



Organic Chemistry II

PHA284

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Ankara University

Faculty of Pharmacy

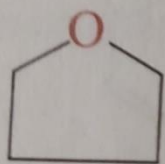
Department of Pharmaceutical Chemistry



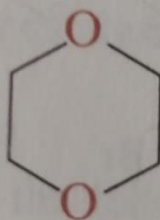
Heterocycles

✓ **Nomenclature**

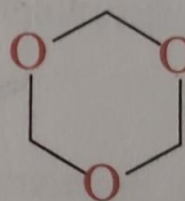
- Hetero-atom is to be counted as 1 or as low as possible
- When there is more than one hetero-atom, preference is given to O, then S, then N, then C. Also N-H presides over -N= .
- When there is more than one hetero-atom, numbering should be as direct as possible from one to the other
- Substituents are numbered as low as possible
- Common suffixes for N- and non-N-heterocycles For partially unsaturated systems, H is (are) are used to indicate the location of saturation
- Hantzsch-Widman System of systematic name of heterocyclic compounds



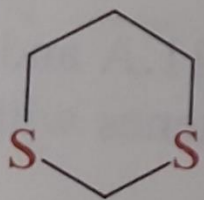
tetrahydrofuran



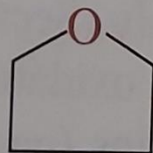
1,4-dioxane



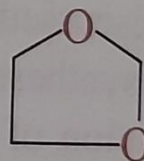
1,3,5-trioxane



1,3-dithiane
(used commonly)



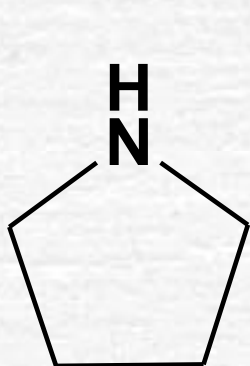
oxolane
(rarely used)



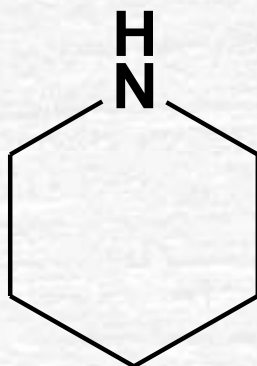
1,3-dioxolane
(used commonly)

Heterocycles

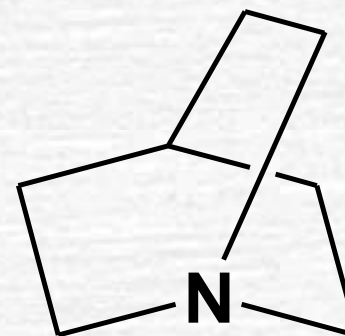
- ✓ **Hantzsch – Widman Nomenclature** (adopted by IUPAC)



pyrrolidine



piperidine



quinuclidine

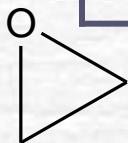
(1-azabicyclo[2.2.2]octane)

- Acceptable prefixes include O=Oxa; S=Thia; N=Aza

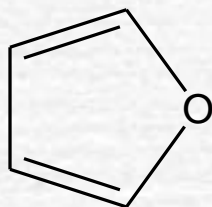
Heterocycles

- ✓ **Hantzsch – Widman Nomenclature** (adopted by IUPAC)

<i>Ring Size</i>	<i>Saturated</i>	<i>Partly Saturated</i>	<i>Unsaturated</i>
3	-irane	-	-irene
4	-etane	(dihydro)	-ete
5	-olane	(dihydro)	-ole
6	-inane	(di or tetrahydro)	-ine
7	-epane	(di or tetrahydro)	-epine
8	-ocane	(di, tetra, or hexahydro)	-ocine

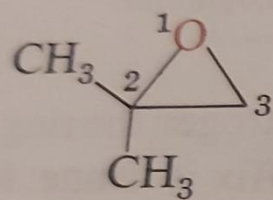


Common name : ethylene oxide
Systematic name : Oxa + irane Oxirane

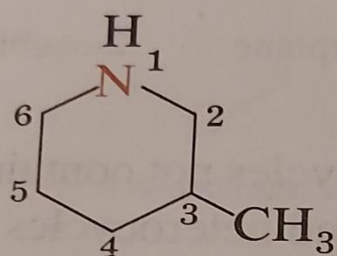


Common name : furan
Systematic name : Oxa + ole Oxole

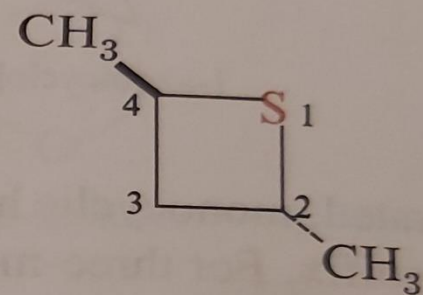
In naming substituted derivatives, the ring is numbered beginning with the heteroatom.



2,2-dimethyloxirane



3-methylpiperidine

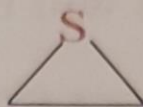


trans-2,4-dimethylthietane

Names in common use of some fully saturated heterocycles containing only one hetero-atom are shown below.



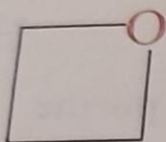
oxirane
(ethylene oxide)



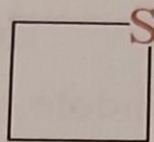
thiirane
(ethylene sulfide)



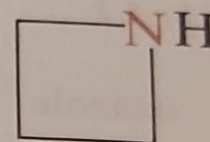
aziridine
(ethyleneimine)



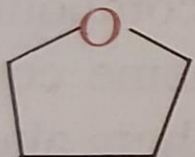
oxetane



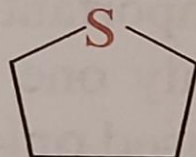
thietane



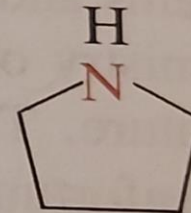
azetidine



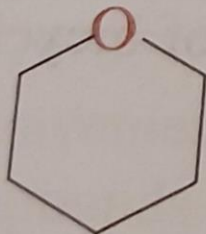
tetrahydrofuran



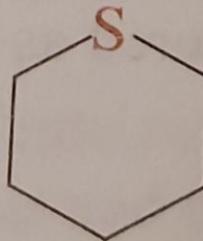
tetrahydrothiophene



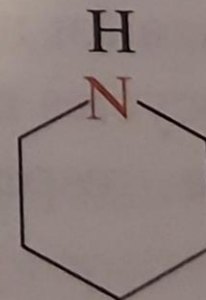
pyrrolidine



tetrahydropyran



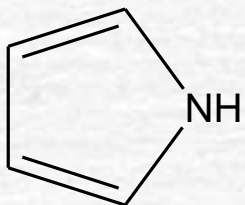
tetrahydrothiopyran



piperidine

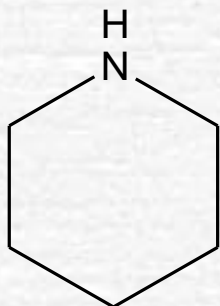
Heterocycles

✓ **Hantzsch – Widman Nomenclature** (adopted by IUPAC)



