

A male scientist with a beard, wearing a white lab coat, safety goggles, and blue gloves, is working in a laboratory. He is pouring a green liquid from a small vial into a flask. The background shows laboratory equipment and shelves. The text "Medicinal Chemistry II" is overlaid on the image.

# Medicinal Chemistry II

# What is Medicinal Chemistry?

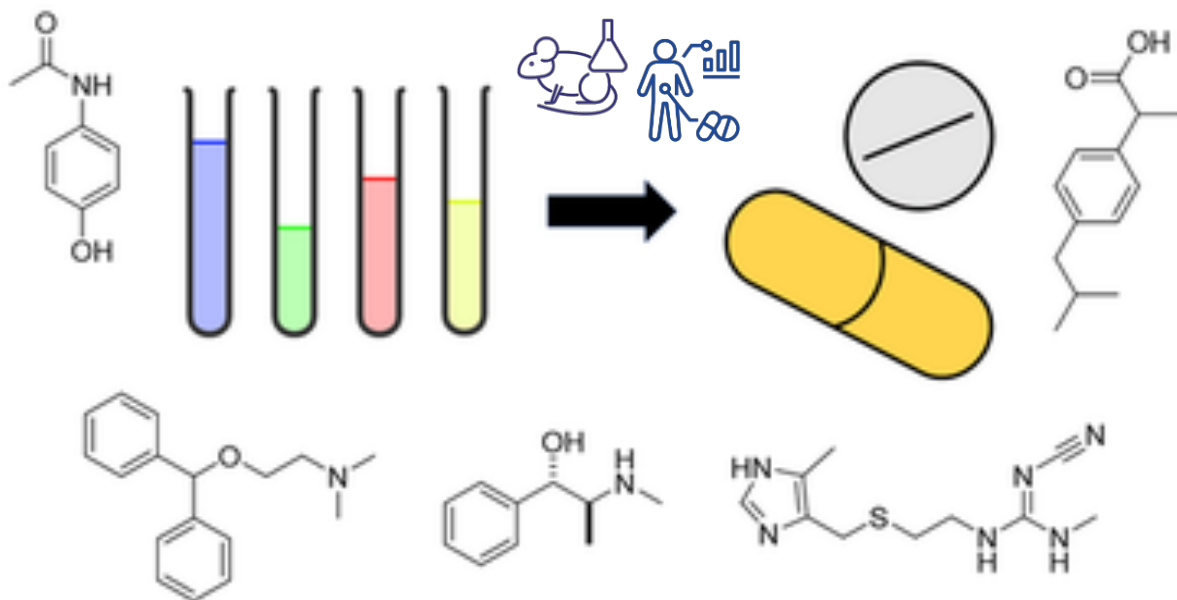
The science that deals with the relationship between the **chemical structure** of the drug and its **behavior in the biological systems**, added to this the aspects of drug design and synthesis.

Biological activity / Side effects  
(Pharmacodynamics)

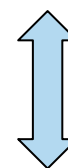


**Chemical structure of a drug**

(organic functional groups, stereochemistry)



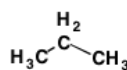
Physicochemical properties of the drug



These properties influence the ADME and toxicity of the drug  
(Pharmacokinetics)

# What is Chemical Structure?

## Functional Groups - The Main Players



alkane



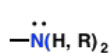
alkene



alkyne



benzene ring  
(phenyl)



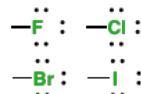
amine



alcohol



ether



alkyl halide



thiol



aldehyde



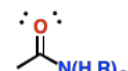
ketone



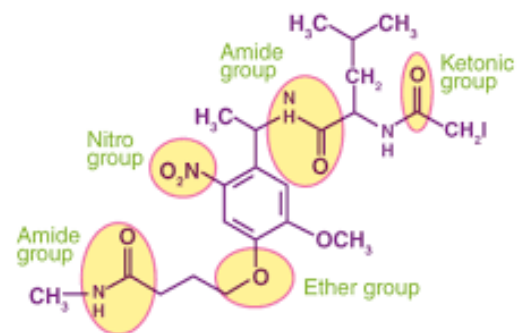
ester



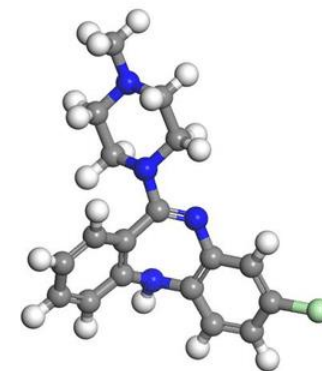
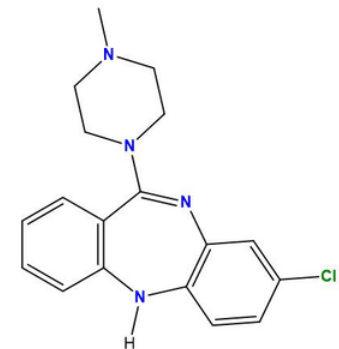
carboxylic  
acid



amide



## Clozapine

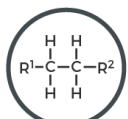




# FUNCTIONAL GROUPS IN ORGANIC CHEMISTRY

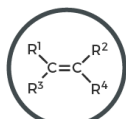
Functional groups are the characteristic groups in organic molecules that give them their reactivity. In the formulae below, R represents the rest of the molecule and X represents any halogen atom.

● Hydrocarbons ● Halogen-containing groups ● Oxygen-containing groups ● Nitrogen-containing groups ● Sulfur-containing groups ● Phosphorus-containing groups



**ALKANE**

Naming: *-ane*  
e.g. ethane



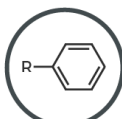
**ALKENE**

Naming: *-ene*  
e.g. ethene



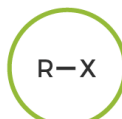
**ALKYNE**

Naming: *-yne*  
e.g. ethyne



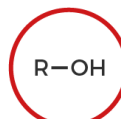
**ARENE**

Naming: *-yl benzene*  
e.g. ethyl benzene



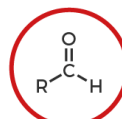
**HALOALKANE**

Naming: *halo-*  
e.g. chloroethane



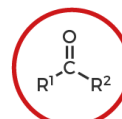
**ALCOHOL**

Naming: *-ol*  
e.g. ethanol



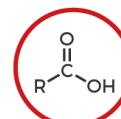
**ALDEHYDE**

Naming: *-al*  
e.g. ethanal



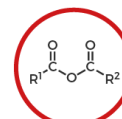
**KETONE**

Naming: *-one*  
e.g. propanone



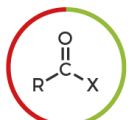
**CARBOXYLIC ACID**

Naming: *-oic acid*  
e.g. ethanoic acid



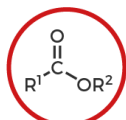
**ACID ANHYDRIDE**

Naming: *-oic anhydride*  
e.g. ethanoic anhydride



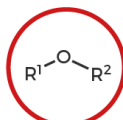
**ACYL HALIDE**

Naming: *-oyl halide*  
e.g. ethanoyl chloride



**ESTER**

Naming: *-yl -oate*  
e.g. ethyl ethanoate



**ETHER**

Naming: *-oxy -ane*  
e.g. methoxyethane



**EPOXIDE**

Naming: *-ene oxide*  
e.g. ethene oxide



**AMINE**

Naming: *-amine*  
e.g. ethanamine



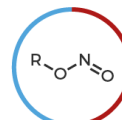
**AMIDE**

Naming: *-amide*  
e.g. ethanamide



**NITRATE**

Naming: *-yl nitrate*  
e.g. ethyl nitrate



**NITRITE**

Naming: *-yl nitrite*  
e.g. ethyl nitrite



**NITRILE**

Naming: *-nitrile*  
e.g. ethanenitrile



**NITRO**

Naming: *nitro-*  
e.g. nitromethane



**NITROSO**

Naming: *nitroso-*  
e.g. nitrosoethane



**IMINE**

Naming: *-imine*  
e.g. ethanimine



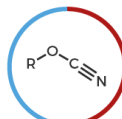
**IMIDE**

Naming: *-imide*  
e.g. succinimide



**AZIDE**

Naming: *-yl azide*  
e.g. phenylazide



**CYANATE**

Naming: *-yl cyanate*  
e.g. methyl cyanate



**ISOCYANATE**

Naming: *-yl isocyanate*  
e.g. methyl isocyanate



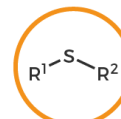
**AZO COMPOUND**

Naming: *azo-*  
e.g. azoethane



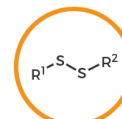
**THIOL**

Naming: *-thiol*  
e.g. methanethiol



**SULFIDE**

Naming: *sulfide*  
e.g. dimethylsulfide



**DISULFIDE**

Naming: *disulfide*  
e.g. dimethyl disulfide



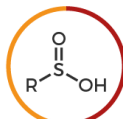
**SULFOXIDE**

Naming: *sulfoxide*  
e.g. dimethyl sulfoxide



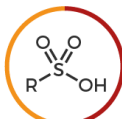
**SULFONE**

Naming: *sulfone*  
e.g. dimethylsulfone



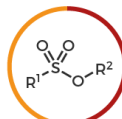
**SULFINIC ACID**

Naming: *-sulfinic acid*  
e.g. benzenesulfinic acid



**SULFONIC ACID**

Naming: *-sulfonic acid*  
e.g. benzenesulfonic acid



**SULFONATE ESTER**

Naming: *-yl sulfonate*  
e.g. methylmethanesulfonate



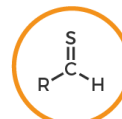
**THIOCYANATE**

Naming: *thiocyanate*  
e.g. ethyl thiocyanate



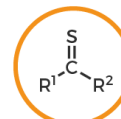
**ISOTHIOCYANATE**

Naming: *isothiocyanate*  
e.g. ethyl isothiocyanate



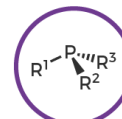
**THIAL**

Naming: *-thial*  
e.g. ethanethial



**THIOKETONE**

Naming: *-thione*  
e.g. propanethione



**PHOSPHINE**

Naming: *phosphane*  
e.g. methylphosphane



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## ***Before we start***

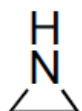
Before we start this course you need to review some previous courses of high relevance to this one. Such things you need to review include:

- Important heterocycles frequently encountered in medicinal chemistry.
- Drug metabolism.
- **Don't forget to revise acidity, basicity, and drug ionization!!**

### ***Examples of common heterocycles.***



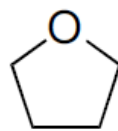
epoxide



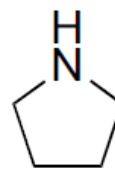
aziridine



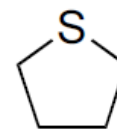
thiirane



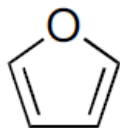
tetrahydrofuran



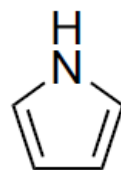
pyrrolidine



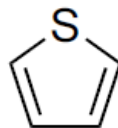
tetrahydrothiophene



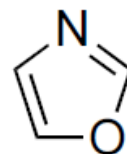
furan



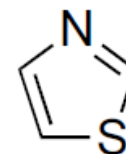
pyrrole



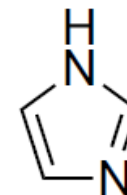
thiophene



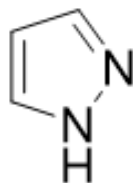
oxazole



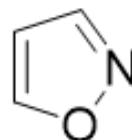
thiazole



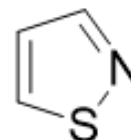
imidazole



pyrazoles

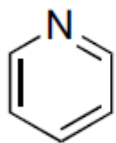


isoxazoles

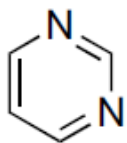


isothiazoles

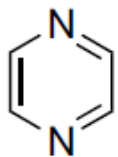
**Examples of common heterocycles.**



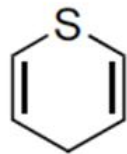
pyridine



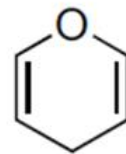
pyrimidine



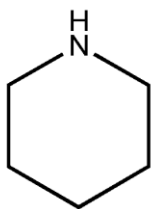
pyrazine



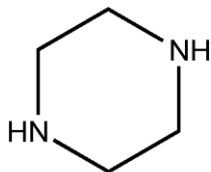
thiopyran



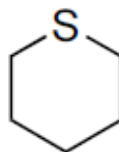
pyran



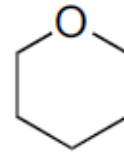
Piperidine



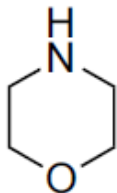
Piperazine



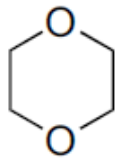
tetrahydrothiopyran



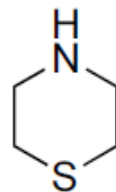
tetrahydropyran



morpholine

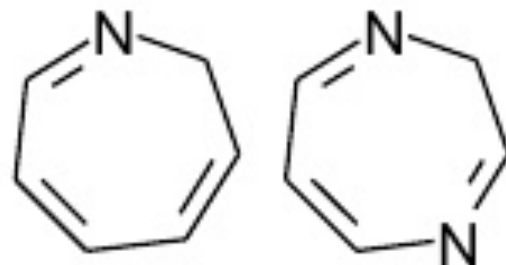


dioxane

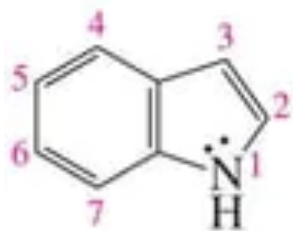


thiomorpholine

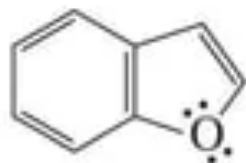
**Examples of common heterocycles.**



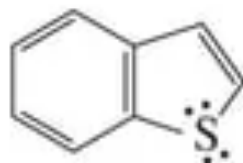
azepine 1,4-diazepine



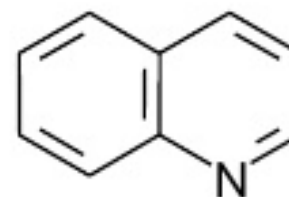
indole



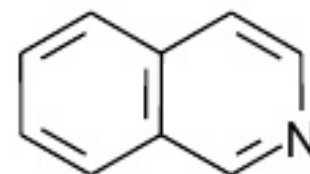
benzofuran



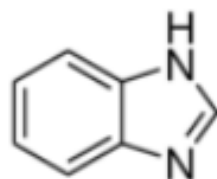
benzothiophene



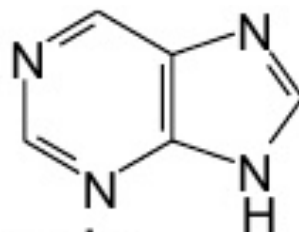
quinoline



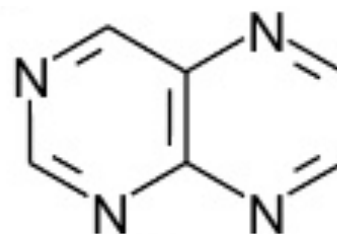
isoquinoline



Benzimidazole



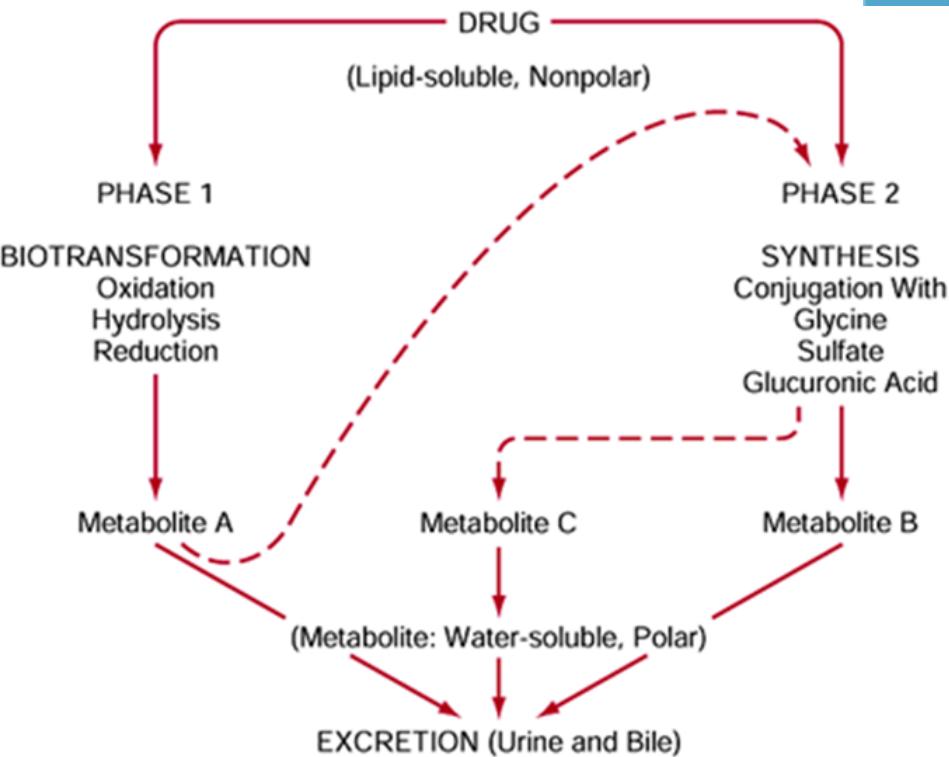
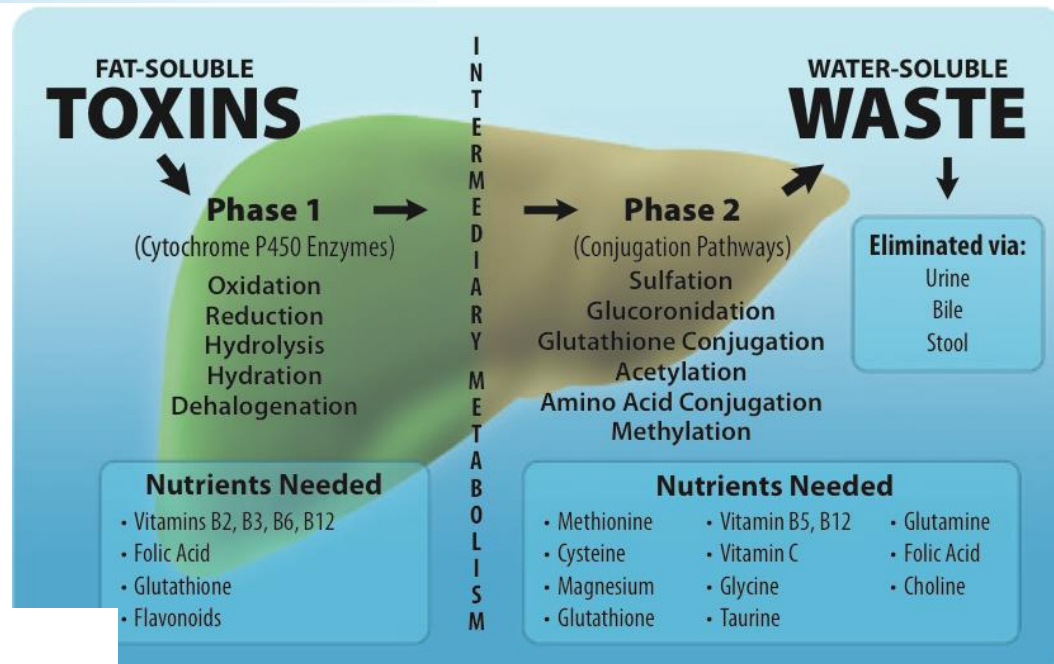
purine



