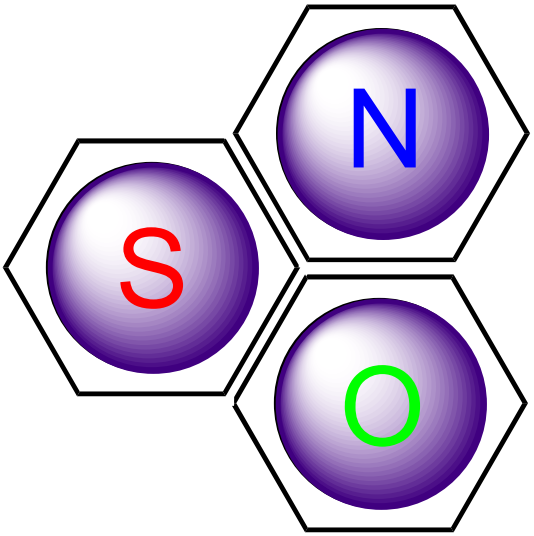
Heterocyclic Chemistry



Nomenclature of Heterocyclic compounds

Nomenclature of heterocyclic compounds

- Three systems for naming heterocylic compounds:

1) The common nomenclature: no structural information but it still widely used.

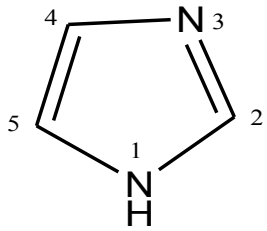
2) The replacement method

3) The Hantzsch-Widman (IUPAC or Systematic) method which is designed so that one may deduce from it the structure of the compound.

I- Common Nomenclature

❖ Each compound is given the corresponding trivial name. This usually originates from the compounds occurrence, its first preparation or its special properties.

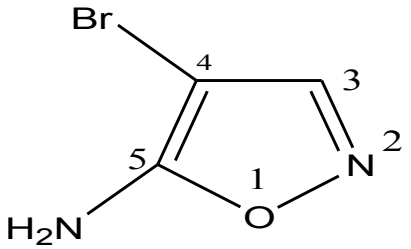
❖ If there is more than one hetroatom of the same type numbering starts at the saturated one, e.g. imidazole.



❖ If there is more than one type of the heteroatoms, the ring is numbered starting at the hetroatom of the higher priority (O>S>N) and it continues in the direction to give the other hetroatoms the lower numbers as possible.

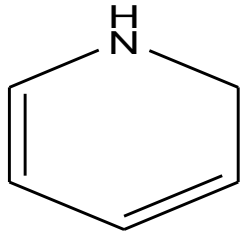
I-Common Nomenclature

- If subsituents present, their position should be identified by the number of the atoms bearing them and then they should be listed in alphabetical order.



5-Amino-4-bromoisoxazole

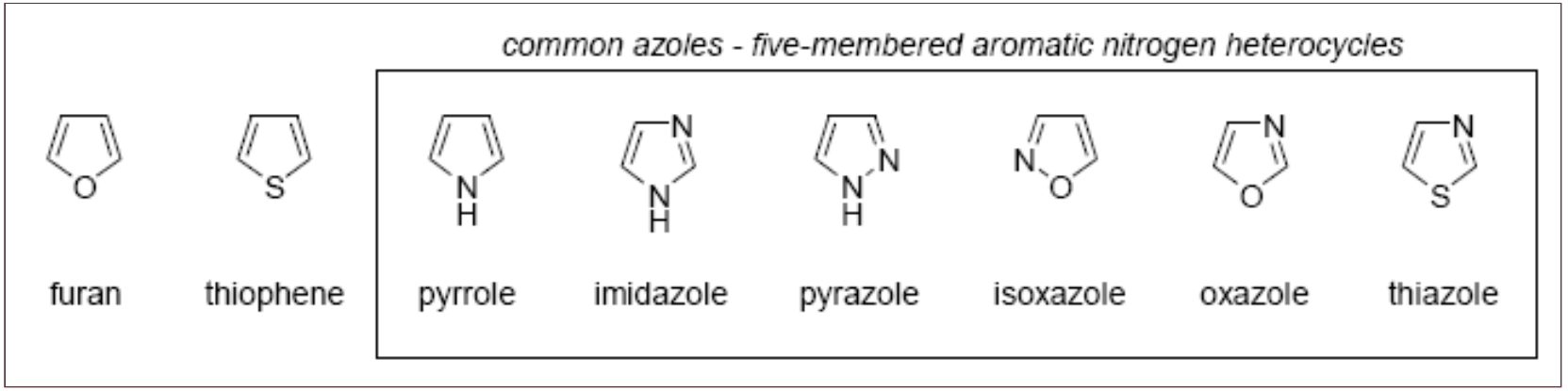
❖ The words dihydro, or trihydro, or tetrahydro are used if two or three or four atoms are saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated trivial name.



1,2-Dihydro-pyridine

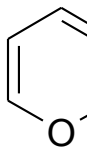
Trivial names

1) 5-membered heterocycles with one or two heteroatoms

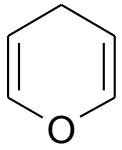


2) 6-membered heterocycles with one or two heteroatoms

Common azines-six-membered aromatic nitorgrn heterocycles



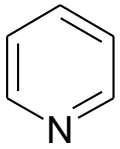
2H-Pyran



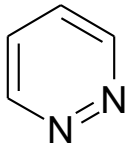
4H-Pyran

These are tautomers

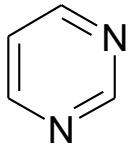
Both are not aromatic



Pyridine

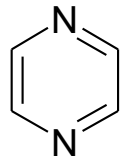


Pyridazine



Pyrimidine

DNA/RNA bases

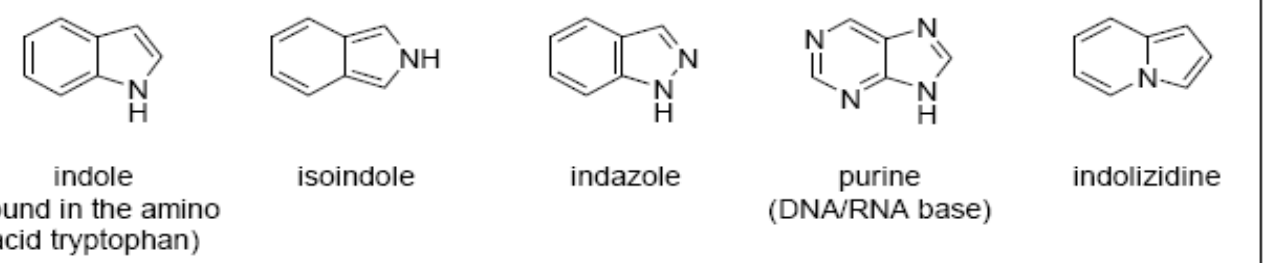


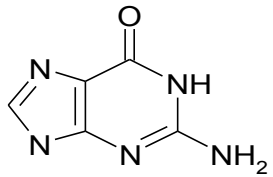
Pyrazine

Trivial names

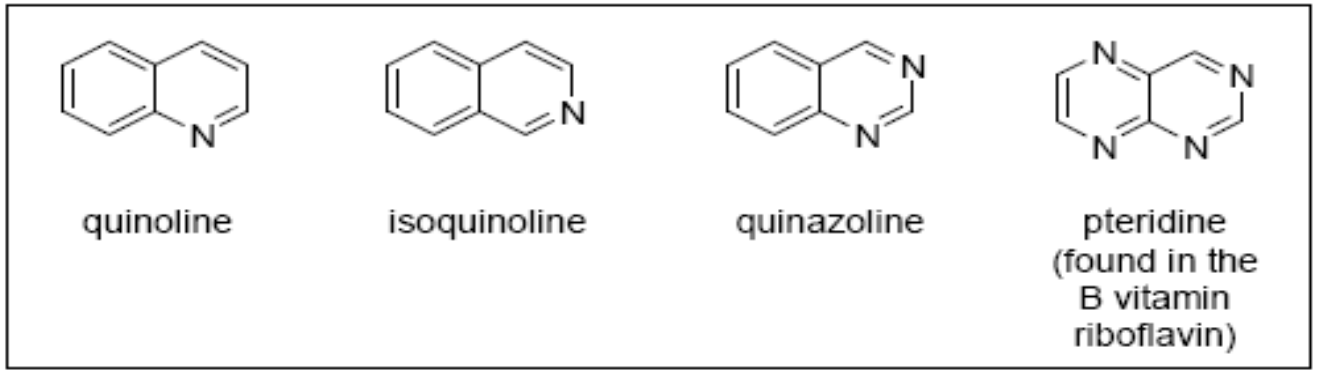
3) Fused heterocycles

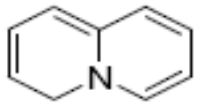
common ring-fused azoles





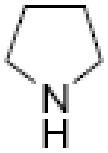
common ring-fused azines



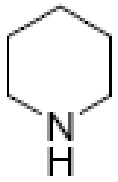


Trivial names

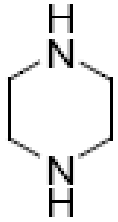
4) Saturated heterocycles



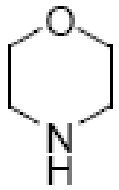
pyrrolidine



piperidine



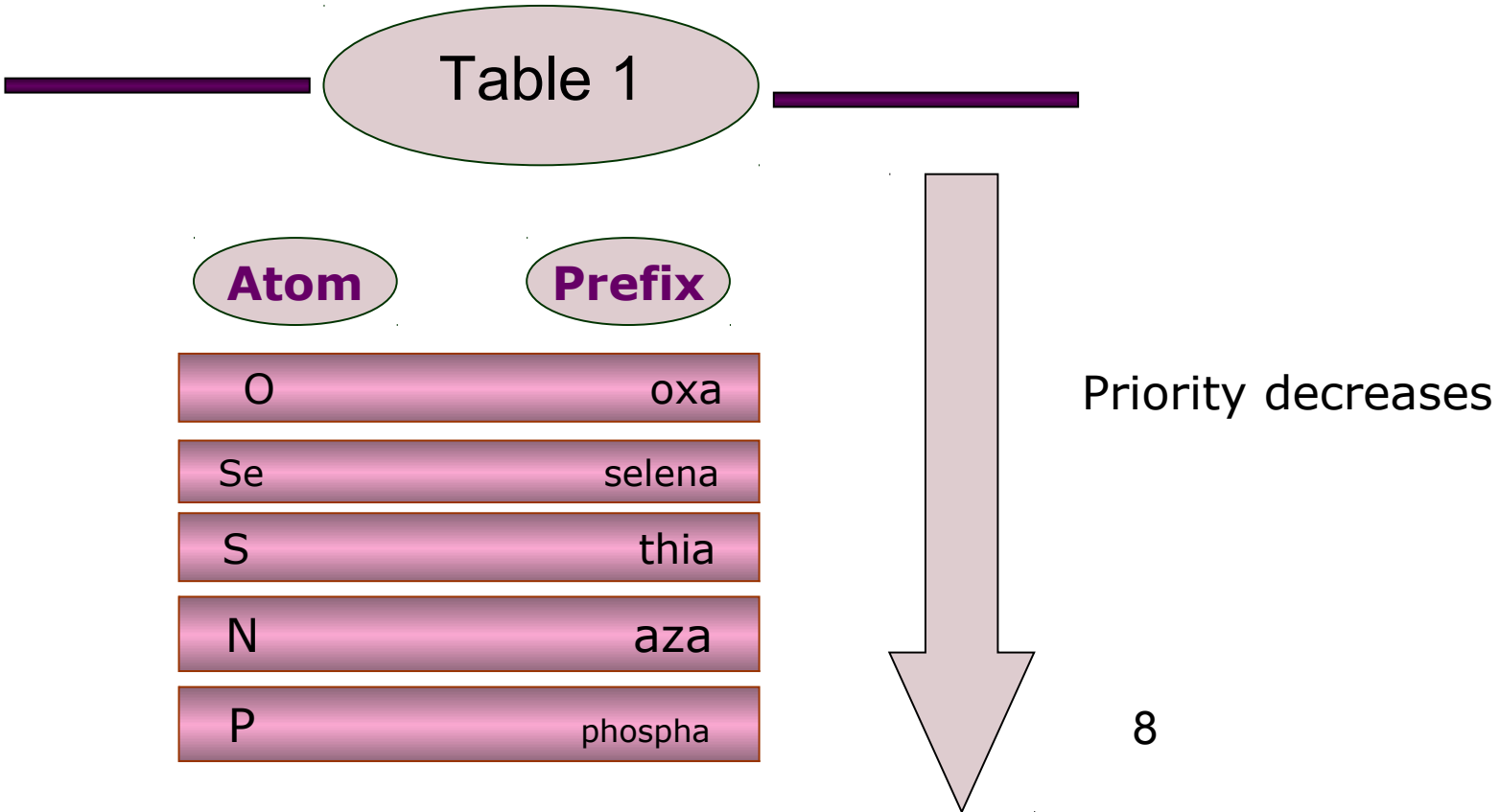
piperazine



morpholine

II- Replacement nomenclature

- Heterocycle's name is composed of the corresponding carbocycle's name and an elemental prefix for the heteroatom introduced (if more than one heteroatom is present they should be listed according to the priority order shown in (table 1).



II- Replacement nomenclature


Benzene


Cyclopentadiene

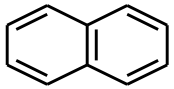

Cyclopentadiene

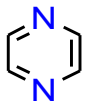

Cyclopropane


Cyclopropene


Cyclopentadiene

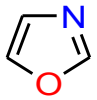

Cyclohexane


Naphthalene



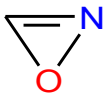
1,4-Diazabenzene

Oxacyclopenta-2,4-diene

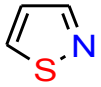


1-Oxa-3-azacyclopenta-2,4-diene

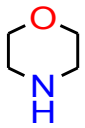
Oxacyclopropane



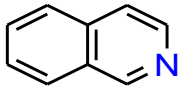
Oxazacyclopropene



1-Thia-2-azacyclopenta-2,4-diene



1-Oxa-4-azacyclohexane



2-Azanaphthalene

III-Hantzsch-Widman nomenclature (IUPAC)

- German chemists Arthur Hantzsch and Oskar Widman, proposed similar systematic naming of heterocyclic compounds in 1887 and 1888 respectively.