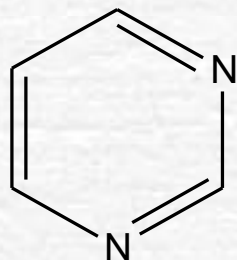
Common name : pyrrole

Systematic name : H at 1 position + Aza + ole 1H-Azole



Common name : piperidine

Systematic name : Aza + inane 1H-Azinane

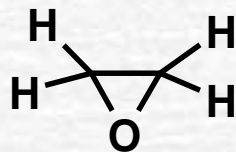


Common name : pyrimidine

Systematic name : two aza at 1, 3 positions + ine [1,3]-diazine

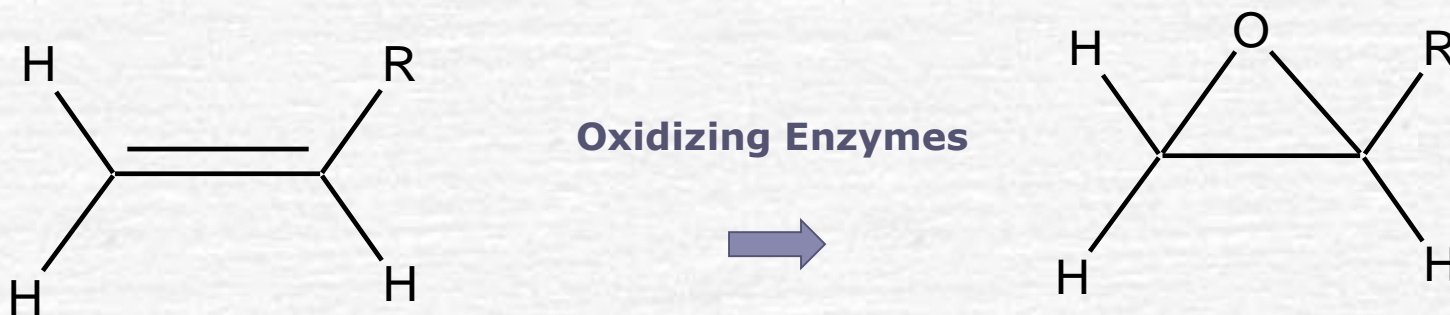
Oxygen Containing Heterocycles

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



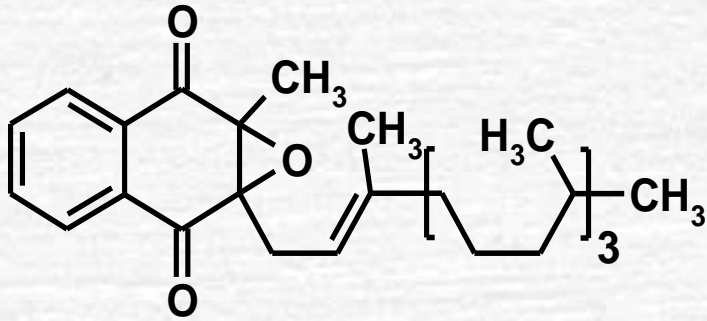
- **Epoxide**, cyclic ether with a three-membered ring. The basic structure of an **epoxide** contains an oxygen atom attached to two adjacent carbon atoms of a hydrocarbon. ... **Epoxides** are easily opened, under acidic or basic conditions, to give a variety of products with useful functional **groups**.

- ✓ **Oxirane formation in our body**



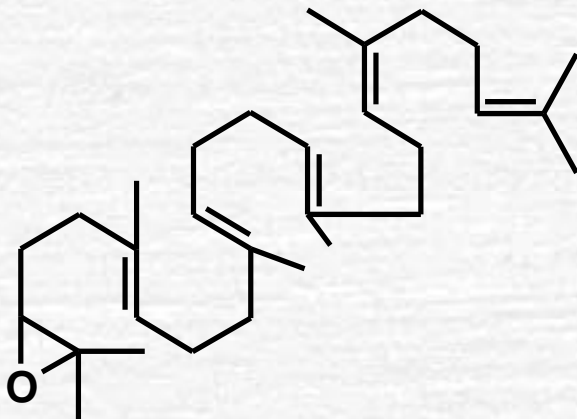
Oxygen Containing Heterocycles

✓ Epoxides in our system



Vitamin K epoxide

Role of Vitamin K epoxide?

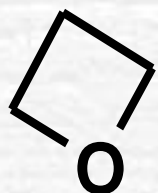


Squalene Epoxide

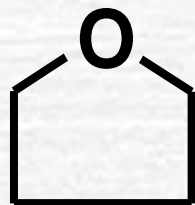
Role of Squalene epoxide?

Oxygen Containing Heterocycles

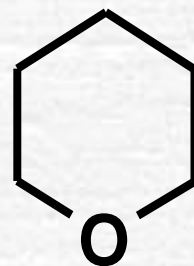
✓ Higher Oxides



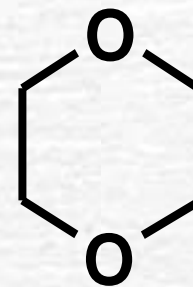
Oxetane



oxolane



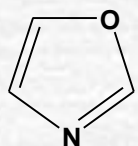
oxane



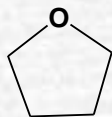
1,4-dioxane

Oxygen Containing Heterocycles

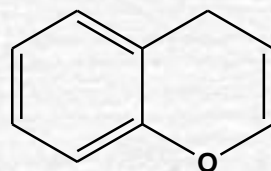
The **oxygen-containing heterocycles** are an important class of **compounds** in organic chemistry. These **compounds** are used as drugs (coumarin and oxazole), solvent (tetrahydrofuran), flavors, and fragrances (lactones). ... Some of the fused **compounds** are coumarin (benzopyrans) and piclozotan (benzoxazepines).



