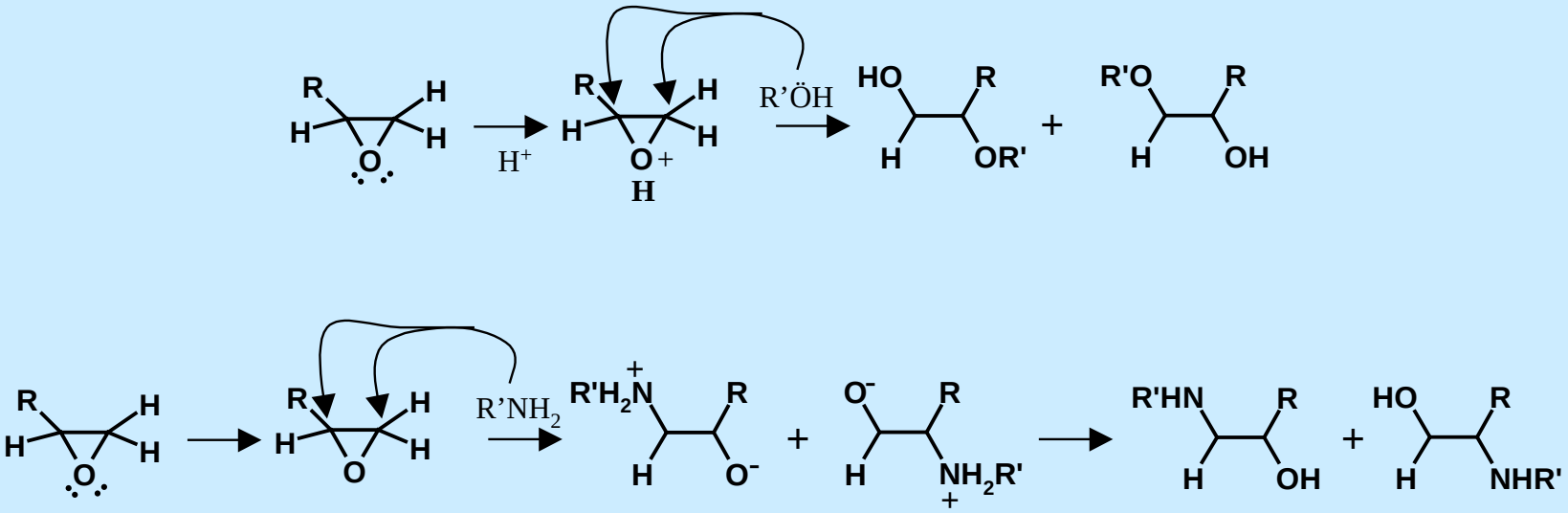
Enzymatic Opening of Epoxides



Oxygen Containing Heterocycles

✓ **Reactions of Epoxides**

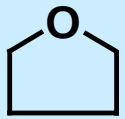
Opening of Epoxides with Amines and Alcohols



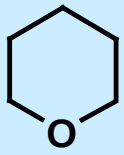
Oxygen Containing Heterocycles

✓ **Higher Oxides**

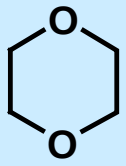
Oxetane



oxolane



oxane

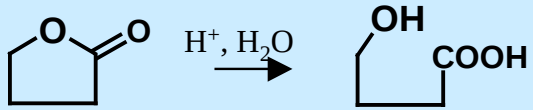


1,4-dioxane

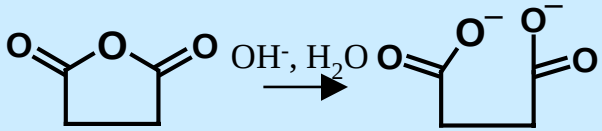
Properties:

- *all non-planar*
- *oxetane has a small pucker*
- *all good solvents and used in place of diethylether*
- *all are generally non-toxic, except for dioxane, which is mutagenic*

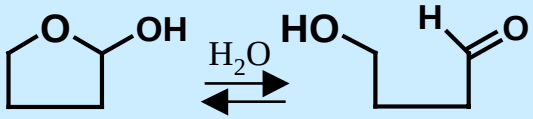
Stability of these oxides change drastically on α-substitution



