Therapeutic Chemistry

M1 Applied Biochemistry & Pharmacology – Toxicology

Foreword

This book is intended for students of the second cycle of university: Master 1 Applied Biochemistry and Pharmacology-Toxicology. It focuses on therapeutic chemistry and is interested in the knowledge of the chemical mechanisms of the drugs responsible for the various therapeutic effects

This book is divided into four chapters: the first recalls the reaction mechanisms in organic chemistry, namely: the mechanisms of substitution, elimination and addition.

In Chapter 2, we present heterocyclic compounds as well as their modes of synthesis and reactivity

Chapter 3 defines drugs, their different drug targets and their mechanisms of action. In Chapter 4, we present some families of drugs.

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CHAPTER I: REACTION MECHANISMS

I.1. General

Organic reactions fall into four broad categories:

- Substitution reactions

$$CH_3Br + KOH \rightarrow CH_3OH + KBr$$

- Elimination reactions: A distinction is made between order 1 and order 2 β-eliminations.

$$CH_3CH_2OH \xrightarrow{H^+} CH_2=CH_2 + H_2O$$

- Addition reactions: these can be electrophilic, nucleophilic, or radical.

$$CH_2=CH_2 + Br_2 \rightarrow CH_2Br\text{-}CH_2Br$$

- Transposition reactions (rearrangement): which occur by the migration of an atom or group of atoms from one site of a molecule to another site.

$$(CH3)_3C\text{-}CH2\text{-}OH \rightarrow (CH_3)_3\text{-}C(OH)\text{-}CH_2\text{-}CH_3$$

A reaction mechanism is described using the following aspects:

1. **<u>Thermodynamic aspect</u>**

Thermodynamics can predict whether or not a reaction can take place, but it cannot tell how to move from reactants to products, the number of steps, and the stereochemical aspect of the reaction. To address all these shortcomings, the mechanism of action must be elucidated in order to describe in detail the path followed by this reaction. Knowledge of the mechanism of a reaction can make it possible to control it, guide it and increase its yield.

- Mechanism≡ Step(s) of the reaction, the nature and structure of the intermediates formed, the nature of the broken and formed bonds, the reaction sites.

2. Kinetic appearance

Kinetics make it possible to follow the evolution of reactions as a function of time. It leads to the determination of reaction rates.

Let be the reaction: **A+B→C**

The speed of this reaction can be defined in relation to the reactants or in relation to the products:

$$V = \frac{d[C]}{dT} = -\frac{d[A]}{dT} = -\frac{d[B]}{dT}$$

If the speed can be written:

- $V = k[A][B]$, the reaction is of order 2 (bimolecular reaction). This reaction occurs by a simple collision between a molecule A and a molecule B.
- $V = k[A]$, The reaction is said to be of order 1 (monomolecular reaction). This equation is compatible with a two-step reaction mechanism:

Slow Stage: **A→X**

Quick Step: **B+X→C**

The slow step of the reaction is the formation of the X intermediate. The action of B on X leads to C in a rapid step. The 1st step is said to be kinetically determining. It is the stage that determines the speed.

Activation Energy

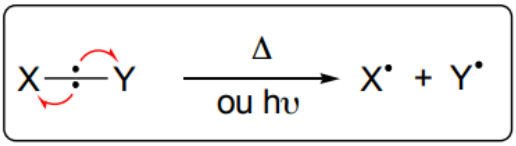
Collision theory: The rate at which a reaction occurs between two molecules A and B is related to the frequency of collisions between these molecules. In order for it to have an effective impact, a certain minimum amount of energy must be provided at the time of collision. This energy is called: Activation Energy.

3. Electronic aspect

This aspect allows us to know the role and fate of electrons in chemical reactions. Thus, a constituent can result, according to the electronic mode, in different entities, namely: free radicals during radical reactions, electrophiles or nucleophiles.

A distinction is made between:

Homolytic mode that is done by thermal or photochemical means, leading to the formation of free radicals:



Heterolytic mode: this is a break or an asymmetrical association resulting in one atom carrying a lone pair and the other with a vacant orbital. This break is called a heterolytic split.

I.2. Nucleophilic Substitution Reactions

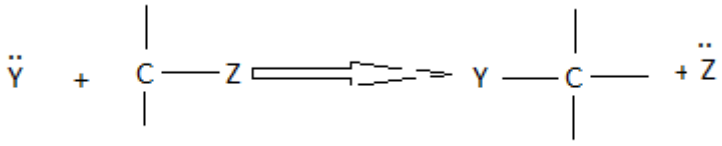
I.2.1. Introduction

Nucleophilic substitution consists of the attack of a nucleophilic reagent on the carbon of a substrate carrying a Z substituent that is likely to be displaced.$\ddot{y}$

$$y + R - Z \overset{..}{\rightarrow} y - C + \ddot{Z}$$

Where y is the nucleophile, z is called the leaving group or nucleofuge.

During the reaction, the nucleophile establishes a bond thanks to its free electron pair, while the leaving group, after breaking the C-Z bond, acquires a free doublet.$y - C$



The nucleophile and the departing group, as well as the substrate and the product, can be neutral or charged entities.

Tables 1 and 2 give the main nucleophiles and starting groups:

Table 1: The main nucleophiles:

Atom carrying the free pair	Nucleophile
Halogen	Cl^-, Br^-, I^-
Oxygen	H_2O, OH^-, ROH, RO^-, RCOOH, $RCOO^-$, NO_3^-
Sulphur	H_2S,HS^-, R_2S
Nitrogen	NH_3, RNH_2, R_2NH, R_3N, N_3^-
Phosphorus	R_3P
Carbon	R_3C^-, $RC\equiv C^-$
Hydrogen	$LiAlH_4$

Table 2: The main starting groups:

Atom carrying the free pair	Nucleophile
Halogen	Cl^-, Br^-, I^-
Oxygen	H_2O, ROH, RCOOH, $RCOO^-$, $HSO3O^-$, RSO_3O^-
Sulphur	SR_2
Nitrogen	N_2

I.2.2. S_N2 bimolecular nucleophilic substitution

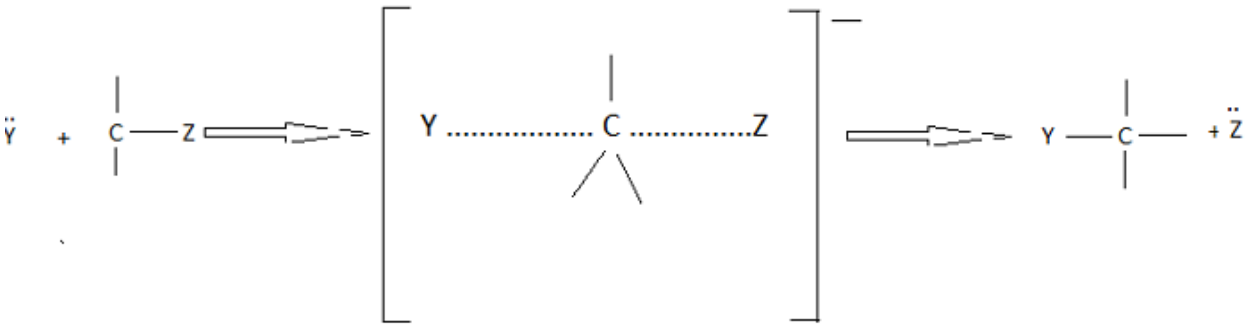
1.2.2.1. The S_N2 mechanism

Features of an S_N2:

Speed is expressed by:

V=k [substrate][nucleophile]

The substitution takes place in a single slow step that is kinetically determinative: breaking of the C-leaving group bond and formation of the C-nucleophilic bond. It is therefore an elementary reaction of the second order.



Example: $CH_3CH_2Cl + Na^+OH^- \rightarrow CH_3CH_2OH + NaCl$

$$V=K[CH_3CH_2Cl][OH^-]$$

If we perform the reaction on an asymmetric carbon, we find that there is a configuration inversion called Walden inversion.

Example

These experimental results can be explained by a mechanism involving a transition state where Y (nucleophile), C (functional carbon) and Z (leaving group) are carried by the same axis.

The nucleophile occurs on the opposite side of the nucleophile, forcing the three substituents of the carbon to be placed in the same plane, perpendicular to the Y-C-Z axis.

3.2.2.2. The determining factors of the S_N2 mechanism

a) Substrate Structure

The functional carbon (carrier of the Z-leaving group) can be primary, secondary or tertiary.

The rate of the S_N2 reaction follows the following reactivity sequence:

$$\mathbf{CH_3Z > R\text{-}CH_2\text{-}Z > R_2CH\text{-}Z > R_3C\text{-}Z}$$

This effect is due to the crowding created by the R group around the carbon reaction site, which the nucleophile must be able to reach during the collision. The greater the number of these groups, the greater the proportion of ineffective collisions.

b) Influence of the nucleophile

The attack of the nucleophile triggers the reaction process, so a good nucleophile **(I^- > Br^- > Cl^-) is needed.**

c) **Leaving group**

He must be able to leave easily.

d) Nature of the solvent

Poorly polar aprotic solvents increase the rate of an S_N2 reaction by solvation of the nucleophile-bound cation.

Features of the S_N2 mechanism

1. The reaction is biomolecular and has a speed of order 2
2. The carbon on which the substitution relates undergoes a configuration reversal. SN2 is stereospecific
3. The reaction is very sensitive to steric crowding.
4. The reaction is favoured by non-polar or slightly polar solvents.

I.3. Monomolecular nucleophilic substitution of order 1

I.3.1. S_N1 mechanism

The speed is given by the expression:

$$\mathbf{V=k\ [substrate]}$$

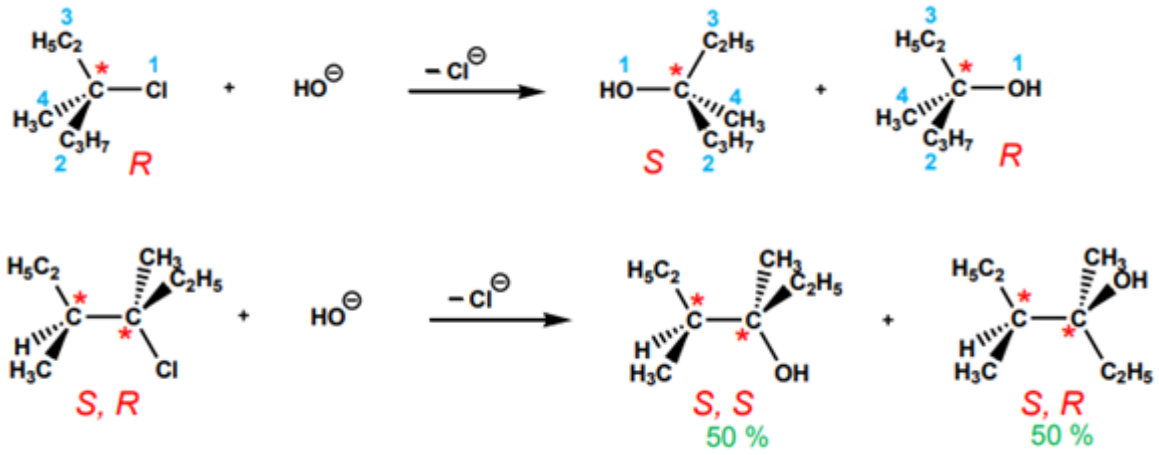
The reaction occurs in two stages:

1st stage; kinetically determinative slow resulting in the formation of a sp2 hybridized plane carbocation.

