

Heterocyclic compounds

Cyclic organic compounds containing at least one element other than carbon, within the ring system. E.g., N, O, S, P, As, etc .

Objectives

- Define heterocyclic compounds
- Describe the nomenclature systems of heterocyclic compounds
 - IUPAC
 - Trivial names/common names
 - Hantzsch–Widman naming system
- Describe the Classification of heterocyclic compounds

Heterocyclic compounds

☐ Books to read

☐ Fundamentals of heterocyclic chemistry

Louis D. Quin and John A. Tyrell

Classification

Can be classified according to;

- Nature and/or number of the hetero-atom(s) present
 - Azoles contain nitrogen, thiophenes S
- Degree of saturation
 - Aromatic, non-aromatic
 - Saturated, unsaturated
- Size of the heterocyclic compound
 - Number of atoms making up the ring system; 3, 4, 5, 6, 7, 8, 9, 10
 - Simple heterocycles
 - Fused ring systems

Heterocyclic compounds

Nomenclature

Four rules

1. The heteroatom is given a name and is used as a prefix: N, aza-; O, oxa-; S, thia-; P, phospho-; As, arsa-; Si, sila-; Se, seleno-, B, bora, and so on. The “a” ending is dropped if the next syllable starts with a vowel. Thus “aza-irine” is properly written “azirine.”
2. Ring size is designated by stems that follow the prefix: 3-atoms, -ir-; 4-atoms, -et-; 5-atoms, -ol-; 6-atoms, -in-; 7-atoms, -ep-; 8-atoms, -oc-; 9-atoms, -on-; and so on.

Heterocyclic compounds

- ❑ 3. If fully unsaturated, the name is concluded with a suffix for ring size: 3-atoms, -ene (except -ine- for N); 4-, 5-, and 6-atoms, -ene; 7-, 8-, and 9- atoms, -ene.
- ❑ 4. If fully saturated, the suffix is -ane for all ring sizes, except for N, which uses -idine for rings of 3-, 4-, or 5-atoms, and for 6-atoms, a prefix of hexahydro- is used. Also, the name oxane, not oxinane, is used for the 6-membered ring with O present.
- ❑ Other exceptions exist for P, As, and Brings, but are beyond our scope.

Size of ring	Rings containing nitrogen		Rings containing no nitrogen	
	<i>Unsaturated^(a)</i>	<i>Saturated</i>	<i>Unsaturated^(a)</i>	<i>Saturated</i>
3	-irine	-iridine	-iren	-iran
4	-ete	-etidine	-et	-etan
5	-ole	-olidine	-ole	-olan
6	-ine	(b)	-in	-ane
7	-epine	(b)	-epin	-epan
8	-ocine	(b)	-ocin	-ocan
9	-onine	(b)	-onin	-onan
10	-ecine	(b)	-ecin	-ecan

a. Corresponding to the no. of non-cumulative double bonds

b. Expressed by prefixing 'per hydro' to the name of the corresponding unsaturated compound

Classification continued

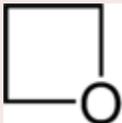
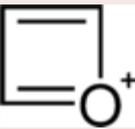
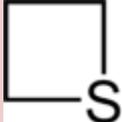
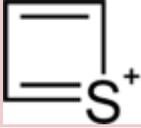
Three- membered rings; one hetero-atom

Hetero-atom	Saturated	Unsaturated
Nitrogen	Aziridine 	Azirine 
Oxygen	Ethylene oxide 	Oxirene 
Sulfur	Thiirane 	Thiirene 

Three membered; two hetero-atoms

Hetero- atom	Saturated	Unsaturated
Oxygen	Dioxirane	
Nitrogen		Diazirine

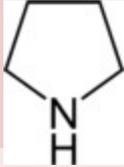
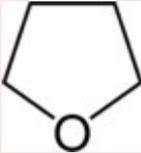
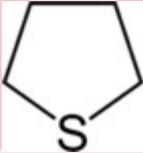
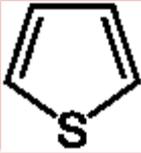
Four membered ring; one hetero-atom

Hetero-atom	Saturated	Unsaturated
Nitrogen	Azetidine 	Azete 
Oxygen	Oxetane 	Oxete 
Sulphur	Thietane 	Thiete 

Four membered ring; two hetero-atoms

Hetero-atom	Saturated	Unsaturated
Nitrogen	Diazetidine	
Oxygen	Dioxetane	Dioxete
Sulphur	Dithietane	Dithiete

Five membered ring; one hetero-atom

Hetero-atom	Saturated	Unsaturated
Nitrogen	Pyrrolidine 	Pyrroline , Pyrrole 
Oxygen	Tetrahydrofuran 	Dihydrofuran, furan 
Sulphur	Tetrahydrothiophene 	Dihydrothiophene, Thiophene 
Phosphorus		Phosphole
Silicon		Silole
Arsenic		Arsole