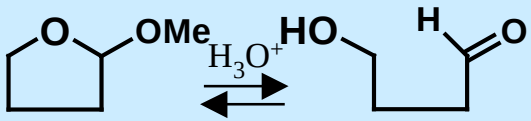
Lactones



anhydrides



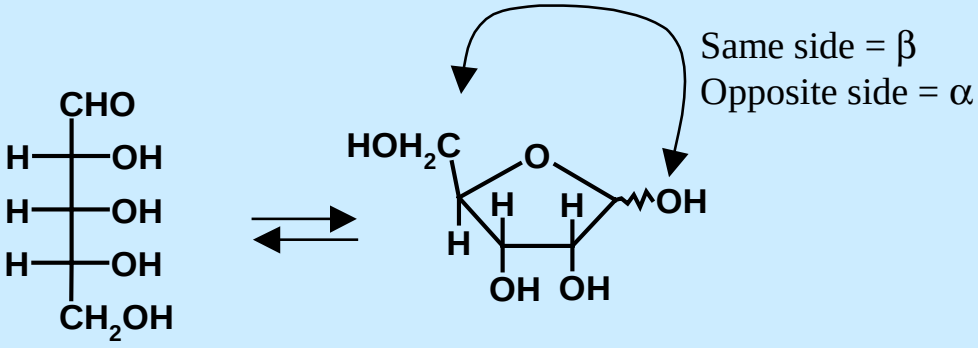
Hemi-acetals



acetals

Oxygen Containing Heterocycles

✓ **Examples of Acetals or Hemi-Acetals in Nature**

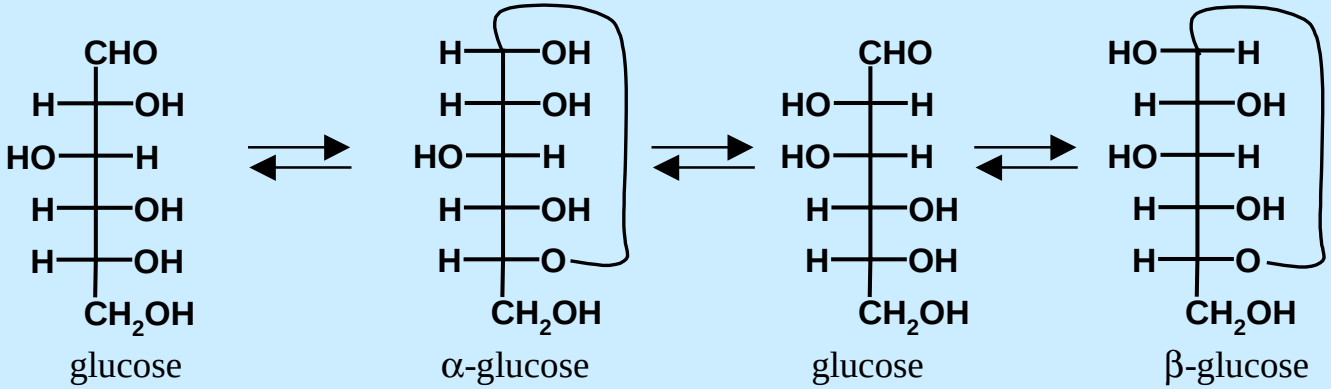


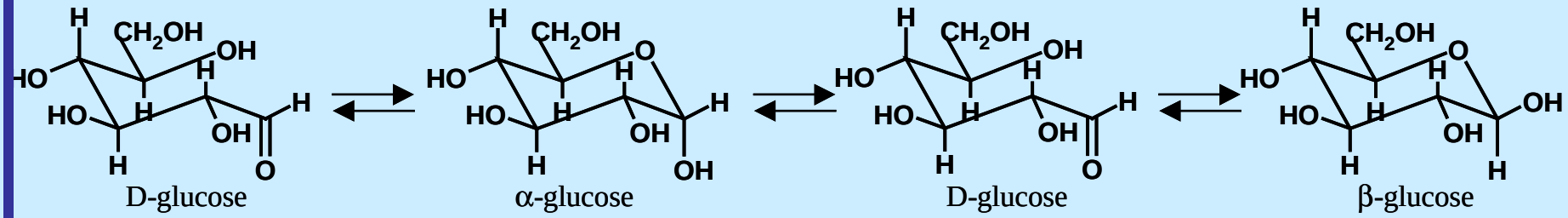
ribose hemiacetal

Oxygen Containing Heterocycles

✓ **Interconversion of α- and β-forms of sugars**

The phenomenon of mutarotation

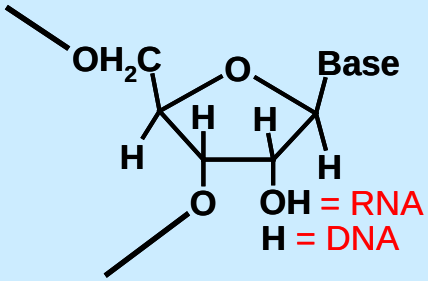


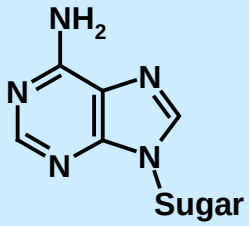


Oxygen Containing Heterocycles

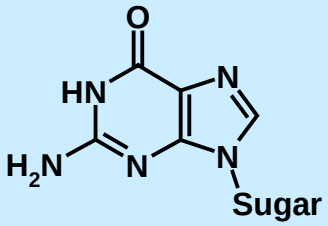
✓ **Examples of sugars in natural systems**