- three to ten-membered rings named by combining the appropriate prefix (or prefixes) that denotes the type and position of the heteroatom present in the ring with suffix that determines both the ring size and the degree of unsaturation

- In addition, the suffixes distinguish between nitrogen-containing heterocycles and heterocycles that do not contain nitrogen

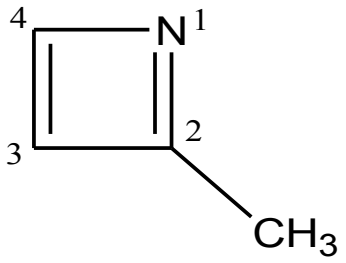
- IUPAC name = locants+ prefix + suffix

Hantzsch-Widman rules for fully saturated and fully unsaturated heterocycles

1) Identify the hetroatom present in the ring and choose from (table 1 on slide 8) the corresponding prefix .

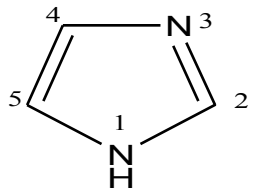
2) The position of a single heteroatom control the numbering in a monocyclic compound. The heteroatom is always assigned position 1 and if substituents present are then counted around the ring in a manner so as to take the lowest possible numbers.

For example:



Hantzsch-Widman rules

3) A multiplicative prefix (di, tri, ect.) and locants are used when two or more similar heteroatoms contained in the ring(two nitrogen indicated by diaza) and the numbering preferably commenced at a saturated rather than an unsaturated atom, as depicted in the following example: 1,3-diaza….

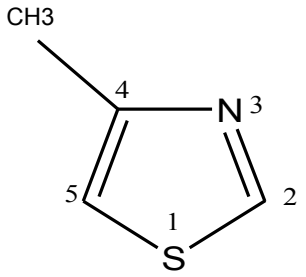


4) If more than one type of hetroatoms present in the ring the name will include more than one prefix with locants to indicate the relative position of the heteroatoms.

- When combining the prefixes (e.g. oxa and aza) two vowels may end up together, therefore the vowel on the end of the first part should be omitted (oxaza).

Hantzsch-Widman rules

- The numbering is started from the heteroatom of the highest priority in such a way so as to give the smallest possible numbers to the other heteroatoms in the ring (the substituents are irrelevant). For example the prefix corresponding to the following compound is 4-Methyl-1,3-Thiaza….



5) Choose the appropriate suffix from (table 2) depending on whether or not nitrogen atom is present in the ring, the size of the ring and presence or absence of any double bonds

6) Combine the prefix(s) and suffix together and drop the first vowel if two vowels came together.

Hantzsch-Widman rules

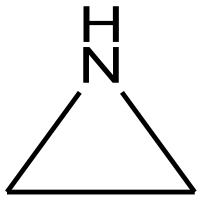
Table 2

Ring size	N-present		N-absent	
	Unsat	sat	Unsat	sat
	irine	iridine	irene	irane
	ete	etidine	ete	etane
	ole	olidine	ole	olane
	ine	a	in	ane
	epine	a	epin	epane
	ocine	a	ocin	ocane
9	onine	a	onin	onane
10	ecine	a	ecin	ecane

a: means use the prefix perhydro followed by the fully unsaturated name

Hantzsch-Widman rules

- Examples

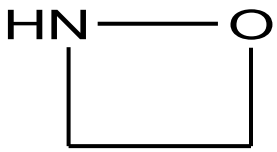


- This ring contains (N) → Prefix is aza

- The ring is 3-membered and fully saturated →
  suffix is iridine

- By combining the prefix and suffix, two vowels ended up together (azairidine), therefore the vowel on the end of the first part should be dropped. This gives the correct name: **Aziridine**

Hantzsch-Widman rules



- This ring contains (O ,N) and (o) has higher priority than (N) and by starting numbering the ring at (O) → Prefix is 1,2-Oxaaza, but the first vowel must be omitted to give

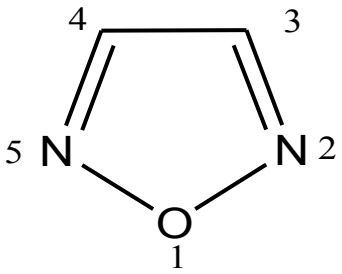
  1,2-Oxaza

- The ring is 4-membered and fully saturated → suffix is etidine

- By combining the prefix and suffix, two vowels ended up together (1,2-oaxazaetidine), therefore the vowel on the end of the first part should be dropped. This gives the correct name:

  1,2-oxazetidine

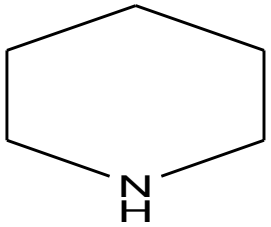
Hantzsch-Widman rules



- This ring contains (O) → prfix1 (oxa), and two (N) → prfix2 diaza
- Locants, since (O) is higher priority than (N) so it is in position 1 by default and the two (N) are therefore at positions 2 and 5, this gives the combined prefixes as 1,2,5-oxadiaza (note that the a in oxa is not dropped)
- It is 5-membered,fully unsaturated ring with (N) → the suffix is ole
- By combining the prefixes and the suffix and dropping the appropriate vowels we get the correct name as

  1,2,5-Oxadiazole

Hantzsch-Widman rules



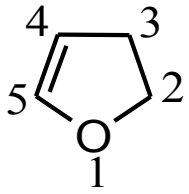
- The ring is 6-memberd, fully saturated with N ⇒
Prefix perhydro followed by the name of fully unsaturated 6-memberd ring with nitrogen ⇒ azine

- Thus the full name is **perhydroazine**

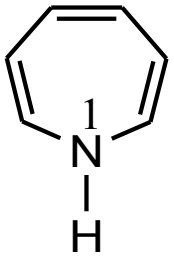
Hantzsch-Widman rules for partially unsaturated heterocycles

❖ Partial unsaturation in heterocyclic compounds can be indicated by one of the following methods:

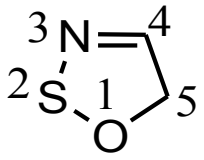
a) The position of nitrogen or carbon atoms which bear extra hydrogen atoms must be indicated by numbers and italic capital H (e.g. 1*H*, 2*H*, etc.) followed by the name of maximally unsaturated ring.



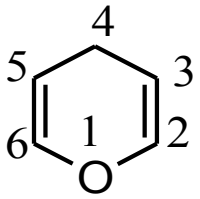
2*H*, 3*H*-Oxole



1*H*-Azepine



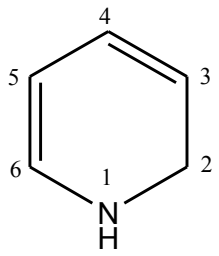
5H-1,2,3-Oxathiazole



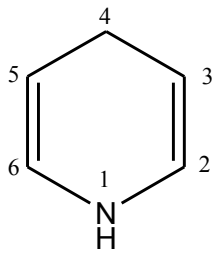
4*H*-Oxin

Hantzsch-Widman rules for partially unsaturated heterocycles

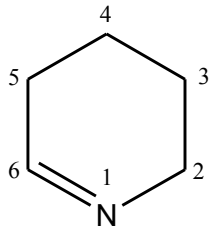
b) The words dihydro, or trihydro, or tetrahydro are used if two or three or four atoms are saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated Hantzsch-Widman name.



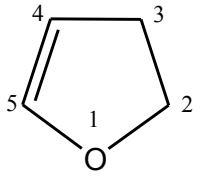
1,2-Dihydroazine



1,4-Dihydroazine



2,3,4,5-Tetrahydroazine

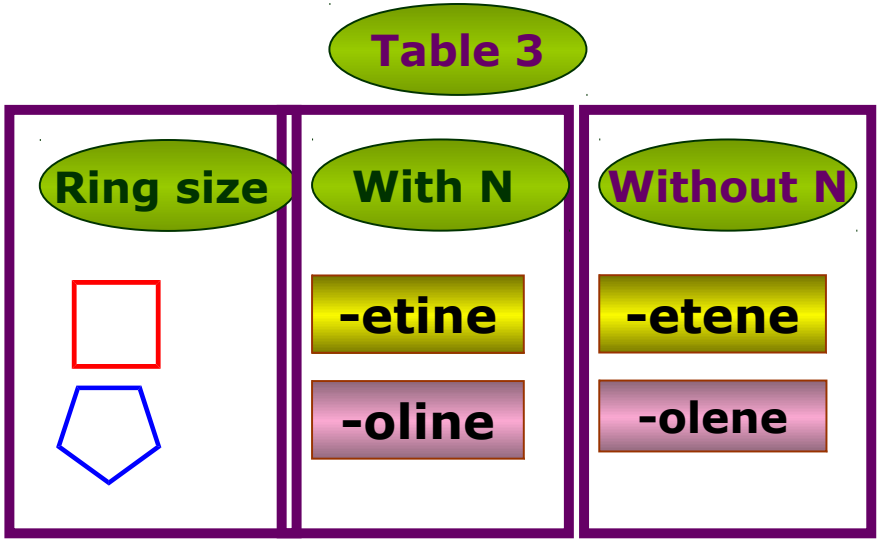


2,3-Dihydrooxole

Hantzsch-Widman rules for partially unsaturated heterocycles

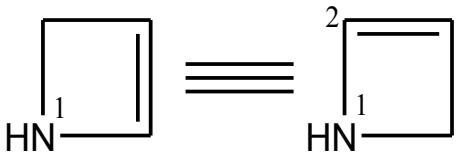
c) Alternatively, the partially unsaturated 4 and 5 rings (i.e. rings contain one double bond) are given special Hantzsch-Widman suffixes as in table 3 and the double bond is specified as Δ^1, Δ^2, Δ^3, etc.. Which indicates 1 and 2; 2 and 3; 3 and 4 atoms respectively have a double bond

(i.e. Name : Δ^x + Prefix + special suffix)
(x= locant of the double bond)

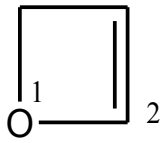


Hantzsch-Widman rules for partially unsaturated heterocycles

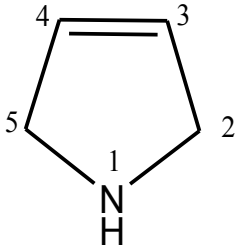
- Examples



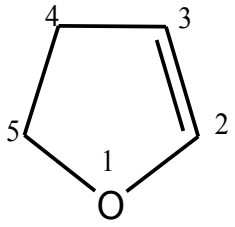
Δ^2 -Azetine



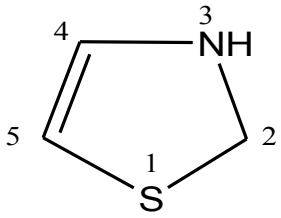
Δ^2 -Oxetene



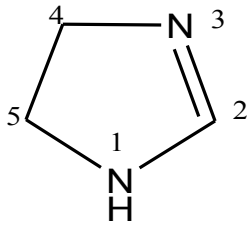
Δ^3 -Azoline



Δ^2 -Oxolene



Δ^4 -1,3-Thiazoline

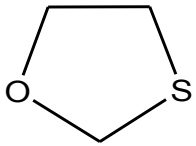


Δ^2 -1,3-Diazoline

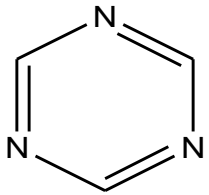
Hantzsch-Widman rules

- Exercise:

  Explain how can you name the following heterocycles.

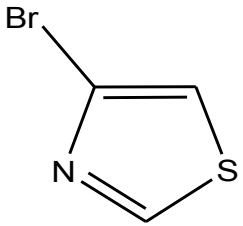


1,3-Oxathiolane



1,3,5 triazine

Oxirene



4 bromo 1,3 thiazole

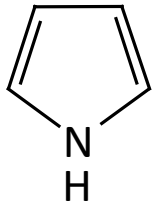
Pharmaceutical Importance of 5-membered Heterocycles

Introduction

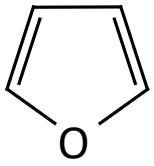
- A heterocyclic compound is a cyclic compound that has atoms of at least two different elements as members of its ring. The counterparts of heterocyclic compounds are homocyclic compound , the rings of which are made of a single element.
- Although heterocyclic compounds may be inorganic, most contain at least one carbon.

Five membered Heterocycles

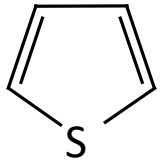
- The most common heterocycles are those having five membered rings and containing heteroatoms of Nitrogen(N), Oxygen(O), Sulfur(S).
- Examples:



Pyrrole



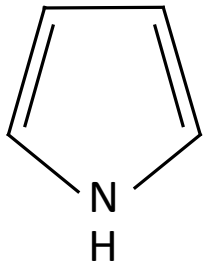
Furan



Thiophene

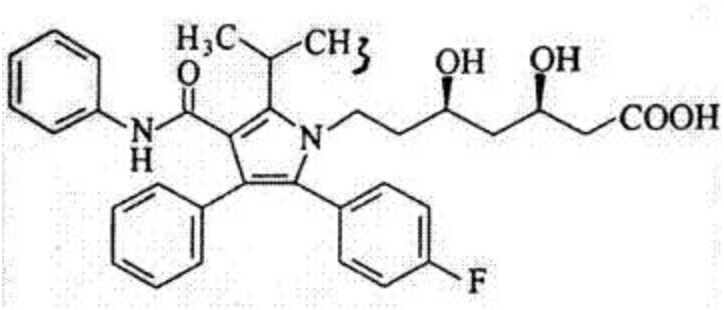
Pyrrole

- Pyrrole is a heterocyclic aromatic organic compound a five-membered ring with the formula C_4H_4NH. Substituted derivatives are also called pyrroles.