2nd step: rapid: Intervention and attack of the nucleophile which is done from two sides with equal probability.

From a stereochemical point of view, SN1 is not stereospecific, it results in the formation of a racemic mixture (50% R+50%siS) when the substrate contains a single asymmetric carbon.

If the substrate has two asymmetric carbons, SN1 gives rise to an equimolar mixture of diastereoisomers. (see examples below).

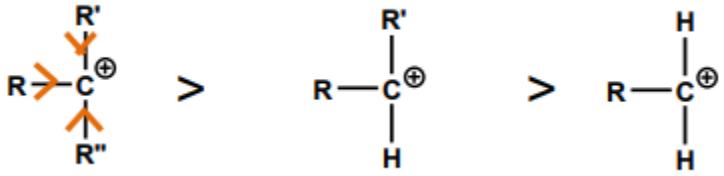


II.3.2. Factors influencing the $S_{N1\ mechanism}$

a) Substrate Structure

The SN1 mechanism is only possible if the carbocation formed is stable. The stability of carbocation is favored by electron-donating electronic effects, namely the inductive (+I) and mesomeric (+M) effect. These allow for an increase in electron density

of the carbon site of the reaction. Thus, the reactivity sequence of an SN2 mechanism is as follows:



Where R, R', R'', are alkyl donor groups by inductive effect (+I).

A carbocation is only stable if it is of a higher class. A substrate giving a tertiary carbocation promotes SN1.

b) Influence of the nucleophile The nucleophile has no influence on an SN1 mechanism, the velocity expression is independent of the concentration of the nucleophile. The kinetically decisive step is the formation of a carbocation.

c) Influence of the departing group

The C-Z bond (Z is a leaving group) breaks more easily when it is more polarizable, especially when it is longer.

d) Nature of the solvent

The speed of an S_N1 reaction increases in the presence of polar protic solvents, capable of interacting through hydrogen bonds with the leaving group, thus facilitating the breaking of the C-Z bond and the formation of carbocation.

Features of the S_N1 mechanism

1. The reaction is monomolecular (unimolecular) and has a speed of order 1.
2. Racemization is the rule when the substrate contains a single C*.
3. SN1 is not stereospecific
4. The reaction is insensitive to steric crowding.
5. The reaction is strongly accelerated by polar solvents.
6. Rearrangements are common.

I.4. Elimination reactions

I.4.1. General

When a compound has at least one hydrogen atom on a carbon adjacent (carbon β) to the C-Z bond (Z is a leaving group carried by carbon α), the action of a base can cause elimination with the formation of a double bond.

Many bases can cause this elimination, strong bases such as OH-, NH2-, RO-, but also weaker bases such as ammonia NH3, R-NH2 amines or R-OH alcohols.

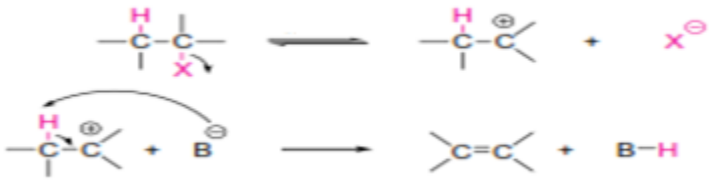
This elimination reaction can be done in two stages, which is called an order 1 elimination reaction (E1) or in a single step, which is called an order 2 reaction (E2).

The elimination reactions are regioselective: if there are several hydrogens carried by β carbons, only one will be attacked in a preferential manner and will result in the formation of the majority compound according to Zaitsev's rule.

Zaitsev's rule: The most substituted alkene is in the majority.

I.4.2. Monomolecular Removal of Order 1 (E1)

a) Mechanism:



Where B^-: a base; X: departing group.

- The E1 reaction occurs in two stages:

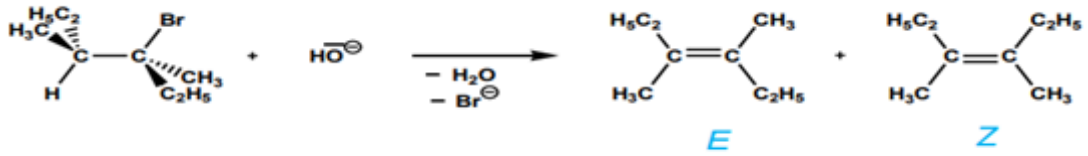
  1st step: slow kinetically determining Formation of a sp2 hybridized plane carbocation.

  2nd stage: rapid: attack on the B- base, which will tear off a hydrogen in β.

- Velocity law: V=k[Substrate]

- The free rotation around the C-C bond gives rise to the formation of the two alkenes (Z+E).

Example:



b) <u>Characteristics of an E1 mechanism:</u>

✔ Monomolecular reaction: 1st order reaction; V=k [substrate]

✔ Removal is carried out in two stages via carbocation.

✔ Reaction favors a tertiary substrate and a protic solvent.

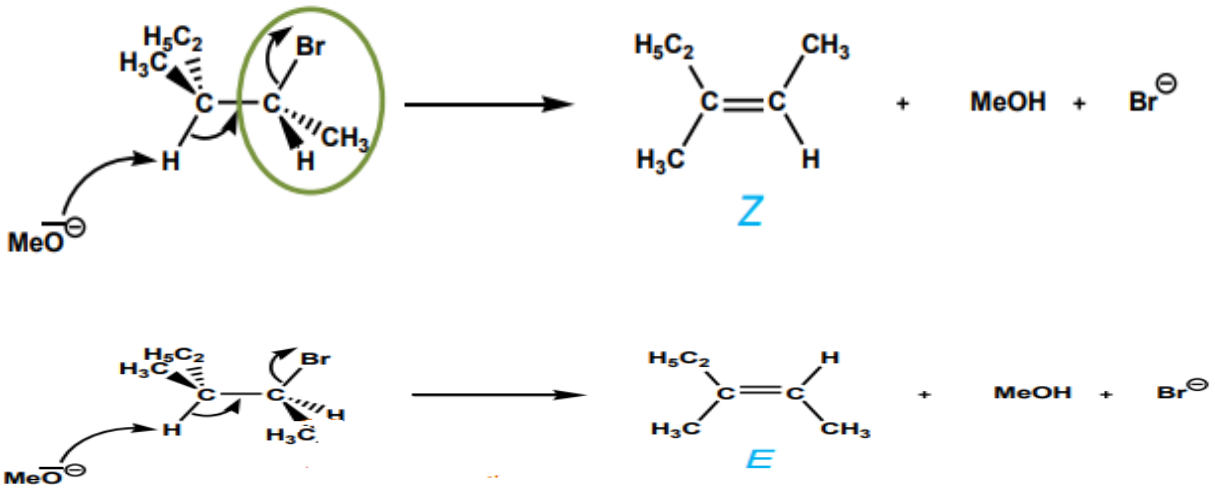
I.4.3. Biomolecular Removal of Order 2 (E2)

a) ***<u>Mechanism:</u>***

A reaction in a single act that is elemental and bimolecular and goes through a state of transition.

- ***<u>Kinetic aspect</u>***: Order is equal to molecularity: V=k[Substrate][Base]
- ***<u>Stereochemical aspect</u>***: The groups to be eliminated during an E_2 (the H+ proton and the leaving group) must be coplanar anti-parallel. E2 is stereospecific anti, it is a trans-elimination.

Examples:



Where MeO^- is the base that will tear off H^+

From the previous examples, we can deduce that the E2 elimination is stereospecific, it results in the formation of a single alkene, according to the absolute configuration of the asymmetric carbons of the substrate.

c) ***Features of an E2 mechanism:***

- ✔ Monomolecular reaction: 1st order reaction; V=k [substrate][base]
- ✔ Elimination is carried out in a single step by passing from a transition state.
- ✔ Stereospecific and stereoselective reaction.
- ✔ Sensitive reaction to steric crowding and solvent polarity.

I.4.4. Study of the influence of the various parameters

Tertiary substrates: E1; Primary substrates: E2; E1 and E2 secondary substrates: in this case the strength of the basic reagent favors an E_2 and the nature of the polar solvent favors an E1

Polar protic solvents: E1; Poorly polar or non-polar aprotic solvents: E2.

I.4.5. S_N-E Competition

In contact with a substrate, the nucleophilic or basic reagent will lead to mixtures of different proportions.

A potent base always has a nucleophilic character whereas a potent nucleophilic may have no basic character in a given solvent such as halide ions (Cl^-, Br^-, I^-). These reagents will only give S_Ns.

Nucleophilic substitution is favored by a strong nucleophile and steric crowding of the carbon β.

Elimination is favoured by a powerful, low-nucleophilic base and a high carbon footprint α.

A rise in temperature promotes elimination.

A cold-diluted reagent promotes nucleophilic substitution. A hot-concentrated reagent promotes elimination.

Factor	**S_N1/E1**	**S_N2/E2**
Mechanism	***V=k[substrate]*** S_N1/E1	***V=k[substrate][nucleophile]*** S_N2 ***V=k[substrate][base]*** E2
Intermediary	Carbocation C^+	Transitional State
Stereochemical aspect	Non-stereospecific S_N1: Racemic mixture E1: Alkenes Z and E With E is the majority (more stable)	Stereospecific S_N2: Configuration Reversal (Walden Inversion) E2: Alkene Z or E
Substrate	Tertiary>Secondary>Primary	Lightly Crowded Substrate (Primary)
Leaving group (nucleof-repellent)	Atoms bonded the same: The strength of the nucleofuge increases with the decrease in basicity.	

	Different bonded atoms but they belong to the same column of the periodic table: the strength of the leaving group increases with increasing atomic radius	
Nucleophile/base	No influence	S_N2: The strength of the nucleophile increases with increasing basicity. The strength of the nucleophile increases with increasing atomic radius. E2 favored by strong bases
Solvent	Polar Protics	Mild or nonpolar aprotic

I.5. Electrophilic addition reactions

I.5.1. General

Addition reactions take place with unsaturated compounds with multiple bonds, such as: C=C; C≡C; C=O; C≡ N....

A π bond of the substrate opens under the action of an A-B type reagent in which the σ bond is broken homolytically (radical addition) or heterolytically (electrophilic or nucleophilic addition).

I.5.2. Electrophilic addition

The substrate has an electron-rich center, usually a carbon–carbon multiple bond. The A+ electrophile comes from the dissociation of the A-B molecule.

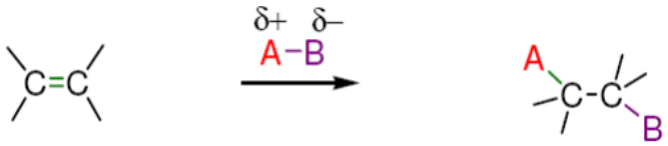
$A\text{-}B \rightarrow A^+ + B^-$

The two ions generated by heterolytic rupture do not add up simultaneously. Since the electrophly reagent has an electron gap, it reacts with the π pair of the multiple bond. Depending on the nature of A+, two cases arise:

- Slow formation of a carbocation

- Or slow formation of a bridged ion.