Deoxynucleic Acids and Ribonucleic Acids

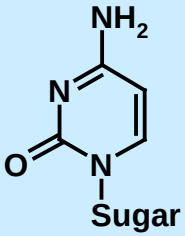




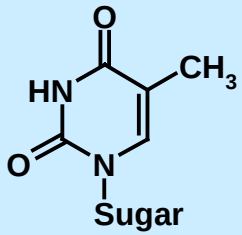
Adenine



Guanine



Cytidine

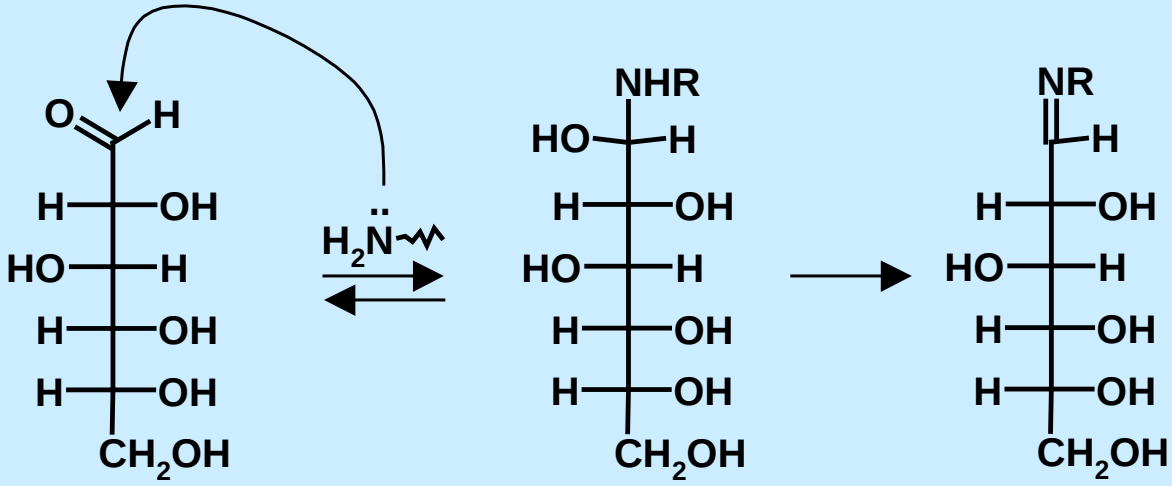


Thymidine

Live link: http://www.bmrb.wisc.edu/referenc/nomenclature/

Oxygen Containing Heterocycles

✓ **Sugars and Diabetes**

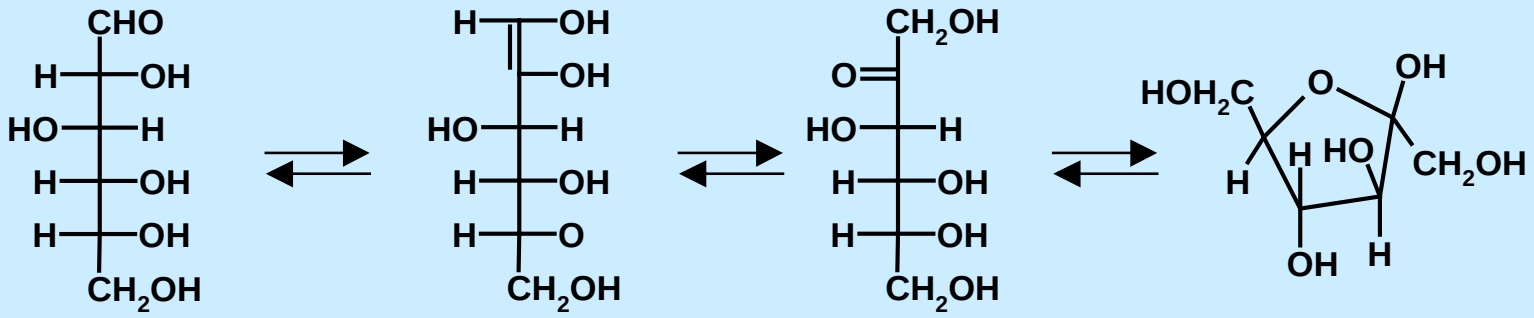


Glycated Hemoglobin (HbA1c or GHb)

Also called glycosylated hemoglobin. The saccharide equilibrium is the reason for the formation of glycated hemoglobin in diabetic patients. Excess free plasma sugar, and therefore the open-chain aldehyde, reacts with the N-terminal NH_2 group of hemoglobin (or lysine side chains) to form glycated adducts, which are detected to confirm and monitor diabetes. The upper limit for a normal individual is 7% HbA1c.

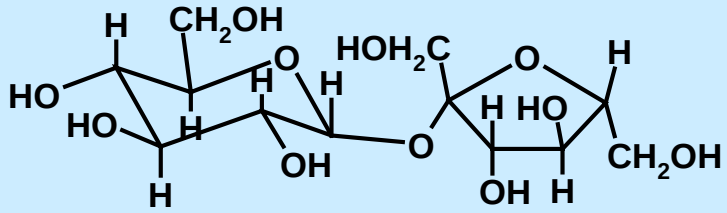
Oxygen Containing Heterocycles

- ✓ **Fructose**



D-glucose ene-diol fructose (open-chain form) fructose (furanose form)