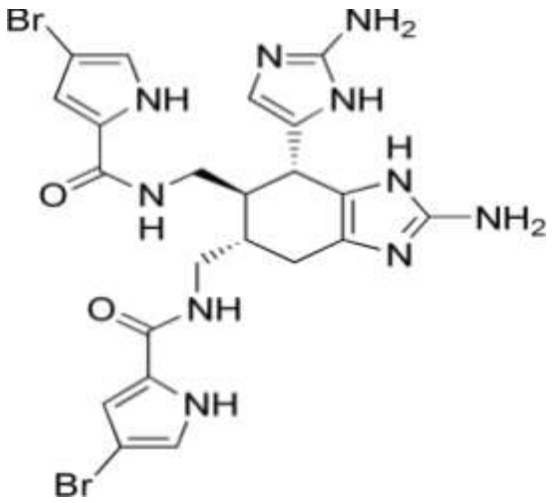


- Pyrrole derivatives drug: Atorvastatin, Ageliferin, Elopiprazole

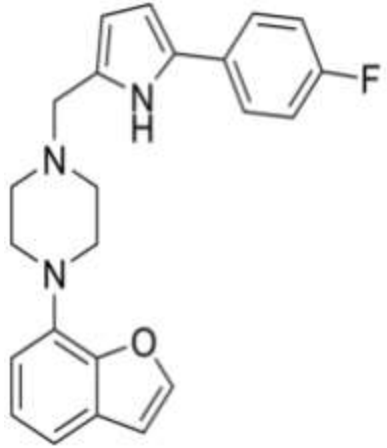
- Structure



atorvastatin



ageliferin



elopiprazole

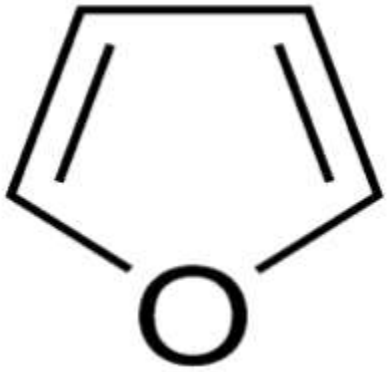
Pharmaceutical Importance

Pyrrole derivatives drug mainly used in-

- Treatment of dyslipidemia & the prevention of cardiac disease.
- Antibacterial agent
- Antipsychotic drug

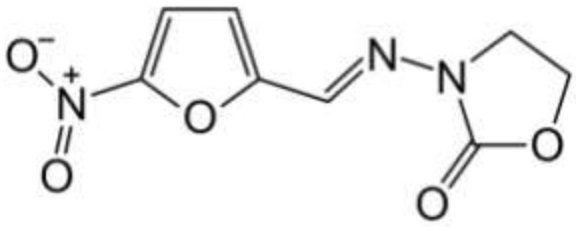
furan

- Furan is a heterocyclic organic compound, consisting of a five-membered aromatic ring with four carbon atoms and one oxygen.

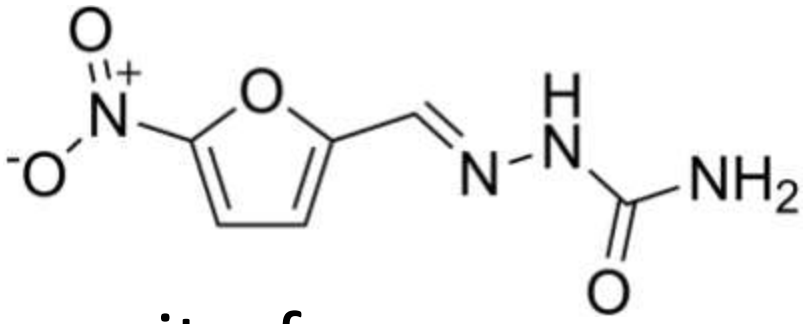


- Furan derivatives drug: Furazolidone, Nitrofurazone, Nitrofurantoin

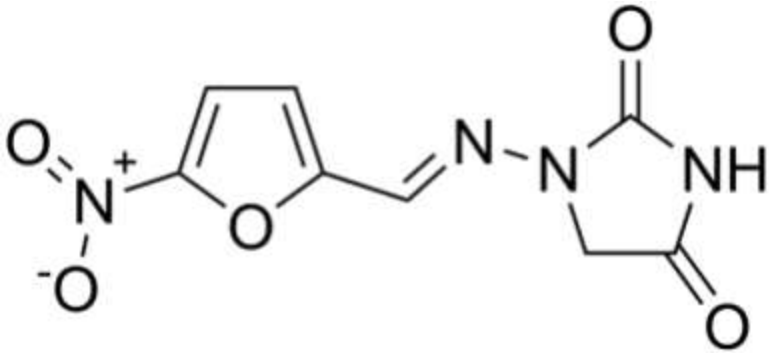
- Structure:



furazolidone



nitrofurazone



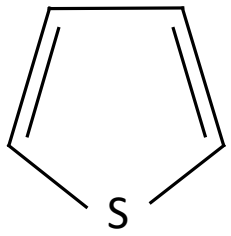
nitrofurantoin

Pharmaceutical Importance

- Used to treat diarrhoea and enteritis caused by bacteria or protozoan infections.
- Batericidal compound used as an antibiotic most commonly in the form of ointments.
- Used as antiparasitic drug.

Thiophene

- Thiophene also commonly called thiofuran, is a heterocyclic compound



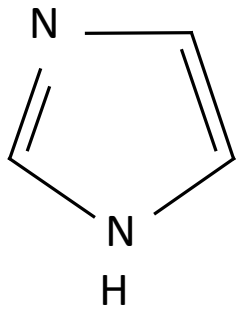
- Consisting of a flat five-membered ring, it is aromatic as indicated by its extensive substitution reactions.

Pharmaceutical Importance

Thiophenes are important heterocyclic compounds that are widely used as building blocks in many agrochemicals and pharmaceuticals. The benzene ring of a biologically active compound may often be replaced by a thiophene without loss of activity. This is seen in examples such as the NSAID lornoxicam the thiophene analog of piroxicam.

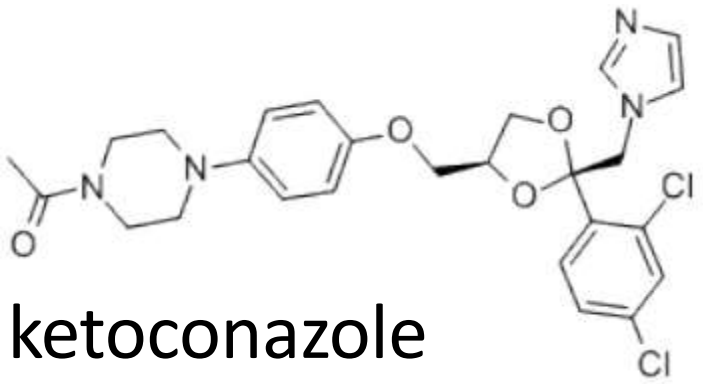
Imidazole

- Imidazole is an organic compound with the formula $(CH)_2N(NH)CH$. It is a colourless solid that dissolves in water to give mildly alkaline solution.

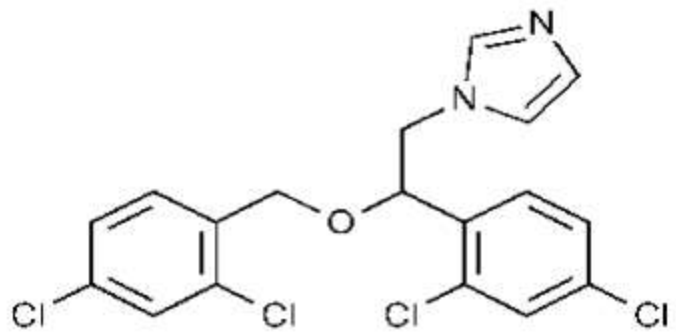


- Imidazole drug: Ketoconazole, Miconazole, Clotrimazole

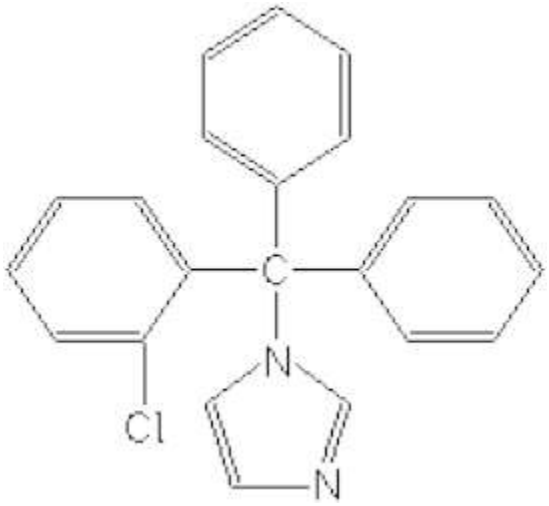
- Structure:



ketoconazole



miconazole



Clotrimazole

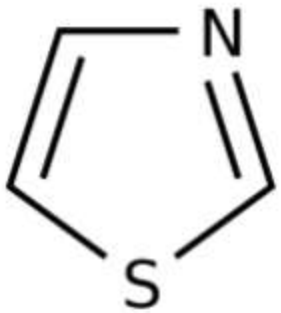
Pharmaceutical Importance

- Imidazole derivatives are potent antifungal agent. •

It is also used in the treatment of mycotic infection of skin.

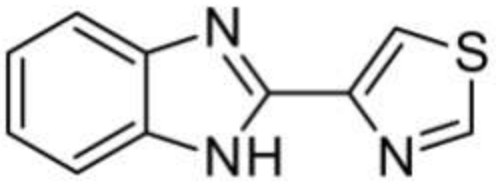
thiazole

- Thiazole is a heterocyclic compound that contains both sulfur and nitrogen; the term 'thiazole' also refers to a large family of derivatives.

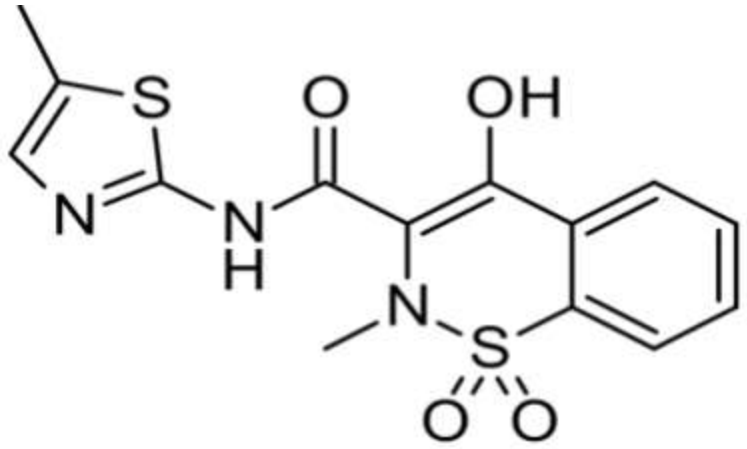


- Thiazole itself is a pale yellow liquid with a pyridine-like odor and the molecular formula C_3H_3NS. The thiazole ring is notable as a component of the vitamin thiamine(B_1).

- Thiazole drug:



Thiabendazole



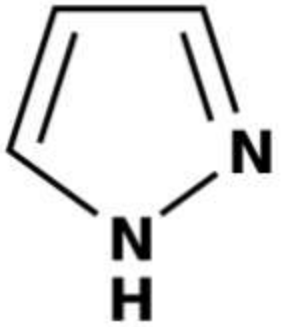
meloxicam

Pharmaceutical Importance

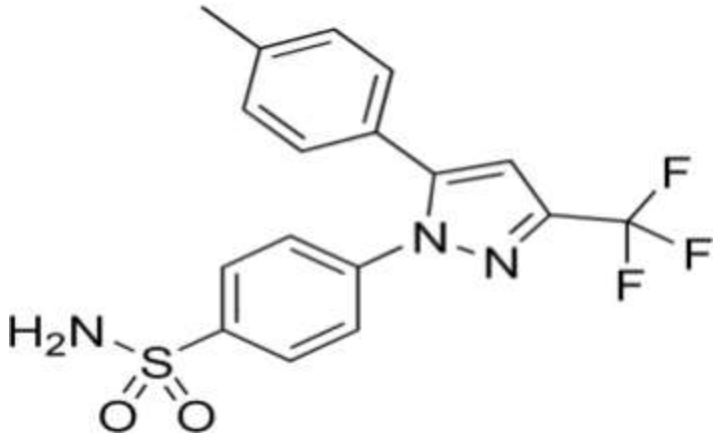
- Used in the disease of dutch elm disease
- Used as paracitiside
- Angiogenesis Inhibitor
- Used as anti microbial agent-sulfathiazole
- Used as antidepressant drug-pramipexole

pyrazole

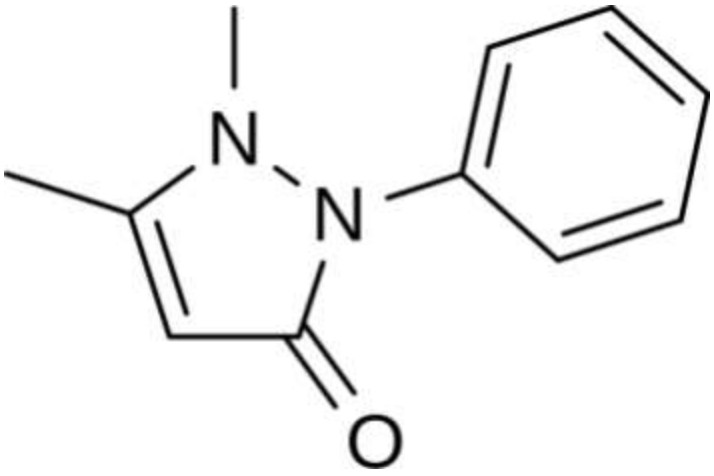
- Pyrazole is the organic compound with the formula $C_3H_3N_2H$.
- It is a heterocycle characterized by a 5-membered ring of three carbon atoms and two adjacent nitrogen centres.



- Pyrazole derivative drug:



celecoxib



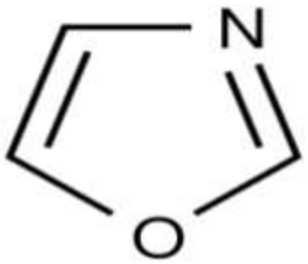
Phenazone

Pharmaceutical Importance

- In medicine, derivatives of pyrazoles are used for their analgesic, anti-inflammatory, antipyretic, antiarrhythmic, tranquilizing, muscle relaxing, anticonvulsant, monoamineoxidase inhibiting, antidiabetic and antibacterial activities.