The balance equation of an electrophilic addition on a double bond is written:

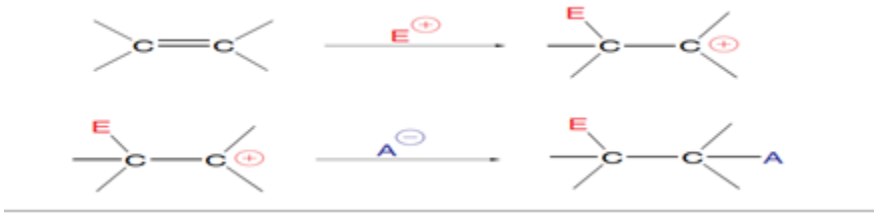


The A-B reactant is either polar or nonpolar but polarizable under the influence of the π cloud.

AEs occur in two stages:

1st stage: electrophilic attack on the double bond.

2nd step: Nucleophilic attack on the other carbon.



I.5.3. Electrophilic reagents

They are Lewis acids with either positively charged centers (C^+, X^+, NO_2^+, H^+) or electronic gaps (BF_3, $AlCl_3$, $FeCl_3$)

I.5.4. Different electrophilic addition reactions

a. Addition of halogenated hydroacids HX (X≡Cl, Br, I)

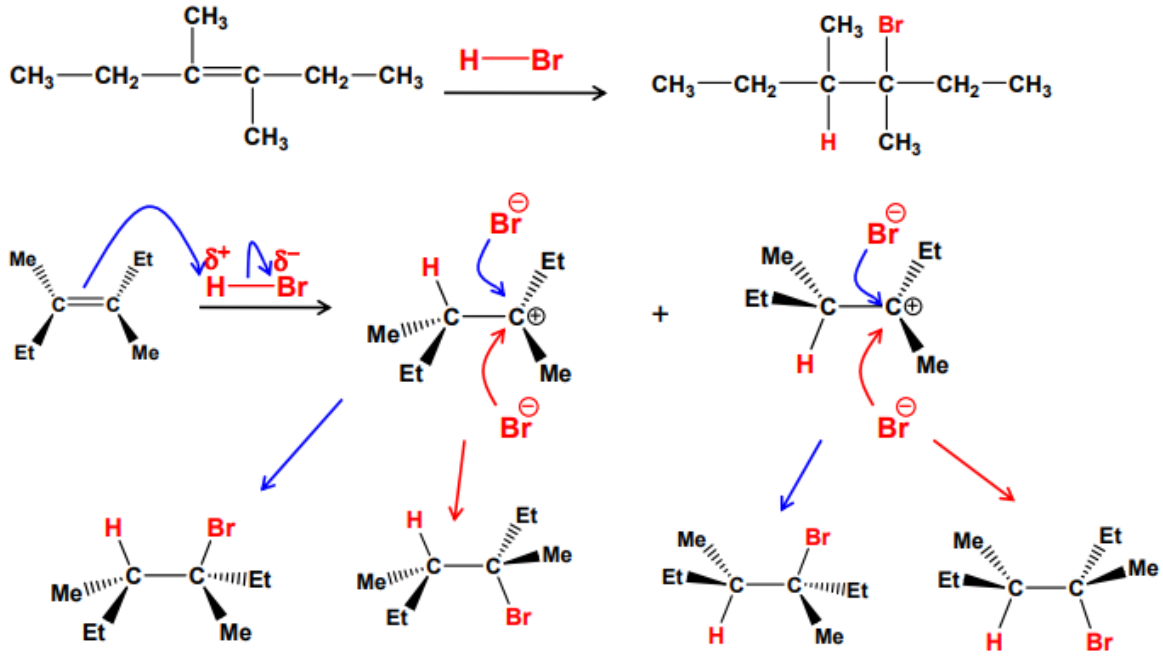
Example: CH_3-CH=CH_2 + HCl →CH_3-CH_2-CH_2-Cl + CH_3- CH(Cl)-CH_3

The reaction gives rise to a mixture of two chlorinated derivatives. It is regioselective and is governed by the Markovnikov rule.

Markovnikov's rule:

When a hydrogenated HA compound is added to an asymmetric alkene, the hydrogen binds to the least substituted carbon

Example: HBr addition on 3,3-dimethylhex-3-ene



The addition of HX can be done according to a radical chain reaction: this is the Karasch effect.

b. Radical addition of HX (karasch effect or peroxide effect)

Some additions of halogenated hydroacids HX take place in the opposite direction of the

Markovnikov, if the reaction is carried out in the presence of peroxides with the formula: R-CO-O-O-CO-R. This is the Karasch effect or the peroxide effect.

The reaction no longer has a heterolytic mechanism but a homolytic chain mechanism.

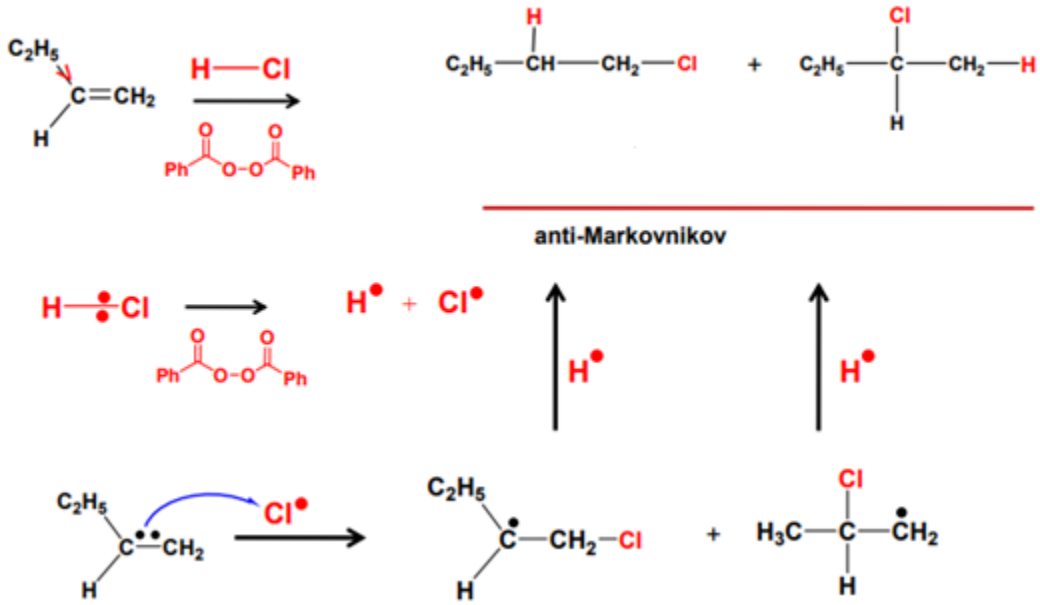
The reaction occurs in three phases:

- Free radical production phase;
- Initiation phase;
- Propagation phase.

During the radical addition of HX to a dissymmetrical alkene, the hydrogen binds to the most substituted carbon: this is a sreeoselective and non-stereospecific addition

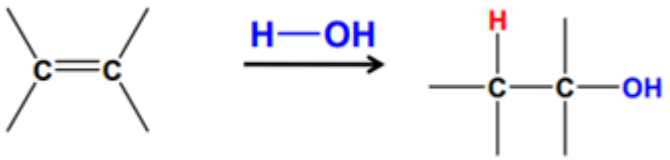
anti Markovnikov

Example:



c. ***Addition of water: hydration***

Hydration of C=C leads to alcohol according to the reaction pattern:



Hydration therefore involves three stages and it occurs in the presence of a strong acid, acting as a catalyst:

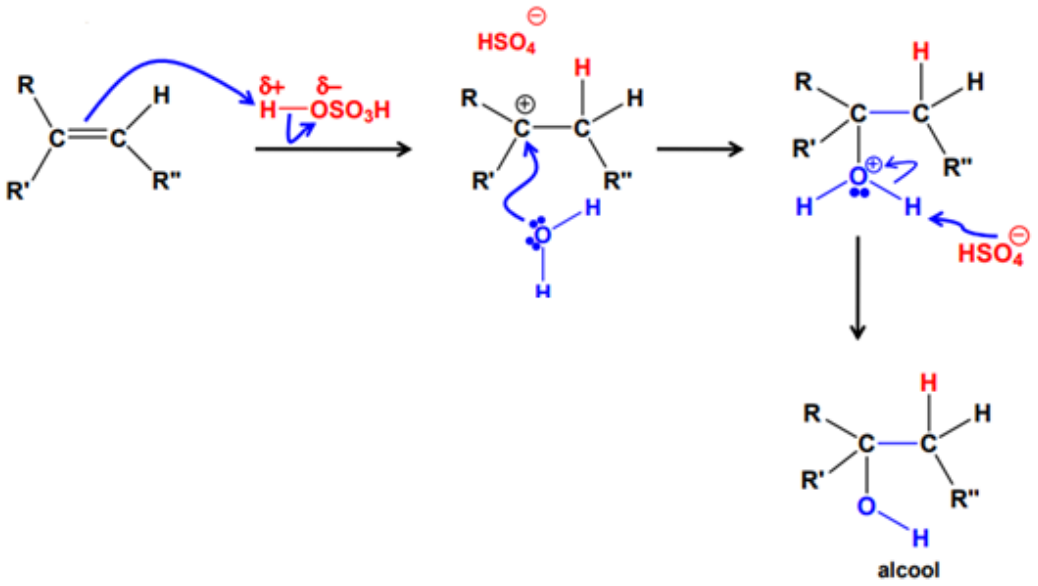
1st step: Protonation of the double bond by sulfuric acid and formation of a carbocation.

2nd step: Intervention of water as a nucleophile that can bind to the carbocation

By one of his free doublets.

3rd step: Elimination of a proton, facilitated by the existence of an electron deficit on oxygen.

The removed proton replaces the one that sulfuric acid initially provided.



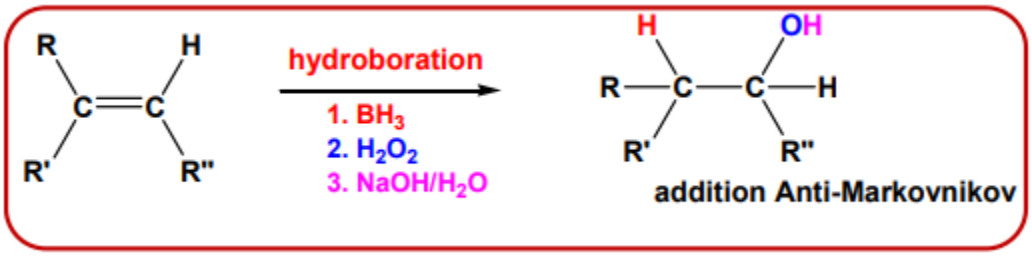
Markovnikov's rule applies at the time of carbocation formation: the electrophile attaches to the least substituted carbon, giving rise to the most stable carbocation.