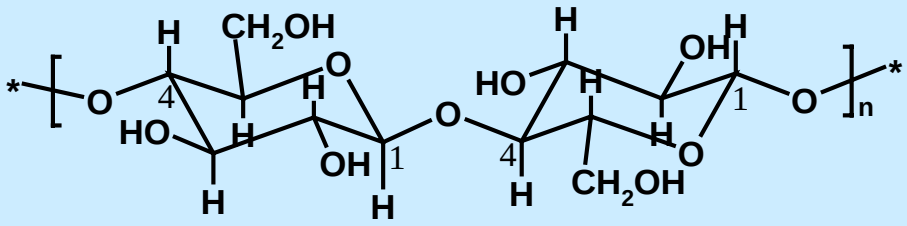
- ✓ **Sucrose**



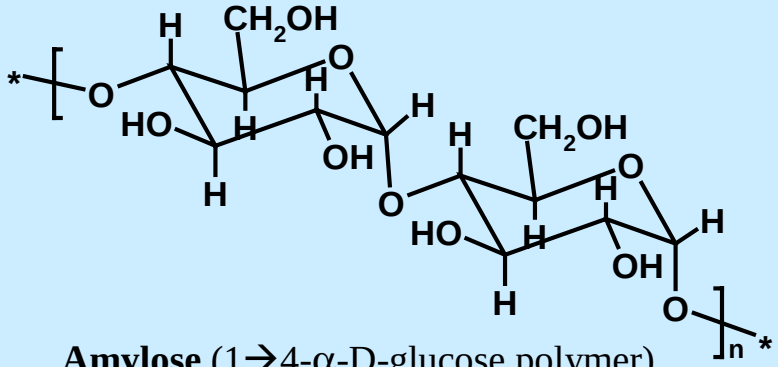
α-D-glucose β-D-fructose

Oxygen Containing Heterocycles

- ✓ **Polysaccharides – Cellulose and Starch**



Cellulose (1→4-β-D-glucose polymer)

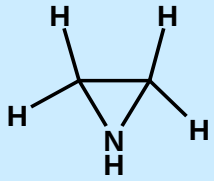


Amylose (1→4-α-D-glucose polymer)
80% constituent of starch; 20% is amylopectin

Nitrogen Containing Heterocycles

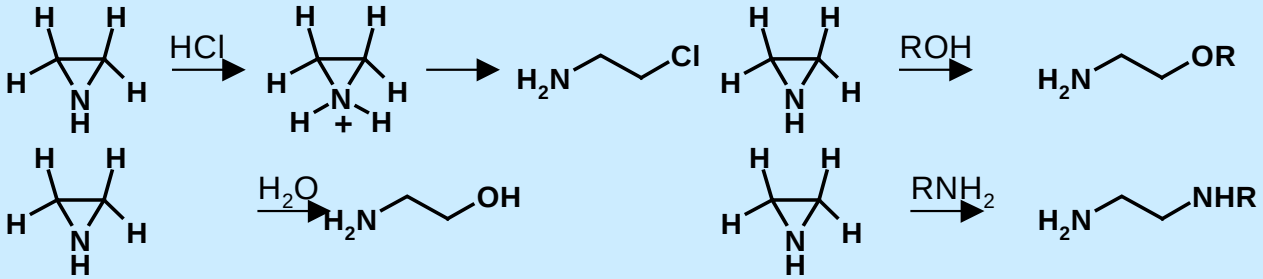
- ✓ **Three-membered**

Aziridine



Planar
Highly strained; highly reactive
Toxic and carcinogenic

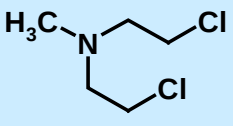
Reactions of Aziridine



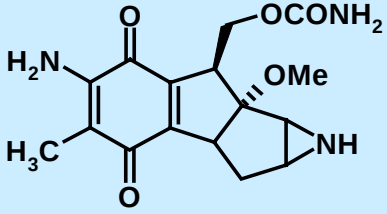
Nitrogen Containing Heterocycles

- ✓ **Three-membered**

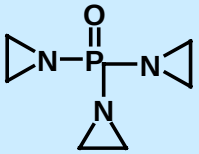
Examples of Aziridine Containing Drugs



Mechlorethamine

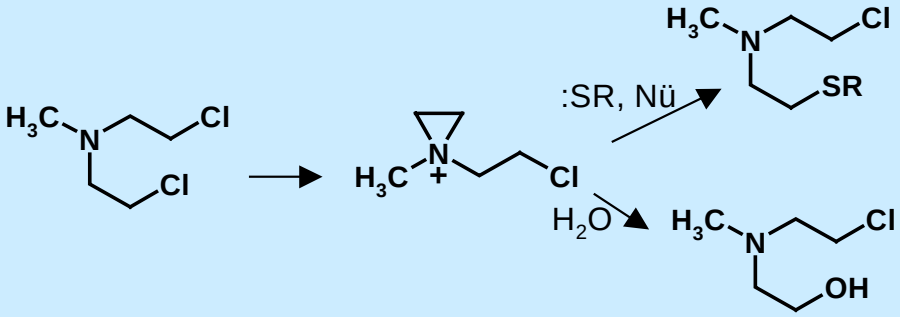


Mitomycin C



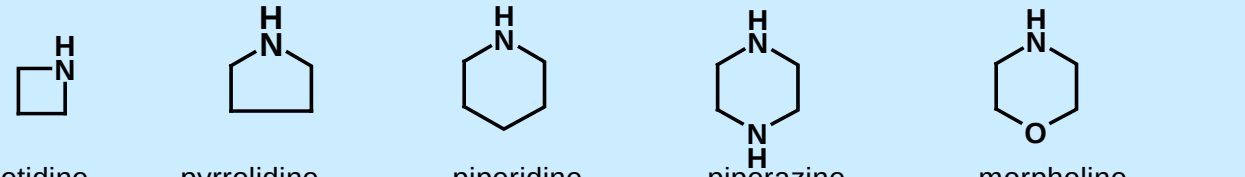
TEPA

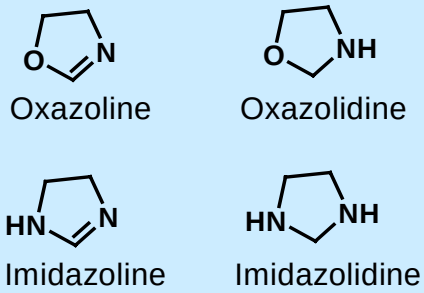
Mechanism of Action of Mechlorethamine – Formation of an Aziridinium Ion