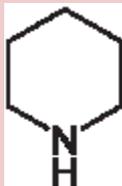
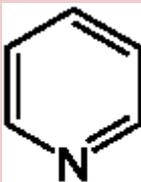
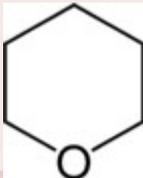
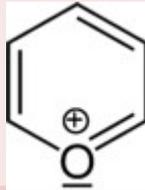
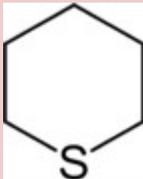
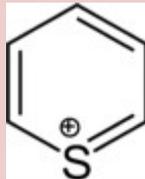
Five membered ring; two hetero-atoms

Hetero-atom	Saturated	Unsaturated
Nitrogen /nitrogen	Imidazolidine Pyrazolidine	Imidazoline ,imidazole Pyrazoline, pyrazole
Nitrogen/oxygen	Oxazolidine Isoxazolidine	Oxazoline, oxazole Isoxazoline, isoxazole
Nitrogen/sulphur	Thiazolidine Isothiazolidine	Thiazoline, thiazole Isothiazoline, isothiazole
Oxygen/oxygen	Dioxolane	
Oxygen /sulphur	Oxathiolane	
Sulphur/sulphur	Dithiolane	

Five membered ring; three hetero-atoms

Hetero-atom	Saturated	Unsaturated
Nitrogen		Triazoles
Nitrogen/two o sulphur		Dithiazole
2 nitrogen/oxygen		Furazan , oxadiazole
2 nitrogen/sulphur		Thiadiazole
Four hetero-atoms		
Nitrogen		Tetrazole
Five hetero-atoms		
Nitrogen		Pentazole –inorganic?

Six membered ring; one hetero-atom

Hetero-atom	Saturated	unsaturated
Nitrogen	Piperidine 	Pyridine 
Oxygen	Tetrahydropyran 	Pyrilium 
Sulphur	Thiane 	Thiopyran 

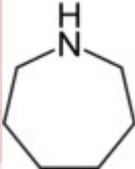
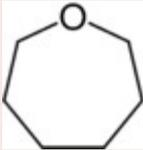
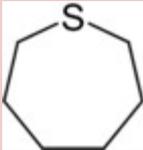
Six membered ring; two hetero-atoms

Hetero-atom	Saturated	Unsaturated
Nitrogen	Piperazine	Diazines
Nitrogen/oxygen	Morpholine	Oxazine
Nitrogen /sulphur		Thiazine
Sulphur	Dithiane	
Oxygen	Dioxane	Dioxin

Three hetero-atoms

Hetero-atom	Saturated	Unsaturated
Nitrogen		Triazine
Oxygen	Trioxane	
Four hetero-atoms		
Nitrogen		Tetrazine

Seven membered; one hetero-atom

Hetero-atom	Saturated	Unsaturated
Nitrogen	Azepane	Azepine
Nitrogen/nitrogen		Diazepine 
Oxygen	Oxepane 	Oxepine 
Sulphur	Thiepane 	Thiepine 

Eight membered ring; one hetero-atom

Hetero-atom	Saturated	Unsaturated
Nitrogen	Azocane	Azocine
Oxygen	Oxecane	
Sulphur	Thiocane	

Heterocyclic compounds

Rings with more than one heteroatom

- The usual rules for stems to indicate ring size and suffixes for degree of saturation are used, as are the prefixes for the various heteroatoms.
- They are listed in the following order of priorities, derived from the main groups of the Periodic System, and then within each group by increasing atomic number:
- Group VI (*O > S > Se > Te*) > Group V (*N > P > As*) > Group IV (*Si > Ge*) > Group III (*B*).
- *This listing can be simplified greatly by taking out the most commonly found heteroatoms in their order,*

Heterocyclic compounds

Rings with more than one heteroatom

- which gives $O > S > N > P$. Each heteroatom is then given a number as found in the ring, with that of highest priority given position 1.
- A saturated heteroatom with an extra-hydrogen attached is given priority over an unsaturated form of the same atom, as in 1H-1,3-diazole (see the following discussion).
- The numbers are grouped together in front of the heteroatom listings (thus, 1,3-oxazole, not 1-oxa-3-azole).
- The heteroatom prefixes follow the numbers in the priorities given previously.

Heterocyclic compounds

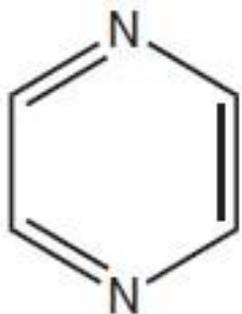
Rings with more than one heteroatom

- ❑ Punctuation is important; in the examples to follow, a comma separates the numbers and a dash separates the numbers from the heteroatom prefixes.
- ❑ A slight modification is used when two vowels adjoin; one is deleted, as in the listing for “oxaaza,” which becomes simply “oxaza.”
- ❑ As for monohetero systems, substituents on the ring are listed alphabetically with a ring atom number for each (not grouped together).