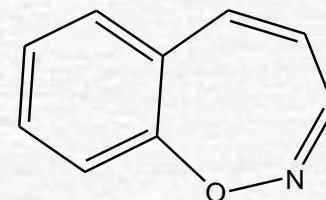
oxazole



tetrahydrofuran



benzopyran

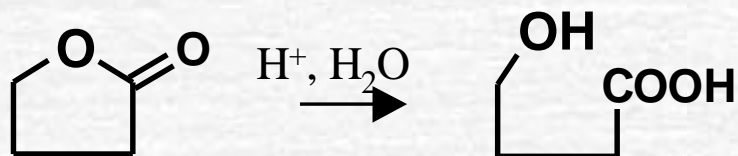


benzoxazepine

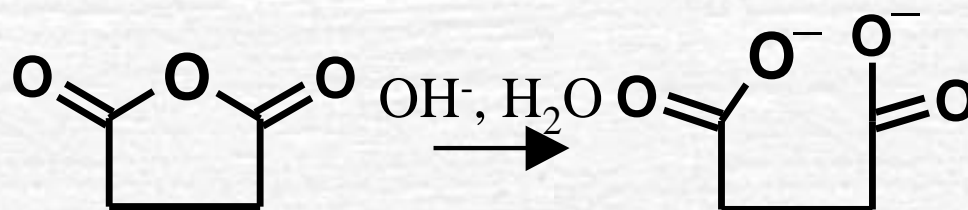
Oxygen Containing Heterocycles

✓ Higher Oxides

Stability of these oxides change drastically on α -substitution



Lactones

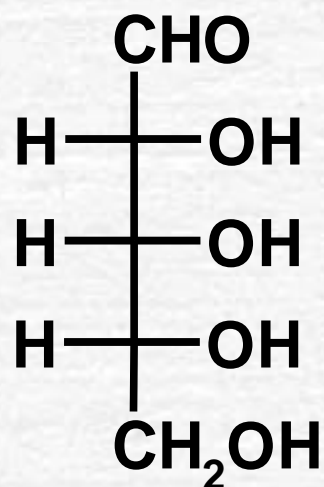


anhydrides

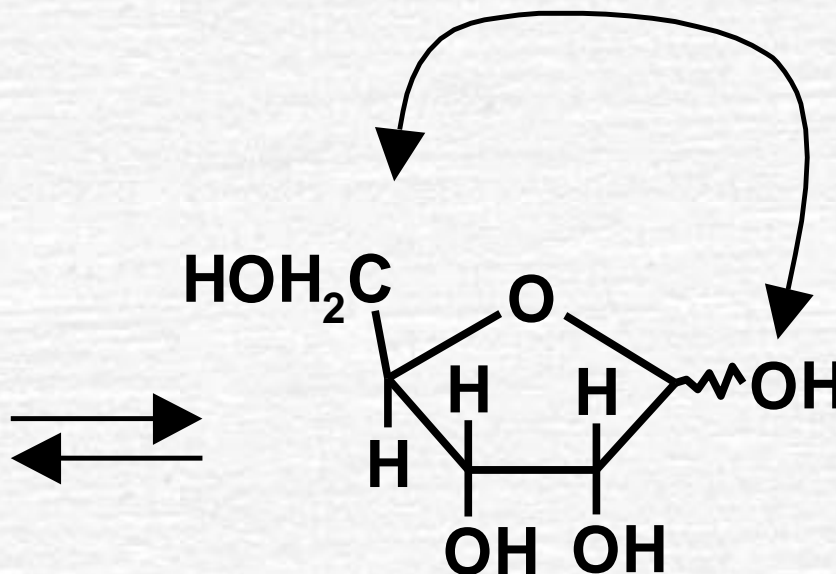
A **lactone** is an ester in which the **functional group** of the ester has become part of a ring structure with carbon atoms.

Oxygen Containing Heterocycles

✓ Examples of Acetals or Hemi-Acetals in Nature



ribose



hemiacetal

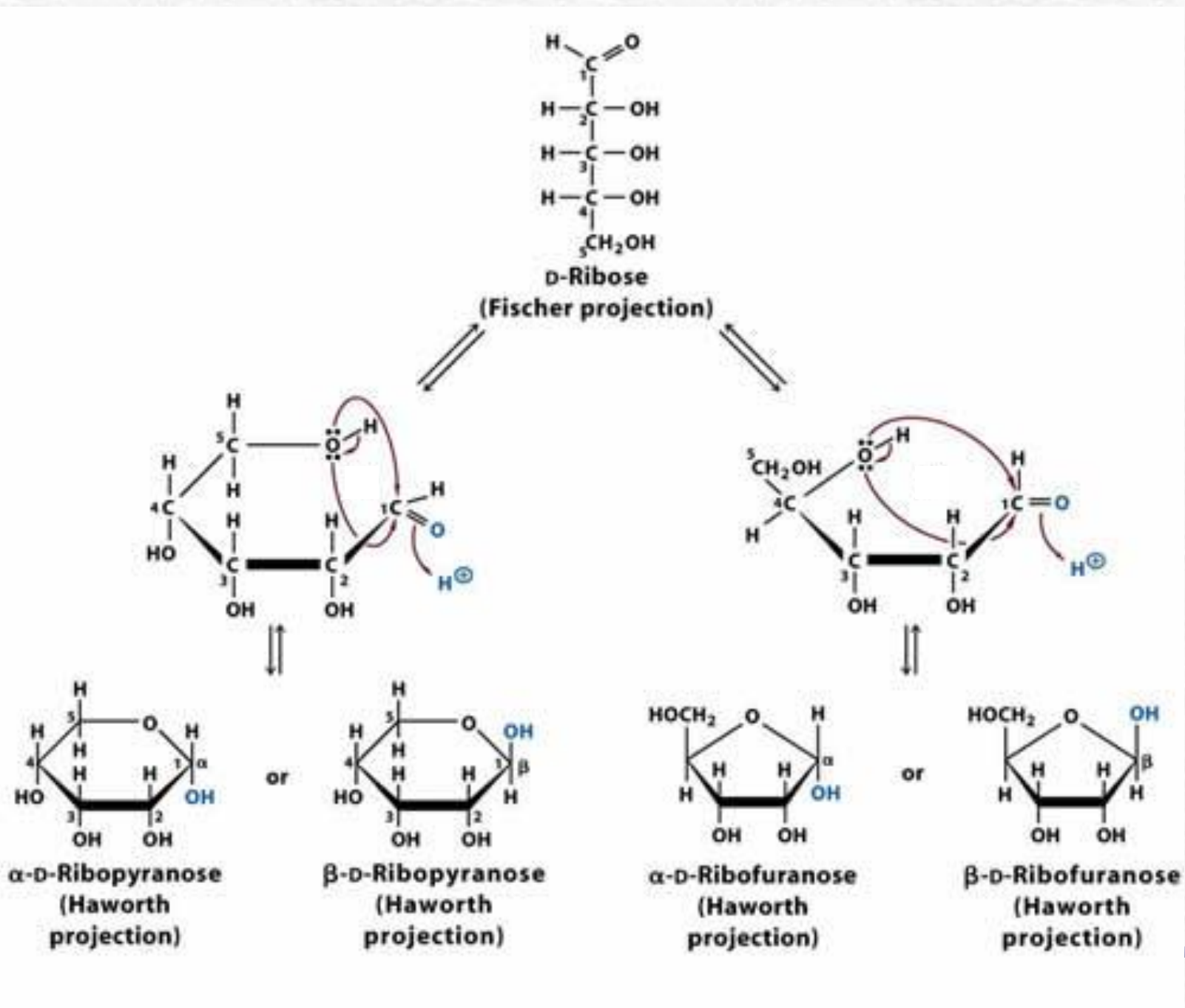
Same side = β
Opposite side = α

In case of the compounds having the OH group on the highest numbered chiral carbon on right side of the viewer, notation D- is used like natural carbohydrates (glucose, ribose).

In the other side it will be L- like natural amino acids.

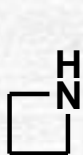
Oxygen Containing Heterocycles

- ✓ **Interconversion of α - and β -forms of sugars**
The phenomenon of mutarotation

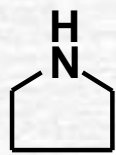


Higher Heterocycles Containing Nitrogen

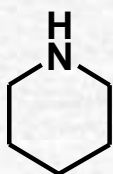
✓ Basic Ring Systems



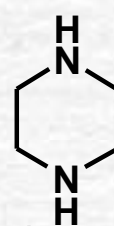
azetidine



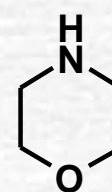
pyrrolidine
(azolidine)



piperidine
(perhydroazine)



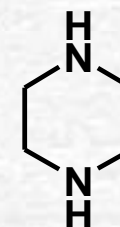
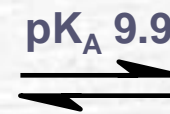
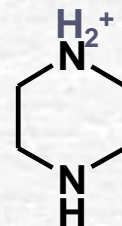
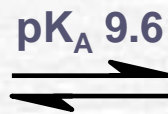
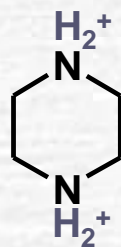
piperazine
(perhydro-1,4-diazine)



morpholine
(perhydro-1,4-oxazine)