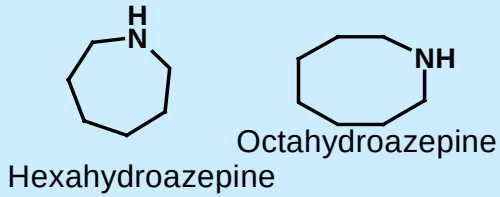


Nitrogen Containing Heterocycles

- ✓ **Higher Membered Ring Systems - Saturated**





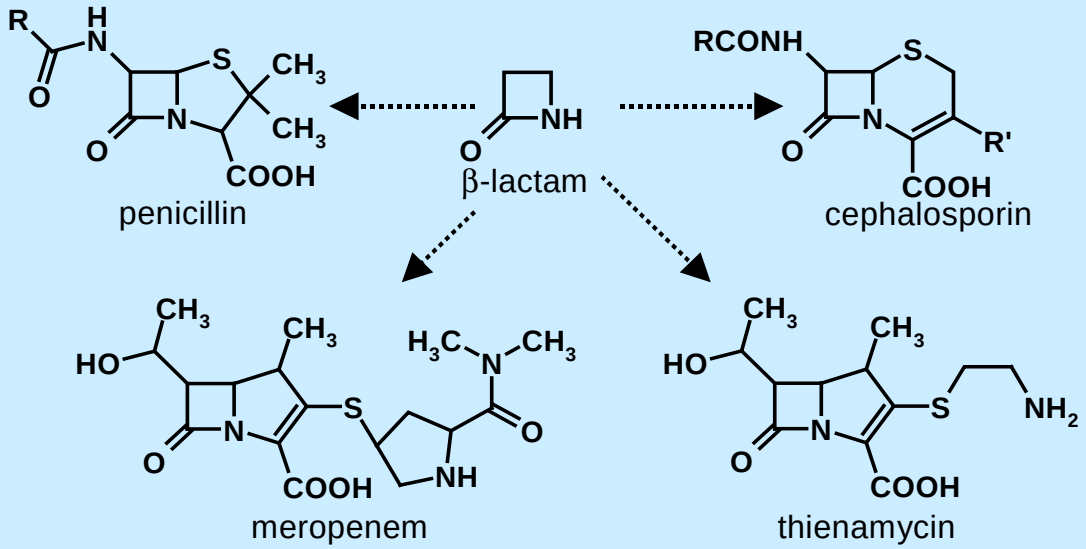


- ✓ *Non-planar molecules*
- ✓ *pK_A same as secondary amines (~8-11)*
- ✓ *Most are liquids with fish-like odor*
- ✓ *Salts are odorless and crystalline*
- ✓ *Some have two pK_A values, e.g., first $(pK_A)_1 > (pK_A)_2$ for imidazolidine*

Nitrogen Containing Heterocycles

- ✓ **Higher Membered Ring Systems - Saturated**

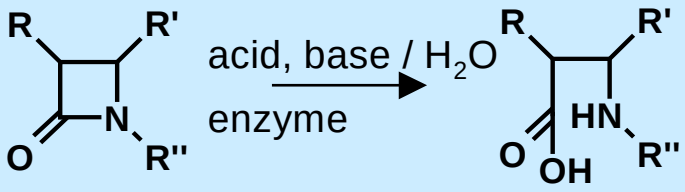
Examples of 4-membered nitrogen containing rings in drugs



Nitrogen Containing Heterocycles

- ✓ **Higher Membered Ring Systems - Saturated**

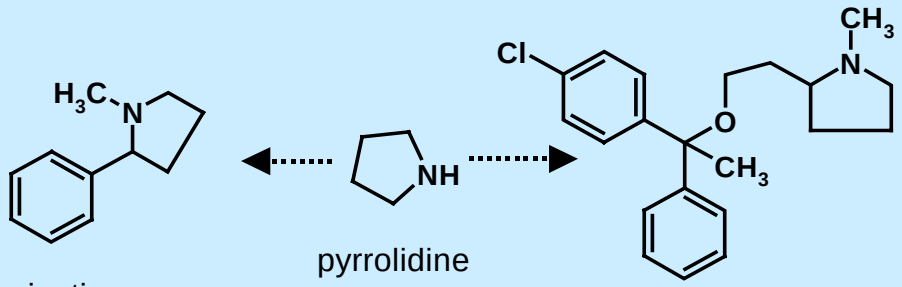
Hydrolysis of β-lactams



Nitrogen Containing Heterocycles

- ✓ **Higher-Membered Ring Systems - Saturated**

Examples of 5-membered nitrogen containing ring in drugs

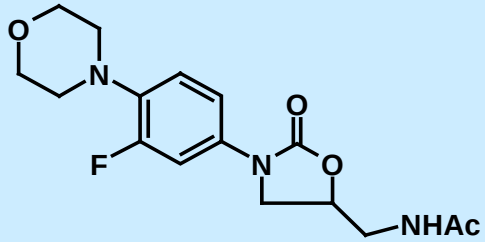


nicotine pyrrolidine clemastine

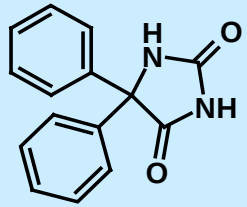
Nitrogen Containing Heterocycles

- ✓ **Higher-Membered Ring Systems - Saturated**

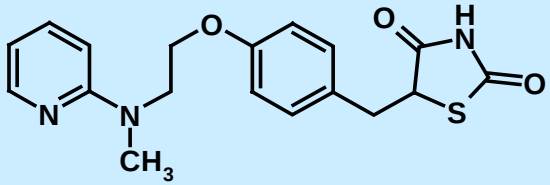
Examples of 5-membered ring containing two heteroatoms in drugs