The reaction is regioselective (according to Markovnikov) but it is not stereospecific (H2O attacks from two sides).

d. Hydroboration hydration

The hydration of the double bonds can also be done indirectly by using boron hydride BH3: this is therefore hydration by hydroboration

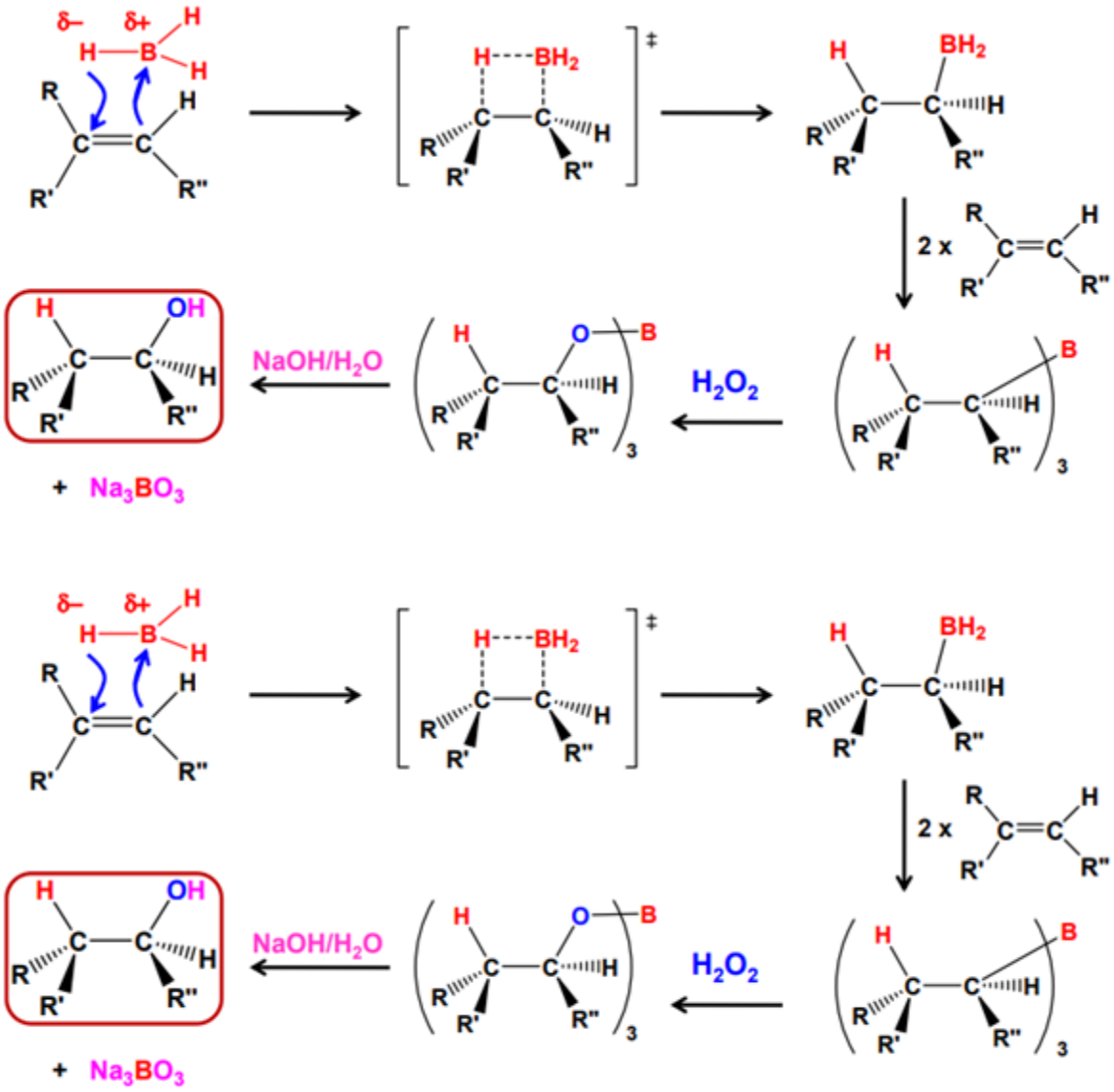
The general balance of a hydroboration is as follows:



The hydroboration reaction goes through two stages:

1st step: Addition of BH_3 on the double bond to give an alkylboran R-BH2 (R≡alkyl group).

2nd step: Oxidation of alkylborane by hydrogen peroxide H_{2O2} in a basic medium.



It is an ***anti-Markovnikov addition***: BH_3 dissociates into BH_2^+ and H^- (boron is less electronegative than hydrogen): it is BH_2^+ that binds first. It is a **stereospecific Cis-addition.**

e. Dihalogenation reaction

Halogens add up on double bonds to give dihalogenated derivatives in which the two halogen atoms are carried by two neighboring carbons in a two-step mechanism:

1st step : The X+ bromine atom (Br+ for example) forms a halonium bridge on the substrate with the formation of a halonium ion with a cyclic structure. In this bridged cation, where rotation between the two carbonsis not possible, the positive charge is distributed among 3 atoms.

2nd step: The bridged ion can only be attacked by the X^{-} ion (Br- for example) on the opposite side (the least congested) and this attack causes the cycle to reopen.

The dihalogen addition reaction is an **anti-stereospecific reaction** : it is a ***stereospecific trans-addition*** "the two halogen atoms attach on either side of the double bond.

f. Addition of HOX hypohalogen acids

Acids of the HOX form, mainly hypochlorous acid HOCl and hypobronous acid HOBr, add to the double bonds and form a halohydrin or α-halogenated alcohol.

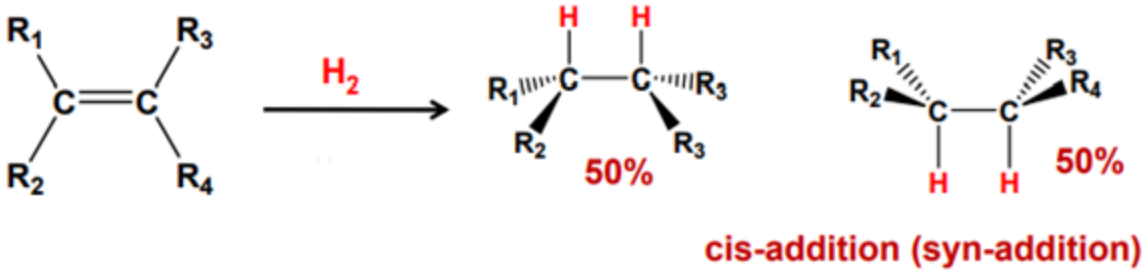
The reaction is **regioselective**: the halohydrin resulting mainly from the fixation of X^{+} on the least substituted carbon and OH^{-} on the most substituted carbon (X is less electronegative than oxygen).

The reaction is **stereospecific**: X+ and OH^{-} attach to each other, it is an **anti** (**trans addition**).

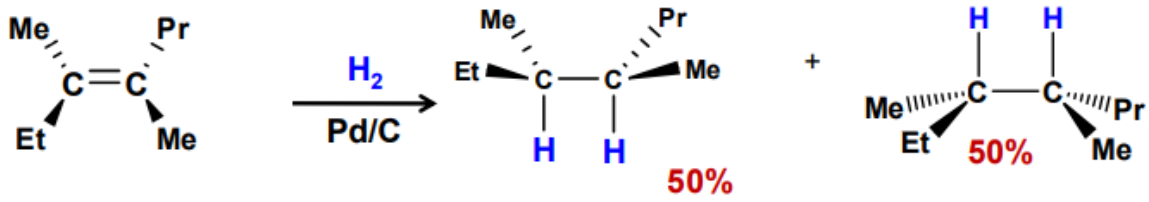
g. Catalytic hydrogenation: Addition of hydrogen H2 to double bonds (alkenes)

The addition of H2 to an alkene leads to the corresponding alkane. This reaction takes place with appreciable speed only in the presence of a catalyst. The catalysts used are nickel (Ni), platinum (Pt), palladium (Pd) etc ...

The reaction taking place between alkene and H2 molecules fixed to the surface of the catalyst: adsorption of H2 and alkene on the surface of the catalyst (heterogeneous catalysis). The two hydrogen atoms attach themselves to the same side of the plane of the double bond: this is a **stereospecific cis-addition.**


R1
R3
C
C
R2
R4
H2
H
H
R1
C
C
R3
R2
R3
50%
R1
R3
R2
C
C
R4
H
H
50%
cis-addition (syn-addition)

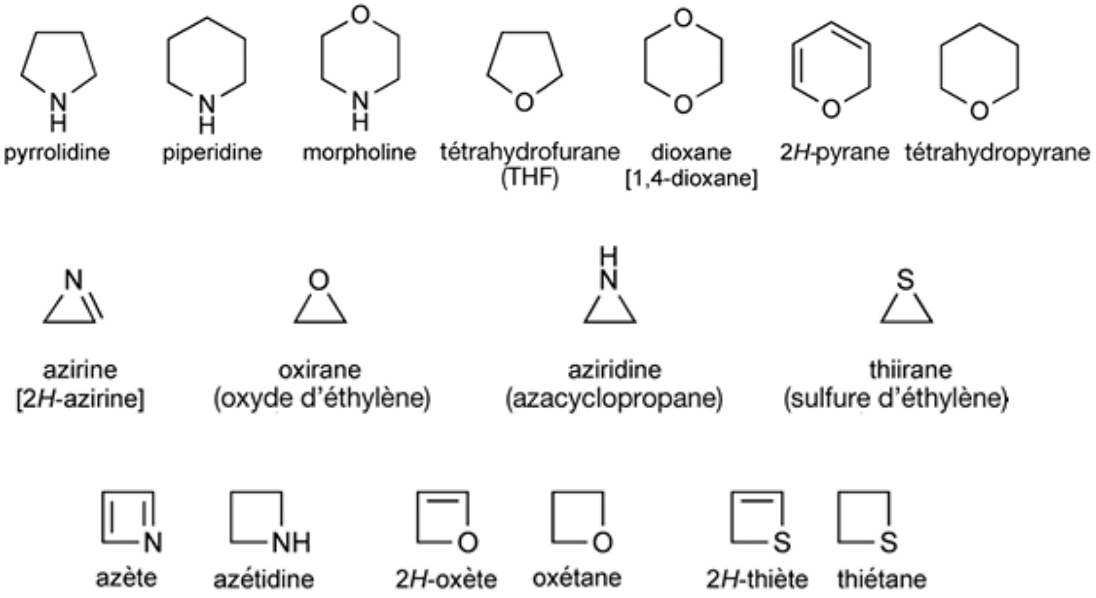
Example:


Me
Pr
C
C
Et
Me
H2
Pd/C
Me
Pr
Et
C
C
Me
H
H
50%
+
H
H
Me
C
C
Pr
Et
50%
Me

II.1. Definition

A heterocycle is a cyclic compound having one or more identical or different heteroatoms. It is the basic noyanu of most natural substances and medicines.

Examples:



II.2. Rules for the nomenclature of heterocycles

Heterocycles are named according to IUPAC, using the Hantzsch-Widman rule and the replacement rule for rings with more than 10 atoms.

According to IUPAC, the name of the heterocycle must have a prefix related to the heteroatom, a suffix, and a root.

The table gathers the prefixes as well as the precedence of the O>S>Se>N) atoms:

Heteroatoms	Prefixes
(O)	Oxa
(S)	Thia
(N)	AZA
(Se)	Selena
(P)	Phospha
(As)	Arsa
(Sb)	Stiba
(Bi)	Bisma
(If)	Sila
(Ge)	Germa
(Sn)	Stanna
(Pb)	Plomba
(B)	Bora
(Hg)	Mercura

The table below summarizes the roots and suffixes of heterocycles according to the size, degree of saturation and nature of the heteroatom.