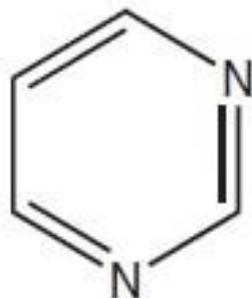
Heterocyclic compounds

Rings with more than one heteroatom

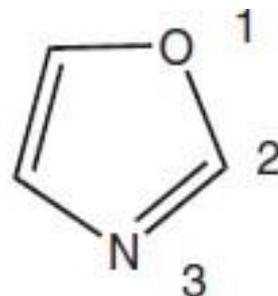
Examples



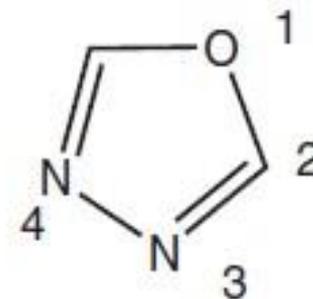
1,4-diazine
(pyrazine)



1,3-diazine
(pyrimidine)



1,3-oxazole

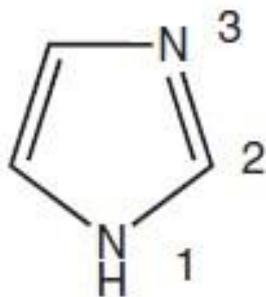


1,3,4-oxadiazole

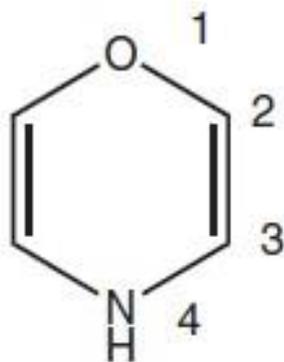
Heterocyclic compounds

❓ Rings with more than one heteroatom

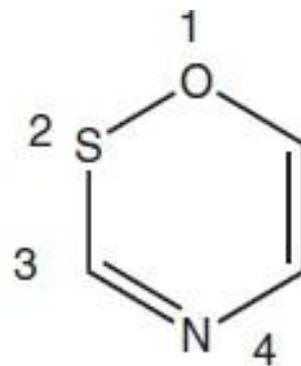
❓ More examples



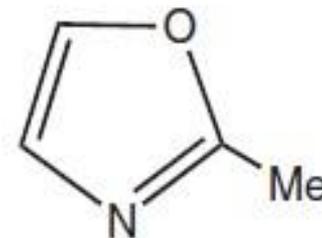
1H-1,3-diazole
(imidazole)



4H-1,4-oxazine



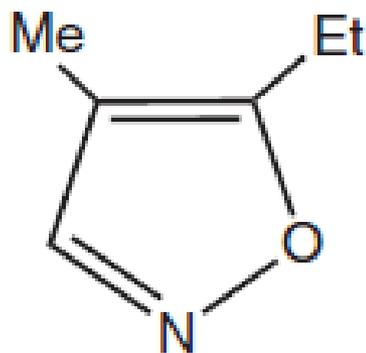
1,2,4-oxathiazine



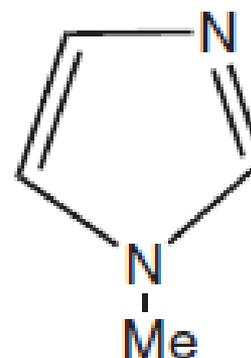
2-methyl-1,3-oxazole

Heterocyclic compounds

? Rings with more than one heteroatom



5-ethyl-4-methyl-1,2-oxazole



1-methyl-1H-1,3-diazole
(N-methylimidazole)

Heterocyclic compounds

❑ Bicyclic compounds

- ❑ Systems where two rings share a common single or double bond, which are said to be fused rings.
- ❑ A common case is where a benzene ring is fused to a heterocyclic ring. The name begins with the prefix “benzo.” The point of attachment is indicated by a letter that defines the “face” of the heterocycle involved.
- ❑ Thus, the 1,2- position on the heterocyclic ring is always the “a-face,” 2,3- is the “b-face,” 3,4- is the “c-face,” and so on. After the name is established, the ring atoms are given new numbers for the entire bicycle.

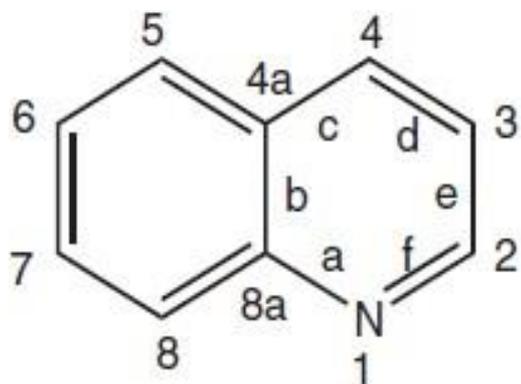
Heterocyclic compounds

- ❑ The letters for the faces of the monocycle are placed inside the ring, and the numbers for ring positions of the bicycle taken as a whole are shown on the outside.
- ❑ The final numbering always begins at a position next to the benzo group and that the heteroatoms are given the lowest numbers possible, observing the $O > S > N > P$ rule.
- ❑ *The positions of ring fusion bear the number of the preceding ring atom with the letter “a” attached.*
- ❑ Brackets are used around the face letter, and the name is put together without spaces, except that a dash separates the bracket from ring numbers if present, as in benzo[d]-1,3-thiazole

