بسم الله الرحمن الرحيم

Heterocyclic Organic Chemistry (2020)

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(Synthesis of Hetero Cyclic)
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Chapter 1

Nomenclature of Heterocyclic compounds

HETEROCYCLIC COMPOUNDS

Most chemical compounds consist of molecules. The classification of such chemical compounds is based on the structure of these molecules, which is defined by the type and number of atoms as well as by the covalent bonding within them. There are two main types of structure:

-The atoms form a chain - aliphatic (acyclic) compounds

-The atoms form a ring - cyclic compounds

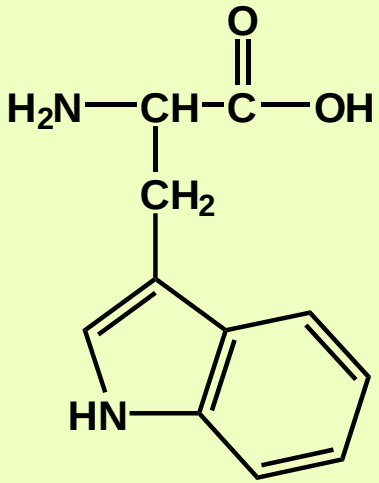
Cyclic compounds with at least two different atoms in the ring are known as heterocyclic compounds. The ring itself is called a heterocycle.

A hetero atom **is an atom other than carbon. The name comes from the Greek word *heteros*, which means "different".**

The N-atom is the most common heteroatom. Next in importance are O- and S-atoms. Heterocycles with Se-, Te-, P-, As-, Sb-, Bi-, Si-, Ge-, Sn-, Pb- or B-atoms are less common.

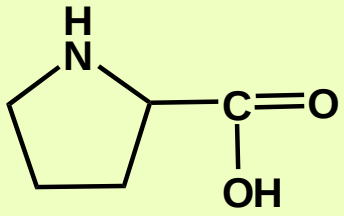
Heterocyclic compounds are widely distributed in nature. Many are of fundamental importance to living systems, for examples:
Chlorophyll and heme،
Essential ingradients such as thiamin (Vitamin B1), riboflavin (Vitamin B2), pyridoxal (Vitamin B6), nicotinamide (Vitamin B3), and ascorbic acid (Vitamin C) are heterocyclic compounds.

Among the twenty amino acids commonly found in proteins, three of them are heterocyclic.



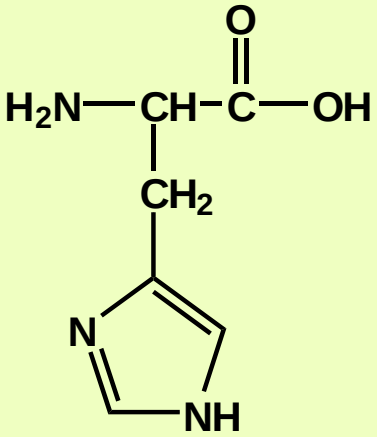
2-amino-3-(1*H*-indol-3-yl)propanoic acid

Trptophan (Trp)



pyrrolidine-2-carboxylic acid

Proline (Pro)



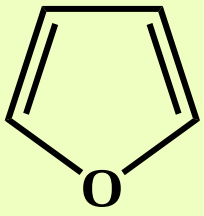
2-amino-3-(1*H*-imidazol-4-yl) propanoic acid

Histidine (His)

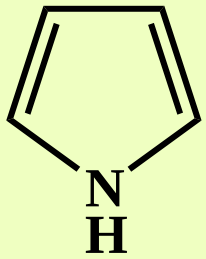
NOMENCLATURE OF HETEROCYCLIC COMPOUNDS

(a) Monocycles

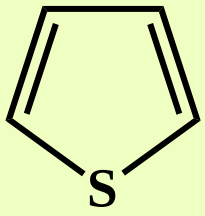
(i) *Trivial Names*



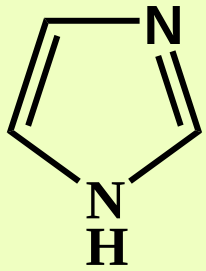
furan



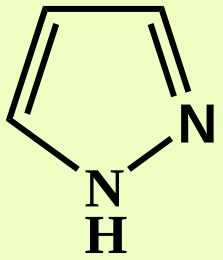
1*H*-pyrrole



thiophene

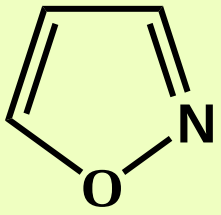


1*H*-imidazole

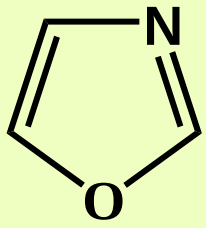


1*H*-pyrazole

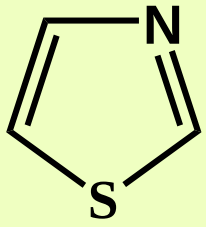
isothiazole



isoxazole

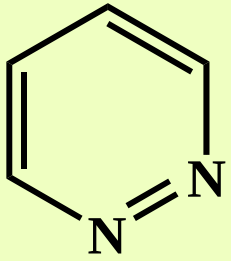


oxazole

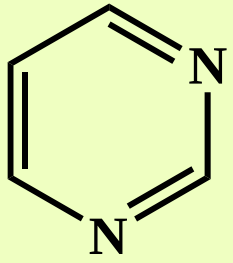


thiazole

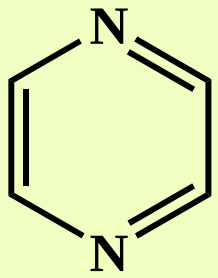
pyridine



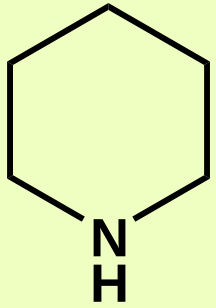
pyridazine



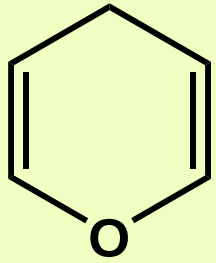
pyrimidine



pyrazine



piperidine



4*H*-pyran

morpholine

Hantzsch-widman system

- The basis for this system were introduced independently by A. Hantzsch and O. Widman .
- **According to this system a prefix is used to *indicate the nature of heteroatom* *in the ring* and**
- **a suffix is used to *indicate the size and the degree of saturation in the ring* .**