Number of links in the cycle	Nitrogen cycle		Non-nitrogenous cycle	
	Unsaturated	Saturated	Unsaturated	Saturated
3	irine	iridine	Irene	ane
4	and	etidine	and	Étane
5	ole	Olan	ole	Olan
6	Ine	inane	Ine	ane
7	thorn	Panic	thorn	Panic
8	ocine	ocane	ocine	ocane

Trivial names are sometimes preferred to systematic names. the case, Example: furan, pyrrole, pyrolidine, pyridine.

II.2.1. Partially or Totally Saturated Heterocycles with a Single Heteroatom

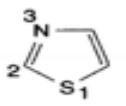
Unsaturated heterocycles with a few saturation positions are named by adding the suffix of the unsaturated ring and the prefixes dihydro, tetrahydro etc., preceded by the numbers indicating the saturation position(s). Numbering always starts with the heteroatom.

II.2.2. The case of heterocycles with several heteroatoms of the same nature

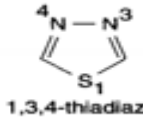
They are named by indicating the number of heteroatoms by the prefixes di, tri, tetra and their positions.

II.2.3. The case of heterocycles with several heteroatoms of different types

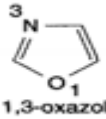
They are named according to the priority of each heteroatom. Position 1 goes to the one who has the higher precedence over the others (O>S>N...) and the suffix of the heterocycle goes to the heteroatom who has the lowest rank.



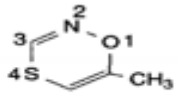
1,3-thiazole



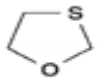
1,3,4-thiadiazole



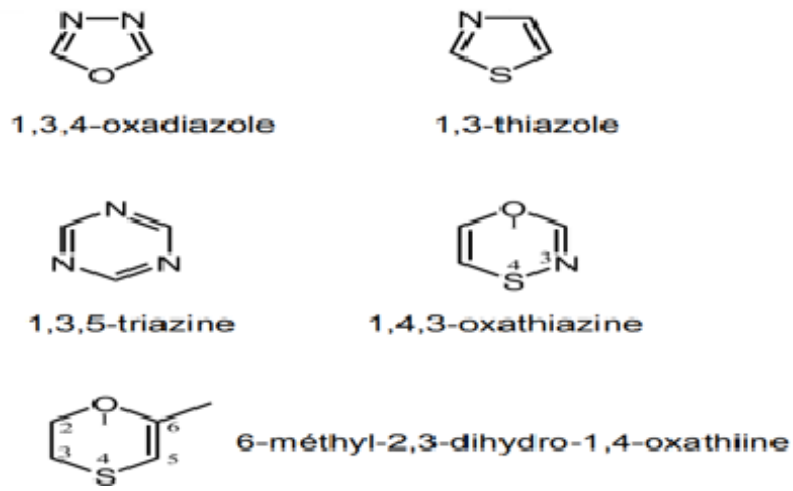
1,3-oxazole



6-méthyl-1,4,2-oxathiazine

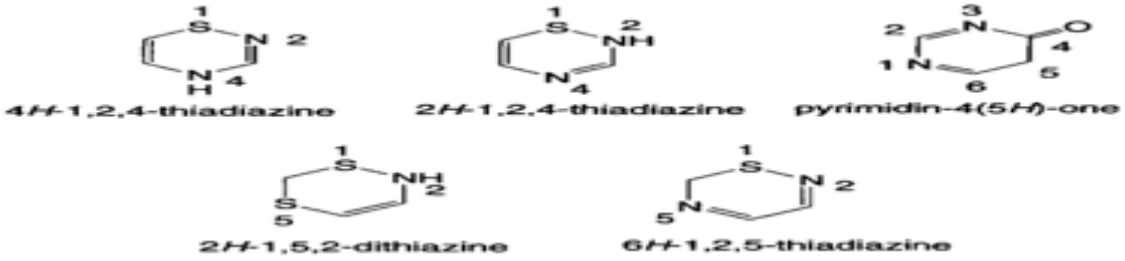


1,3-oxathiolane



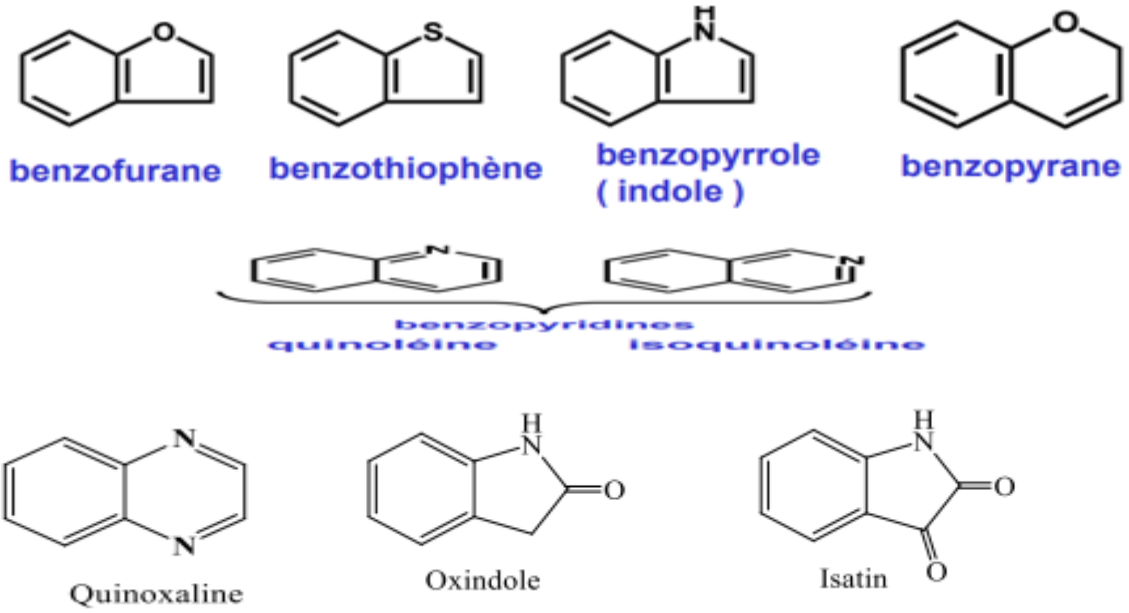
II.2.4. Position of a hydrogen for certain structural isomers

When several isomers differ from each other in the position of a hydrogen in the ring, this is indicated by an H in italics preceded by the position of the atom to which it is linked.

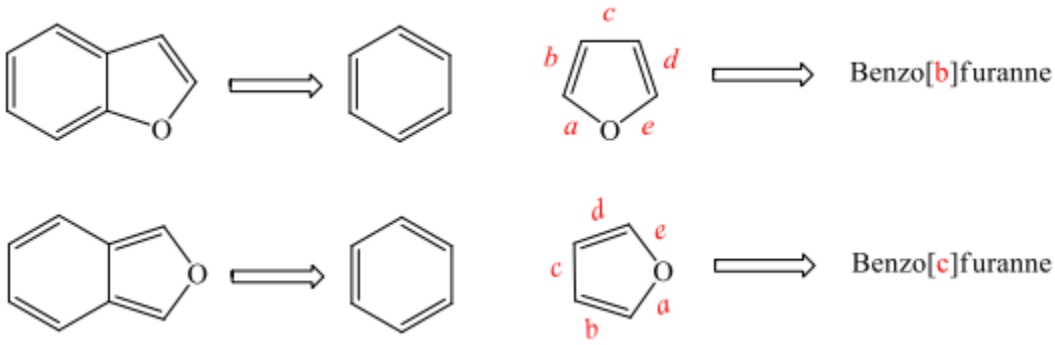


II.2.5. Bicyclic systems

This condensed heterocyclic system consists of a basic (heterocycle) and secondary (benzene) cycle. These compounds often have common names (quinoline, isoquinoline, indole, etc.)

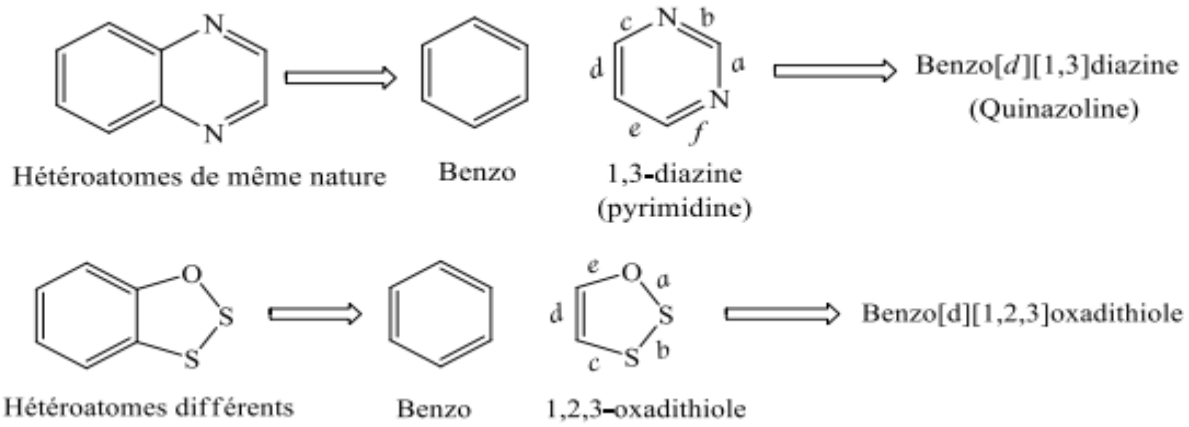


The name of the condensed heterocycle is preceded by the prefix benzo followed by a letter in square brackets which designates the bond common to the two rings defined from the heteroatom.



For a bicyclic system comprising a heterocycle with several heteroatoms, the heterocycle is first named according to the preceding rules. The letters a, b, c.. ; to the bonds of the heterocycle starting from the heteroatom with higher precedence. The place where the benzene ring is attached to the heterocycle is designated by this letter. The nomenclature is therefore:

Benzo[letter][positions of heteroatoms]name of the heterocycle



II.2.6. Multi-Heterocycle Compounds

The nomenclature of these molecules is often complex, requiring the use of many rules. First of all, it is necessary to define the structure that will be considered as the basic constituent. It will be preceded by the prefix that designates the secondary heterocycle.

Choice of the base constituent

Rule 1: The heterocycle containing a nitrogen atom must be chosen as the basic constituent.

Rule 2: If both cycles contain nitrogen, the larger cycle is taken as the base.

Rule 3: If both rings do not contain nitrogen, the ring with the priority atom should be chosen.

Rule 4: The ring with a large number of heteroatoms is taken as the base ring.