linezolid
(Anti-infection)



phenytoin
(anti-psychotic)

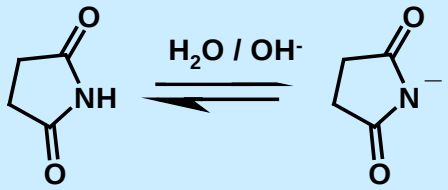


Rosiglitazone
(pyridine + thiazolidine2,4-dione)
Anti-diabetic

Nitrogen Containing Heterocycles

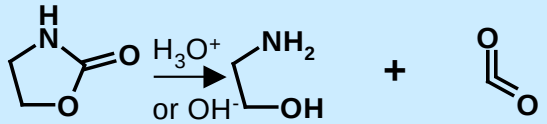
✓ Higher-Membered Ring Systems - Saturated

Acidity of –NH in Imides

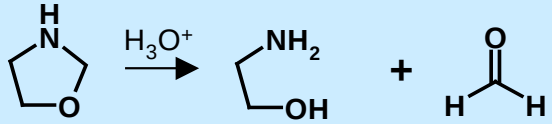


pK_A = 8 - 10

Instability of Carbamates



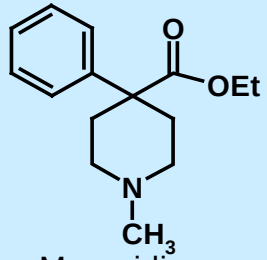
Instability of Oxazolidines



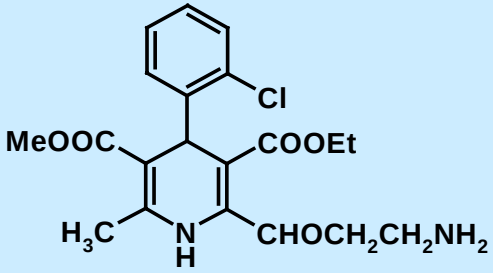
Nitrogen Containing Heterocycles

- ✓ **Higher-Membered Ring Systems - Saturated**

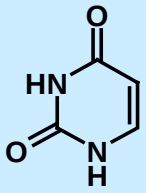
6-membered systems – piperidines, dihydropyridines



Meperidine
(piperidine)
relieves pain,
narcotic analgesic

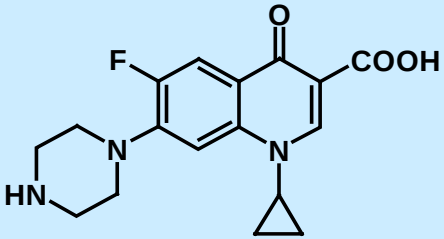


Amlodipine
(dihydropyridine)
Ca^{2+} channel blocker,
Antihypertensive, antianginal

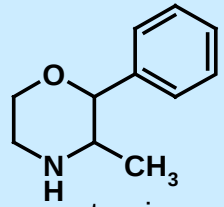


Uracil
(pyrimidine)
One of the bases
of RNA and DNA

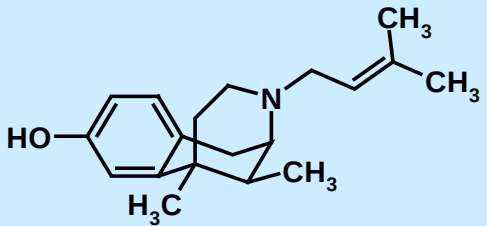
Phenobarbital
(pyrimidine)
controls epilepsy, seizures,
as a sedative to relieve anxiety



Ciprofloxacin
(piperazine)
Antibacterial
(anthrax)



Phenmetrazine
(morpholine)
Appetite suppresant
CNS stimulant
Amphetamine-like

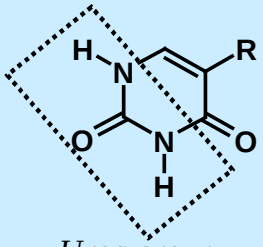


Pentazocine
(octahydroazepine)
Pain reliever

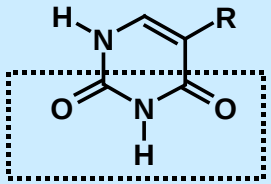
Nitrogen Containing Heterocycles

✓ Higher-Membered Ring Systems - Saturated

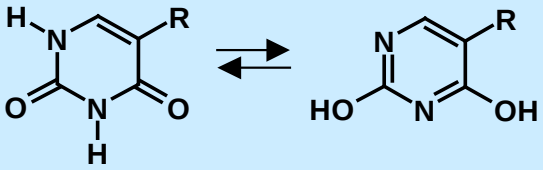
Tautomerism in Barbituric Acids – Enhanced Acidity of -NH