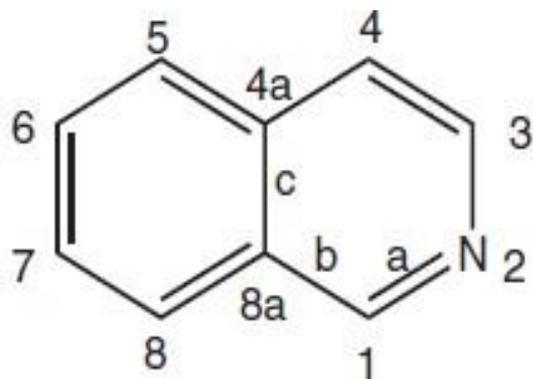
Heterocyclic compounds

- ❑ A convention frequently followed is to write the structure with the hetero ring on the right and with its heteroatom at the bottom
- ❑ If two heterocyclic rings are fused, additional rules are required.
- ❑ A parent ring is selected, and the other ring is considered fused on, as was observed for benzene fusion. Some rules are as follows:
- ❑ If one ring contains N, it is considered the parent, and its name is placed last in the compound's name.

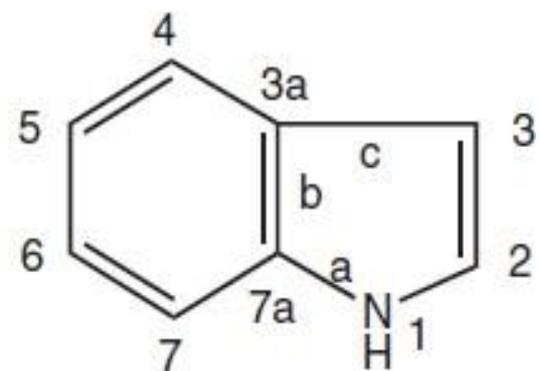
Heterocyclic compounds



benzo[b]pyridine
(quinoline)



benzo[c]pyridine
(isoquinoline)



1H-benzo[b]pyrrole
(indole)

Benzo-fused rings

Heterocyclic compounds

- ❑ If both rings contain N, the larger ring is the parent.
- ❑ If both rings are of the same size, that with the most N atoms is the parent, or if the same number of N atoms is present, that fusion of the rings that gives the smallest numbers for N when the bicycle is numbered is chosen.
- ❑ If no N is present, O has priority over S over P, and then the above rules are applied.
- ❑ The ring fused onto the parent has the suffix “o”; common names are used (with modification) where possible to simplify the name.

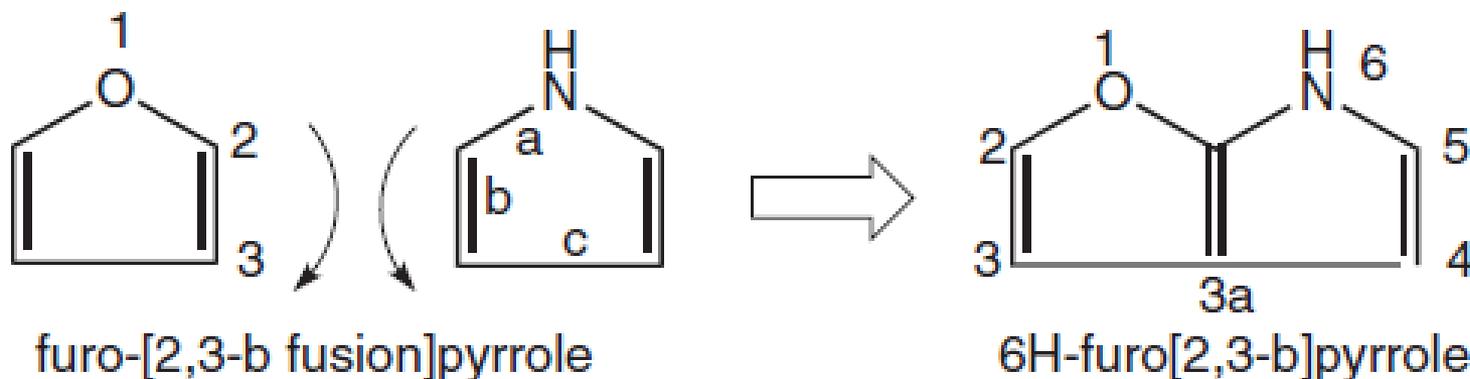
Heterocyclic compounds

- ❑ Some examples are pyrido for pyridine, pyrrolo for pyrrole, thieno for thiophene, furo for furan, imidazo for imidazole, pyrimido for pyrimidine, pyrazino for pyrazine, among others
- ❑ The face letter of the parent ring where the fusion occurs is placed in brackets preceding the name of that ring.
- ❑ The position numbers of the fused ring are placed inside the brackets before the face letter of the parent ring, separated by a comma.
- ❑ The proper numbers for the fused ring are those that are encountered as one goes around the ring in the same direction as going alphabetically around the faces of the parent. These need not be in numerical order.