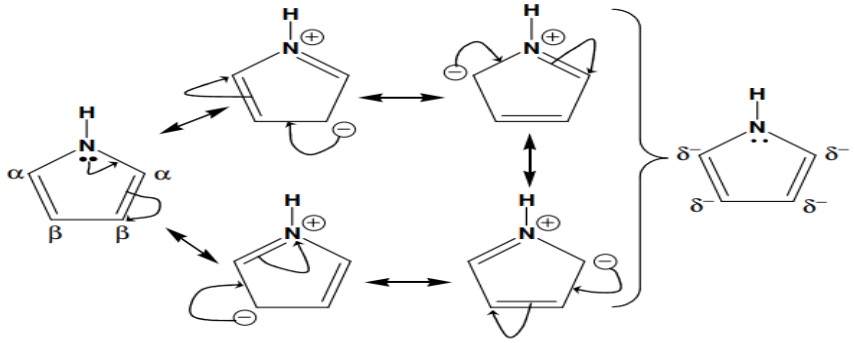
Rule 5: The name of each secondary constituent is added as a prefix to the name of the basic structure by replacing the terminal "e" of the trivial name with "o"

II.3. Synthesis and reactivity of heterocyclic compounds

II.3.1. Pyrrole

I.3.1.1. Reactivity of pyrrole

Pyrrole is an aromatic heterocycle, with five mesomeric limit forms, resulting from the delocalization of the nitrogen free pair and the two π bonds:



✔ **Electrophilic substitution on pyrrole**

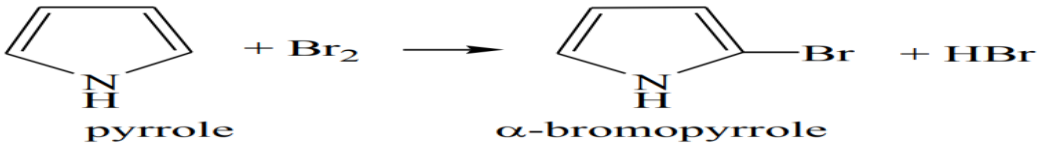
The ES of pyrrole occurs in two stages:

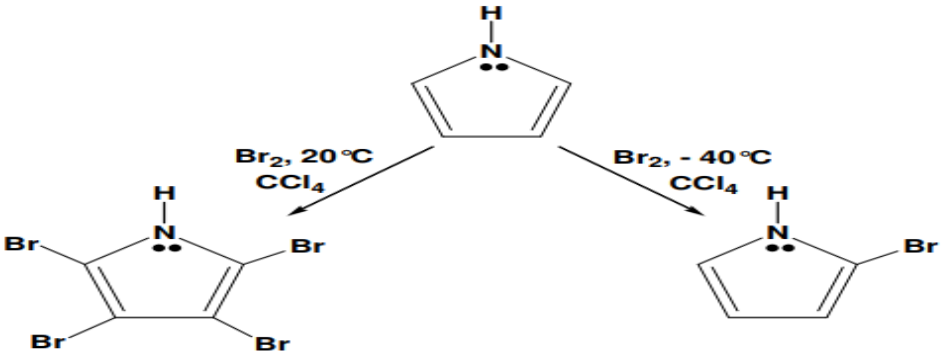
1st step: Addition of the electrophile on a preferential carbon atom with the formation of a non-aromatic cation;

2nd step: Loss of proton bound to this carbon, to bring the system back to an aromatic state.

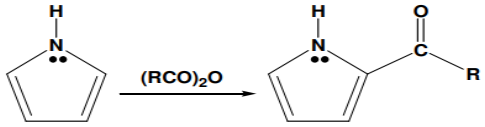
The 1st stage is usually the slowest

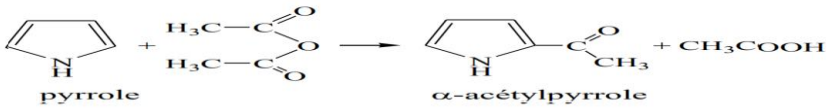
✔ **Halogenation (bromination) of pyrrole**





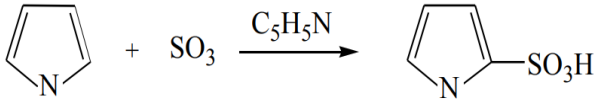
✔ Acylation of Freidel and Crafts

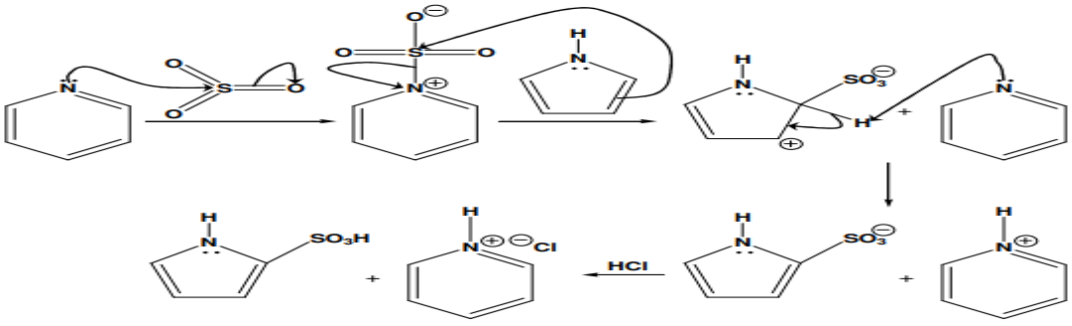




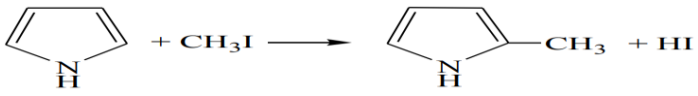
pyrrole — α-acétylpyrrole

✔ Pyrrole sulfonation reaction



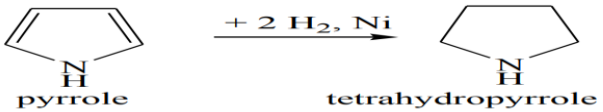


✔ Alkylation



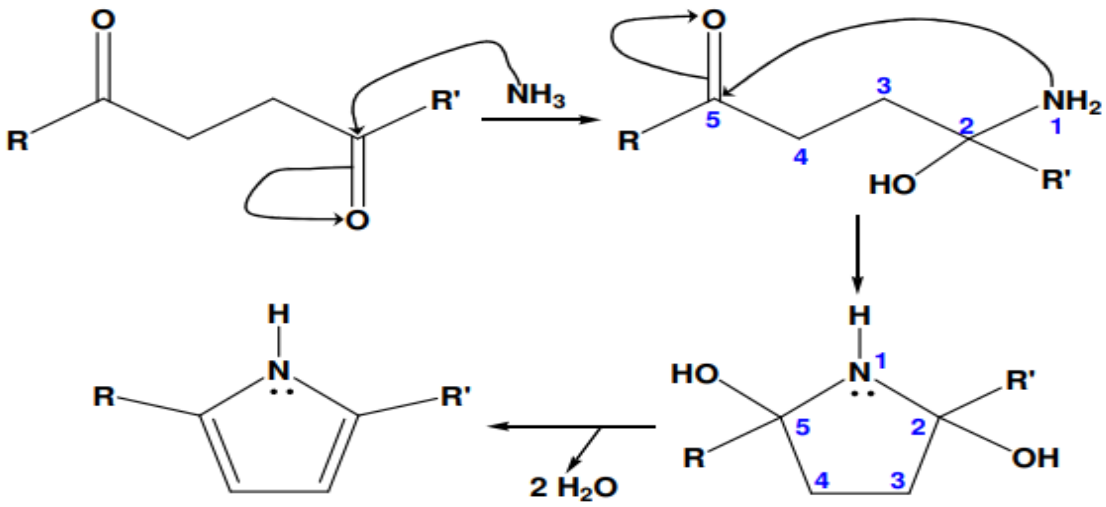
pyrrole — α-méthylpyrrole

✔ **Catalytic hydrogenation of pyrrole**

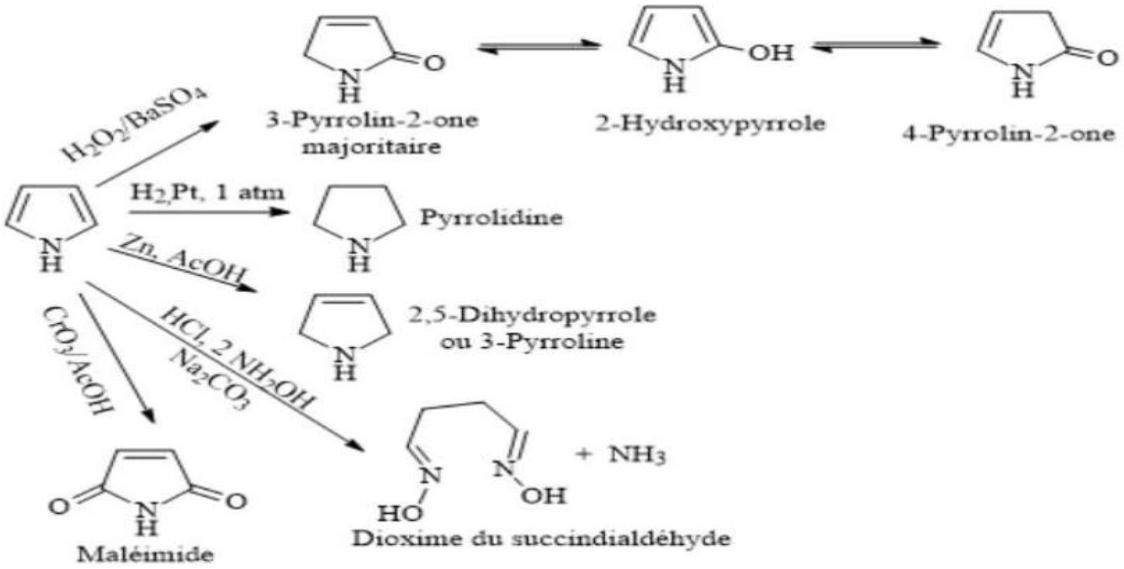


II.3.1.2. Synthesis of pyrroles from dicarbonyl compounds

- **Interaction of ammonia or a primary amine with a dicarbonyl compound (Paal-Knorr synthesis)**



Examples of reactions occurring with pyrrole



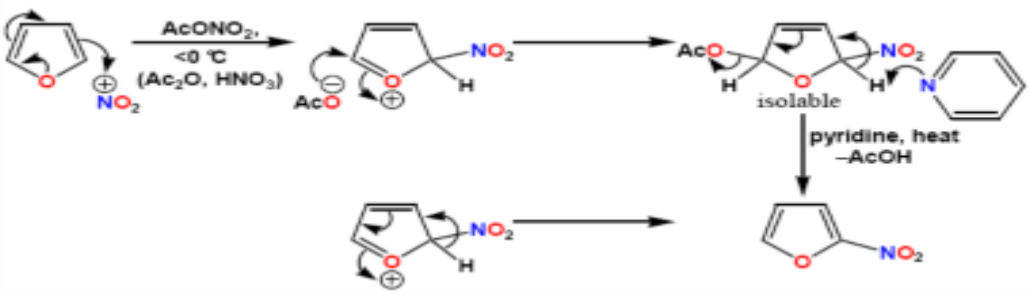
II.3.2. Furane

It is a group of compounds with interesting chemical and biological properties. Interest in furan and its derivatives continues to grow due to their biological and pharmacological properties, and in particular their action as enzyme inhibitors and their anticancer potential.