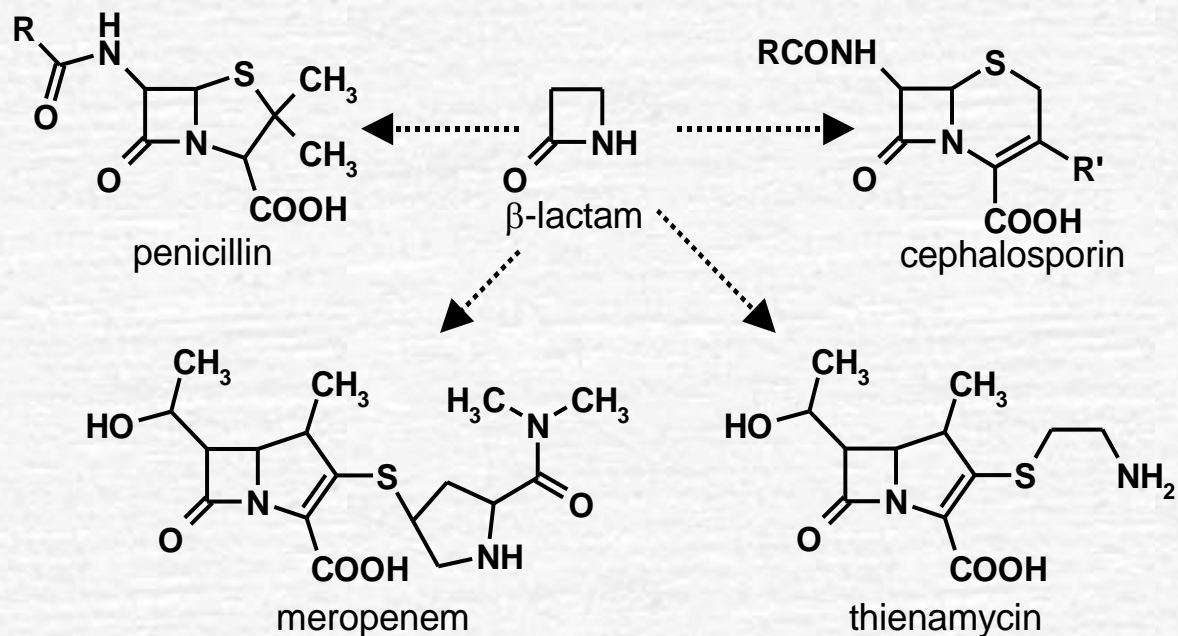
✓ Acid – Base Properties

Ist pK_A ?
IInd pK_A ?

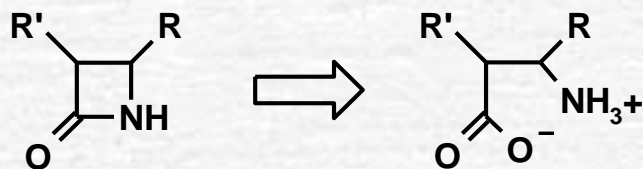


Higher Heterocycles Containing Nitrogen

✓ Examples of Drugs ... 4-membered ring



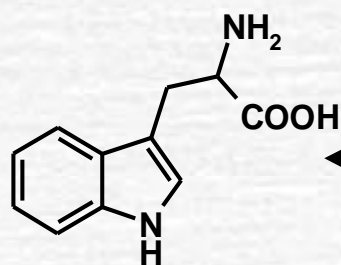
✓ Hydrolysis of β -lactams acid/base and enzymatic conditions



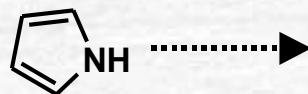
A **lactam** is an amide in which the **functional group** of the amide has become part of a ring structure with carbon atoms.

Higher Heterocycles Containing Nitrogen

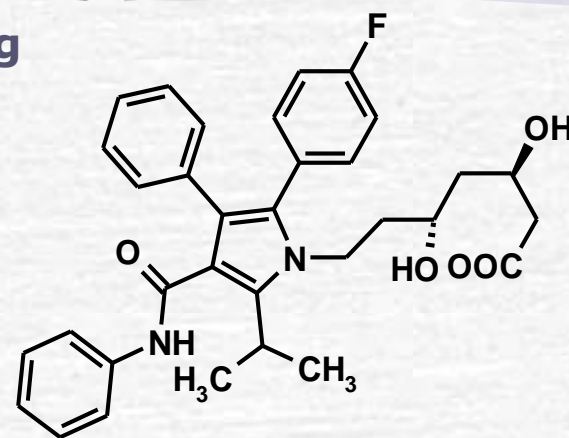
✓ Examples of Drugs ... 5-membered ring



tryptophan

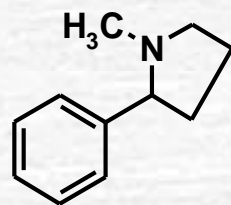


pyrrole



atorvastatin

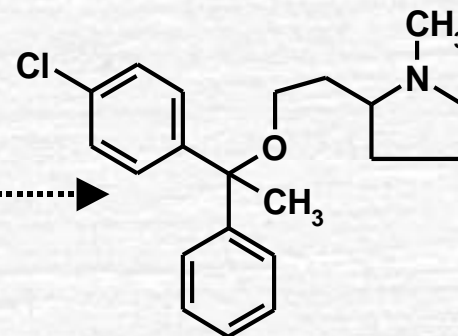
(anti-hyperlipidemic agent)



nicotine



pyrrolidine

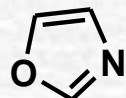


clemastine

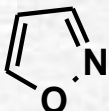
(anti-histaminic)

Five-membered Rings Containing Nitrogen and Another Heteroatom

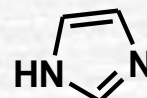
✓ Nitrogen and Oxygen



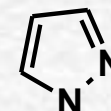
Oxazole
(1,3-oxazole)



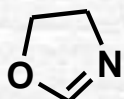
Isoxazole
(1,2-oxazole)



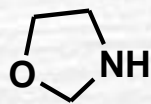
Imidazole
(1,3-diazole)



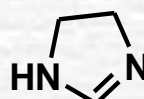
Pyrazole
(1,2-diazole)



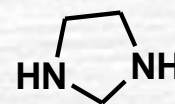
Oxazoline
(1,3-oxazoline)



Oxazolidine
(1,3-oxazolidine)



Imidazoline
(1,3-diazoline)



Imidazolidine
(1,3-diazolidine)

✓ Acid – Base Properties

Ist pK_A ?

IInd pK_A ?

Why is imidazole not strongly basic ?