Heterocyclic compounds

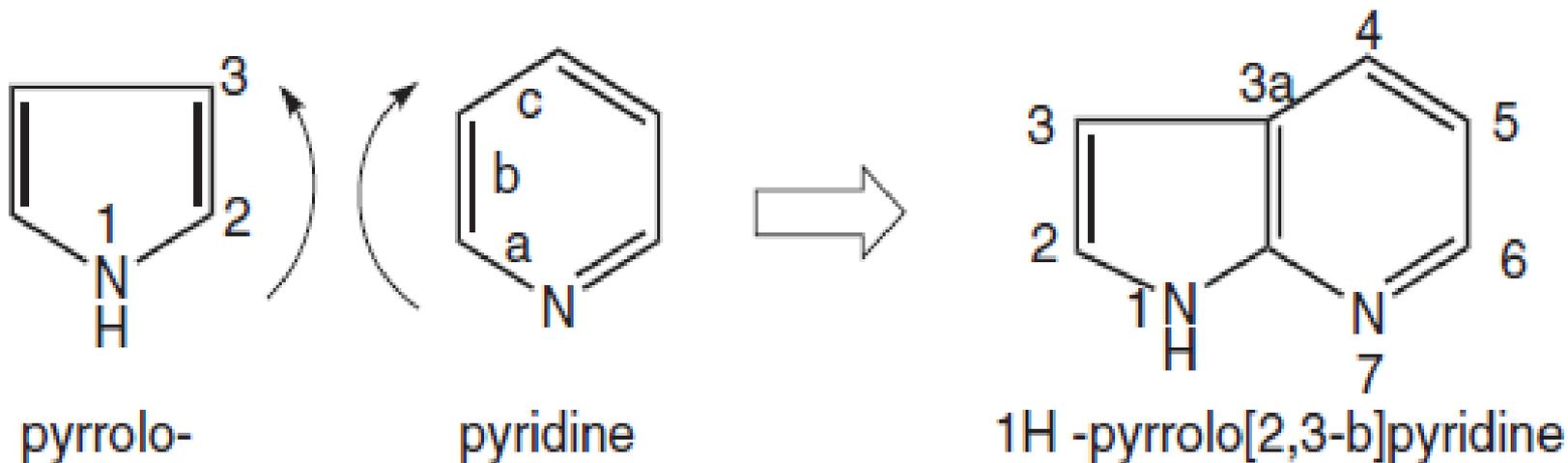
❓ Consider the examples below

❓ Fusing the 2,3-bond of furan onto the b-face of pyrrole, taken as the parent, results in the name 6H-furo[2,3-b]pyrrole.



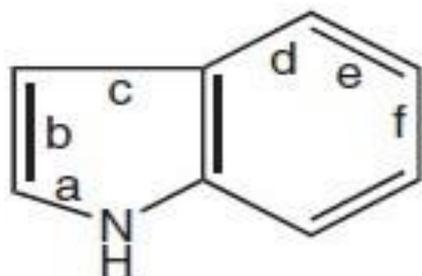
Heterocyclic compounds

Similarly, fusing the 2,3-bond of pyrrole onto the b-face of pyridine results in a pyrrolo[2,3-b]pyridine.

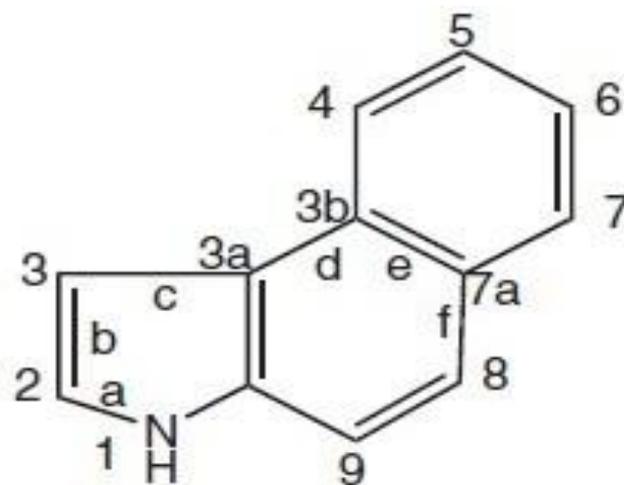
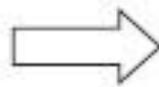