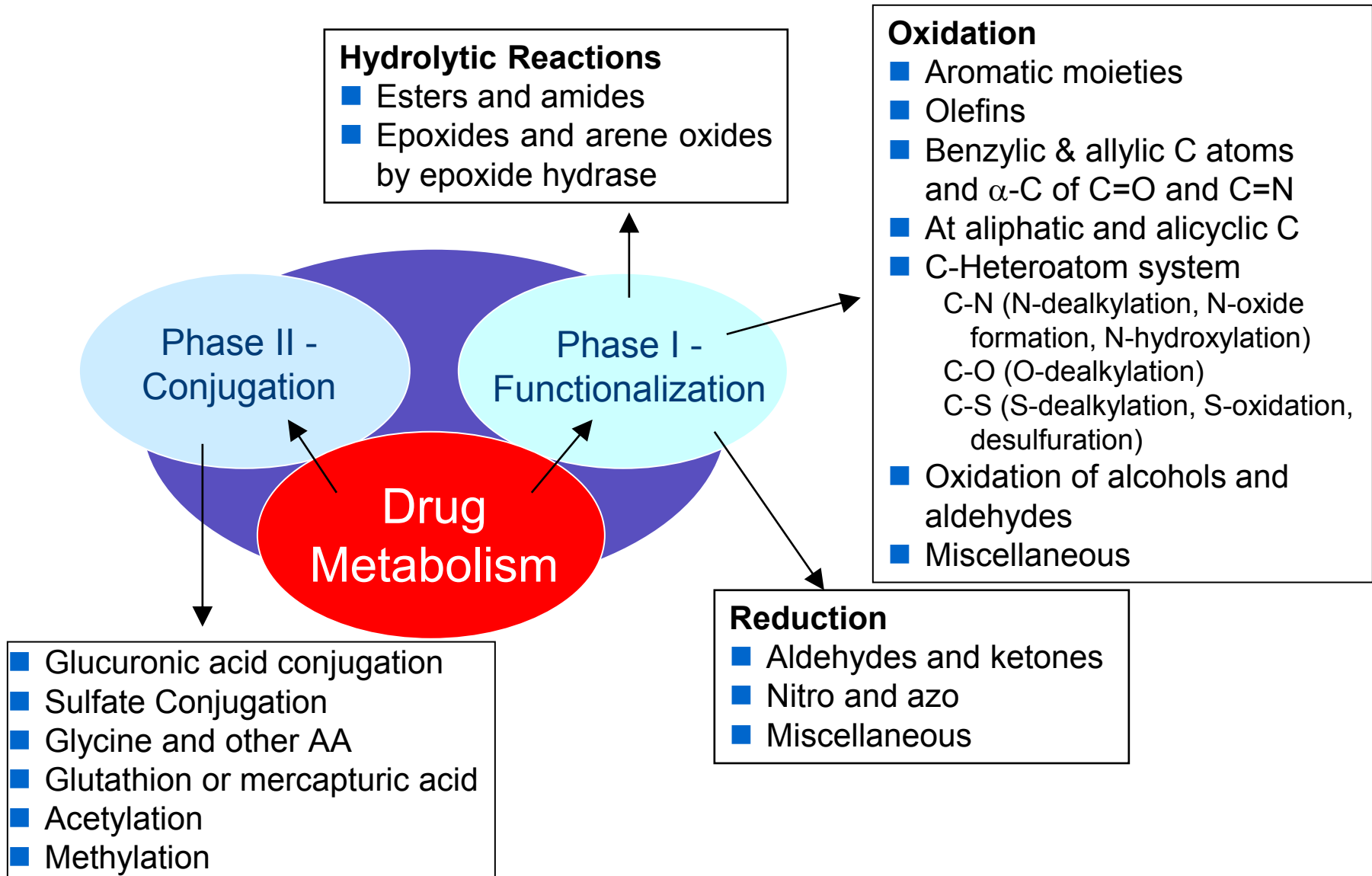
pteridine

# Drug Metabolism

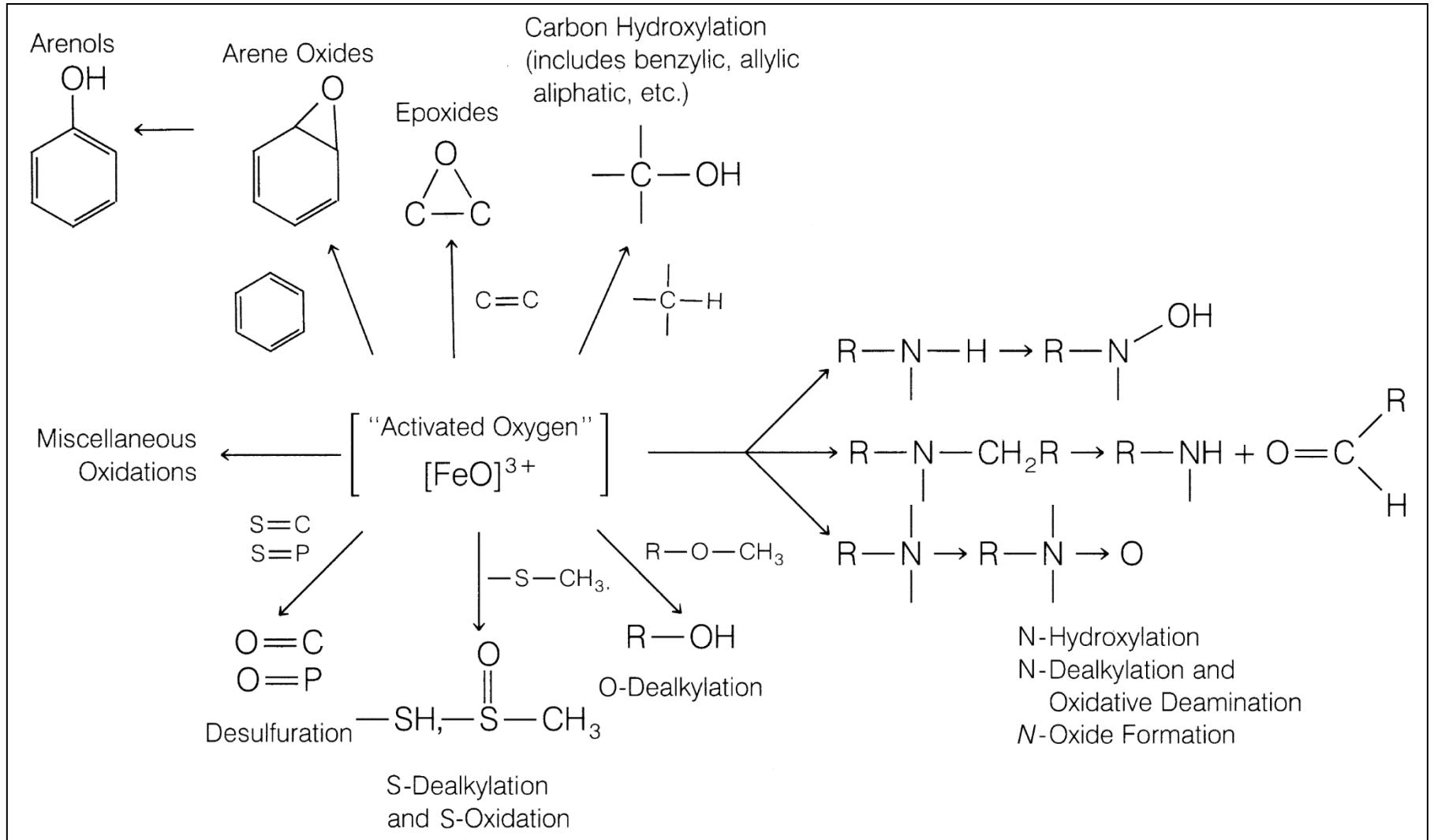
- Biochemical modification or degradation, usually through specialized enzymatic systems, often converts **lipophilic** chemical compounds into more readily excreted **polar** products.