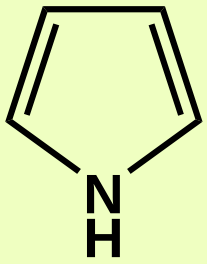
- ***Type of heteroatom***

Elements	**Valence**	**Prefix**	**Elements**	**Valence**	**Prefix**
1) Flour (F)	1	floura	10)Phosphorous (P)	3	phospha
2) Chlore (Cl)	1	chlora	11)Arsenic (As)	3	arse
3) Bromine (Br)	1	broma	12)Antimony (Sb)	3	stilba
4) Iodine (I)	1	ioda	13) Bismuth (Bi)	3	bisma
5) Oxygen (O)	**2**	**oxa**	14) Silicon (Si)	4	sila
6) Sulphur (S)	**2**	**thia**	15) Germnium (Ge)	4	germa
7) Selenium (Se)	2	selena	16) Tin (Sn)	4	stanna
8) Tellurium (Te)	2	tellura	17) Lead (Pb)	4	plumba
9) Nitrogen (N)	**3**	**aza**	18) Boron (B)	3	bora
			19) Mercury (Hg)	2	mercura

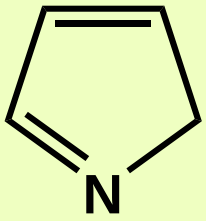
- ***Ring size***

Ring size	Rings containing Nitrogen		Rings containing no Nitrogen	
	Unsaturated	**Saturated**	**Unsaturated**	**Saturated**
3	**irine**	**iridine**	**irene**	**irane**
4	**ete**	**eidine**	**ete**	**etane**
5	**ole**	**olidine**	**ole**	**olane**
6*	**ine**	**ane****	**ine**	**inane*****

When the name obtained utilizing these rules is not satisfactory a locant H is used e.g.

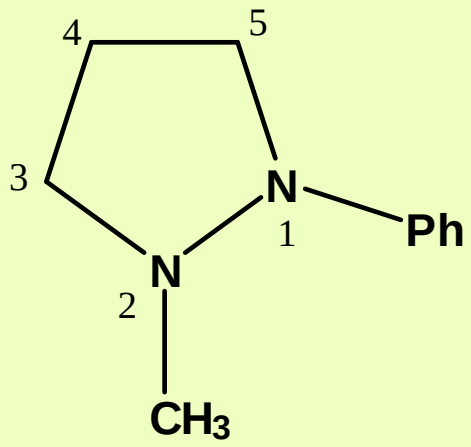


1*H*-pyrrole



2*H*-pyrrole

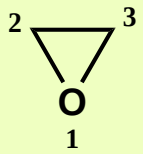
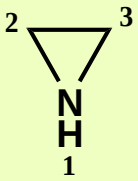
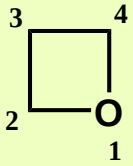
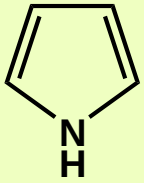
*** When a heterocycle contains two similar atoms, the one carrying the heavier substituent is numbered first .eg.**

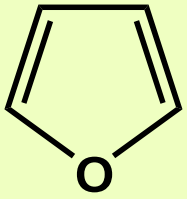


Phenyl-2-methyl-1,2-diazolidine -١

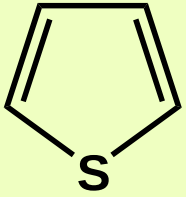
Monocyclic systems, with one heteroatom

The numbering of such systems starts at the heteroatom.

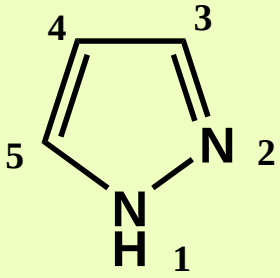
			
Oxiran	**Aziridine**	**Oxetane**	**Azole**



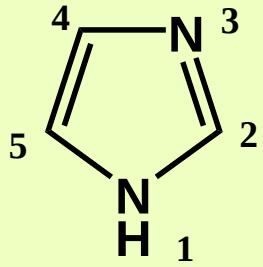
Oxole



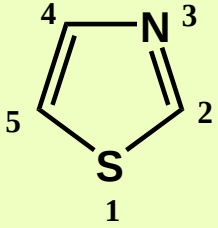
Thiole



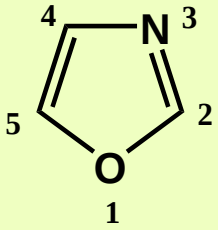
1,2-Diazole
(Pyrazole)



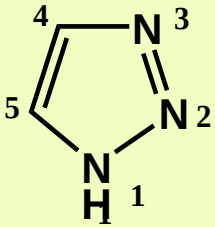
1,3-Diazole
(Imidazole)