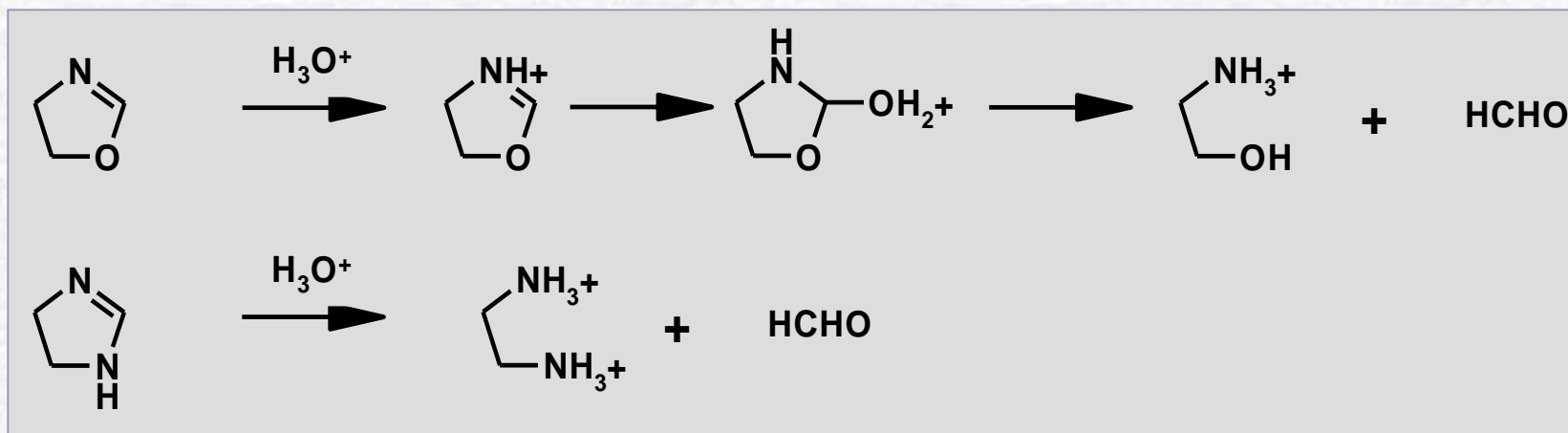
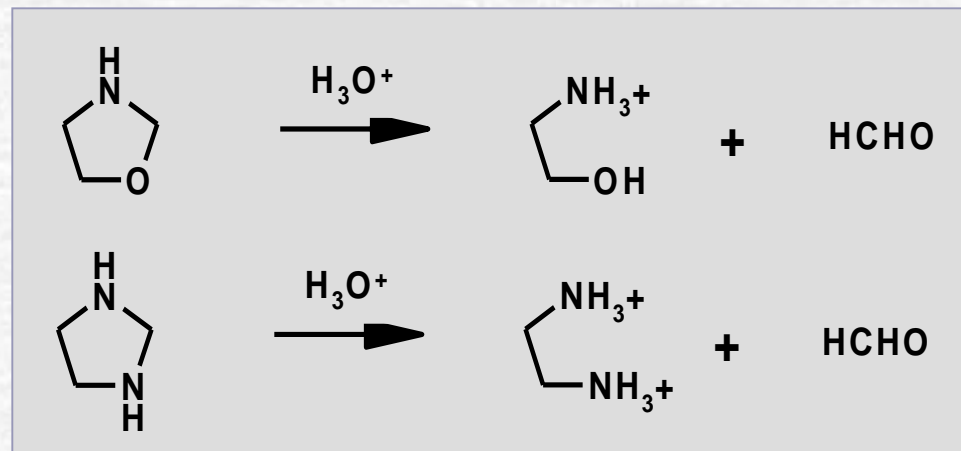
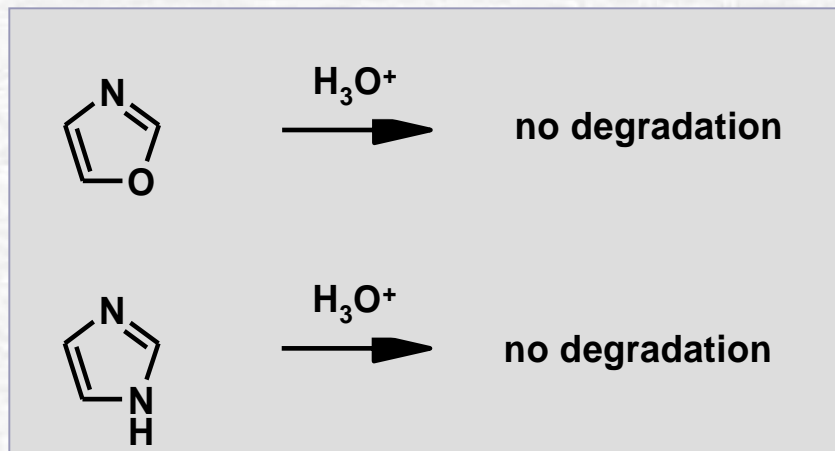
pK_A with greater substitution ?

Higher Heterocycles Containing Nitrogen and Another Heteroatom

✓ Stability to Water, Acid and Base

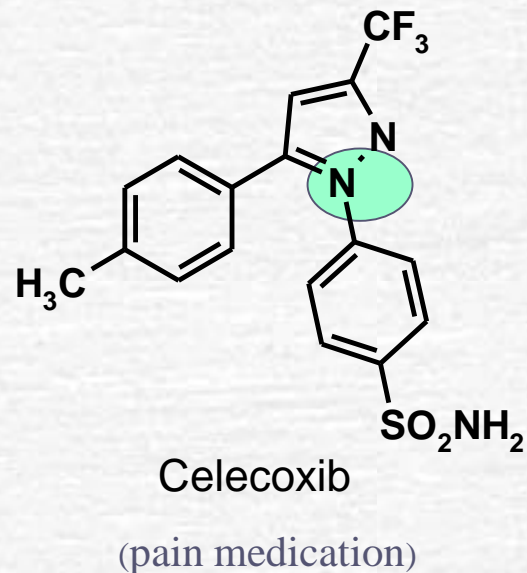
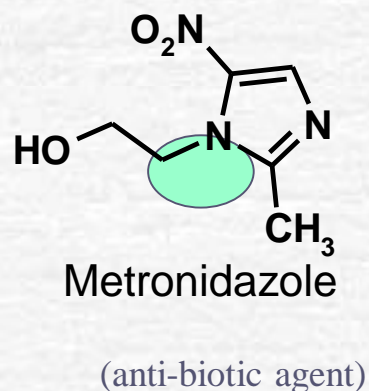
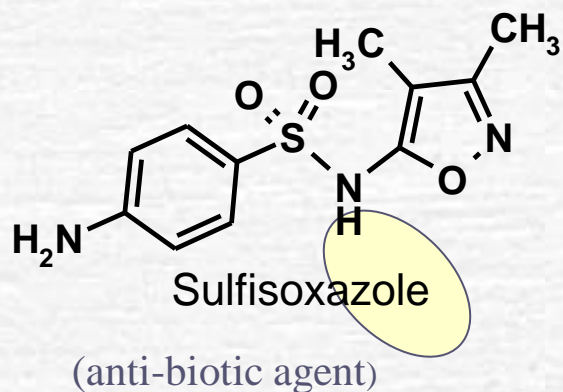
Without substituents ?

With substituents ?

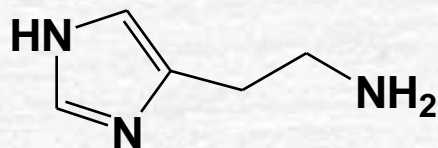


Higher Heterocycles Containing Nitrogen and Another Heteroatom

✓ Examples of such heterocycles in Drugs



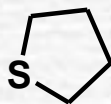
The imidazole molecule is actual extremely important in biochemistry, so let's take a look at a famous molecule that contains the imidazole ring, and this molecule is called **histamine**, which, anyone who has allergies, has heard of histamine.



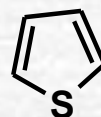
Histamine

Heterocycles Containing Sulfur

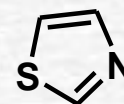
✓ Basic Ring Systems



Tetrahydrothiophene
(thiolane)

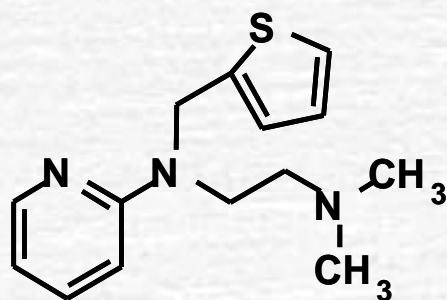


Thiophene
(Thiole)

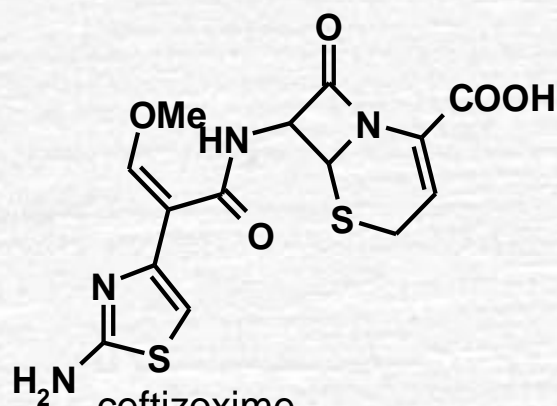


1,3-thiazole

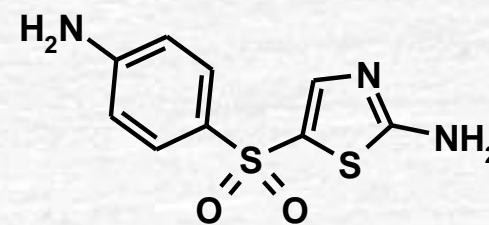
✓ Examples in Drugs



methapyrilene
(Antihistamine)