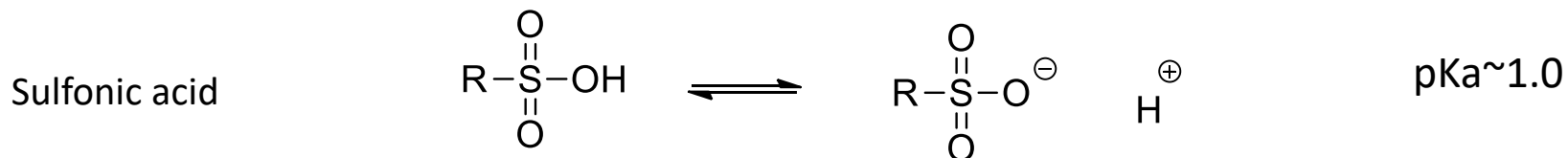
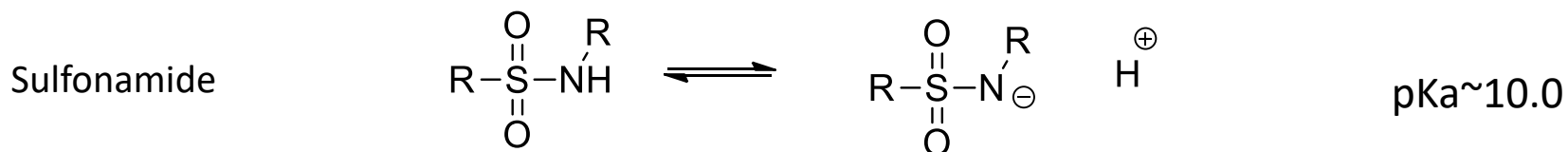
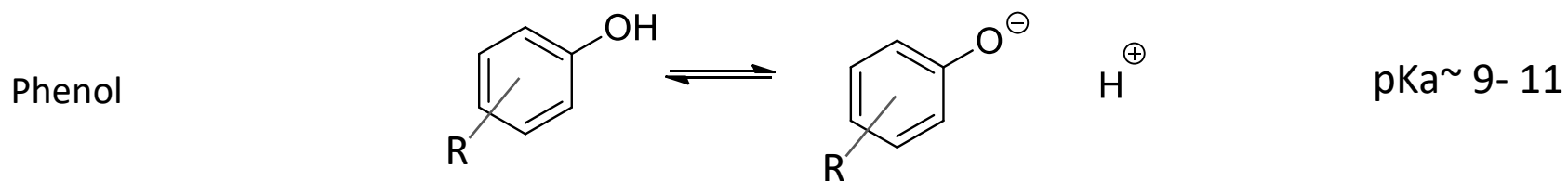
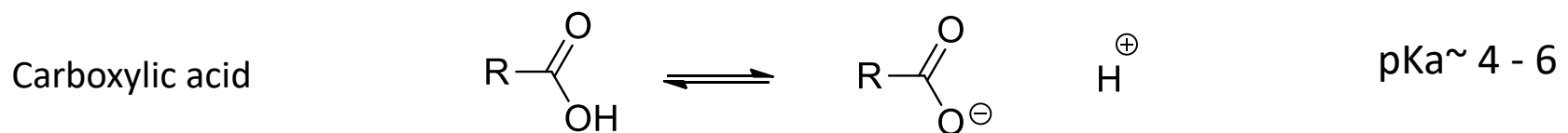
# Summary of phase I and II biotransformations



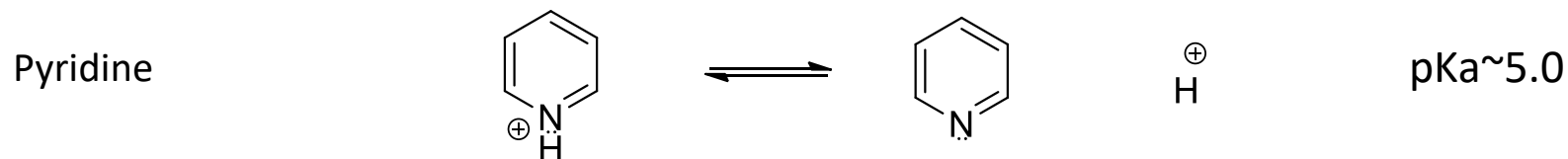
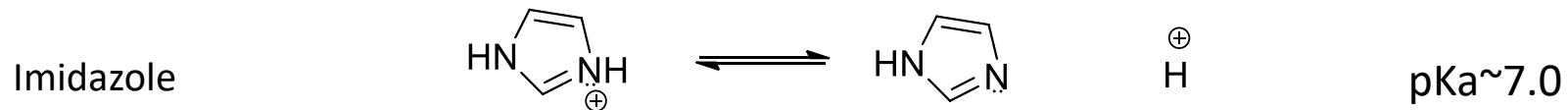
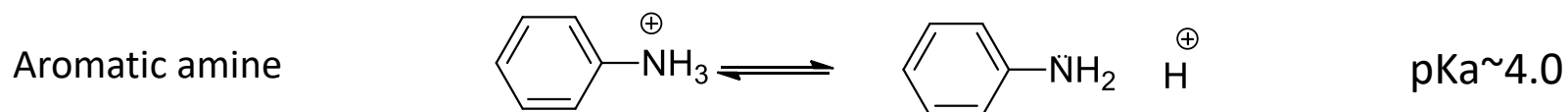
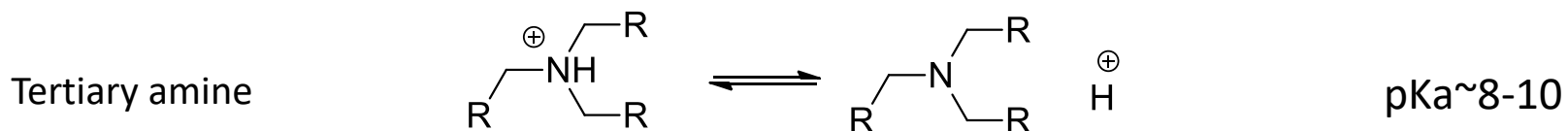
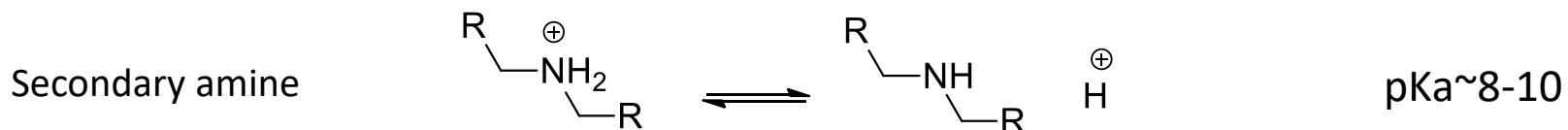
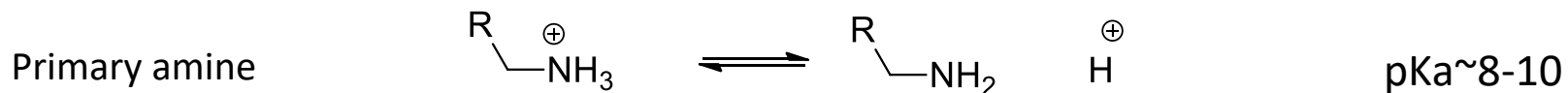
# Summary of the many types of oxidative reaction carried out by CYP.



# Common *acidic* functional groups in pharmaceutical chemistry and their pKa values



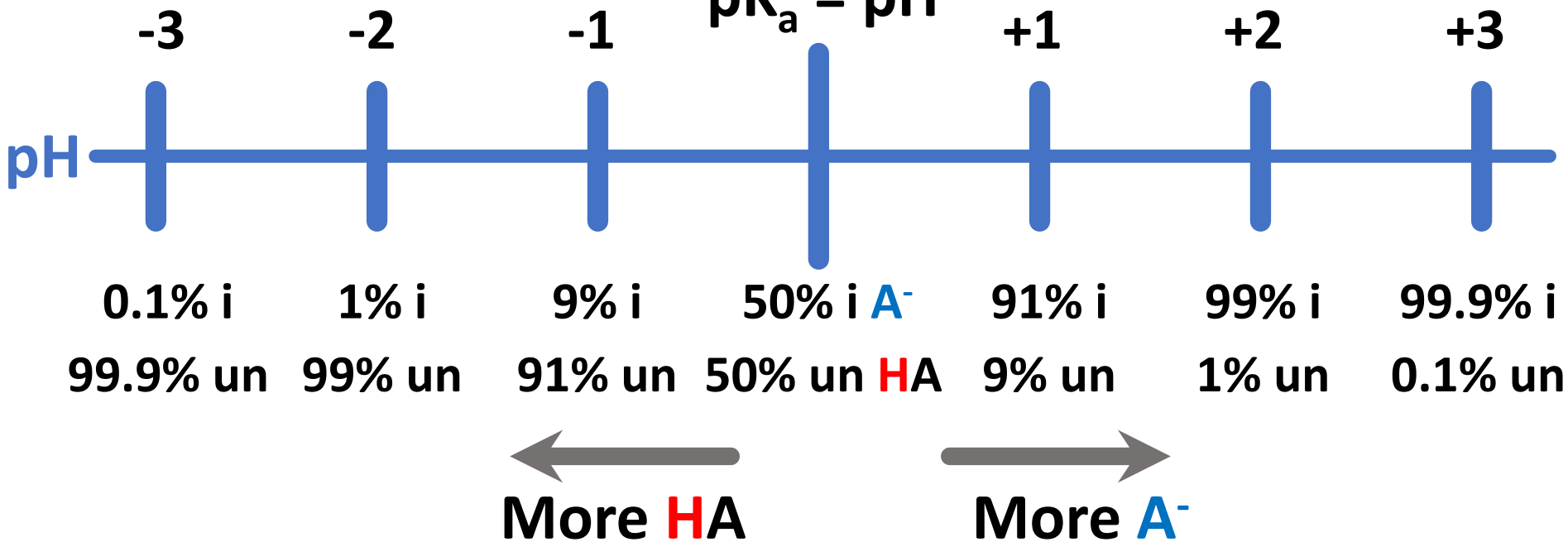
# Common *basic* functional groups in pharmaceutical chemistry and their pKa values