Oxazole

- Oxazoles are heterocyclic aromatic compounds containing an oxygen atom and a nitrogen atom separated by one carbon atom.
- Oxazole derivatives have become increasingly important because of their use as intermediates for the preparation of new biological materials.



Pharmaceutical Importance

The wide range of biological activities of oxazoles includes anti-inflammatory, analgesic, antibacterial, antifungal, hypoglycemic, antiproliferative, anti-tuberculosis, muscle relaxant and HIV inhibitor activity.

Heterocyclic compounds

are organic compounds that contain rings composed of carbon and **other atoms** – **heteroatoms** – in natural heterocycles mostly **nitrogen**, **sulfur**, and **oxygen**.

Heterocycles exist as three-, four-, five-, six-, and multi-membered rings.

The stability of heterocycles increases

- with less distorted bond angles (**less strain**) that are in **five- and six-membered rings**, and
- with maximum number of conjugated double bonds, because the delocalized π-bonding electron pairs form a **molecular π orbital** filled with six electrons and the compound have the **aromatic character**.

Some rings, in spite of being five- or six-membered, are **not stable heterocycles**, e.g.

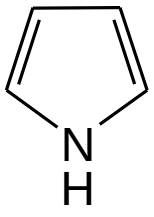
cyclic hemiacetals (cyclic forms of monosaccharides) are in equilibria with their open (acyclic) forms,

cyclic esters (lactones), **amides** (lactams), and cyclic dicarboxylic **acid anhydrides** can undergo hydrolytical splitting.

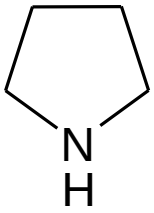
Nonaromatic heterocycles – **cyclic ethers**, **amines**, and **sulfides** behave like their acyclic analogs with the same functional group and do not require special discussion.

Aromatic heterocycles (with the maximum number of conjugated double bonds) are much more important.

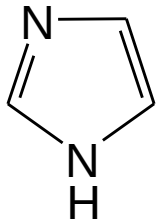
Survey of the most important heterocycles



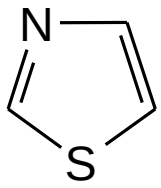
pyrrole



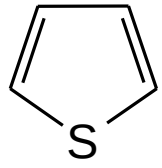
pyrrolidine



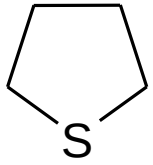
imidazole



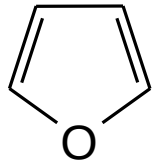
thiazole



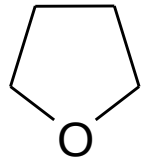
thiofene



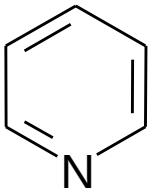
thiolane



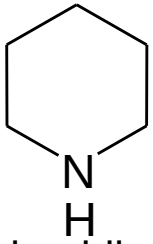
furan



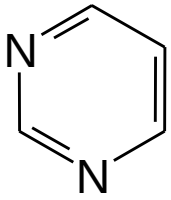
tetrahydro-furan



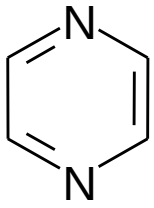
pyridine



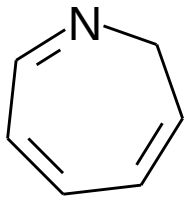
piperidine



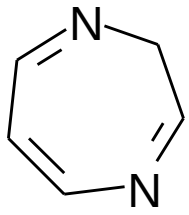
pyrimidine



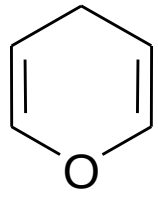
pyrazine



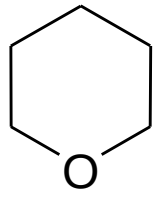
azepine



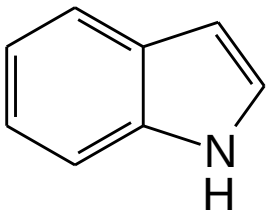
1,4-diazepine



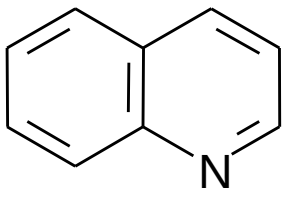
4H-pyran



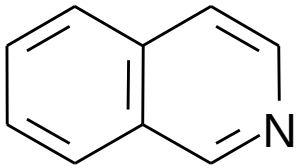
tetrahydro-pyran



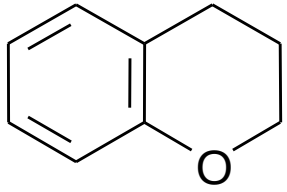
indole



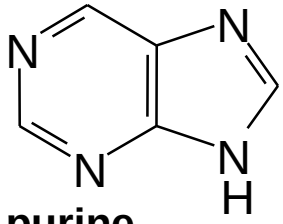
quinoline



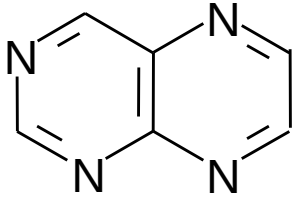
isoquinoline



chroman



purine



pteridine

Nomenclature of heterocycles

Common names for many ring systems are accepted by the IUPAC rules:

- rings with maximum double bonds

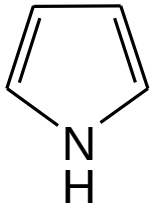
  furan, pyrrole, indole, pyridine, etc.

- saturated ring systems

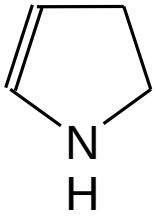
  either prefixes dihydro-, tetrahydro-, perhydro-,

  or in five-membered rings pyrrol**in**e, pyrrol**idin**e,

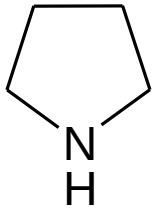
  in six-membered rings pi**per**idine, pi**per**azine.



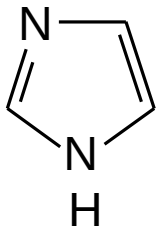
pyrrole



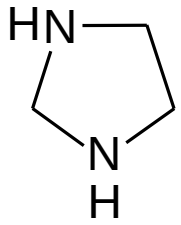
pyrroline



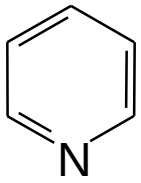
pyrrolidine



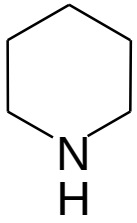
imidazole



imidazolidine



pyridine



piperidine

Systematic names according to **Hantzch-Widman** for monocyclic heterocycles:

prefixes indicating the number of heteroatoms,
stem of the name indicates the type of heteroatom,
endings for number of ring members and saturation.

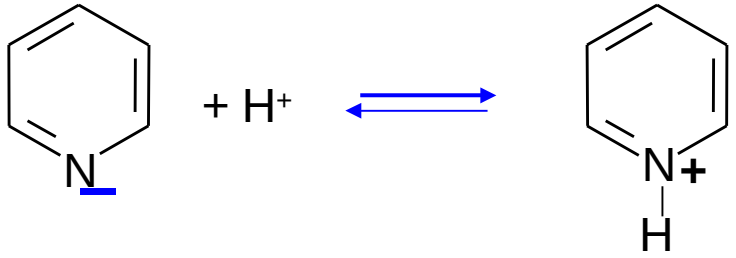
Some examples from the rules (used for some compounds in biochemistry:

Number of heteroatoms	Heteroatom	Number of ring members	Unsaturated	Saturated	
				nitrogenous	oxygenous sulfurous
		1	-irine, -irene	-irane	-irine
		2	-ete	-etidine	-etane ..
di-	**az-**	**5**	**-ole**	**-olidine**	**-olane**
tri-	**thi-**	**6**	**-ine**	(-**per**-)	**-ane**
	ox-	**7**	**-epine**	-epane	-epane
		8	-ocine	-ocane	..

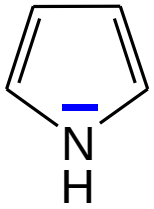
Replacement names may also be used occasionally.

Nitrogen-containing heterocycles are basic, unless the unshared electron pair of nitrogen is conjugated with π-electron pairs of double bonds, i.e. unless it takes part on the formation of an aromatic six-electron π cloud..

Pyridine is a weak base. The unshared electron pair of nitrogen atom can bind a proton by coordination to give **pyridinium cation**:

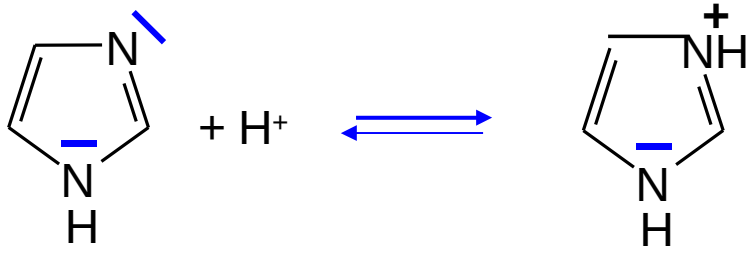


Pyrrole is not a base:

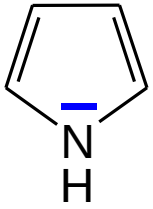


The unshared electron pair of nitrogen is not able to add proton.

Imidazole is a weak base;
One of the two nitrogen atoms can add proton:



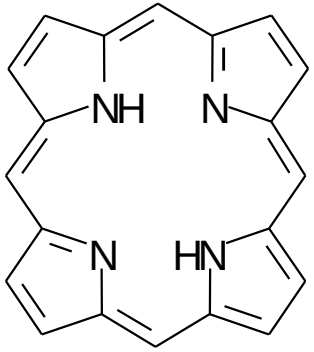
Pyrrole



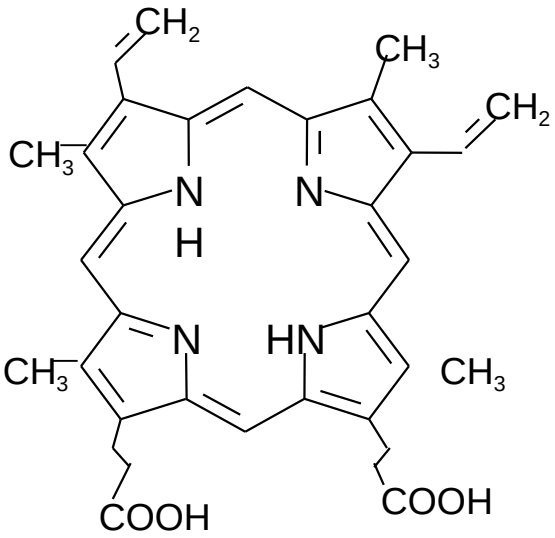
is <u>not a basic compound</u>!

The most important pyrrole derivatives are cyclic tetrapyrroles (haem, chlorophyll) and linear tetrapyrroles (bile pigments).

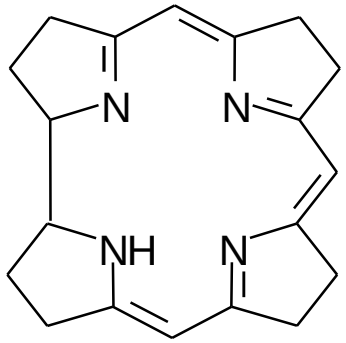
Cyclic tetrapyrroles



porphin

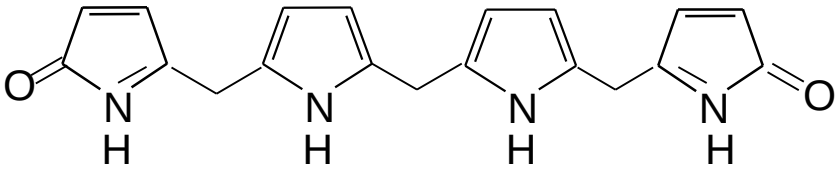


protoporphyrin IX

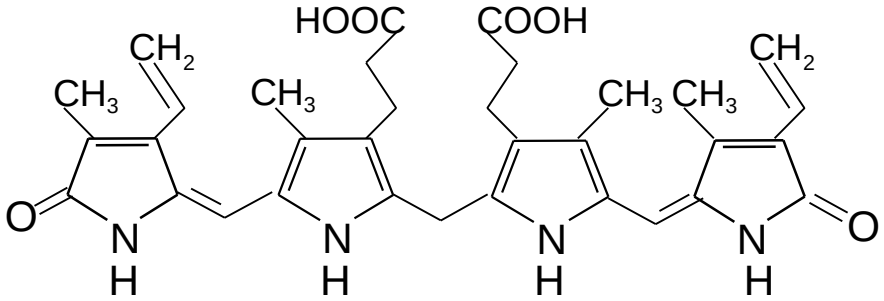


corrin

Linear tetrapyrroles



bilanes (with substituents at β-positions)



bilirubin

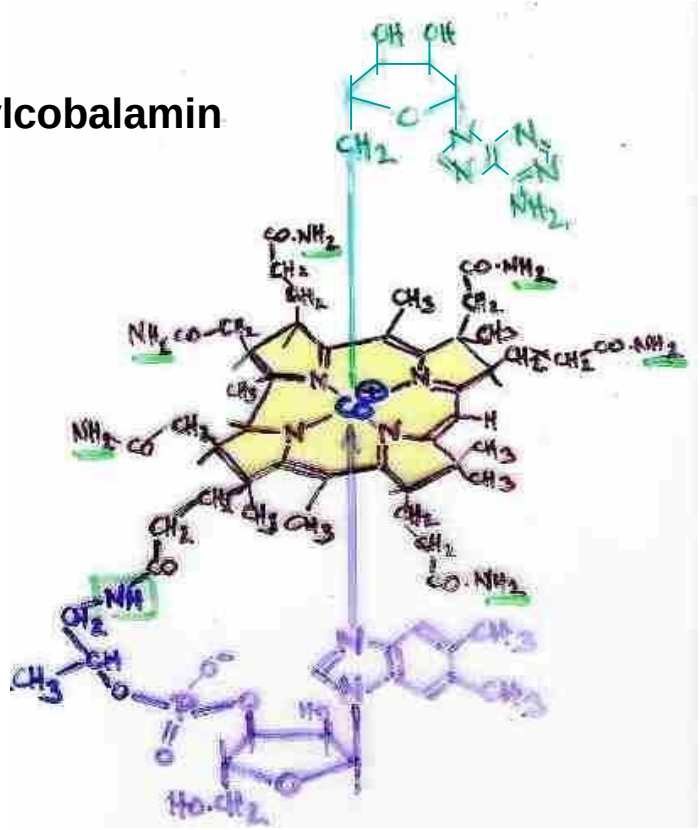
Vitamin B_{12} (cobalamin)

is essential for the maturation and development of red blood cells.