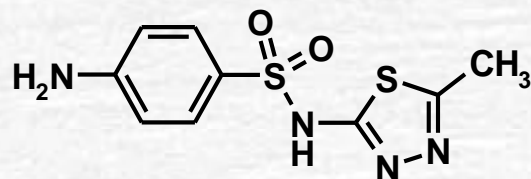
ceftizoxime
(Antibiotic)



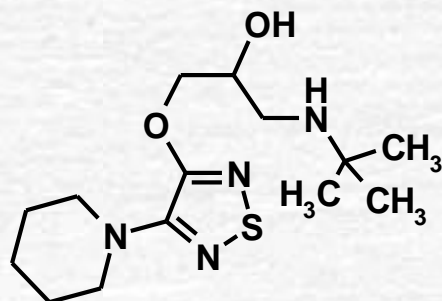
thiazolsulfone
(Antimalarial)

Complex Heterocycles

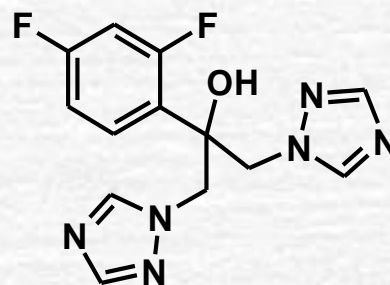
✓ Examples in Drugs



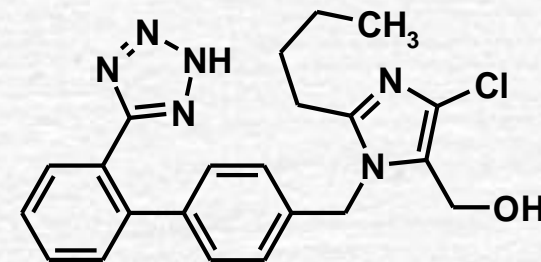
sulfamethizole
(Antibiotic)



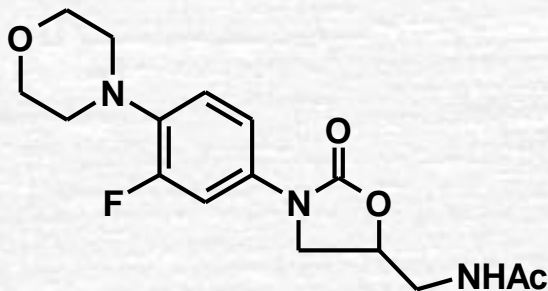
timolol
(Antihypertensive)



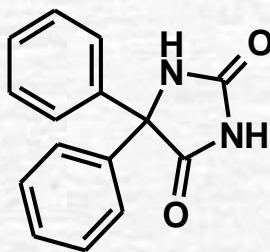
fuconazole
(for pneumonia)



losartan
(Antihypertensive)



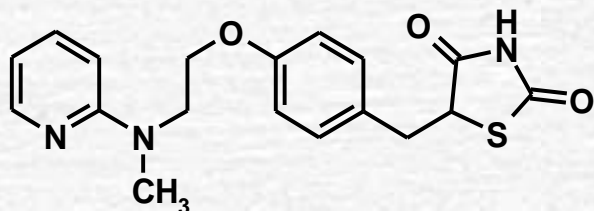
linezolid
(Anti-infectious)



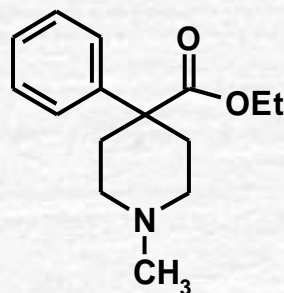
phenytoin
(Anti-seizure)

6 Membered Rings Containing One Nitrogen

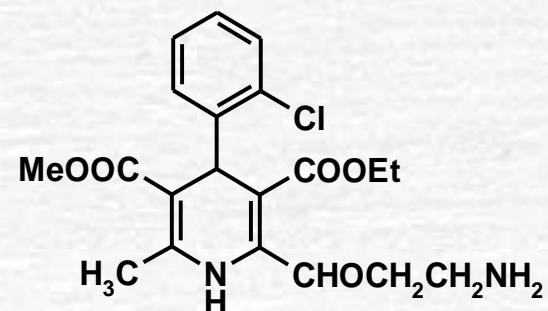
✓ Examples in Drugs



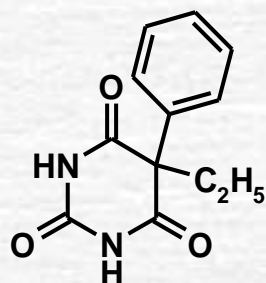
Rosiglitazone
(pyridine + thiazolidine 2,4-dione)
Anti-diabetic



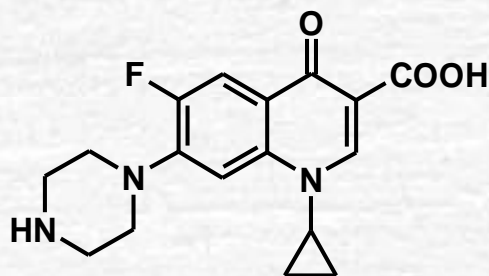
Meperidine
(piperidine)
relieves pain,
narcotic analgesic



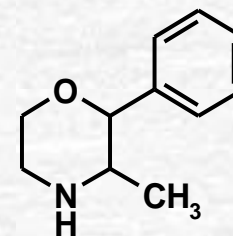
Amlodipine
(dihydropyridine)
Ca²⁺ channel blocker,
Antihypertensive, antianginal



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



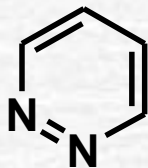
Ciprofloxacin
(piperazine)
Antibacterial
(anthrax)



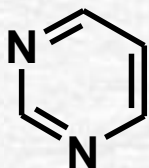
Phenmetrazine
(morpholine)
Appetite suppressant
CNS stimulant
Amphetamine-like

6 Membered Rings Containing Two Nitrogens

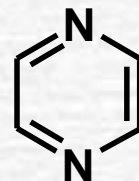
✓ Diazines



1,2-diazine
(pyridazine)



1,3-diazine
(pyrimidine)



1,4-diazine
(pyrazine)

✓ Acid – Base Properties

Ist pK_A ?

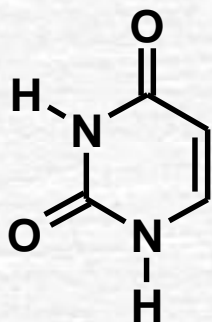
IInd pK_A ?

Why are these dibasic compounds not strongly basic ?