# Ionization



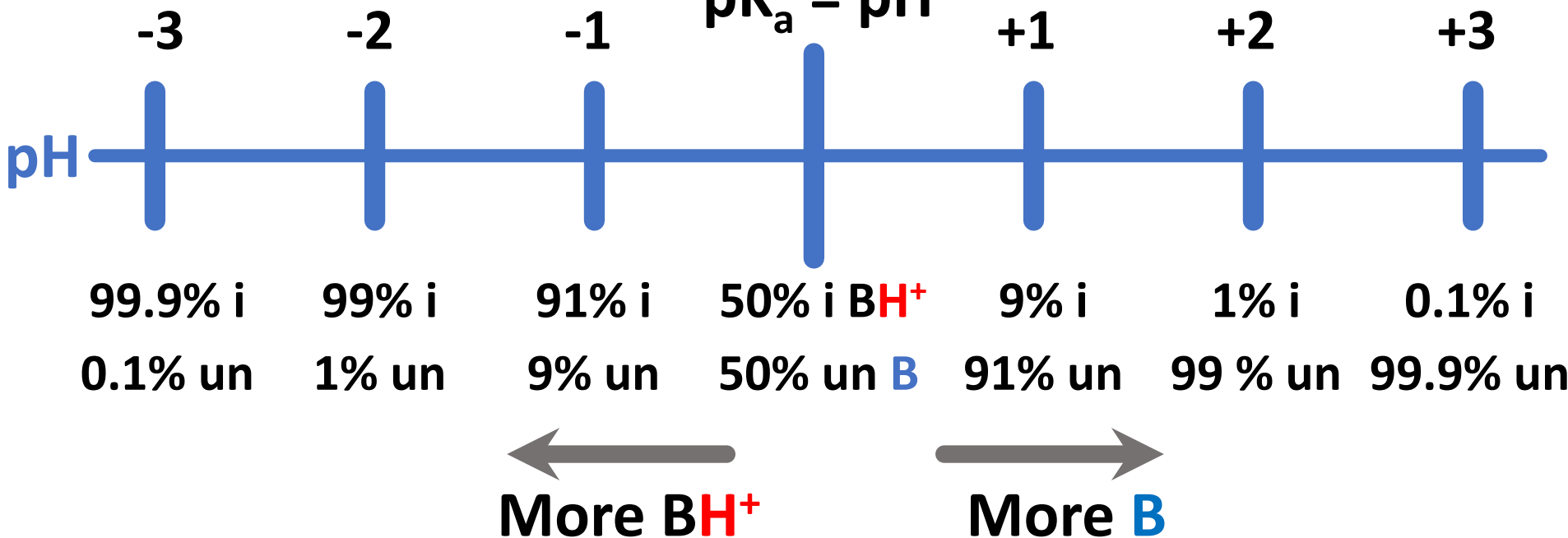
$\text{pK}_a = \text{pH}$



# Ionization

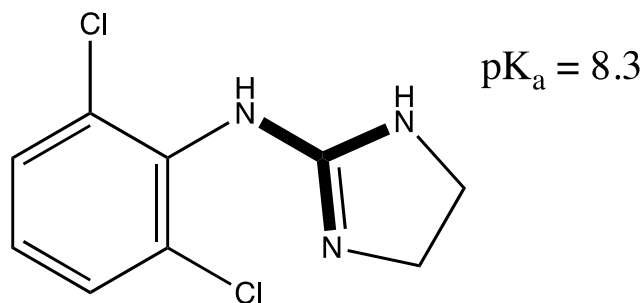


$\text{pK}_a = \text{pH}$

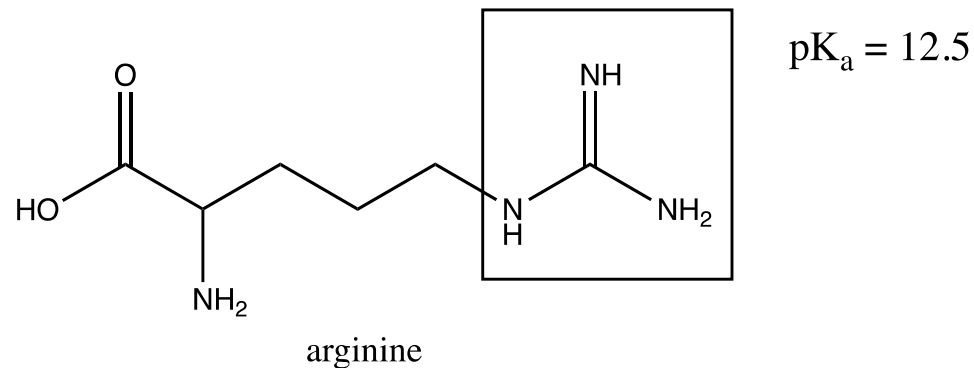


## Self assessment:

Shown below is the structure of clonidine, an alpha2 agonist used to treat hypertension. Clonidine contains a guanidine functional group (highlighted in bold) that has a  $pK_a = 8.3$ . Other guanidine functional groups, such as that seen with arginine, are much more basic with a  $pK_a = 12.5$ . Provide a chemical explanation for this difference.



Clonidine

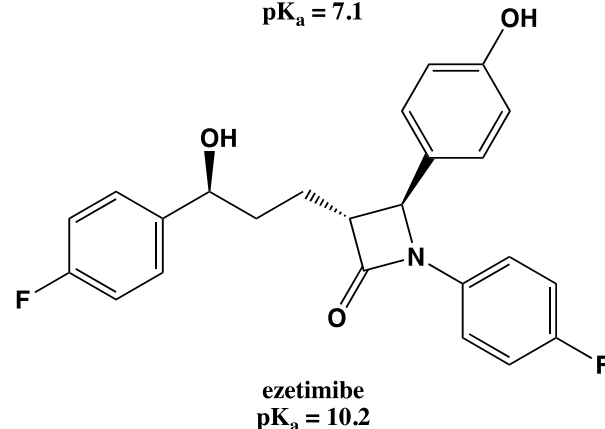
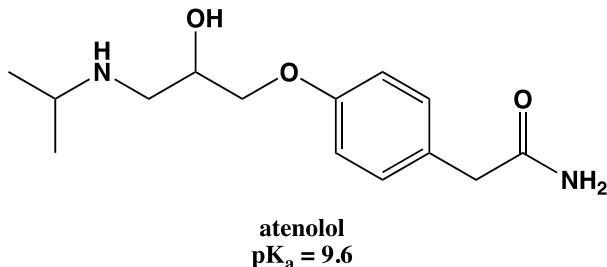
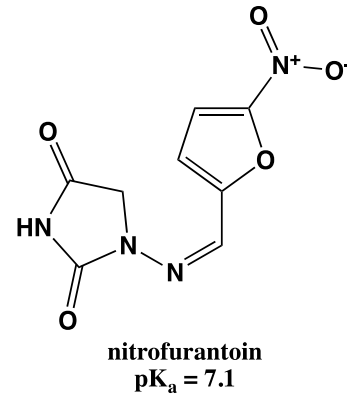
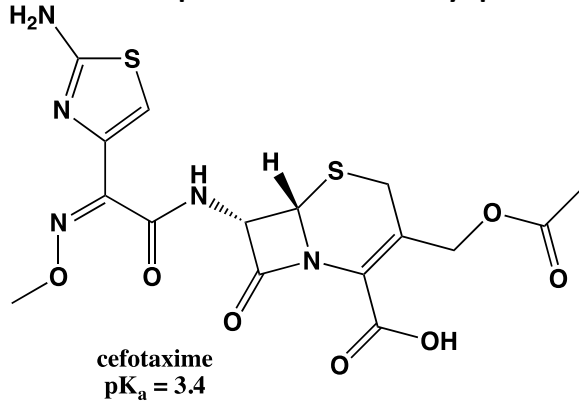


arginine

## Self assessment:

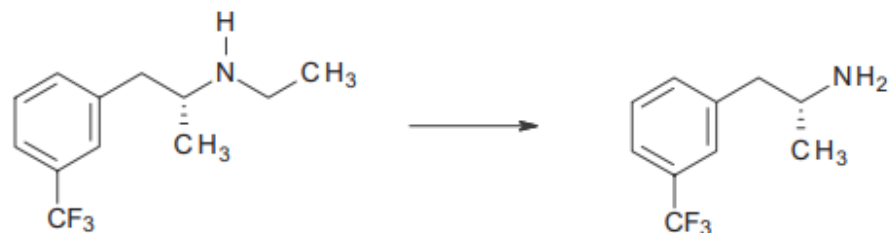
Shown below are the structures of cefotaxime, nitrofurantoin, atenolol and ezetimibe. Each of these drug molecules contains one ionizable functional group. The pKa values have been provided.