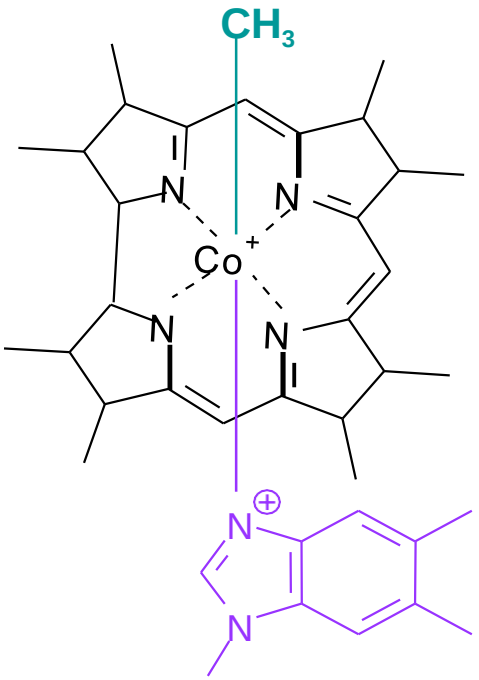
Coenzyme B_{12}

(cobamide cofactors 5´-deoxyadenosylcobalamin, methylcobalamin)

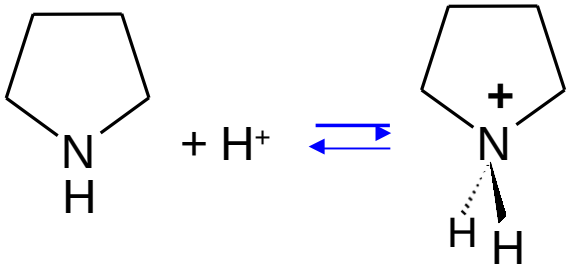
5´-deoxyadenosylcobalamin



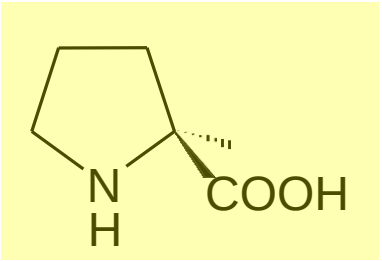
methylcobalamin
(part of the molecule)



Pyrrolidine is a cyclic secondary amine ($pK_B = 2.7$).



pyrrolidine pyrrolidinium ion

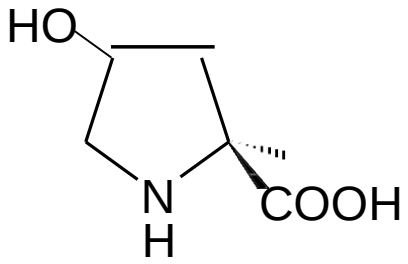


proline
(pyrrolidine-2-carboxylic acid)

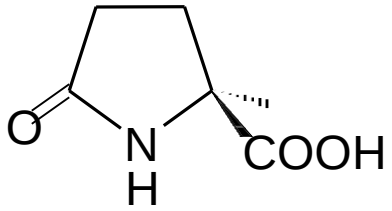
Proline is the only standard α-amino acid that has a secondary amino group:

Hydroxyproline (proline hydroxylated in position 4 or 3) is the characteristic constituent of <u>collagen</u> – the most abundant protein of connective tissue.

5-Oxoproline (lactam of glutamic acid) is formed in the group translocation of amino acids (γ-glutamyl cycle).



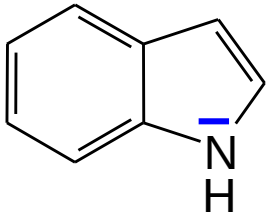
4-hydroxyproline



5-oxoproline
(pyroglutamate)

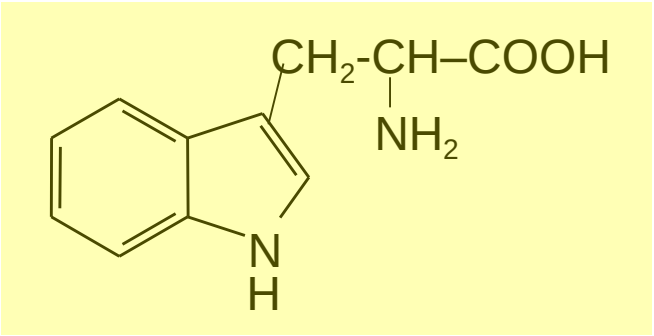
Indole

(2,3-benzopyrrole)



is <u>not a basic compound</u>!

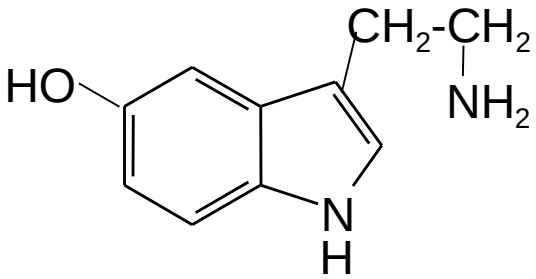
Tryptophan (2-amino 3-(3-indolyl)-propanoic acid) is a standard amino acid from which biologically active compounds are derived.



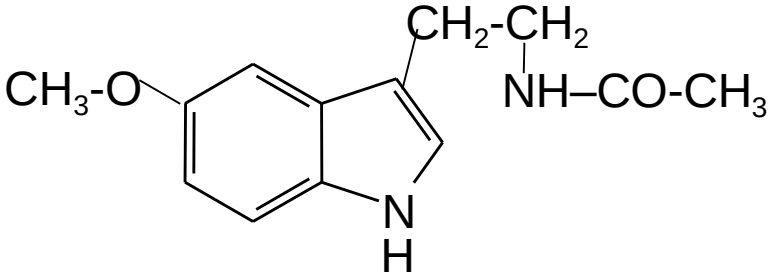
tryptophan

Serotonin (5-hydroxytryptamine) is a neurotransmitter in the central nervous system; it also acts as a vasoconstrictor released from blood platelets.
Melatonin (*N*-acetyl-5-methoxytryptamine) is released from the pineal gland and has a role in the control of diurnal biorhythms.

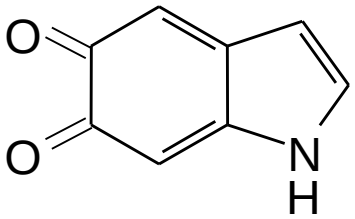
Indole-5,6-quinone that originates from tyrosine is a melanogen.



serotonin

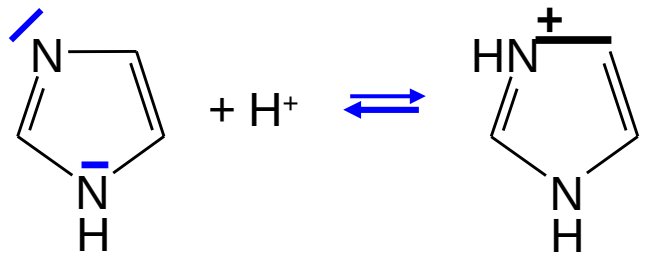


melatonin

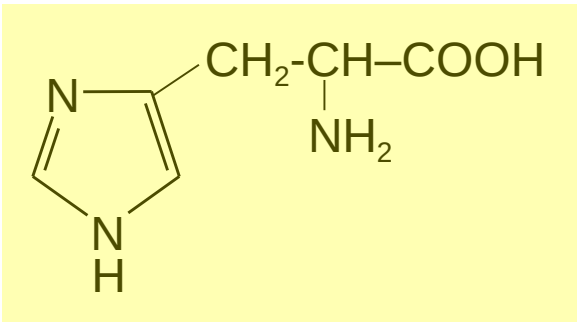


indole-5,6-quinone

Imidazole (1,3-diazole) is a weak base, one of the nitrogen atoms can add proton:



imidazole imidazolium cation

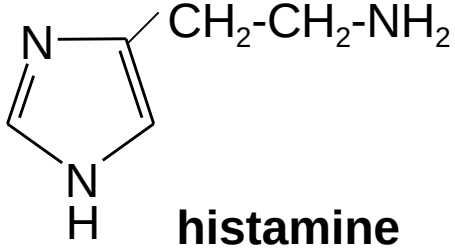


histidine

Histidine (2-amino-3-(4-imidazolyl)-propanoic acid) is an essential amino acid.

The side chains of histidyl residues are responsible for the buffering ability of proteins at physiological pH values, because only the imidazolyl groups (p$K_B \approx 8.0$) can take part in protolytic reactions under those conditions.

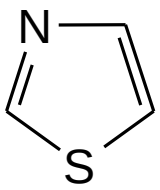
Histamine originates by decarboxylation of histidine and acts as a vasodilator in inflammations and allergic reactions. It also causes contraction of smooth muscles of the bronchial stem and the acidic stomach secretion.



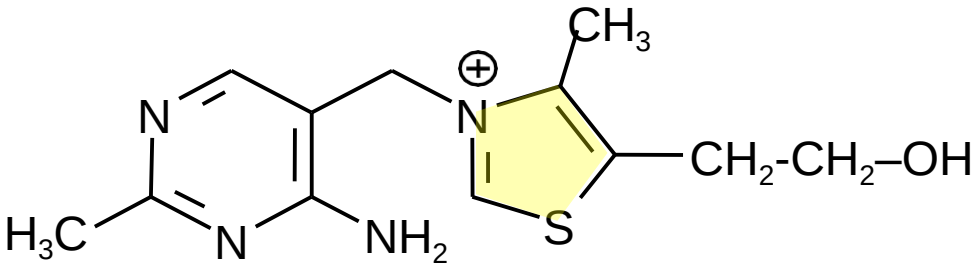
histamine

The **imidazolidine** occurs in the structure of creatinine and biotin.

Thiazole

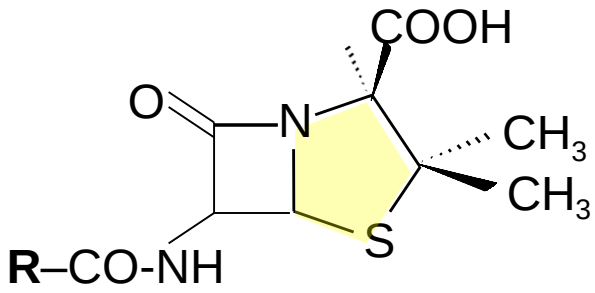


The thiazole ring occurs in **thiamin** (**vitamin B_1**) that also contains a pyrimidine ring.



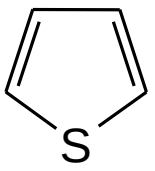
Thiamin diphosphate is the coenzyme that transports "active aldehyde" groups in the course of oxidative decarboxylations of pyruvate and other α-ketocarboxylic acids.

The fully saturated **thiazolidine** (tetrahydrothiazole) ring appears in the structure of antibiotics **penicillins**, the effect of which is caused by the unusual β-lactam ring.

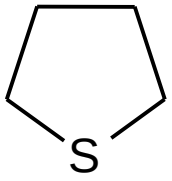


N-acylaminopenicillanic acid

Thiolane is completely hydrogenated thiophene.

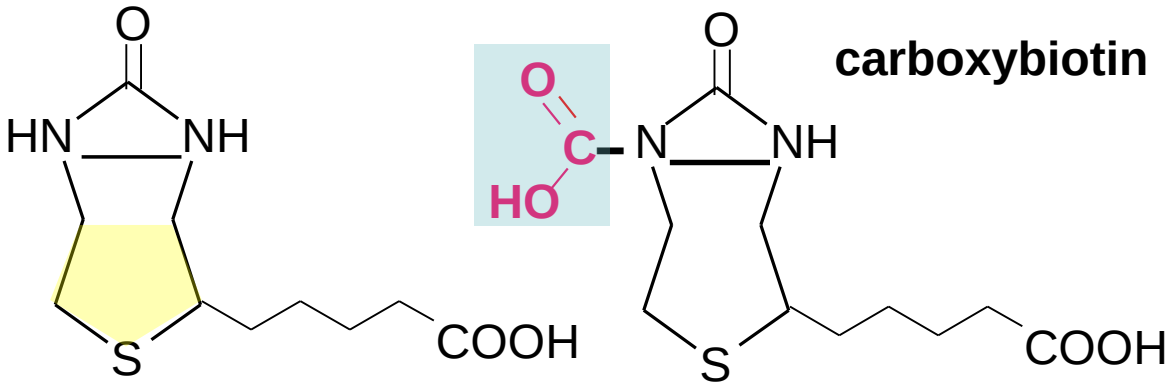


thiophene



thiolane

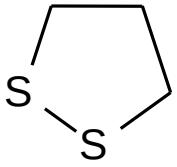
This ring structure appears (fused with imidazolidone) in **biotin**:

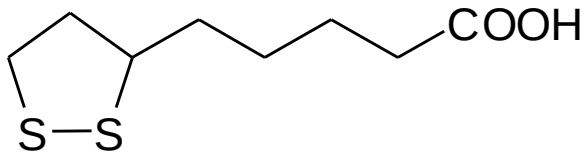


carboxybiotin

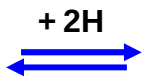
In the cells, biotin may bind CO_2 and resulting carboxybiotin serves as a donor of carboxyl in important carboxylations (e.g., biosynthesis of fatty acids, synthesis of oxaloacetate from pyruvate).