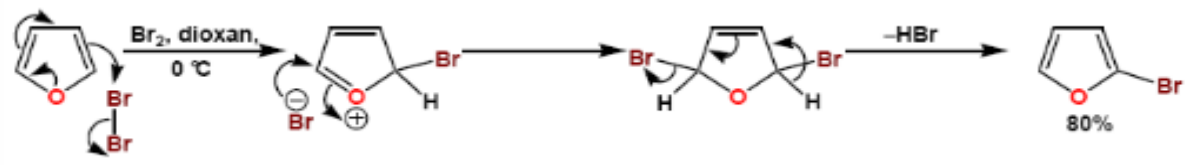
II.3.2.1. Reactivity

A. Electrophilic substitution

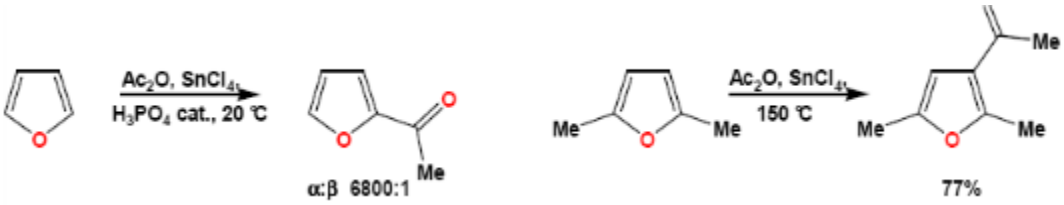
✔ **Nitration**



✔ **Bromination**

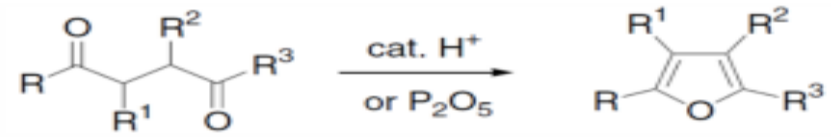


✔ **Acylation by Friedel and Crafts**

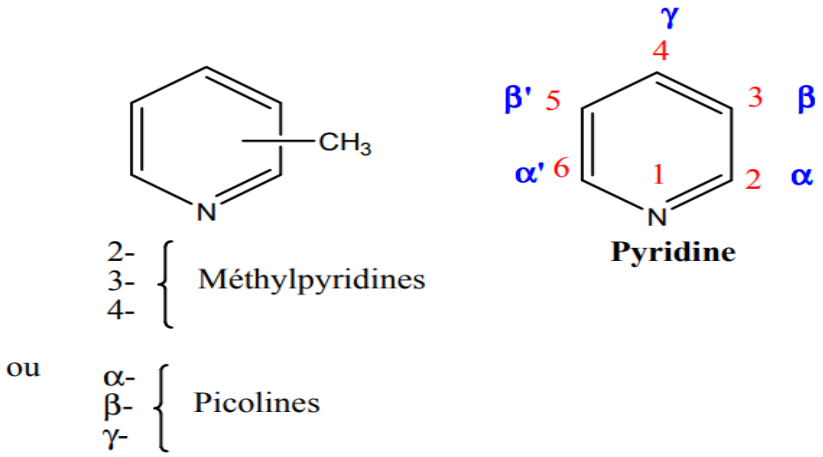


II.3.2.2. Synthesis of furan

<u>Paal-Knorr's summary</u>



II.4. Six-Membered Heterocycles: Pyridine and Derivatives



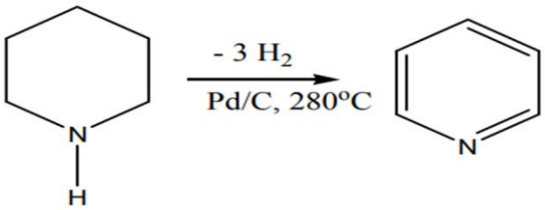
Azine is a heterocyclic aromatic compound with the formula C5H5N. It exists in the form of a liquid, slightly yellowish with an unpleasant odor. It is widely used in chemistry as a ligand in coordination chemistry and as a solvent in organic chemistry.

II.4.1. Azine Synthesis Mode

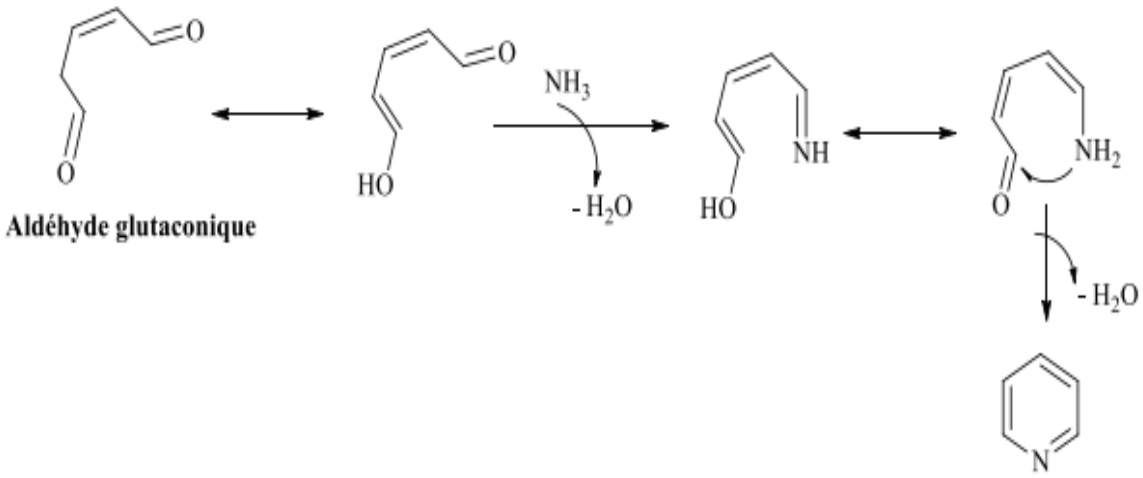
It is generally extracted from tars that also contain the isomeric methylpyridines (picolines).

✔ ***Zelinskyi-Borisov synthesis***

This synthesis consists of the dehydration of piperidine or its derivatives in the presence of Pt or Pd/C at 280°C.

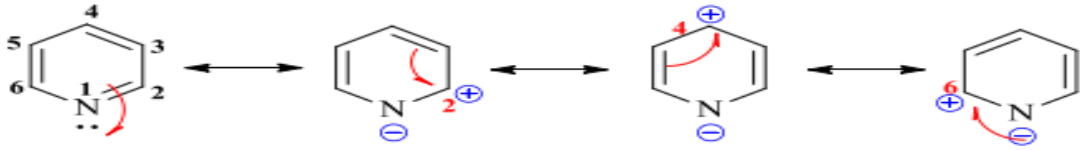


✔ ***Preparation of pyridine from glutaconic aldehyde***



II.4.2. Structure

Pyridine (azine) bears a resemblance to benzene. Its hexagonal and planar molecule has three π delocalized electron pairs.



The ring can therefore be attacked by a nucleophile and the negative charge can be better accommodated by the heteroatom than by a carbon, hence the reactivity of these rings as electrophilic.

- **Carbons 2, 4 and 6 are positively charged;**
- **Pyridine is insensitive to electrophiles.**
- **Pyridine is very sensitive to nucleophilic reagents**

II.4.3. Reactivity

✔ ***Basicity***

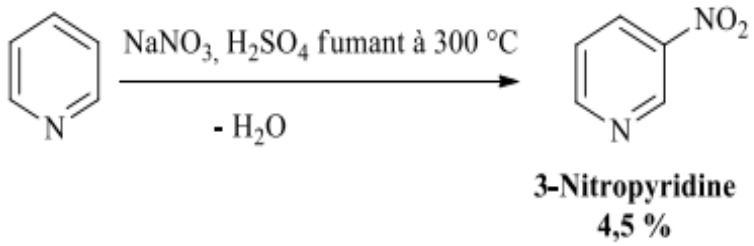
Pyridine is a very strong base than pyrrole. The N doublet does not participate in the delocalization, it is no longer available and the electron density on the nitrogen is not weakened, on the other hand, the conjugated acid of pyridine retains its aromatic character.

✔ ***Surrogate reactions***

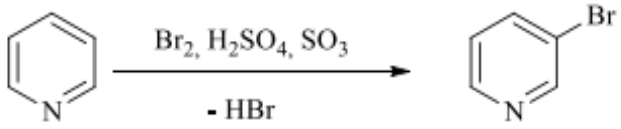
Unlike pyrrole, the nitrogen atom of pyridine does not exert a donor mesomere effect and instead plays a deactivating role through its inductive attractor effect. As a result, the pyridine nucleus is low in electrons, so it is very resistant to nucleophiles.

SE (nitration, sulfonation, bromination) is difficult and preferentially done on carbons 3 or 5 that are less deactivated than the other positions. Freidel and Crafts' reaction is impossible.

In addition, electrophilic reagents bind preferentially to the nitrogen atom of pyridine by giving a pyridinium ion.