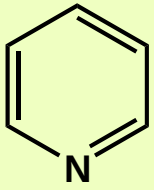
1,3-Thiazole



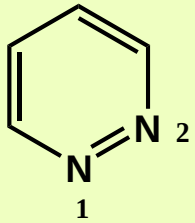
1,3-Oxazole



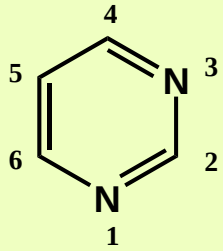
1,2,3-Triazole



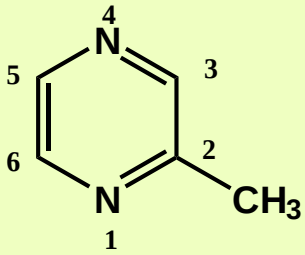
Azine



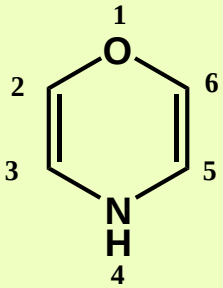
1,2-Diazine



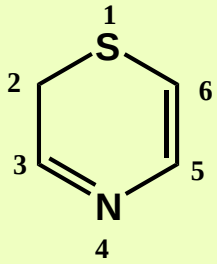
1,3-Diazine



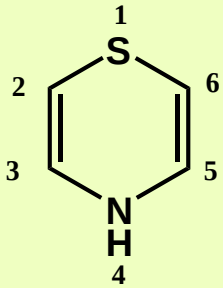
2-Methyl-1,4-Diazine



4*H*-1,4-Oxazine



2*H*-1,4-thiazine



4*H*-1,4-thiazine

Replacement Nomenclature

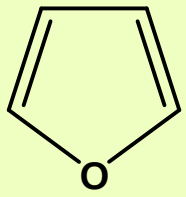
Heterocyclic systems are named by considering them to be derived from cyclic hydrocarbons by replacing a carbon corner by heteroatom.

The heteroatoms are indicated by the same prefixes used in the Hantzsch-Widman nomenclature.

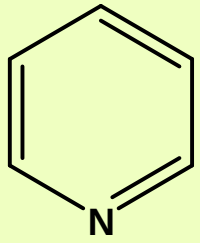
When more than one heteroatom is present citation numbers are used .The same priority rules used in Hantzsch-Widman system are applied.

(O, S, N)

1-Oxa-4-azacyclohexane



Oxacyclopent-2,4-diene

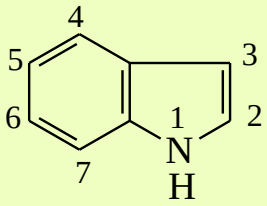


Azabenzene

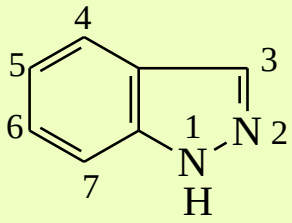
Fusion Names

A)- Bicyclic systems with one benzene ring

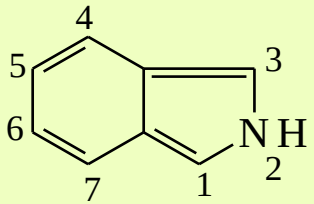
Systems in which at least two neighboring atoms are common to two or more rings are known as fused systems. For several bicyclic benzo-fused heterocycles, trivial names are permitted, e.g:.



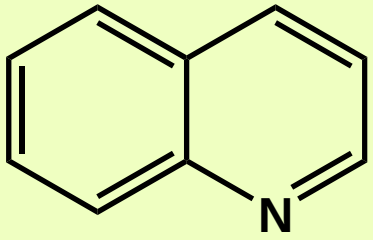
1H-Indole



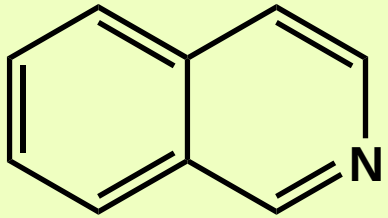
1H-Indazole



Isoindole

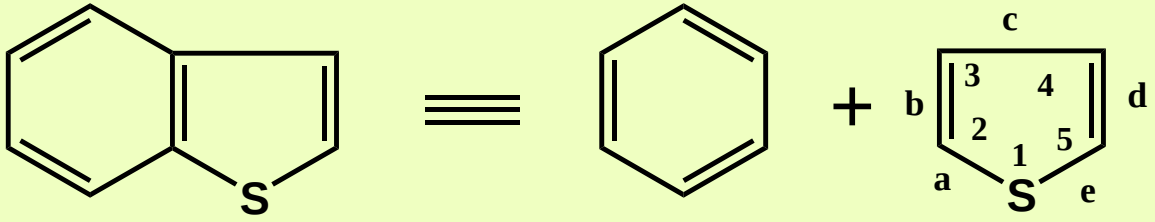


quinoline



isoquinoline

If the heterocycle has a trivial name, then the systematic name is formulated from the prefix benzo- and the trivial name of the heterocyclic component as follows:

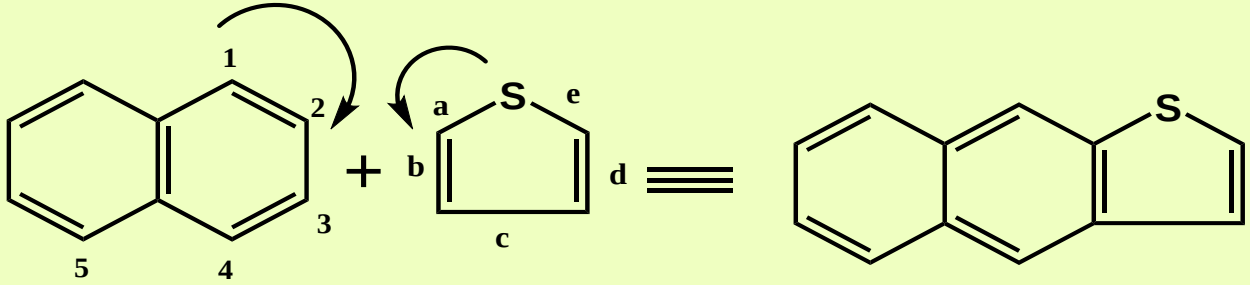


benzo[*b*]thiophene

The heterocyclic component is regarded as the *base component*

The bonds between the ring atoms are denoted according to the successive numbers of the ring atoms by the letters *a, b, c,* etc.
The letter *b* in brackets between benzo and the name of the base component denotes the atoms of the base component which are common to both rings .

The letter must be as early as possible alphabetically and hence benzo[*d*]thiophene is incorrect.



base component

naphtho[2,3-*b*]thiophene

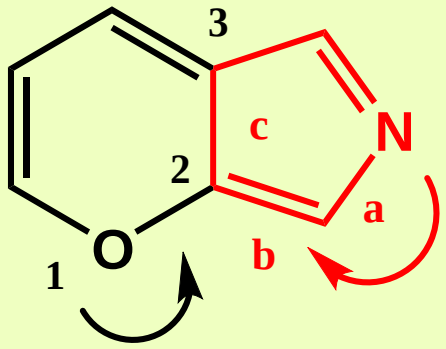
- ***Bi- and polycyclic systems -with two or more heterocycles***

The base component is chosen as that in the Hantzsch-Widman nomenclature except that of nitrogen is given the highest priority.

Prefixes are formed by changing the terminal (e) of the trivial or the Hantzsch-Widman names of the components into (o)

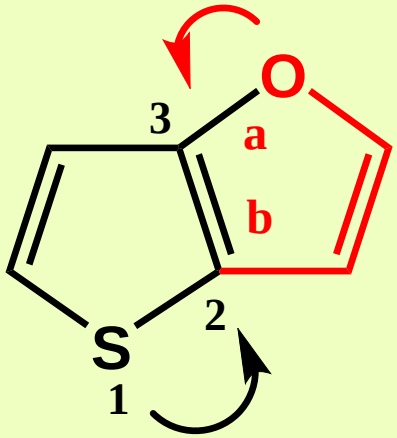
Chosen of the base component.

The base component is:-
- A nitrogen-containing component



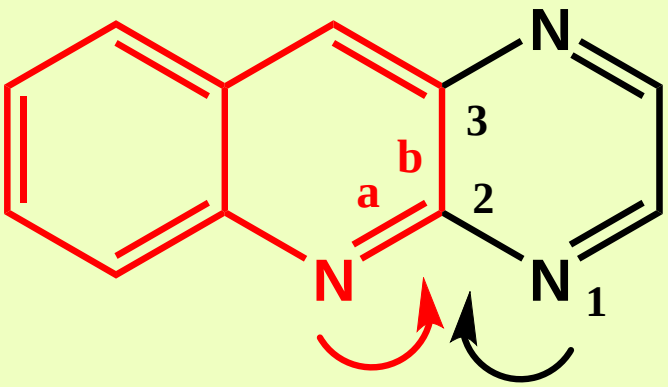
pyrano[2,3-*c*]pyrrole

A component with a heteroatom, other than nitrogen, which is as high as possible in Table 1.



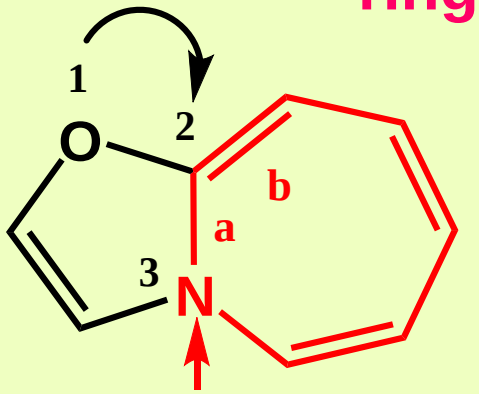
thieno[3,2-*b*]furan

A component with as many rings as possible (e.g. bicyclic condensed systems or polycyclic systems which have trivial names).