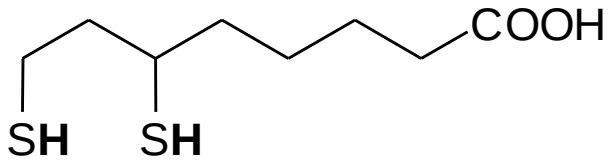
1,2-Dithiolane is a cyclic dlsulfide that can be easily reduced. to acyclic alkan-1.4-dithiol. It occurs as a part of **lipoic acid**.





lipoic acid (an **oxidant**)

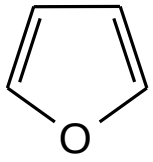




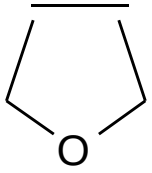
dihydrolipoic acid (**transfer of acyls**)

Oxygen containing five- and six-membered heterocycles

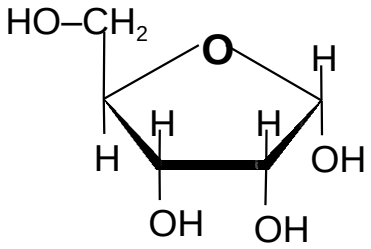
Furan derivatives are rather rare in natural compounds. On the contrary, **tetrahydrofuran** ring is quite common in cyclic forms of sugars.



furan



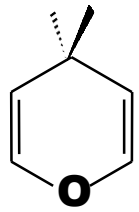
tetrahydrofuran



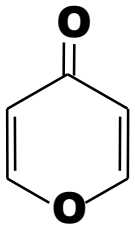
D-**ribofuranose**

Pyran is a labile ring (without the aromatic electron sextet), but it is stabilized through oxidation to pyrone;

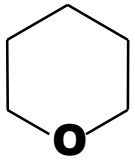
tetrahydropyran ring occurs in cyclic forms of monosaccharides:



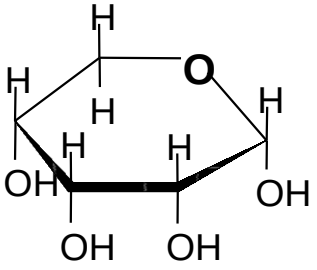
4*H*-pyran



4-pyranone
(γ-pyrone)

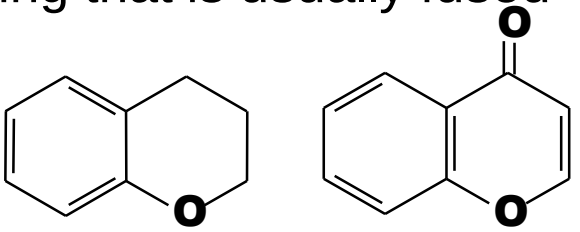


tetrahydropyran



D-**ribopyranose**

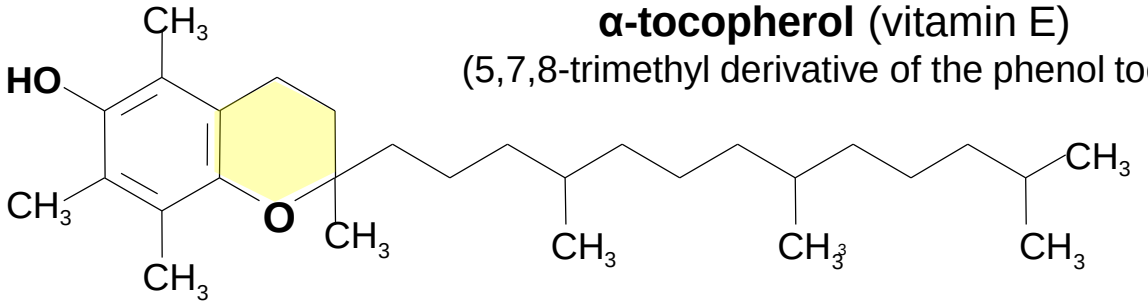
Many plant substances comprise the pyran ring that is usually fused condensed with the benzene ring:



chroman chromone

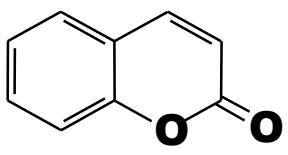
Those structures appear, e.g., in **flavonoids**, in the active component of hemp **tetrahydrocannabinol** (THC), tocopherols, and derivatives of coumarin.

Tocopherols are important exogenous lipophilic antioxidants, which prevent oxidation of membrane lipids and lipoproteins by reactive oxygen species.



α-tocopherol (vitamin E)
(5,7,8-trimethyl derivative of the phenol tocol)

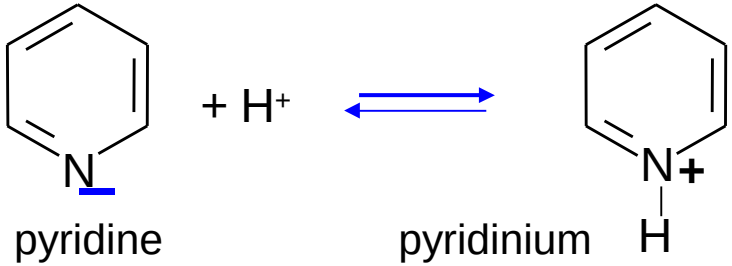
Derivatives of coumarin (warfarin, biscoumarins) prevent *in vivo* coagulation of blood. They act as antivitamins K by inhibition of biosynthesis of vitamin K-dependent coagulation factors.



coumarin
(2-hydroxycinnamic lactone)

Coumarin appears in spoiled sweet-clover hay.

Pyridine is a weak base ($pK_B = 8.7$).

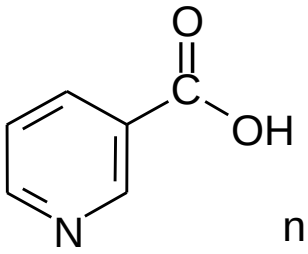


pyridine pyridinium

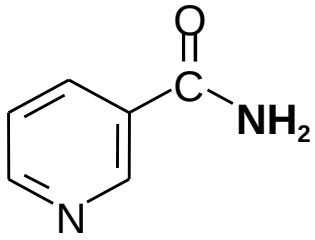
The most important derivatives of pyridine are two essential factors:

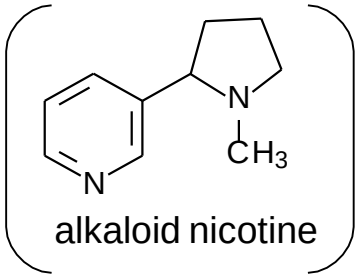
Nicotinic acid and **nicotinamide** is called **niacin** or pellagra-preventing factor (PPF); they are included in the group of vitamins B.

nicotinic acid
(pyridine-3-carboxylic acid)



nicotinamide

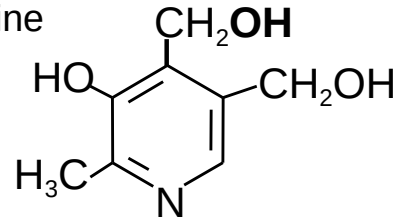




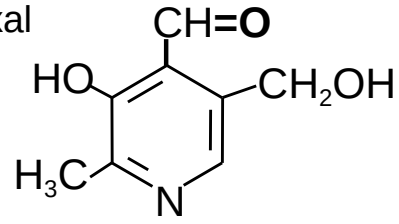
alkaloid nicotine

Vitamin B_6 is the group name for three related derivatives pyridoxine, pyridoxal, and pyridoxamine.

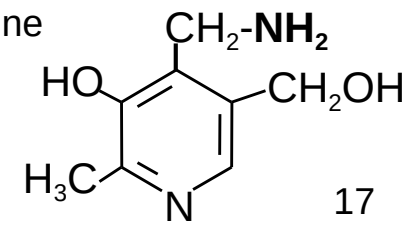
pyridoxine



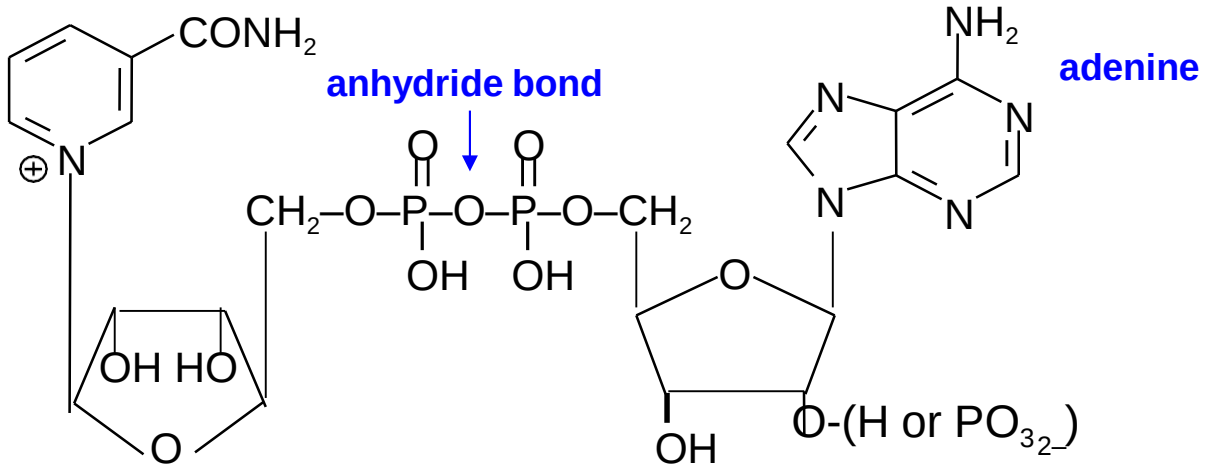
pyridoxal



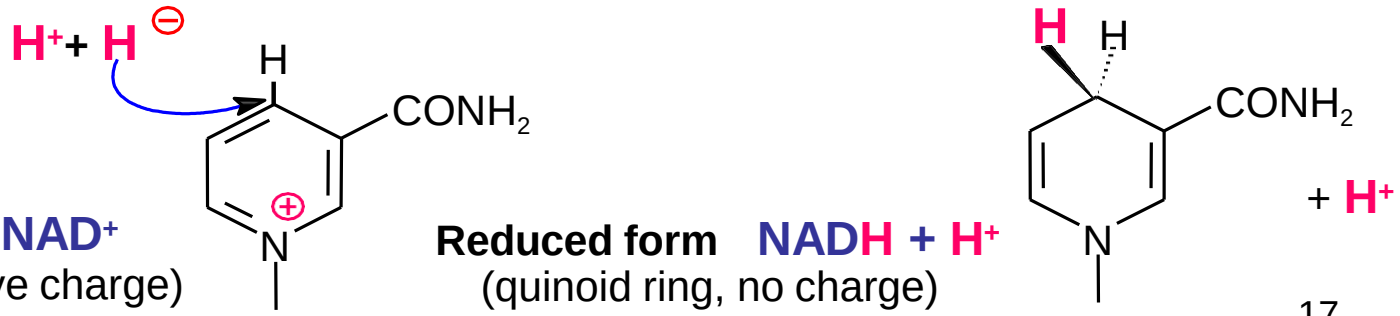
pyridoxamine



NAD$^+$ (nicotinamide adenine dinucleotide) and **NADP$^+$** (NAD phosphate) are **coenzymes of dehydrogenases**:



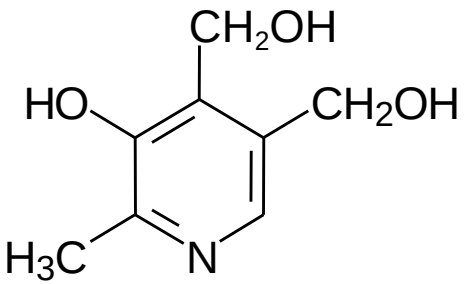
The active group of NAD$^+$ (as well as of similar NADP$^+$) is nicotinamide: It acts as an **oxidant** that takes off **two atoms of hydrogen** from the substrate. One atom plus one electron (**hydride anion H$^-$**) is added to the *para*-position of the pyridinium ring, the remaining H$^+$ binds to the enzyme.



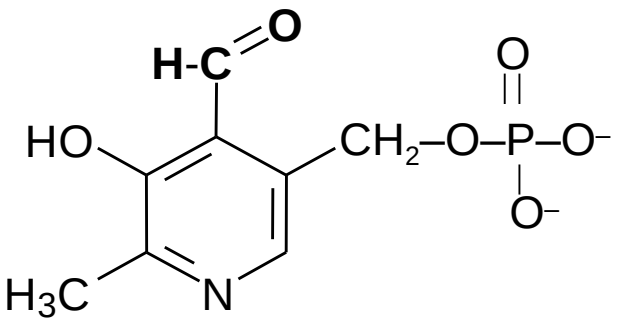
Oxidized form **NAD$^+$**
(aromatic ring, positive charge)

Reduced form **NADH + H$^+$**
(quinoid ring, no charge)

Pyridoxal phosphate



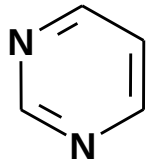
pyridoxine (vitamin B_6)



pyridoxal phosphate

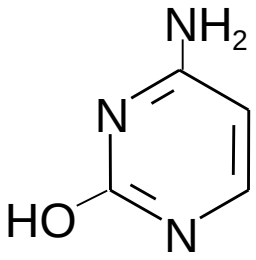
Pyridoxal phosphate is the prosthetic group in many enzymes taking significant part in α-amino acid metabolism namely. They catalyze, e.g., **transamination** and **decarboxylation of amino acids.**
The aldehyde group of pyridoxal coenzyme binds to α-amino group of an amino acid forming an **aldimine intermediate** (Schiff base).

Pyrimidine
(1,3-diazine)

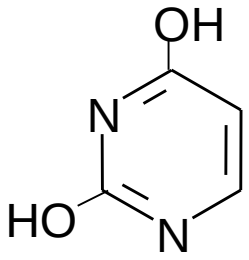


is a dibasic compound.