1. Match the pKa values with the appropriate functional groups. For each functional group identify the name of the group and whether it is acidic or basic.
2. For each functional group indicate whether it would be primarily ionized or primarily unionized at a stomach pH 1.8, urinary pH 6.1 or plasma pH 7.4

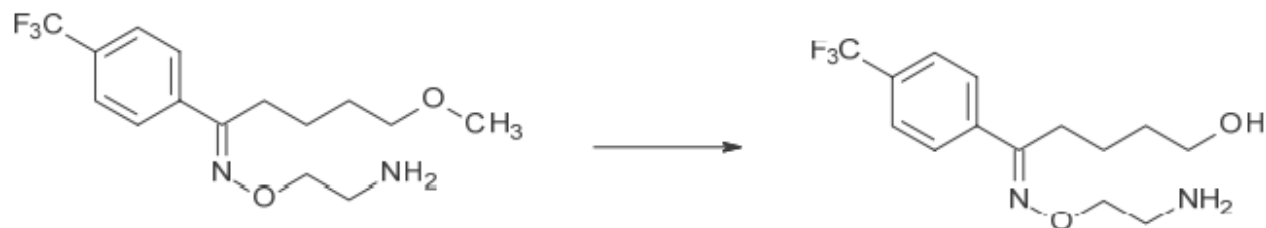


## Self assessment:

Evaluate each of the following metabolic transformations and determine which phase I metabolic transformation has occurred.



Dexfenfluramine



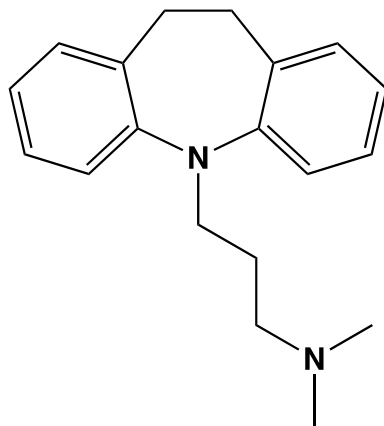
Fluvoxamine



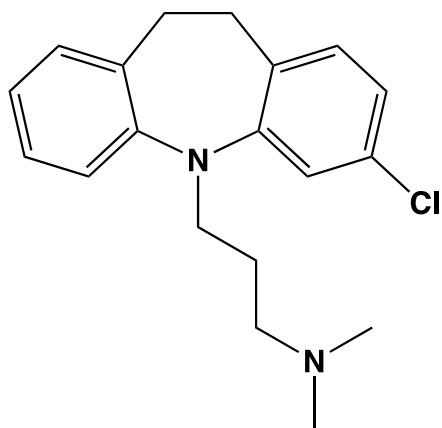
Baclofen

## Self assessment:

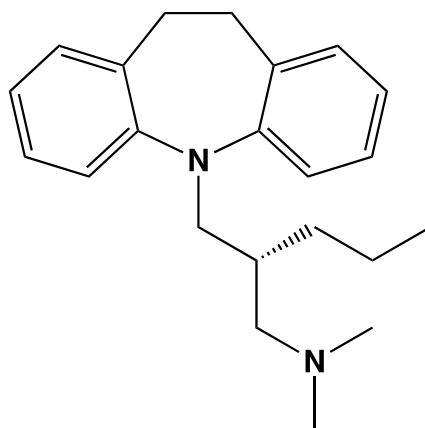
Shown below is the structure of imipramine as well as three analogs. Evaluate each analog and provide an overall evaluation of how each change affects the chemical properties of imipramine.



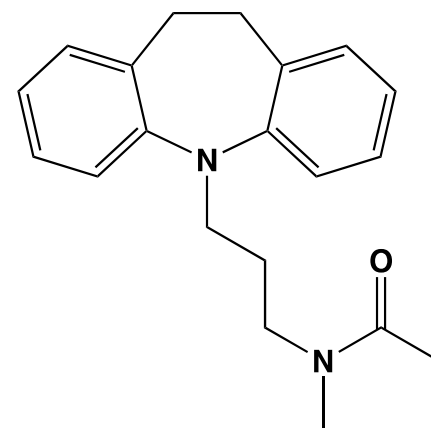
imipramine



Analog A



Analog B

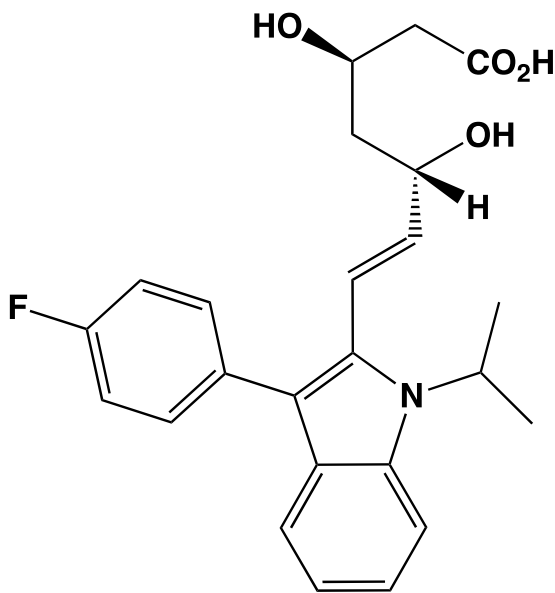


Analog C

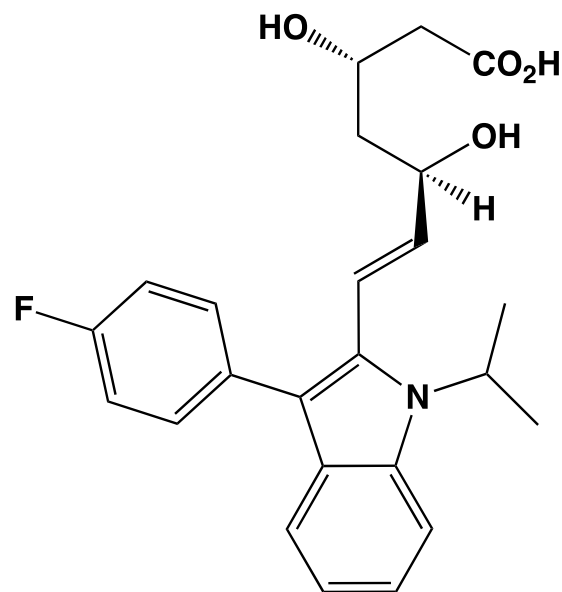
## Self assessment:

Shown below is the enantiomer of Fluvastatin. Which of the following properties/actions would be expected to be identical for Fluvastatin and its enantiomer and which would be expected to be different?

1. Hepatic metabolism
2. Water solubility
3. Adverse side effects
4. Active renal reabsorption by transport proteins
5. Potency
6. % ionization at pH 7.4