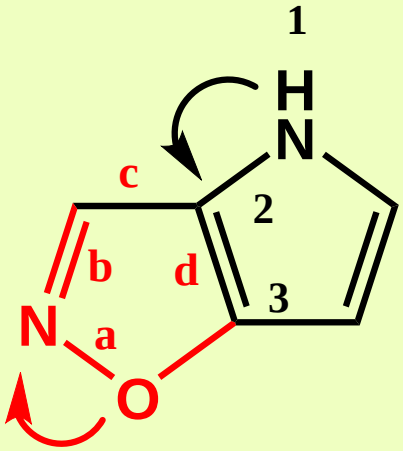
pyrazino[2,3-*b*]quinoline

The component with the largest ring



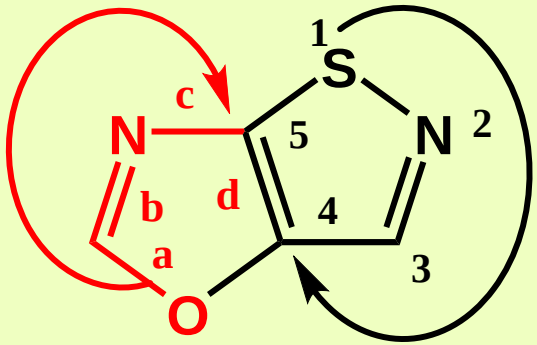
oxazolo[3,2-*a*]azepine

The component with the largest number of heteroatoms of different kinds



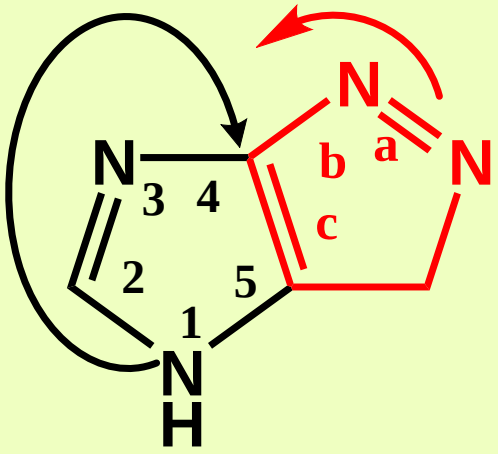
4*H*-pyrrolo[2,3-*d*]isoxazole

The component with the greatest number of heteroatoms which are highest in Table 1 (O, S, ..)

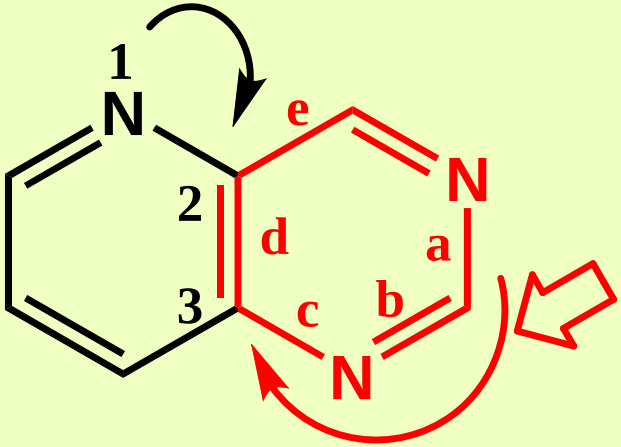


isothiazolo[5,4-*d*]oxazole

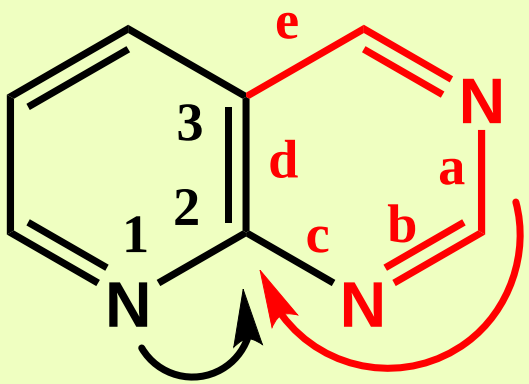
The component with heteroatoms which have the lowest locant numbers.



imidazo[4,5-*c*]pyrazole



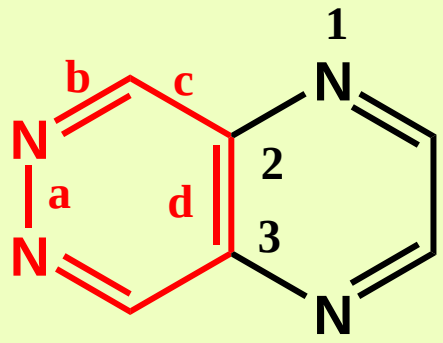
pyrido[3,2-*d*]pyrimidine



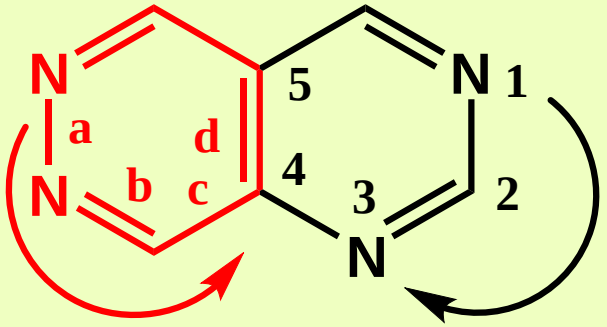
pyrido[2,3-*d*]pyrimidine

Bridge Specification

*In case of two heterorings of the same size and containing the same number and type of heteroatoms, the base component is the one with *lower separation between the heteroatoms*.