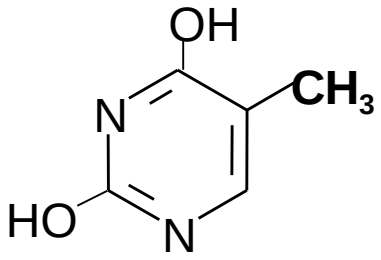
Three pyrimidine bases are components of nucleic acids:



cytosine
4-amino-2-hydroxypyrimidine



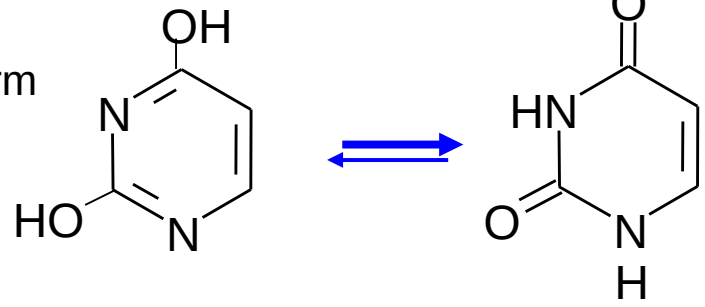
uracil
2,4-dihydroxypyrimidine



thymine
5-methyluracil

They exist in two tautomeric forms. Only the lactam forms can be ribosylated to give nucleosides:

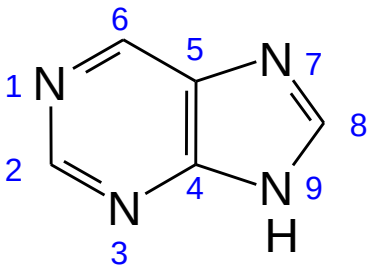
lactim form



lactam form of uracil

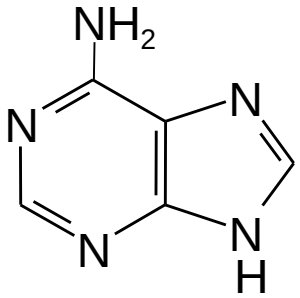
Pyrimidine ring is comprised also in the structure of **thiamin** and **barbituric acid**.

Purine
(pyrimidinoimidazole)

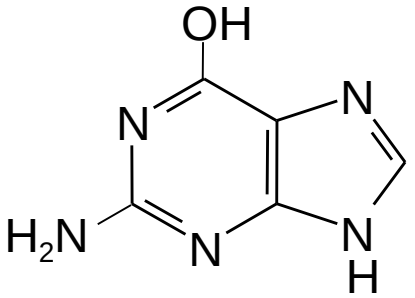


atypical numbering!

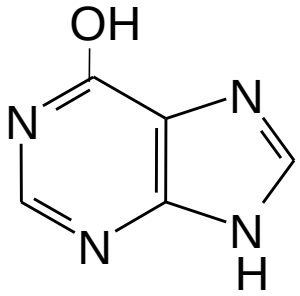
Two purine bases of nucleic acids:



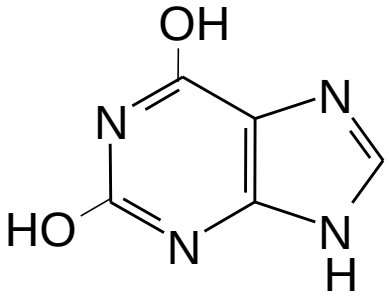
adenine
6-aminopurine



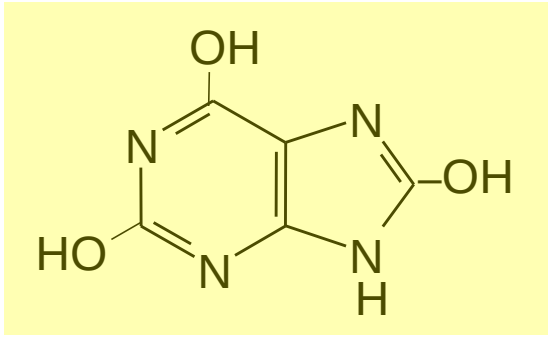
guanine
2-amino-6-hydroxypurine



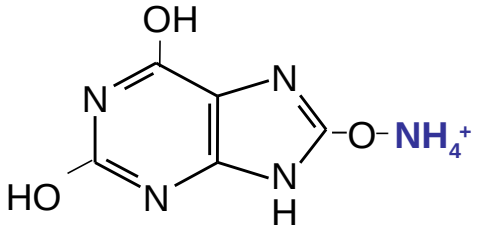
hypoxanthine
6-hydroxypurine



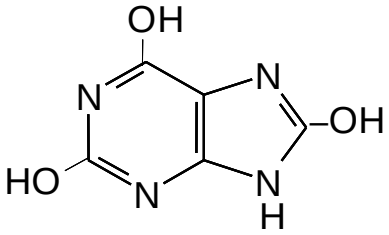
xanthine
2,6-dihydroxypurine



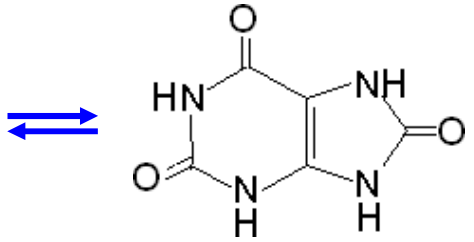
uric acid (2,6,8-trihydroxypurine)



ammonium hydrogen urate

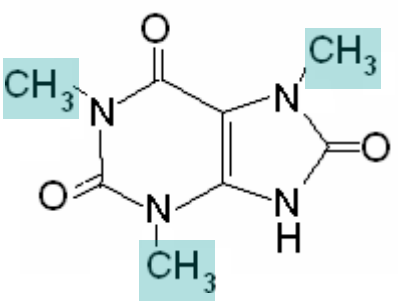


lactim form

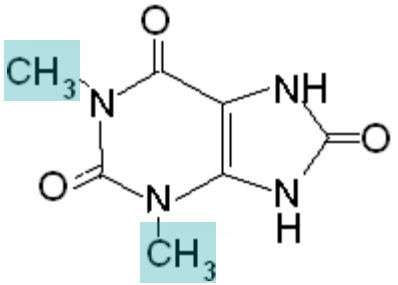


lactam form of uric acid

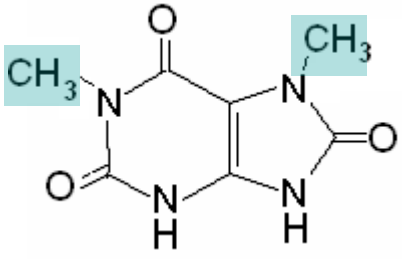
Methylxanthines are *N*-methyl derivatives of xanthines, known alkaloids in coffee, tea, and cocoa.



caffeine
1,3,7-trimethyxanthine



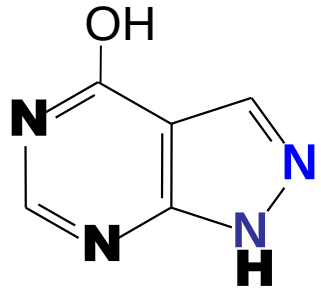
theophylline
1,3-dimethylxanthine



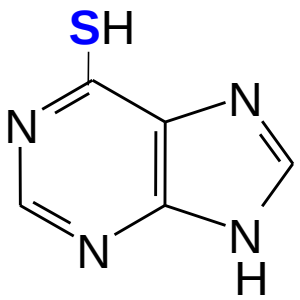
theobromine
1,7-dimethylxanthine

Allopurinol is an isomer of hypoxanthine, which is used in treatment of hyperuricacidaemia and gout. It inhibits xanthine oxidase – the enzyme that transforms hypoxanthine and xanthine to urate.

Mercaptopurine (6-sulfanylpurine) inhibits the biosynthesis of purine bases and is used in chemotherapy of cancer.



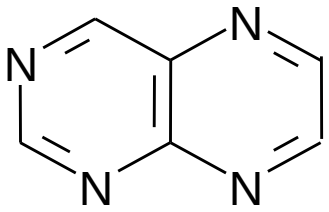
allopurinol

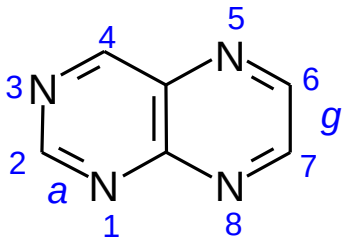


mercaptopurine

Pteridine

(pyrimidinopyrazine)

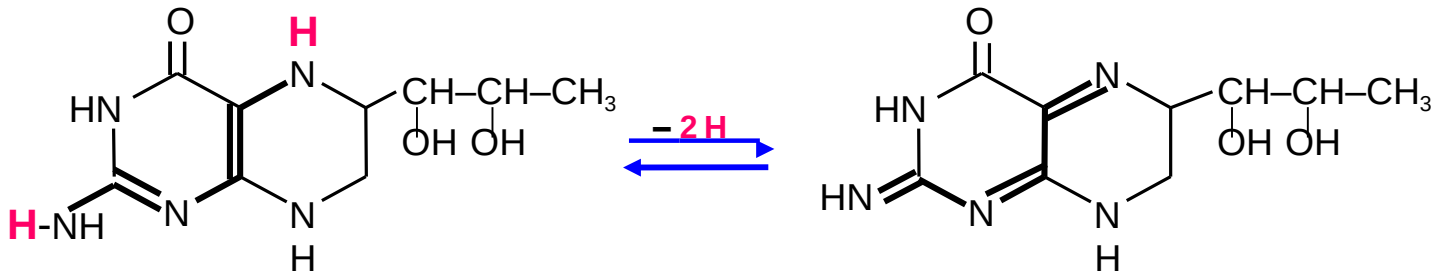




Three important coenzymes are derived from pteridine: pterin coenzyme, folic acid, and flavine coenzymes.
In the cells, the pteridine system originates from guanine!

Tetrahydrobiopterin (BH_4)

acts as the **reducing coenzyme** in certain hydroxylations catalyzed by monooxygenases. It supplies two atoms of hydrogen and is oxidized to the quinoid form of **dihydropterin**:

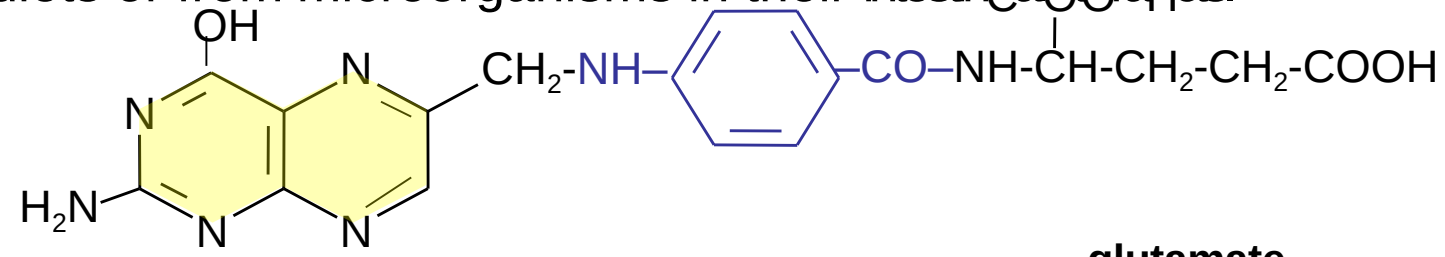


tetrahydrobiopterin (BH$_4$)
reduced form

dihydrobiopterin (**qBH$_2$**)
oxidized (quinoid) form

Folic acid (folate)

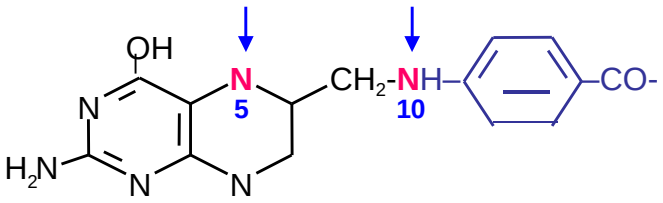
is *N*-**pteroylglutamic acid**; the number of attached glutamyl residues may
be higher. Although synthesizing the pteridine ring, mammals are unable to conjugate it with PABA and glutamate. They have to obtain folate from their diets or from microorganisms in their intestinal flora.



Tetrahydrofolate

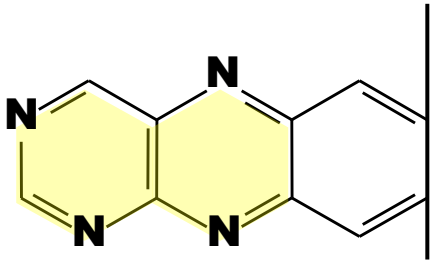
(**H_4folate**) is an cofactor that **transports one-carbon groups** (e.g. –CH=O, –CH_2OH, –CH_3) inevitable namely for the biosynthesis of purine bases and thymine.

Sites for bonding of one-carbon units

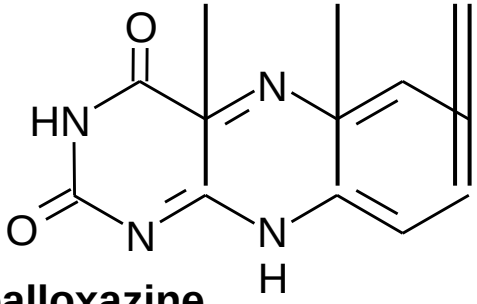


Methotrexate (4-amino-10-methylfolate) and **aminopterin** (4-aminofolate) are antifolate drugs used as cytostatics in oncology.

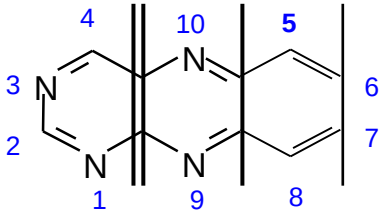
By condensation with benzene ring, pteridine gives **benzopteridine**, the 2,4-dioxoderivative of which is **isoalloxazine**.