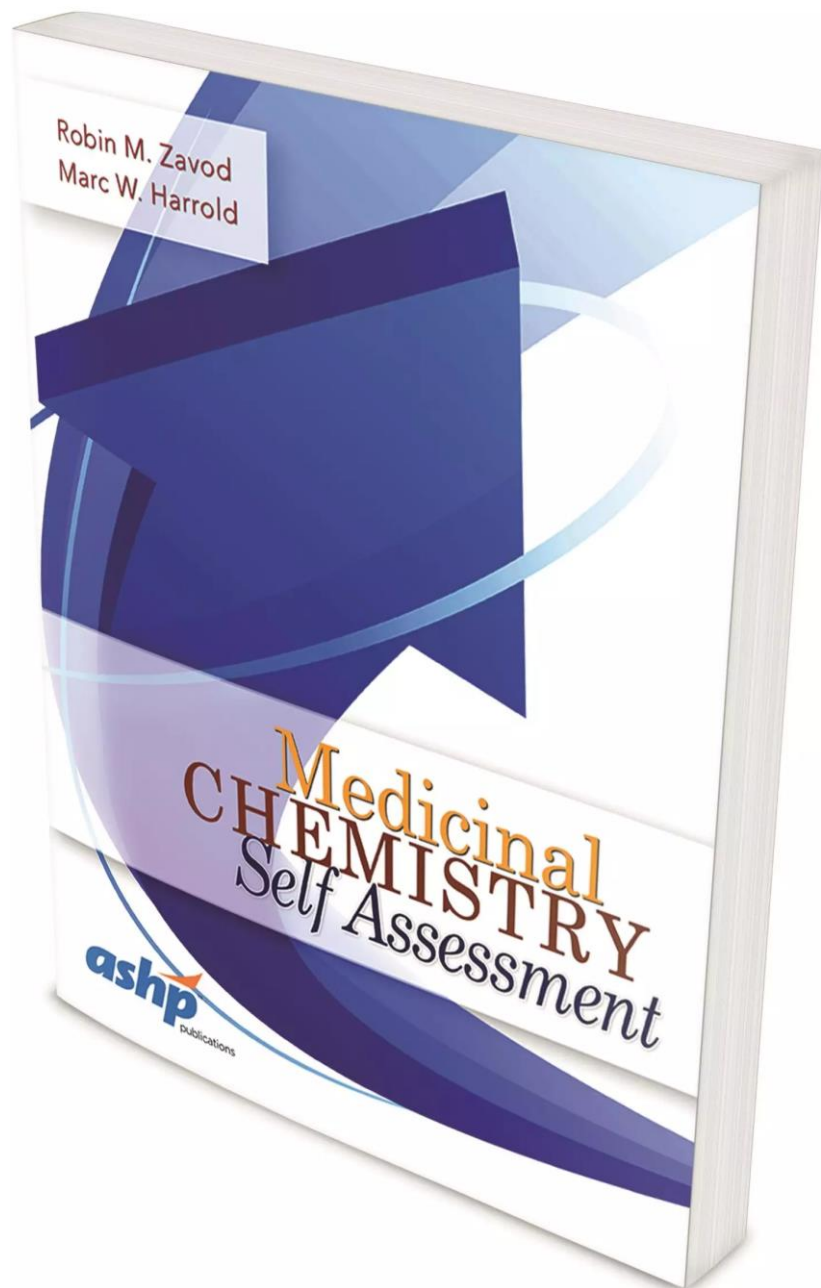


Fluvastatin



Enantiomer of Fluvastatin

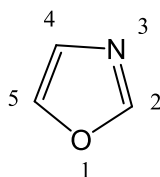
## Recommended book to assess yourself in medicinal chemistry:



<http://library.lol/main/1CDF08C85B46AD66DD24652FFBE57179>

Now, heterocyclic compounds are named **systematically** by the International Union of Pure and Applied Chemistry (IUPAC). One of these IUPAC systems of nomenclature is called **Hantzsch-Widman** method and is used for simple, one-ring heterocycles, and is summarized by the following rules:

1- The name is constructed by combining prefixes that indicate the heteroatoms present with suffixes that indicate the ring size and the degree of unsaturation.



**The name consists of: Prefix + Suffix**

Defines the heteroatoms and their position

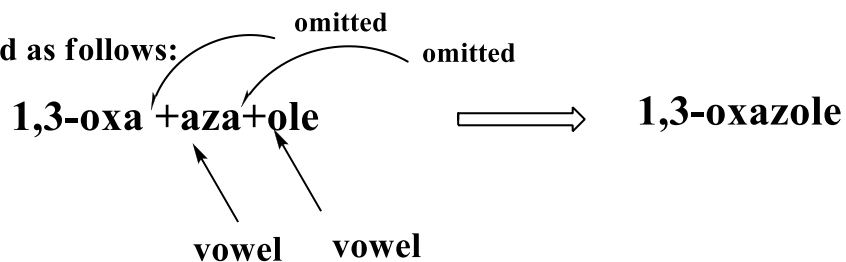
Defines the ring size and degree of unsaturation

} From the table

**Name and order of priority**

**in numbering and inclusion in the name** O (oxa) > S (thia) > N (aza)

**The name is constructed as follows:**



2-**The prefixes** for the heteroatoms are: oxa (O), thia (S), and aza (N).

3- When two or more different heteroatoms are present, prefixes are listed in order of priority and numbering starts at the highest priority atom as follows.

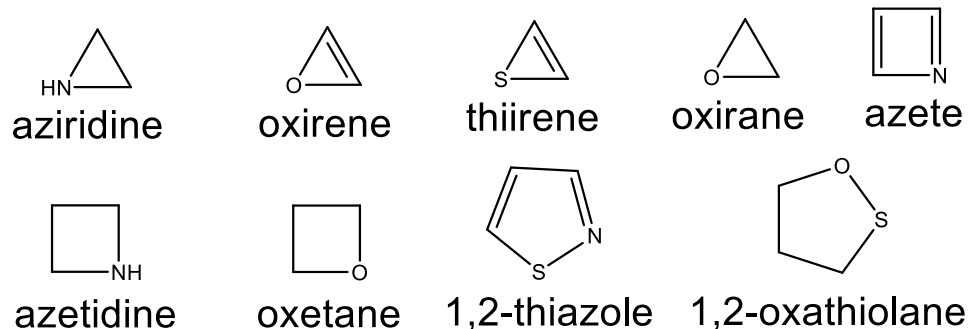


4- The letter **a** in the prefix is omitted when the prefix is followed by a vowel (the first letter in the suffix).

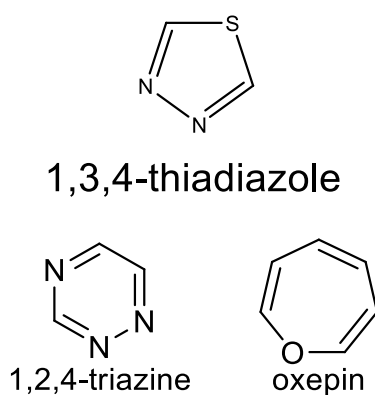
5- **The suffixes** used are listed in the table below.

***Name suffixes (determines ring size and degree of Unsaturation).***

Ring size	Nitrogen present			Nitrogen absent		
	Unsat.	Partial	Sat.	Unsat.	Partial	Sat.
3	irine	----	iridine	Irene	----	irane
4	ete	etine	etidine	ete	etene	etane
5	ole	oline	olidine	ole	olene	olane
6	ine	----	ine	in	----	ane
7	epine	----	epine	epin	----	epane



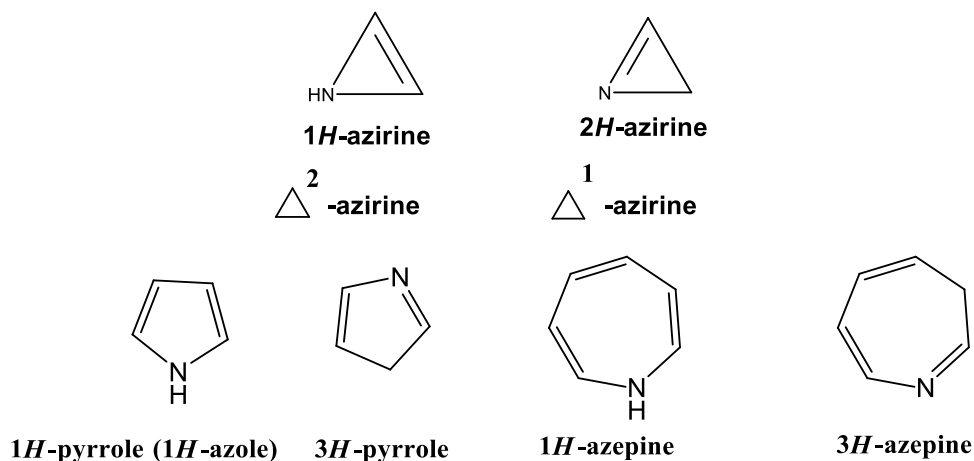
6- Two or more heteroatoms of the same kind are indicated by the prefix di, tri, .etc.



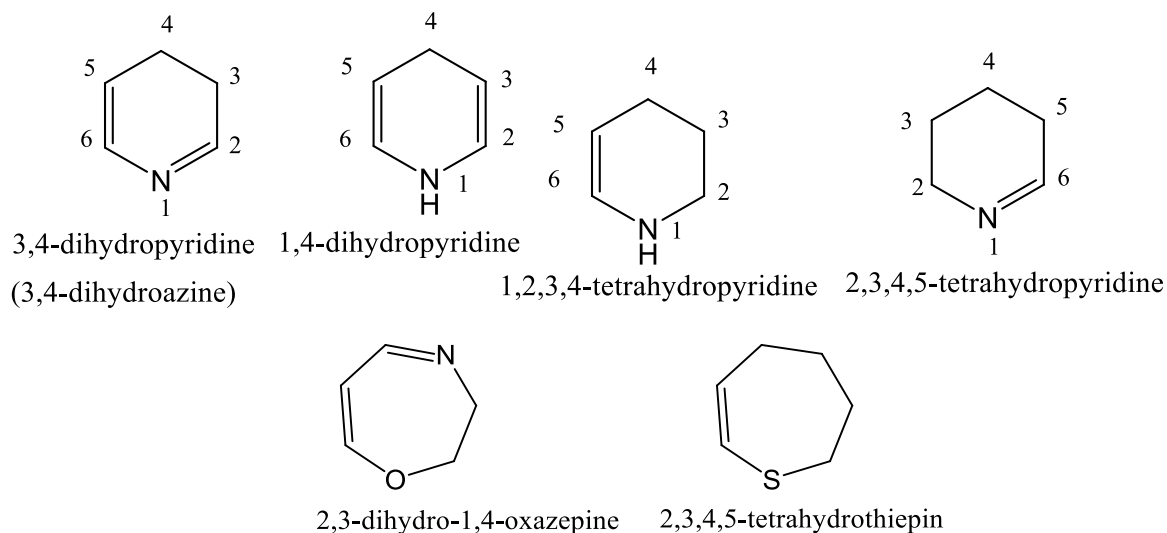
7- When compounds are partially unsaturated ( 4 and 5 ) and differ in the position of a double bond, the position of that double bond is specified.