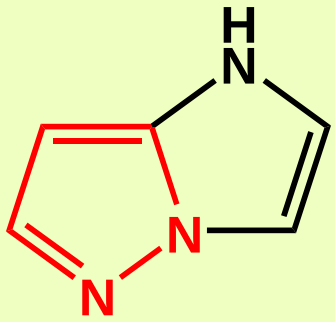
pyrazino[2,3-*d*]pyridazine



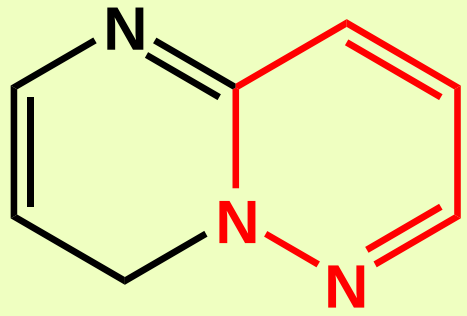
pyrimido[4,5-*d*]pyridazine

not
pyrimido[5,4-d]pyridazine

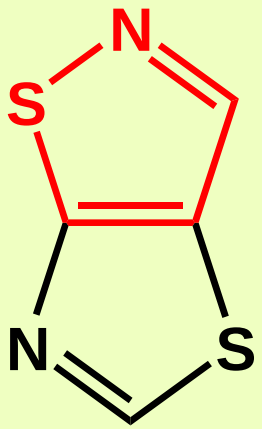
Other examples



1*H*-imidazo[1,2-*b*]pyrazole

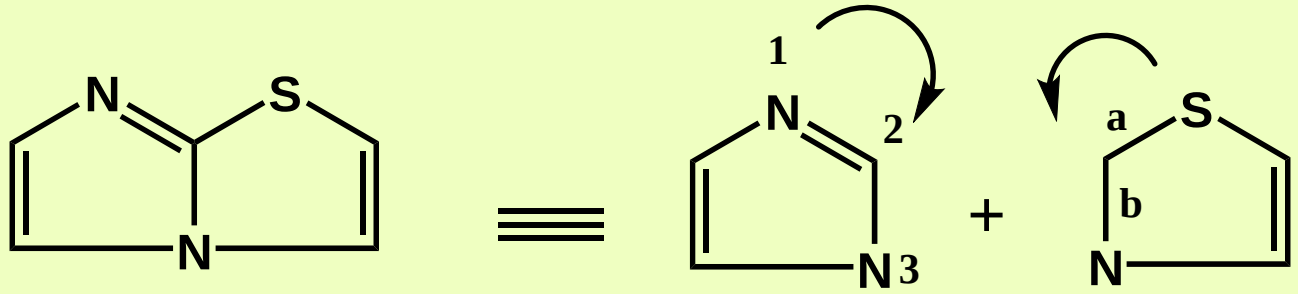


4*H*-pyrimido[1,2-*b*]pyridazine



thiazolo[5,4-*d*]isothiazole

**If a position of fusion is occupied by a heteroatom, the name of the two component rings are chosen in a way that both contain this heteroatom.