Heterocyclic compounds

☐ Multicyclic systems



indole



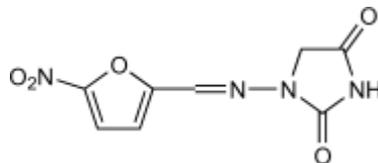
1H-benzo[e]indole

Examples of drugs

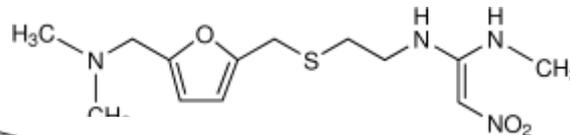
Five membered with one heteroatom

Furan derivatives

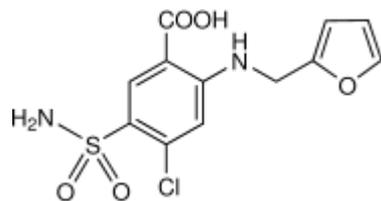
☐ Nitrofurantoin



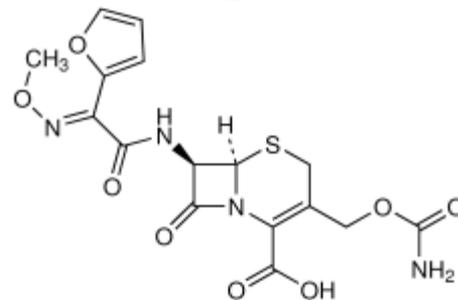
☐ Ranitidine



☐ Furosemide

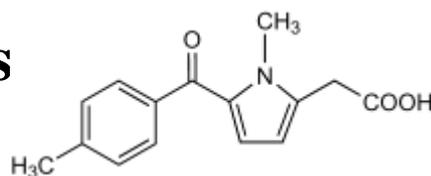


☐ Cefuroxime



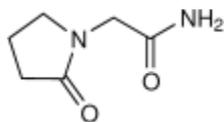
Pyrrole derivatives

☐ Tolmetin

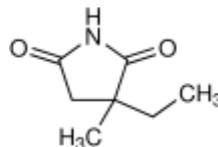


Pyrrolidine derivatives

☐ Piracetam

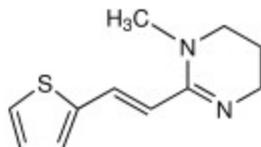


☐ Ethosuximide

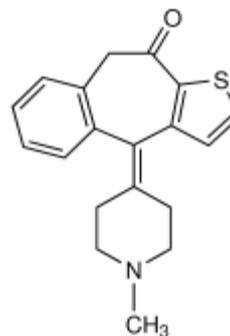


Thiophene derivatives

☐ Pyrantel



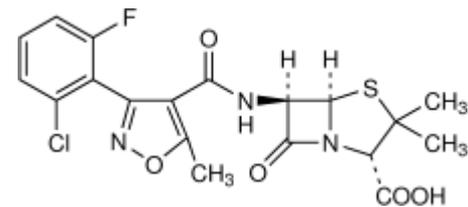
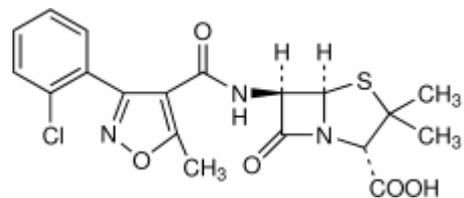
☐ Ketotifen



Five membered with two heteroatoms

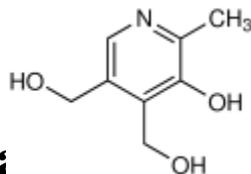
Isoxazole derivatives

- ☐ Cloxacillin, Flucloxacillin, Oxacillin



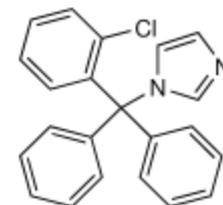
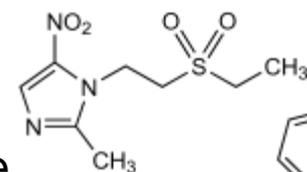
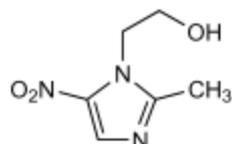
Oxazoles

- ☐ Pyridoxine



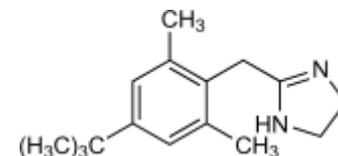
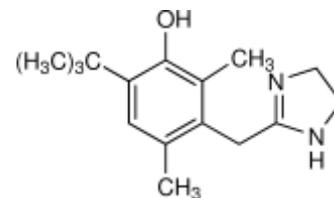
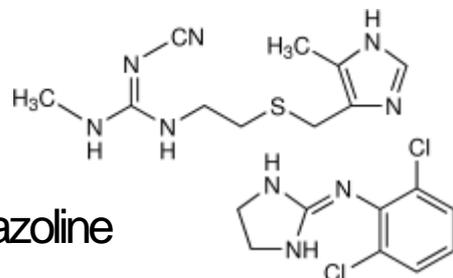
Imidazole deriva:

- ☐ Antibacterials; Metronidazole, Tinidazole
- ☐ Antifungals ; Clotrimazole, Econazole, Isoconazole, Itraconazole
- ☐ Antiulcer; Cimetidine



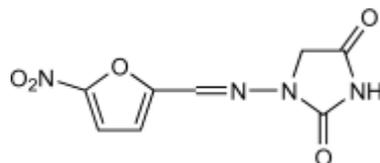
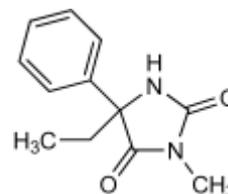
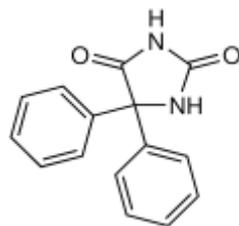
Imidazoline derivatives