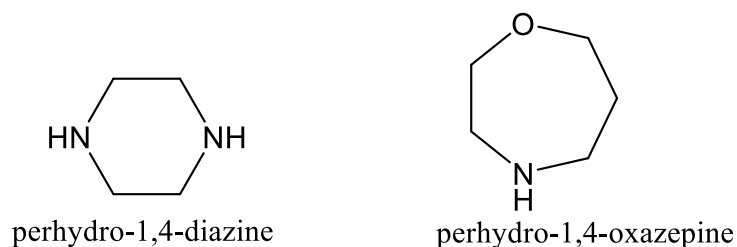
8- When a ring system with the maximum number of double bonds still has a saturated atom in the ring, the position of this atom is numerically indicated, together with the prefix *H* (italic) as a part of the name of the ring system (the position of the double bond can also be indicated using the symbol  $\Delta$ , capital delta, instead of the hydrogen *H*).



9- Partial unsaturation for six or seven membered ring structures is indicated by the prefix dihydro or tetrahydro.

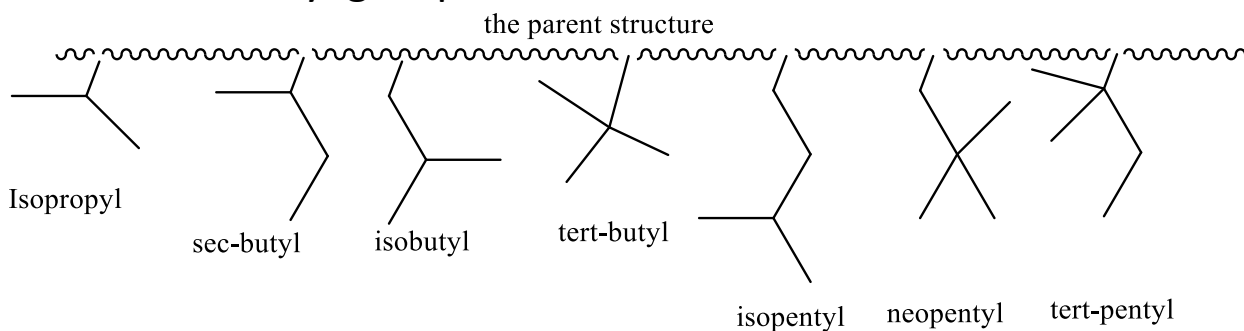


10- Fully saturated six or seven membered ring structures containing nitrogen is indicated by the prefix perhydro.



10- Substitutions on the heterocyclic ring are named as prefixes and arranged alphabetically. Some substituents are always named as prefixes such as:

- The alkyl groups, the following are common names for some of the alkyl groups:



- The halogens ( named as fluoro, chloro, bromo and iodo )
- nitroso ( - NO )
- nitro ( -NO<sub>2</sub> )
- alkyloxy ( RO- )
- alkylthio ( RS- )
- alkyl

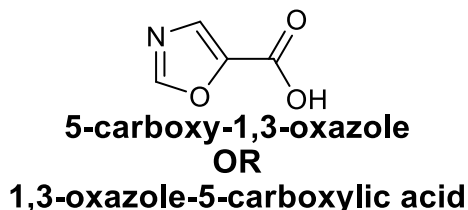
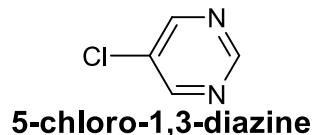
Those that can be named as either prefixes or suffixes. The following is a list of some functional groups and their names as prefixes, and suffixes :

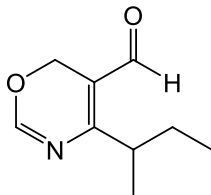
### Naming functional groups

<u>Functional group</u>	<u>prefix</u>	<u>suffix</u> **
Carboxylic acid (- COOH )	carboxy	carboxylic acid OR oic acid
Ester of carboxylic acid (-COOR)	alkoxycarbonyl	carboxylate OR oate
Acid chlorides (-COCl )	chlorocarbonyl	carbonyl chloride OR oyl chloride
Amide (- CONR <sub>2</sub> )	carbamoyl(or amido)	carboxamide OR amide
Nitrile (-CN )	cyano	carbonitrile OR nitrile
Aldehyde (-COH )	formyl(or oxo)	carbaldehyde OR al
Ketone (-CO- )	oxo	one
Alcohol (-OH )	hydroxy	ol
Thiol (-SH )	mercapto	thiol
Amine (-NH <sub>2</sub> )	amino	amine

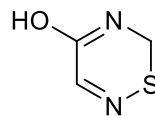
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\*\* The suffix used when the functional group is directly attached to the ring



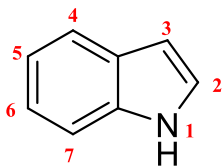


4-s-butyl-5-formyl-6H-1,3-oxazine OR  
4-s-butyl-6H-1,3-oxazine-5-carbaldehyde

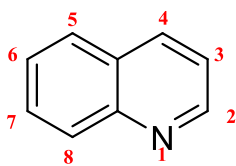


4-hydroxy-6H-1,2,5-thiadiazine

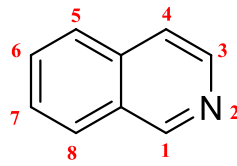
11- Fused–polyheterocyclics have non systematic names, and numbering is similar to the analogous non heterocyclic compound.



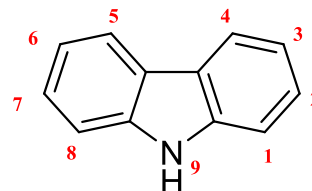
Indole



quinoline

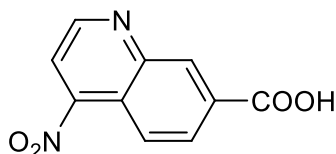


Isoquinoline

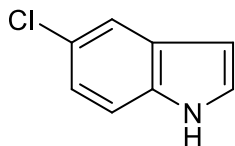


Carbazole

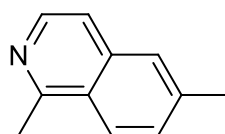
The position of substitutions does not change regardless of the nature of substituent. Examples:



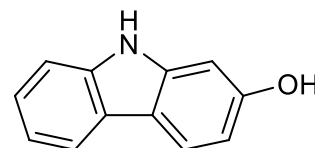
7-carboxy-4-nitroquinoline



5-chloroindole



1,6-dimethylisoquinoline



2-hydroxycarbazole

## Replacement nomenclature

Another method of nomenclature, and is summarized by the following rules:

1. The name of heteroatoms, their sequence and numbering is the same as in Hantzsch – Widman method.

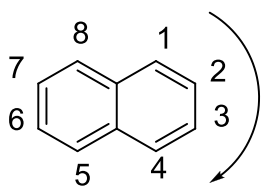
O (oxa) > S (thia) > N (aza)

2. When there is a choice, priority in numbering is given to the heteroatom, then un-saturations, then to substituents in alphabetical order.

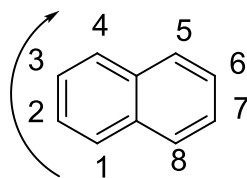
3. The position and prefix for each heteroatom is written in front of the name of the corresponding hydrocarbon, which represents the parent name.

4. In fused heterocycles, numbering of the corresponding hydrocarbon is retained, irrespective of the position of the heteroatom, except when there is a choice, low numbers are assigned to the heteroatoms

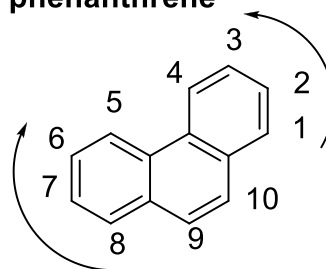
Numbering system in naphthalene



Note that: position 1, 4, 5, and 8 are equivalent

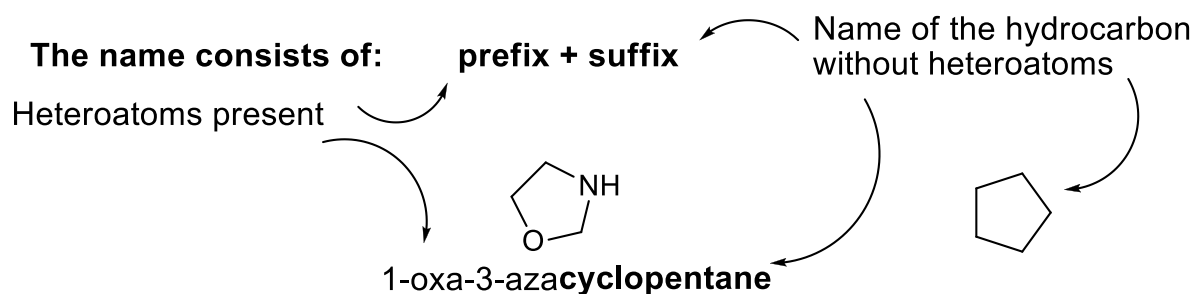


& phenanthrene



Note that: position 1 and 8 are equivalent

Few examples as an application of the replacement method of nomenclature are given below.



The position of each kind of heteroatom is written directly in front of it