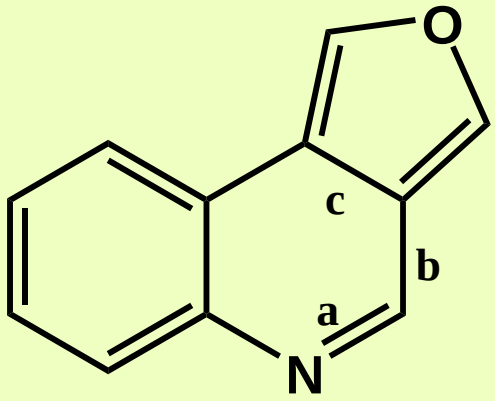


imidazo[2,1-*b*]thiazole

base component

**The attached component should be simples as possible, the following contracted fusion prefixes may be used

furo, thieno, imidazo, pyrido, quino and isoquino…

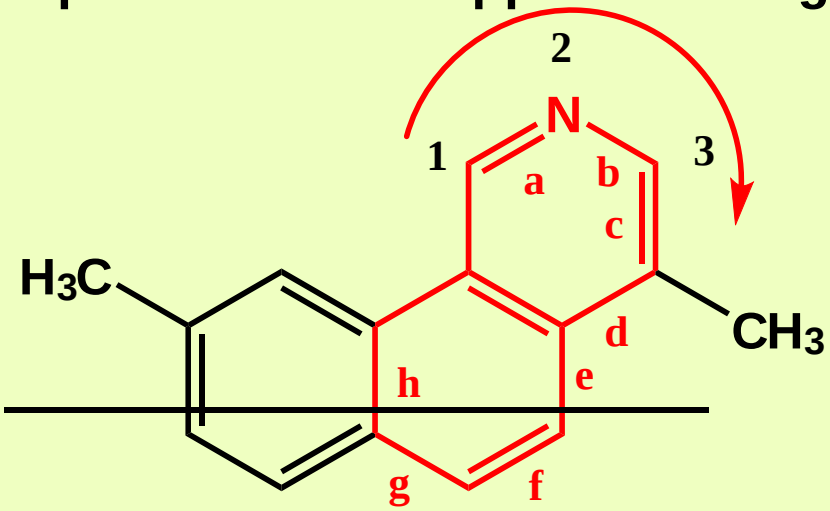


furo[3,4-*c*]quinoline

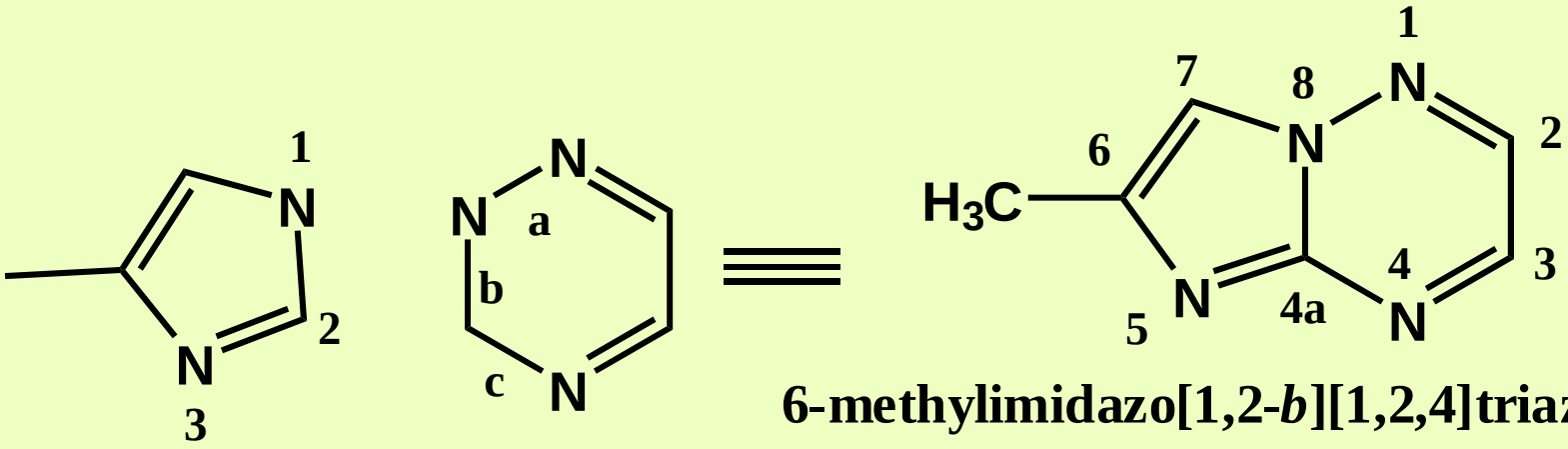
Numbering fused heterocycles

The numbering of the complete fused structure does not depend on the original numbering systems of its components .

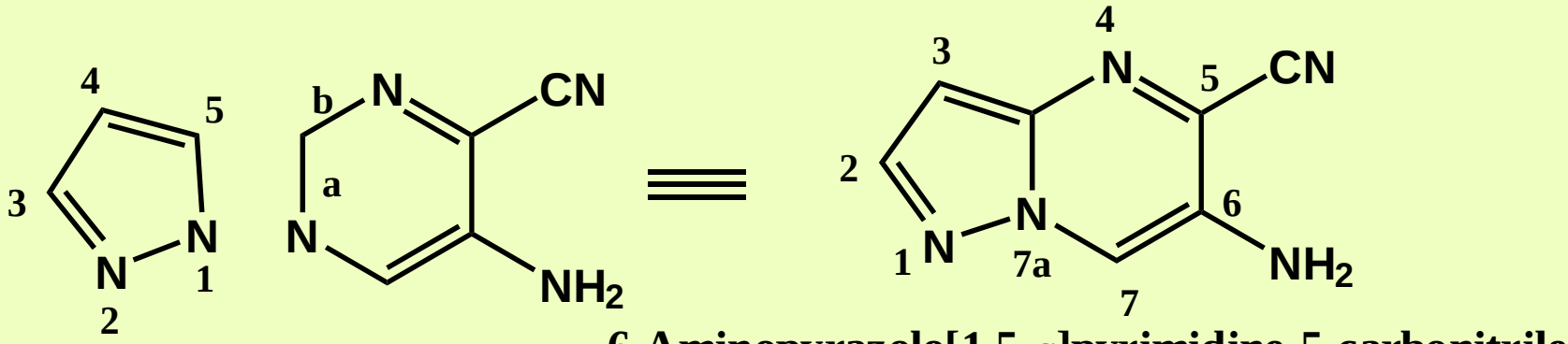
1. **The greatest number of rings should be on a horizontal line, then the maximum number of rings should be above and to the right of this a horizontal line.**
2. **Numbering is carried out usually in a clockwise (*Not in all cases*) starting with the atom not engaged in the ring fusion in the most counter-clockwise position of the uppermost ring.**



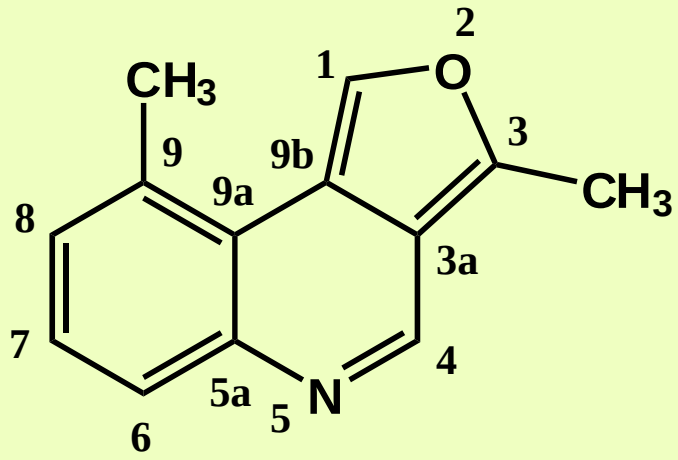
4,9-dimethylbenzo[*h*]isoquinoline



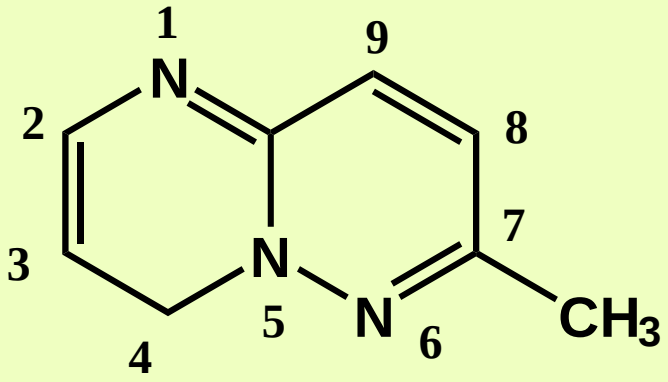
6-methylimidazo[1,2-*b*][1,2,4]triazine



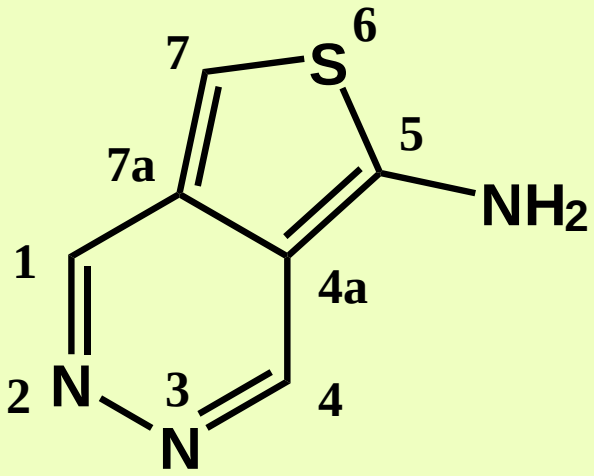
6-Aminopyrazolo[1,5-*a*]pyrimidine-5-carbonitrile