- ☐ Clonidine
- ☐ Oxymetazoline, Xylometazoline



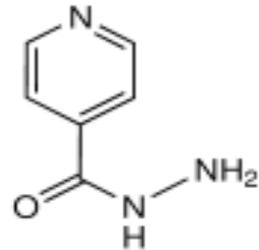
Imidazolidines

- ☐ Phenytoin, Mephénytoin
- ☐ Nitrofurantoin



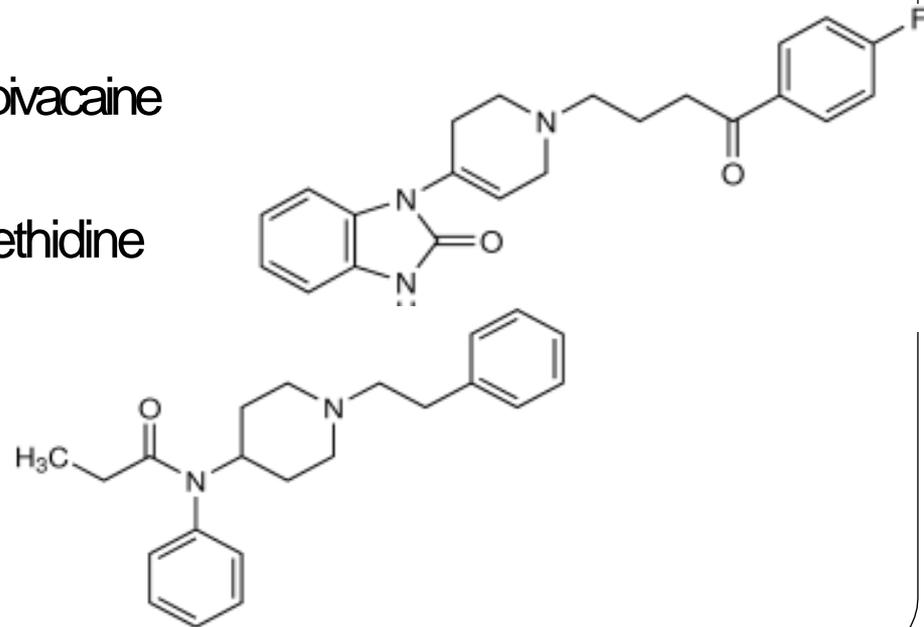
Pyridines

- Pyridine
- Pyridoxine
- Nicotinic acid and derivatives i.e. nicotinamide, nicethamide, etofibrate.
- Isonicotinic acid and derivatives i.e. **isoniazid**, ipraniazid, ethionamide, prothionamide
- Pyridine containing anti histamines
 - Pheniramine, chlorpheniramine ,dexchlorpheniramine , mepyramine , triprolidine.
- Others; betahistine, bisacodyl, cetylpyridium chloride, disopyramide, distigmine, nifedipine, pyridostigmine, nalidixic acid, pyroxicam



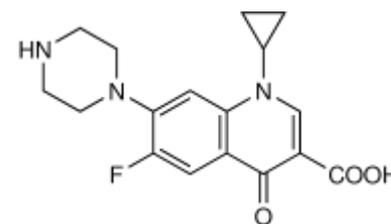
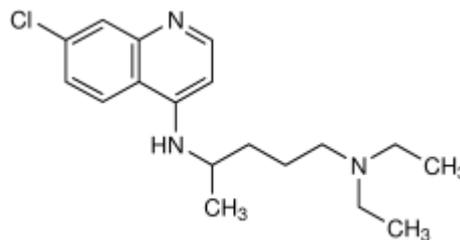
Piperidine derivatives

- Amide local anesthetics mepivacaine, bupivacaine
- Droperidol**, haloperidol, tirfluperidol
- Alfentanil , **fentanyl**, diphenoxylate , pethidine



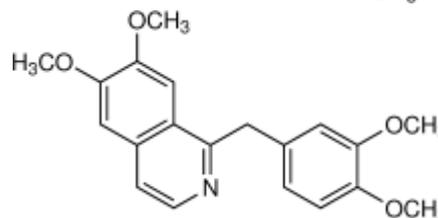
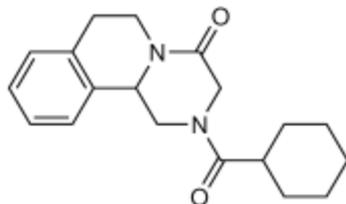
Quinolines

- ? Chloroquine , hydroxychloroquine,
- ? Ciprofloxacin, norfloxacin



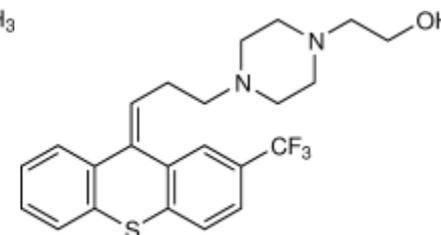
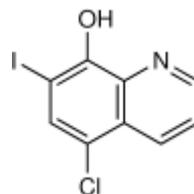
Isoquinolines

- ? Praziquantel
- ? Papaveime



Thioxanthenes

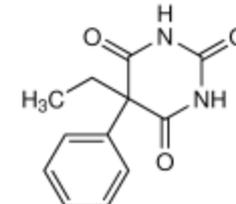
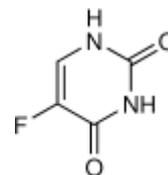
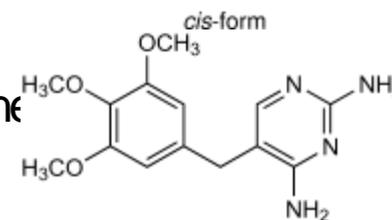
- ? Clioquinol, haloquinol, oxyquinol
- ? Clopenthixol , flupenthixol