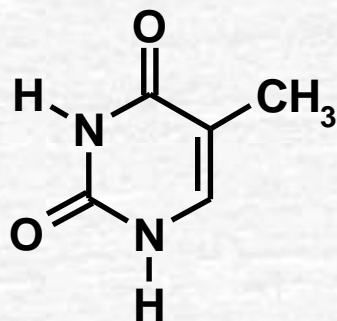
6 Membered Rings Containing Two Nitrogens

✓ **Pyrimidines**

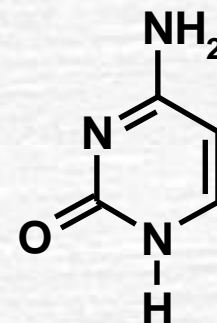
Three derivatives are important for RNA/DNA



Uracil

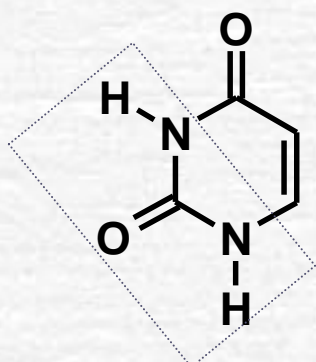


Thymine

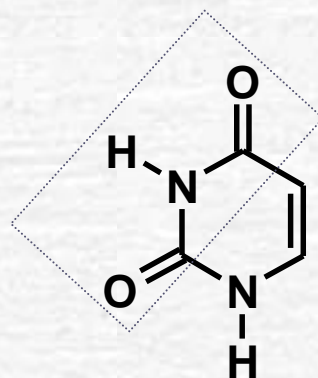


Cytosine

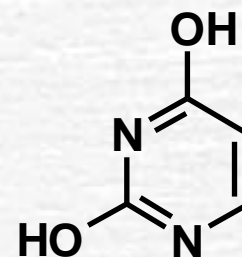
✓ **Forms of Pyrimidines**



Urea
(neutral)



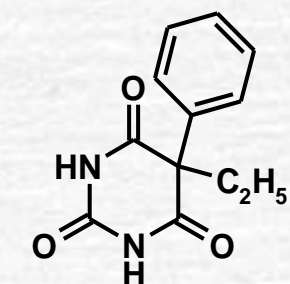
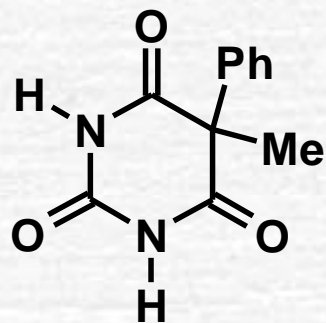
Imide or Keto form
(acidic)



Enol form
(acidic)

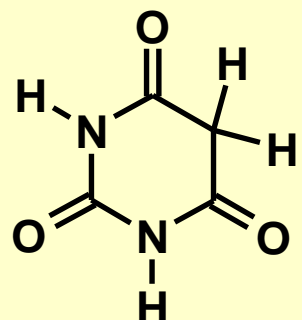
6 Membered Rings Containing Two Nitrogens

✓ Special Pyrimidines ... Barbituric Acid

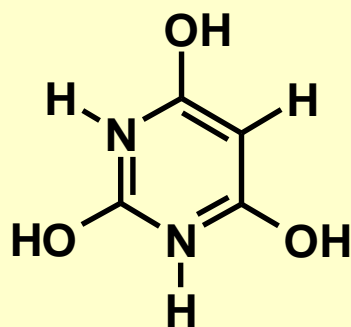
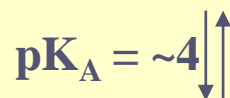


Phenobarbital
(pyrimidine)

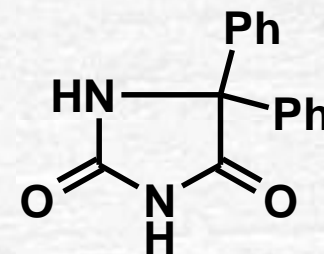
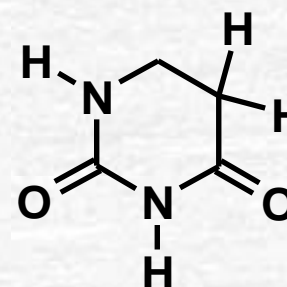
controls epilepsy, seizures,
as a sedative to relieve anxiety



(Keto form)



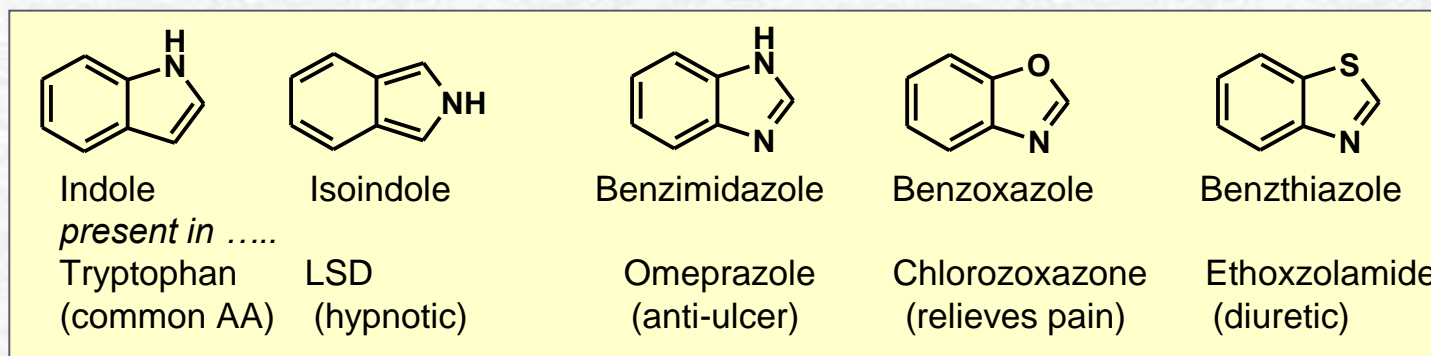
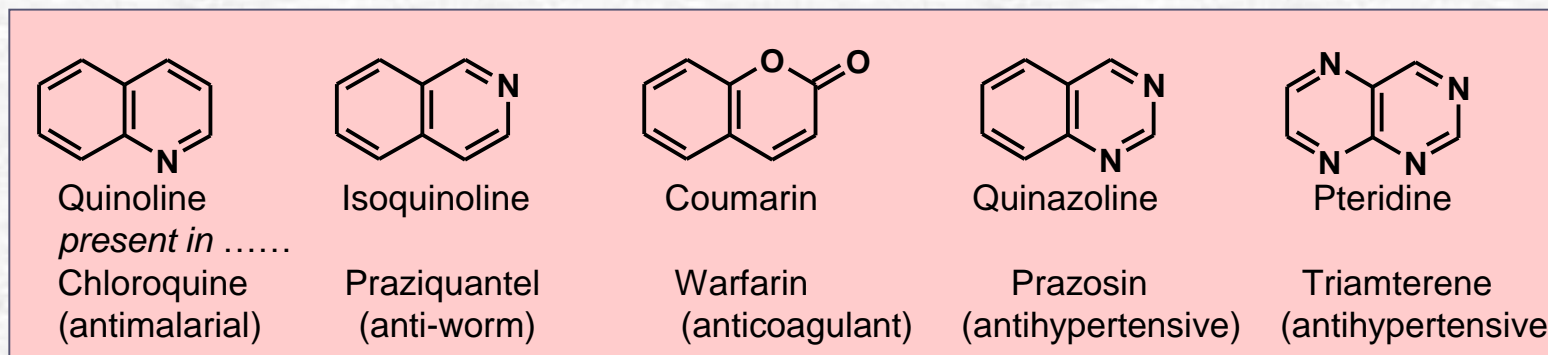
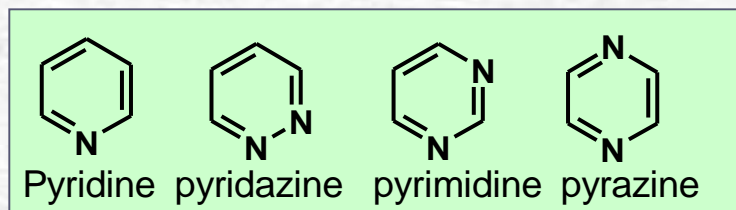
(Enol form)