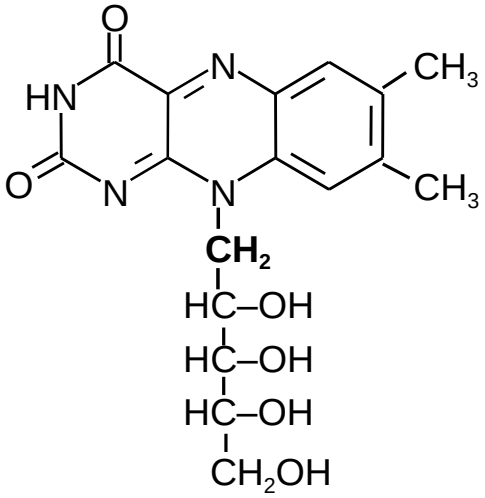
benzo[*g*]pteridine



isoalloxazine



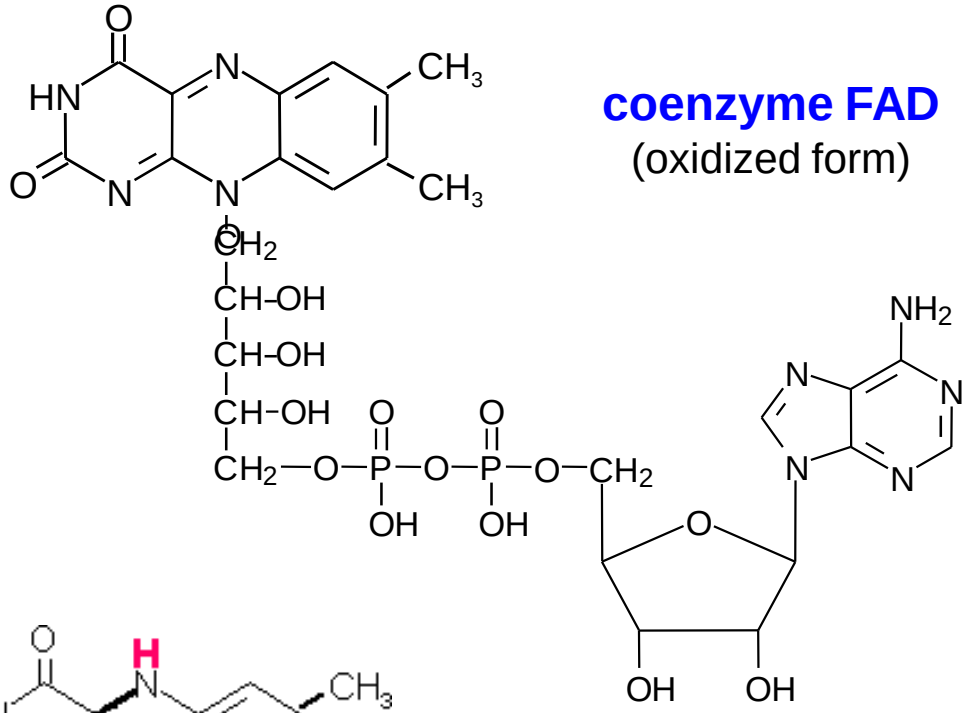
Riboflavin (vitamin B_2) is 6,7-dimethyl-9-(1-ribityl)isoalloxazine.



Ribityl is the remainder of sugar alcohol ribitol. Riboflavin is the only coloured hydrophilic vitamin (intensive yellow).

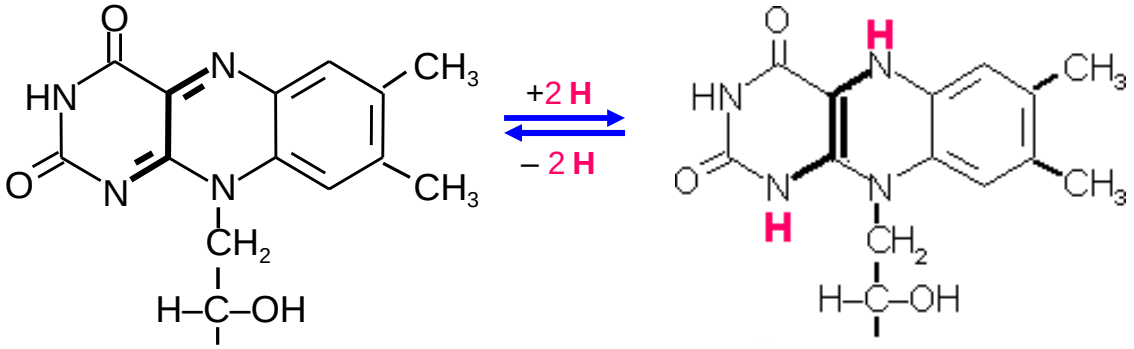
It is a part of **coenzymes FAD and FMN.**

FAD (flavin adenine dinucleotide) and
FMN (flavin mononucleotide)



coenzyme FAD
(oxidized form)

Flavin prosthetic groups act as **oxidants** in certain types of reactions catalyzed by dehydrogenases or oxidases.

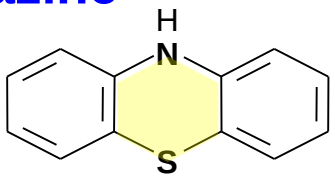


oxidized form
FAD or **FMN**

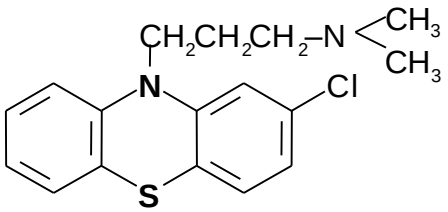
reduced form
FADH$_2$ or **FMNH$_2$**

Heterocycles in major psychotherapeutic agents (examples):

Thiazine



phenothiazine

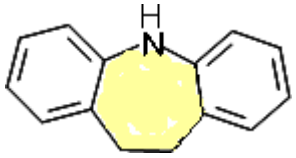


chloropromazine

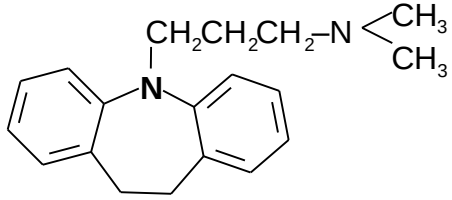
Tranquilizers
(neuroleptics, psychostatics)

Azepine, thiepine, and diazepine

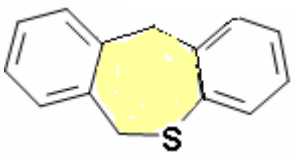
Antidepressants
(thymoleptics, psychostimulants)



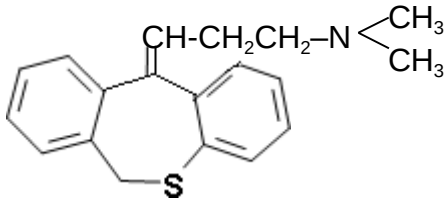
dihydrodibenz[b,f]azepine



imipramine

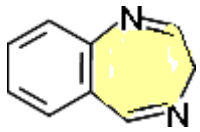


dibenzothiepine

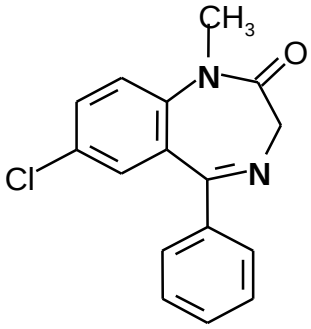


dosulepine

Anxiolytics



benzo[f]diazepine



diazepam (Valium)

Some other derivatives of benzo-diazepam are **hypnotics** (e.g. flunitrazepam, Rohypnol) or **myorelaxants**.

Alkaloids

Alkaloids are

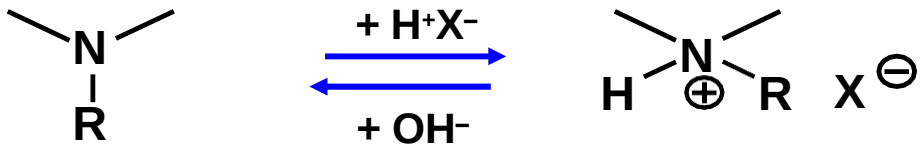
- natural **nitrogenous bases** originating from amino acids (sometimes called "secondary" metabolites),
- occurring **mostly in higher plants**;
- most of them are **heterocyclic compounds**,
- they exhibit extraordinary **variety of structural features**,
- many of them have marked **biological effects**
  (quite a number of them possess curative properties).

It is not yet known, whether alkaloids are unwanted by-products or products of detoxification, protective or reserve compounds, or useful regulators.

Alkaloids are **weak bases**

Alkaloid	pK_B	Alkaloid	pK_B
Atropine	4.35	Nicotine	6.16; 10.96
Ephedrine	4.64	Morphine	6.13
Quinine	5.07; 9.70	Papaverine	8.00
Cocaine	5.59	Caffeine	13.40

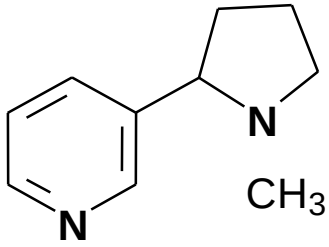
pK_B (ammonia) 4.75



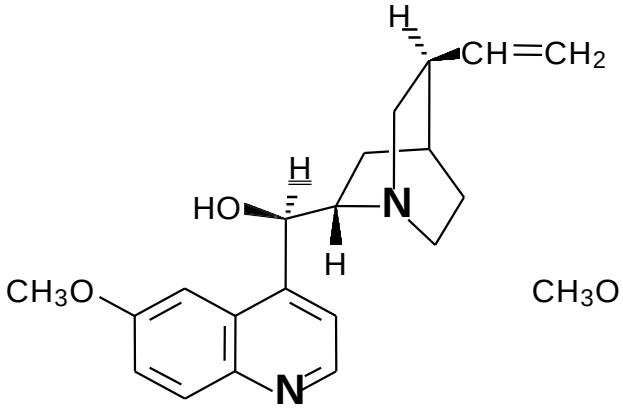
free alkaloid base
(purely soluble in water)

salt
(soluble in water)

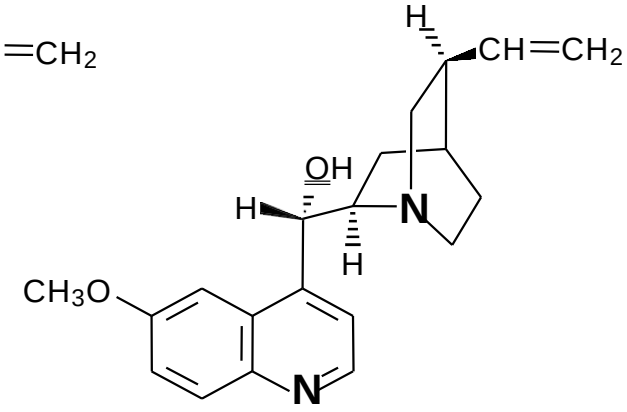
Examples of basic alkaloids:



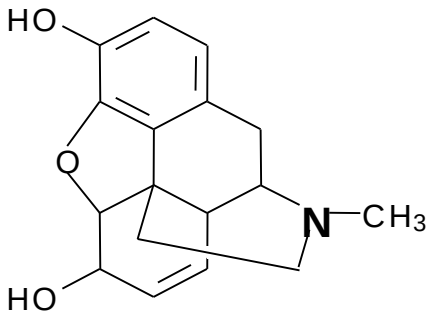
nicotine
(vasoconstrictor, stimulant)



quinine
(antimalarial)

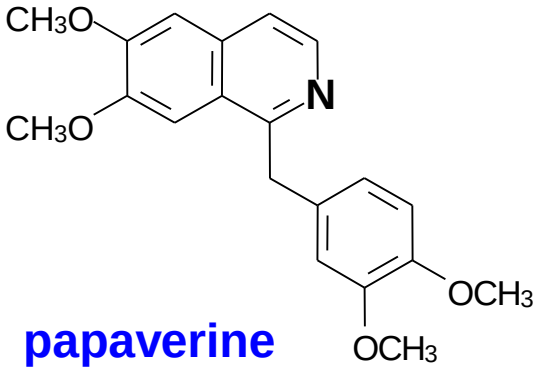


quinidine
(antiarrhytmic)

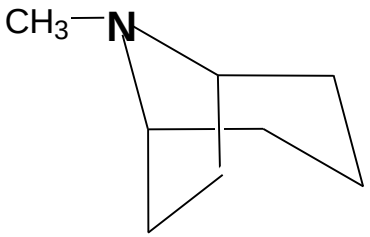


morphine
(narcotic action)

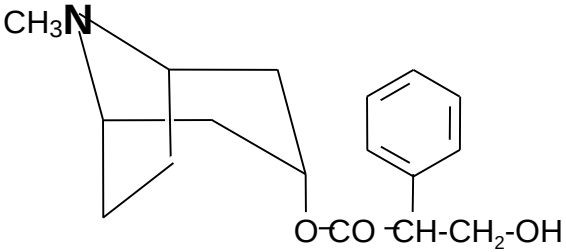
codeine (3-*O*-methylmorphine,
antitussic action)



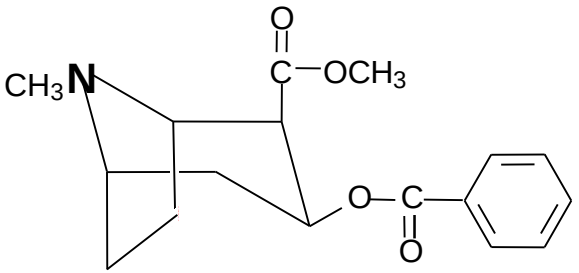
papaverine
(antispasmodic action)



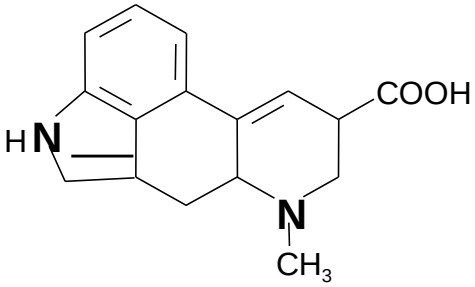
tropane
8-methyl-8-azabicyklo[3,2,1]octane



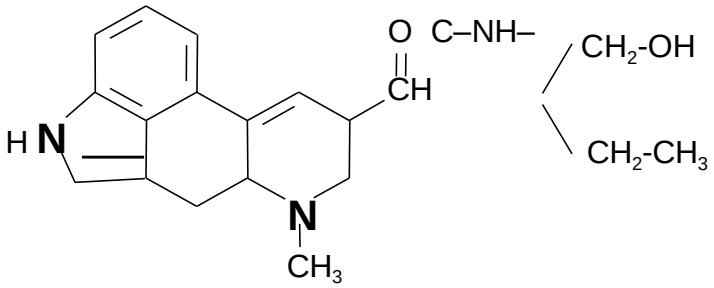
atropine
(antispasmodic action)



cocaine
(local anaesthetic, psychostimulant)



lysergic acid



methylergometrine
(uterotonic)