With two heteroatoms

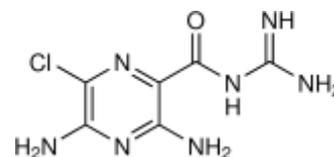
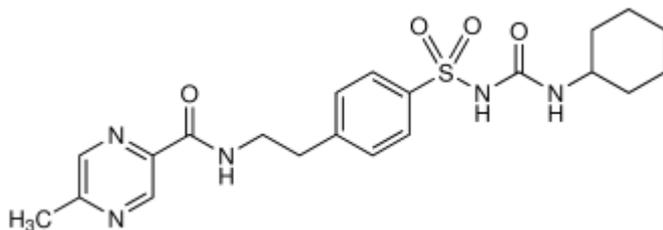
Pyrimidines

- ? Pyrimidines and hexahydropyrimidines; trimethoprim, thiamine
- ? Uracils; fluorouracil, idoxuridine,
- ? Barbiturates; phenobarbital, pentobarbital etc.



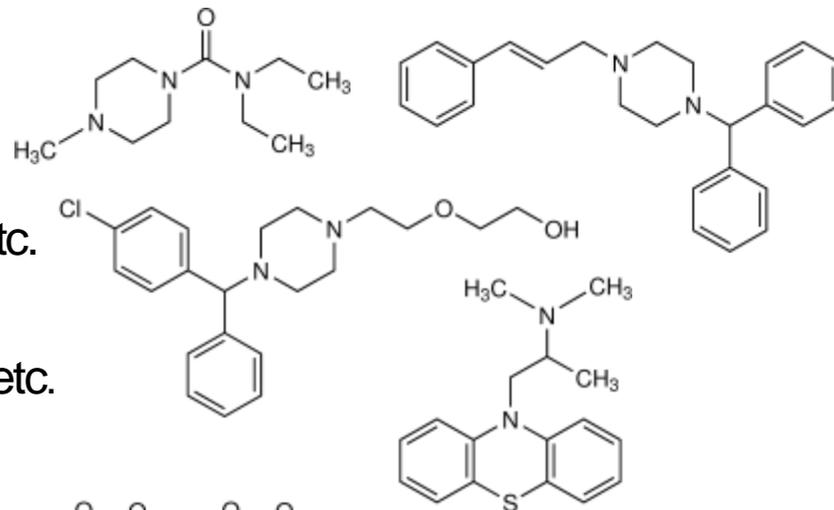
Pyrazines

- ? Glipizide,
- ? amiloride



Piperazines

- ❑ Piperazine, diethylcarbamazine
- ❑ Cinnazirine, flunarizine
- ❑ Hydroxyzine, buspirone, trifluoperazine, etc.



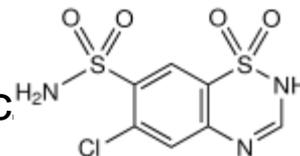
Phenothiazines

- ❑ Promethazine, chlorpromazine, thioridazine etc.

With three heteroatoms

1, 2, 4-benzothiadiazines

- ❑ Thiazide diuretics; Chlorthiazide, butizide, etc.
- ❑ Oxazaphosphorines; Cyclophosphamide, ifosfamide

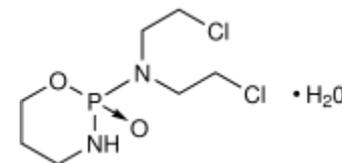
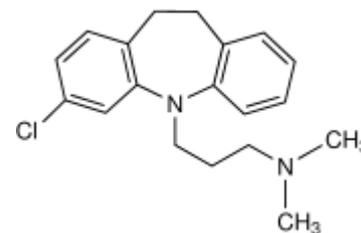
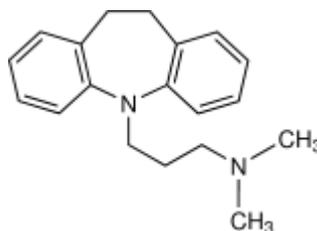
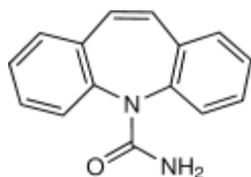


Seven membered

With one heteroatom

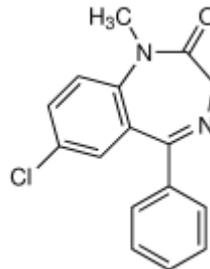
5H-Dibenzo [b,f] azepine

- ❑ Imipramine, chlomipramine
- ❑ Carbamazepine



With two heteroatoms

- 1, 4-Benzodiazepines; chlordiazepoxide, diazepam, prazepam, lorazepam, Nitrazepam, donazepam etc.
- 1, 5-benzodiazepines; dobazam



Poly heterocyclic systems

Purines

- Thanthines; theophylline, theobromine, caffeine
- Theophylline derivatives; aminophylline, etophylline, propoxyphylline, diprophylline
- Anti cancers; mercaptopurine, thioguanine, azathioprine
- Anti virals acyclovir

Pteridines

- Triamterene
- folinic acid, methotrexate