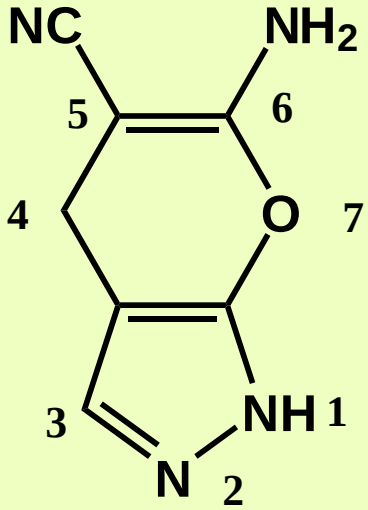
3,9-dimethylfuro[3,4-*c*]quinoline



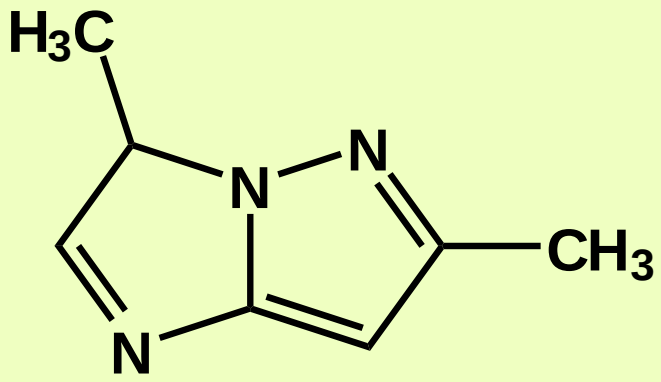
7-methyl-4*H*-pyrimido[1,2-*b*]pyridazine



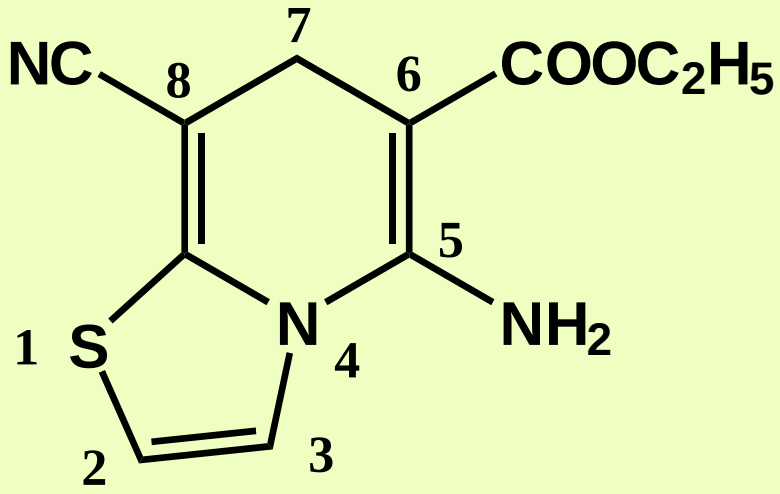
thieno[3,4-*d*]pyridazin-5-amine



6-amino-1,4-dihydropyrano[2,3-*c*]pyrazole -5-carbonitrile



3,6-dimethyl-3*H*-imidazo[1,2-*b*]pyrazole



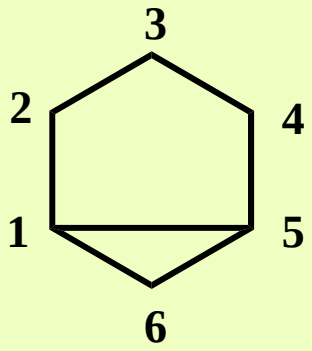
Ethyl 5-amino-8-cyano-7H-thiazolo[3,2-a]pyridine-6-carboxylate

Von Bayer names

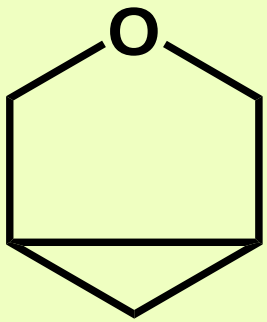
This method is highly convenient for naming bicyclic saturated heterocycles.

The names originally for hydrocarbons, converted into names of heterocycles by application of replacement principals.

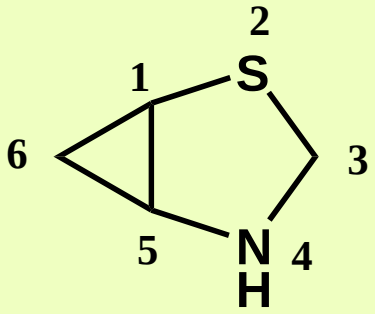
prefix (bicyclo)followed in square brackets by the number of carbon atoms separating the bridgeheads on three possible routes from one bridgehead to the other, followed by the name of alkane containing the same number of atoms in the chain as the whole bicyclic skeleton.



bicyclo[3.1.0]hexane



3-oxabicyclo[3.1.0]hexane



2-thia-4-azabicyclo[3.1.0]hexane