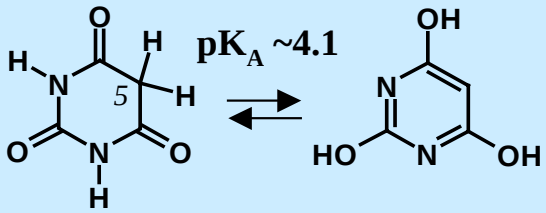
Urea group (neutral)



Imide group (acidic)



Keto form *Enol form*

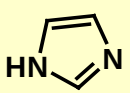


Barbituric Acid (Keto form) *Barbituric Acid (Enol form)*

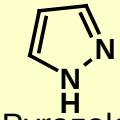
Nitrogen Containing Heterocycles

✓ Unsaturated Ring Systems

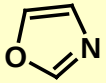
5-membered ring systems



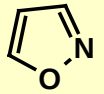
Imidazole
(1,3-diazole)



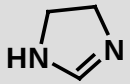
Pyrazole
(1,2-diazole)



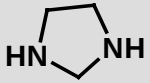
Oxazole
(1,3-oxazole)



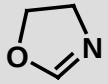
Isoxazole
(1,2-oxazole)



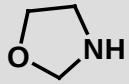
Imidazoline
(1,3-diazoline)



Imidazolidine
(1,3-diazolidine)



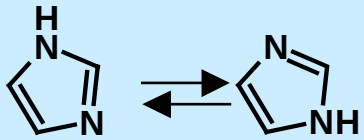
Oxazoline
(1,3-oxazoline)

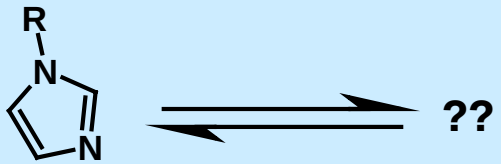


Oxazolidine
(1,3-oxazolidine)

Partly/fully saturated ring structures here are only for reference

Resonance in imidazole – the movement of a hydrogen

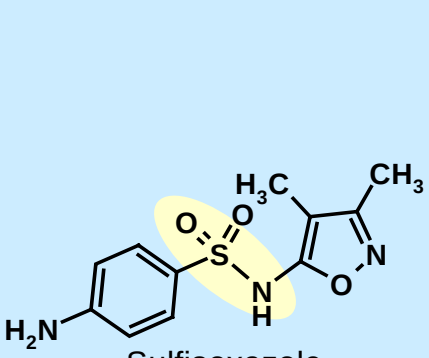




Nitrogen Containing Heterocycles

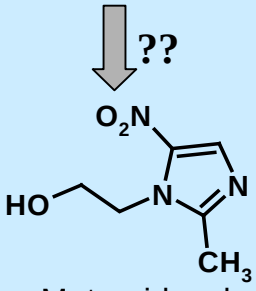
- ✓ **Unsaturated Ring Systems**

  Examples of these ring systems in drugs



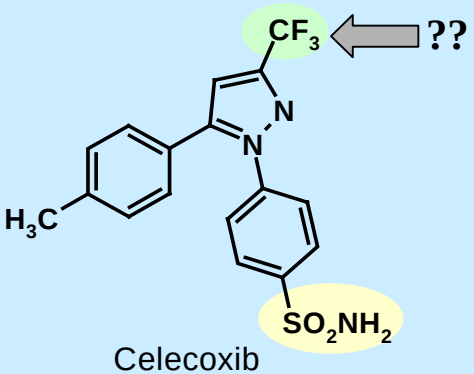
Sulfisoxazole

sulfa-drug
anti-bacterial



Metronidazole

anti-bacterial,
anti-protozoan



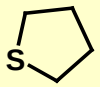
Celecoxib

COX-2 inhibitor
anti-inflammatory

Heterocycles

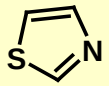
✓ Unsaturated Ring Systems Containing Sulfur

5-membered ring systems

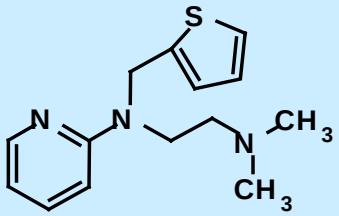


Tetrahydrothiophene
(thiolane)

Thiophene
(Thiole)