Phenytoin
(anti-psychotic)

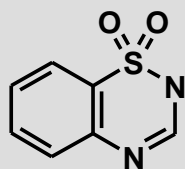
✓ More Complex Unsaturated Ring Systems

➤ 6-membered and higher heterocycles

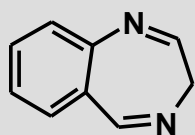


✓ More Complex Unsaturated Ring Systems

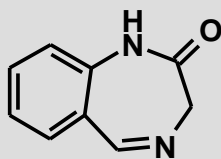
➤ 6-membered and higher heterocycles



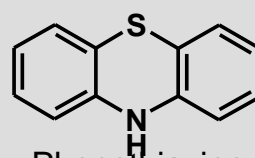
1,2,4-benzothiazine-1,1-dioxide
present in
Chlorothiazide
(antihypertensive)



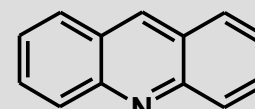
3H-1,4-Benzodiazepine



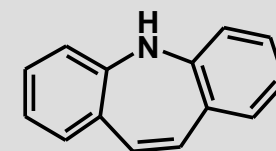
1,3-Dihydro-2H-1,4-benzodiazepin-2-one



Phenothiazine



Acridine



5H-dibenz[b,f]azepine

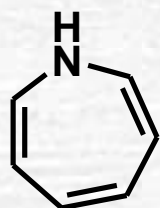
Chlordiazepoxide
(sedative, hypnotic)

Diazepam
(sedative, anxiolytic)

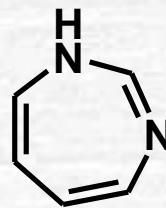
Chlorpromazine
(anxiolytic)

Quinocrine
(antibiotic)

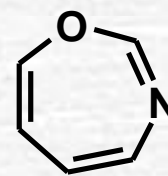
Imipramine
(anti-depressants)



Azepine

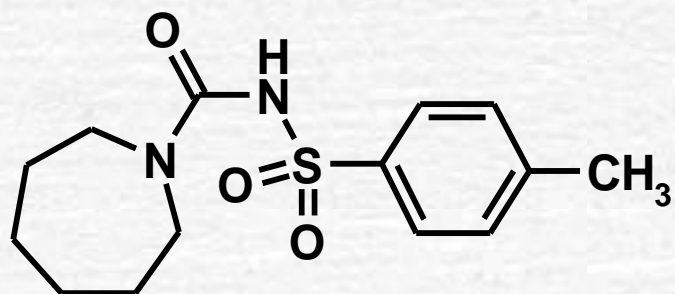


diazepine

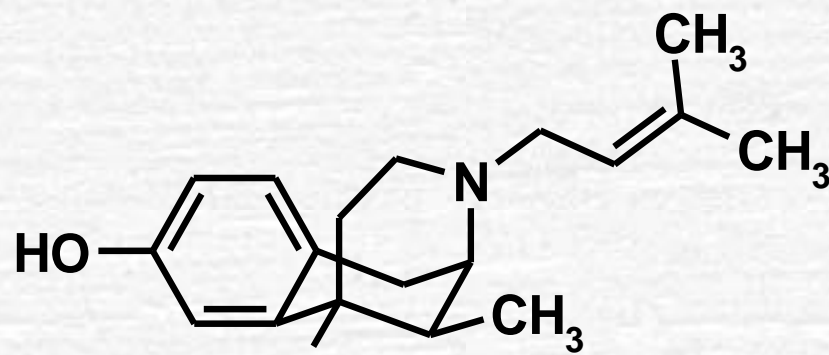


oxazepine

7 and 8 Membered Nitrogen Containing Heterocycles



Tolazamide
(hexahydroazepine)
Oral hypoglycemic

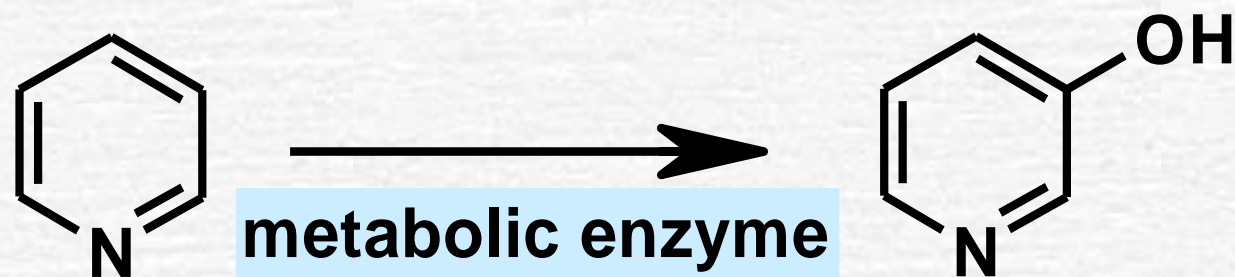
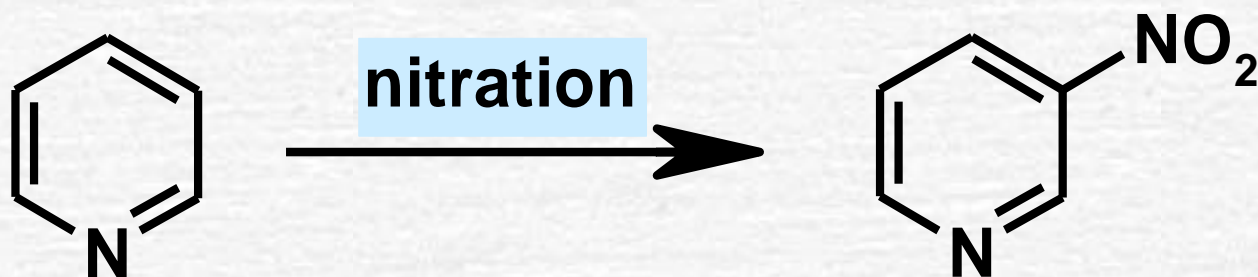


Pentazocine
(octahydroazepine)
Pain reliever

Six Membered Aromatic Heterocycles

✓ Metabolism of Pyridines

- Pyridines are less reactive toward electrophiles than benzene
- Stability to metabolic enzymes is generally higher than their carbocyclic analogs



LITERATURES

1- <https://slideplayer.com/slide/4727988/>

2- A. Streitwieser, C.H. Heathcock, (1985), Introduction to Organic Chemistry, 3th edition, London.

References

- ***Organic Chemistry 11e***, T.W. Graham Solomons, Craig B. Fryhle, Scott A. Snyder, John Wiley & Sons, Inc., 2014, ISBN 978-1-118-13357-6 (cloth) Binder-ready version ISBN 978-1-118-14739-9
- ***Organic Chemistry: A Short Course, 13th Ed.***, D.J. Hart, C.M. Hadad, L.E. Craine, H. Hart, Brooks/Cole, Cengage Learning, 2012, ISBN-13: 978-1-111-42556-2
- ***Organic Chemistry, 6th Ed.***, L. G. Wade, Pearson Education, Inc., 2006, ISBN 0-13-147871-0
- ***Organic Chemistry, 2nd Ed.***, Jonathan Clayden, Nick Greeves, and Stuart Warren,, Oxford University Press, 2012, ISBN: 9780199270293
- ***Organic Chemistry***, Mukherjee, S.M., et al., New Age International Ltd, 2008. ProQuest Ebook Central, <http://ebookcentral.proquest.com/lib/ankara/detail.action?docID=3017383>.