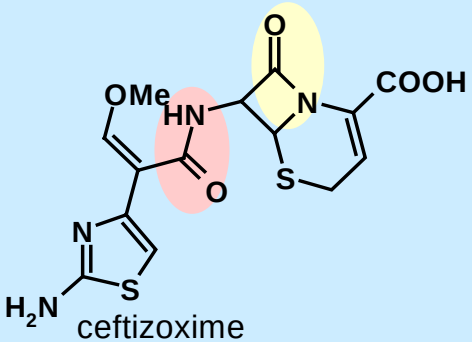


1,3-thiazole



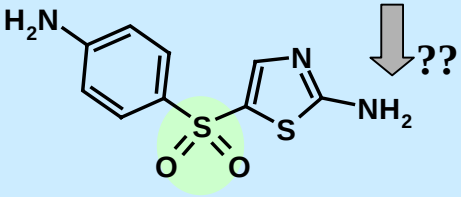
Methapyrilene

Anti-histaminic



ceftizoxime

Anti-biotic

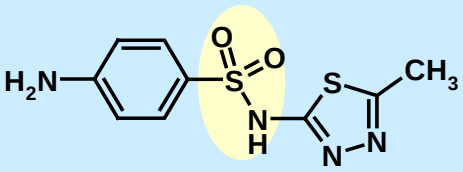


thiazolsulfone

anti-malarial

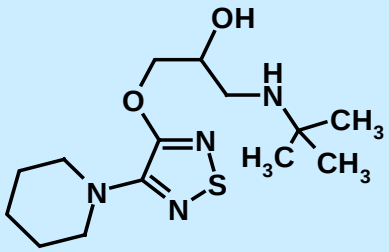
Heterocycles

- ✓ **More Complex Unsaturated Ring Systems**
  - **the 1,3,4- and 1,2,5-thiadiazoles**
  - **the 1,3,4-triazoles**
  - **the 1,2,3,5-tetrazoles**



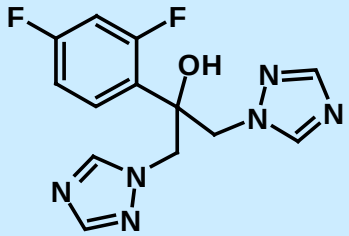
sulfamethizole

Anti-bacterial
Anti-protozoan



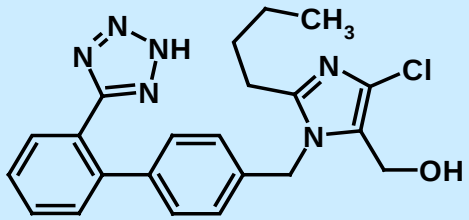
timolol

Anti-hypertensive



fuconazole

Anti-fungal



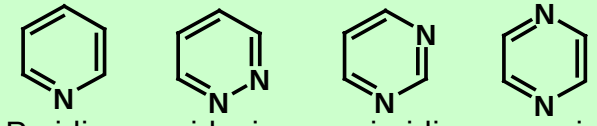
losartan

Anti-hypertensive

Heterocycles

✓ More Complex Unsaturated Ring Systems

➢ 6-membered and higher heterocycles



Pyridine pyridazine pyrimidine pyrazine

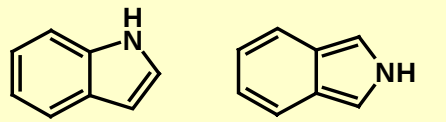
Quinoline — *present in ……* Chloroquine (antimalarial)

Isoquinoline — Praziquantel (anti-worm)

Coumarin — Warfarin (anticoagulant)

Quinazoline — Prazosin (antihypertensive)

Pteridine — Triamterene (antihypertensive)



Indole — *present in …..* Tryptophan (common AA)

Isoindole — LSD (hypnotic)

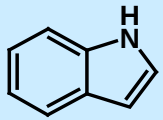
Benzimidazole — Omeprazole (anti-ulcer)

Benzoxazole — Chlorozoxazone (relieves pain)

Benzthiazole — Ethoxzolamide (diuretic)

Heterocycles

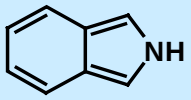
- ✓ **More Complex Unsaturated Ring Systems**
  - ➢ **6-membered and higher heterocycles**



Indole

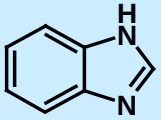
present in …..

Tryptophan (common AA)



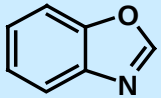
Isoindole

LSD (hypnotic)



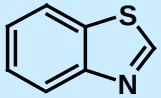
Benzimidazole

Omeprazole (anti-ulcer)



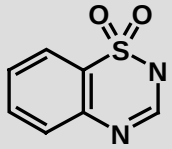
Benzoxazole

Chlorozoxazone (relieves pain)



Benzthiazole

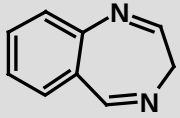
Ethoxzolamide (diuretic)



1,2,4-benzothia diazin-1,1,-dioxide

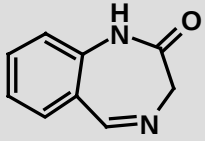
present in …..

Chlorothiazide (antihypertensive)



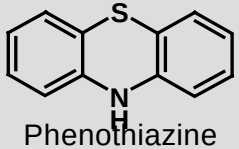
3H-1,4-Benzo diazepine

Chlordiazepoxide (sedative, hypnotic)



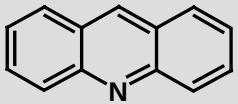
1,3-Dihydro-2H-1,4-benzodiazepin-2-one

Diazepam (sedative, anxiolytic)



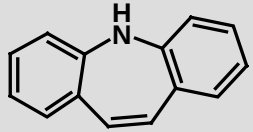
Phenothiazine

Chloropromazine (anxiolytic)



Acridine

Quinocrine (antibiotic)



5H-dibenz [b,f]azepine

Imipramine (anti-depressants)

Heterocycles

✓ Electrophilic Aromatic Substitution in Heterocycles

- heterocycles generally react well with electrophiles; better than benzene (except for pyridines)
- their stability to metabolic enzymes is generally lower than their carbocyclic analogs
- EAS occurs at the 2-position of 5-membered heterocycles
- EAS occurs at the 3-position of 6-membered heterocycles