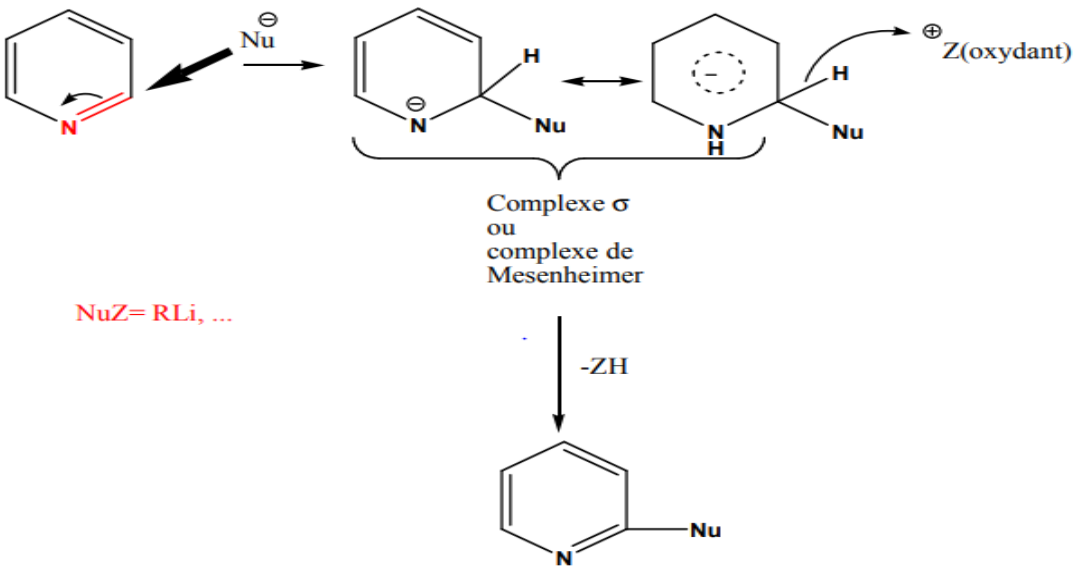
3-Nitropyridine
4,5 %

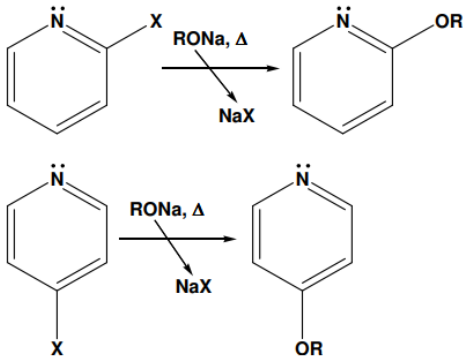


3-Bromopyridine
86 %

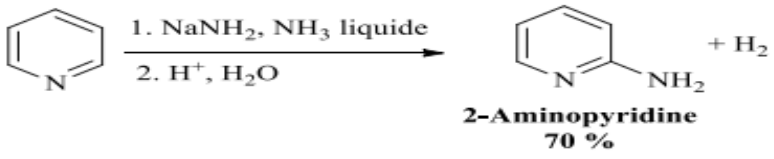
✔ **Nucleophilic Substitution**

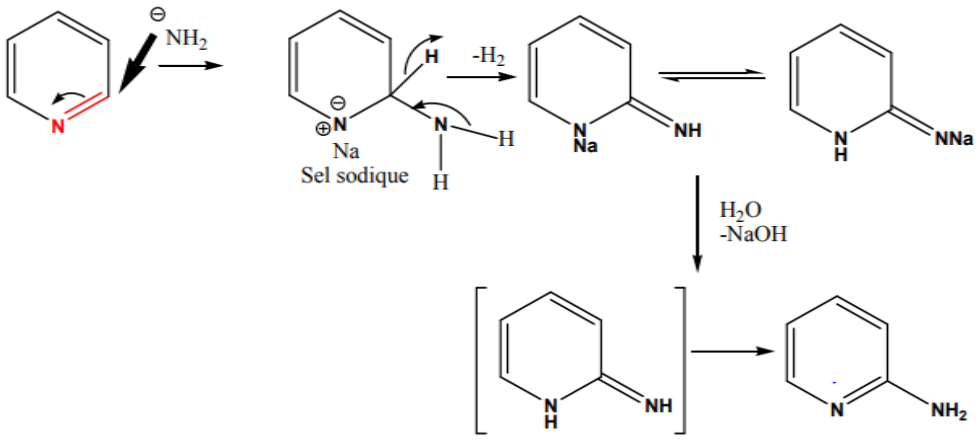
Nucleophilic substitutions are preferably made on positions 2 and 4 (and 6):





✔ **<u>Chichibabin's reaction: hot amination of pyridine in the presence of $NaNH_2$</u>**





✔ ***Addition reactions***

Dihydrogen in the presence of platinum as a catalyst or sodium in ethanol, reduce pyridine to piperidine.

✔ ***Oxidation***

✔ The pyridine cycle is highly resistant to oxidizing agents, but the side chains oxidize easily.

CHAPTER III: MEDICINES

III.1. Definition of pharmacology

Pharmacology makes it possible to analyse physicochemical characteristics and their influence on the biochemical and physiological effects and on the modes of action of drugs.

Pharmacology is divided into six disciplines:

- **The pharmacy**

It studies the physicochemical properties of drugs, their form of administration, their preparation and conditioning.

- **Pharmacognosy**

It studies the sources of the active ingredients.

- **Pharmacoconetics**

It studies the fate of chemical substances within living organisms.

- **Pharmacodynamics**

It allows the understanding of the mechanisms of action, the biochemical and physiological effects of drugs.

- **Clinical Pharmacology**

It is interested in the effects of drugs on human beings and the evaluation of their properties (efficacy, tolerability, pharmacokinetics, etc.).

- **Therapeutic**

It uses the drug in the treatment, prevention and diagnosis of diseases.

- **Toxicology**

Branch for gathering data on the harmful effects of drugs.

III.2. General information on medicinal products

III.2.1. Definition

A drug is a natural, semi-synthetic or synthetic entity administered for the purpose of treating or preventing a disease or function, it is also used for the establishment of a medical diagnosis.

It is a molecular or ionic species that binds to a molecular target through different types of intermolecular interactions, for electrostatic complementarity and can then interact through the establishment of one or more chemical bonds. A drug is often a carbon copy of a neurotransmitter or a natural hormone, whose action it is supposed to reproduce in the body.

The drug can affect the process of life by modifying or exploring physiological systems or disease states. Its binding to the target modifies its conformation, resulting in a cascade of cellular events, which are responsible for its beneficial and secondary effects.

For all drugs, the therapeutic effect results from a pharmacological action between the ligand and the receptor, schematized as follows:

$$\boldsymbol{M + R \leftrightarrow M - R \rightarrow Action\ pharmacodynamique \rightarrow Effet\ th\acute{e}rapeutique}$$

Where M is the molecule of the drug, R is the receptor; the pharmacological action is also called the intrinsic activity.

The action is therefore a biological consequence of the prior binding of the active molecule to a receptor.

III.2.2. Name of a medicinal product

1. **A chemical name** : developed by the International Union of Pure and Applied Chemistry IUPAC.

2. **INN**: nomenclature given by the medical health office, it allows the grouping of medicines belonging to the same pharmaceutical class.

Example: -floxacin for fluoroquinolones.

3. **A trade name, or "brand name".** Example: Doliprane

III.2.3. The different dosage forms of medicinal products

Galenic pharmacy is the science of changing a species into a quality and therapeutically effective drug. It manufactures it in forms appropriate to the administration (type and circumstances) and to the patient.

1. **Oral or nasal forms**

1.a. Liquid forms

They can be solutions, or emulsions.

- ✓ **The solutions**:

These are aqueous solutions, contained in vials.

Example: Diprosone: a skin lotion composed of betamethazone dipropionate, isopropyl alcohol, carbopol, sodium hydroxide and purified water.

- ✓ **Suspensions**

Suspensions form a two-phase system where fine solid particles are dispersed into a liquid in which they are insoluble.

To obtain a good consistency, thickeners such as polysaccharides are added.

Example: **Augmentin**

The excipients of the powder are: colloidal silica, flavorings, xanthan gum and compounds such as aspartame, mannitol and saccharin.

- ✓ **Syrups**

A thick and sweet viscous solution containing one or more active ingredients is called syrup, and they are usually prepared with sucrose. Antioxidants are added to prevent the phenomenon of decomposition by hydrolysis that leads to an acidic syrup. The antioxidants in question are: ascorbic acid or sodium metabisulfite Na2S2O5.

The formulation also includes colouring agents: differentiation or acceptance elements, flavourings and preservatives: chloroform, benzoic acid, bacteriostatic compounds such as sodium methyl parahydroxybenzoate (sodium methyl parahydroxybenzoate)

Example: bicalyptol: active ingredient: pholcodine, excipients: sucrose, ethanol, purified water, cineole: mint green dye.

1-b Solid Forms

- ✓ **Tablets**

They are obtained by agglomeration by compression of a volume of particles (powder or granule) of a mixture containing one or more active ingredients, an excipient and various additives such as: disaggregants, lubricants, dyes and flavourings.

The excipient's function is to make the tablet large enough to allow it to be swallowed more easily. Among the additives: starch, which has the role of accelerating the dissolution of the tablet.

- ✓ **The sugared almonds**:

They are composed of a core, the tablet covered with a coating.

The coating of the tablet is used to hide an unpleasant taste, to maintain gastro-resistance, to hide the color or to have a commercial color.

- ✓ **Capsules**

These are solid preparations, containing a unit dose of active ingredients.

1.c. Parenteral forms

This is the direct introduction of the drug into the internal environment.

- ✓ **Aerosols**: An aerosol is either a gas or a vapor.

Example: **Bricanyl**: used as a bronchodilator in case of asthma attack.

- ✓ **Suppositories**

These are solid single-dose preparations where one or more active ingredients are dispersed or dissolved in an excipient such as glycerin or polyethylene glycol.

Example: active ingredient: potassium sulfogaiacolate; Perfume and disinfectant: Cineole

- ✓ **Eggs**

These are solid preparations administered vaginally for a local therapeutic effect. The excipient used in suppositories is composed of gelatin, water, and glycerin.

1 .d. Topical Forms

Like dermatological preparations. A distinction is made between:

- ✓ **External solutions**

These are disinfectant liquids; anti-septicles (containing antimicrobial substances)

Example: Eosine in aqueous solution containing eosin disodium diluted in purified H2O.

- ✓ **The ointments**

The molecule penetrates the skin layer for topical action or passes through it for a systematic effect.

- ✓ **Eye drops**

The active substance is mainly absorbed transcorneally or transconjunctival.

III.2.4. Drug excipients or adjuvants

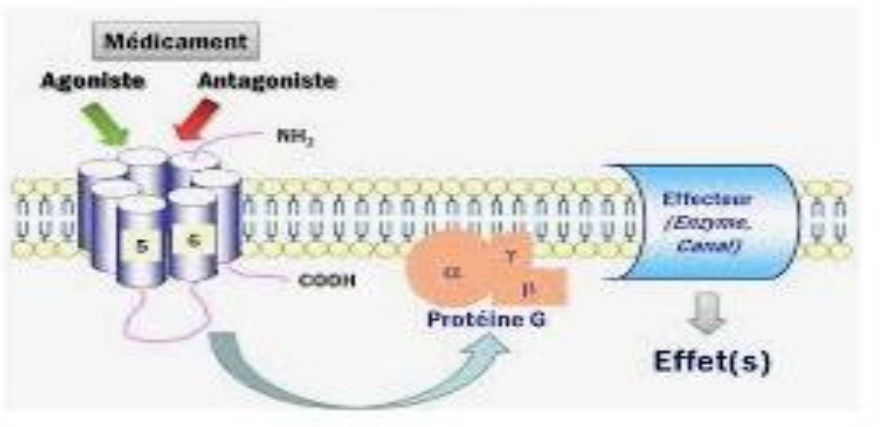
Excipients are inactive substances, characterized by their inertia. These are hydrocarbons and silicones, water, alcohols, glycols, sugars, proteins, surfactants, etc.

III.3. Target of Medicinal Products

III.3.1. Receivers

These are macromolecules present on the cell membrane or in the cytoplasm. When binding to a ligand, receptors regulate various cellular biochemical processes, such as ion conductance, protein phosphorylation, DNA transcription, and enzyme activity. Drug and receptor binding can be reversible or irreversible.

a) G protein-coupled receptors



They do not have a direct effect on ion channels or enzymes. In fact, they activate an informative protein called the G protein.

Structure

The 7-TM receptors are embedded in the plasma membrane. The protein chain folds back on itself seven times across the plasma membrane, hence the term 7-TM.

Each of the 7 transmembrane segments is hydrophobic and helical in shape. Folding seven times reveals three extracellular loops and three other intracellular loops. The N-terminal chain points to the outer side of the cell and has a length varying according to the nature of the receptor, while the C-terminal end is inside the cell.

In this family, we find the best known receptors in pharmaceutical chemistry, such as dopaminergic, cholinergic and adrenergic receptors.

The sequence of events from the combination of a ligand (the chemical messenger) to its receptor and the final activation of the target enzyme is quite long.

Interaction of the 7-TM ligand-receptor complex with G proteins: the process occurs as follows:

Anchoring the ligand to its receptor

Binding of a G protein to the ligand-receptor complex. The G proteins carry the message received by the receiver to the next target in the cascade of events allowing the signal to be transducted.

First, the neurotransmitter or hormone attaches to its receptor with a modification of its conformation, allowing the G protein specific to it to recognize it and associate with it. This process of association induces a conformational change in the latter .

b) Receptors that control ion channels

They are transmembrane proteins responsible for transmembrane ion balances involved in the transmission of signals between neurons or muscle cells.

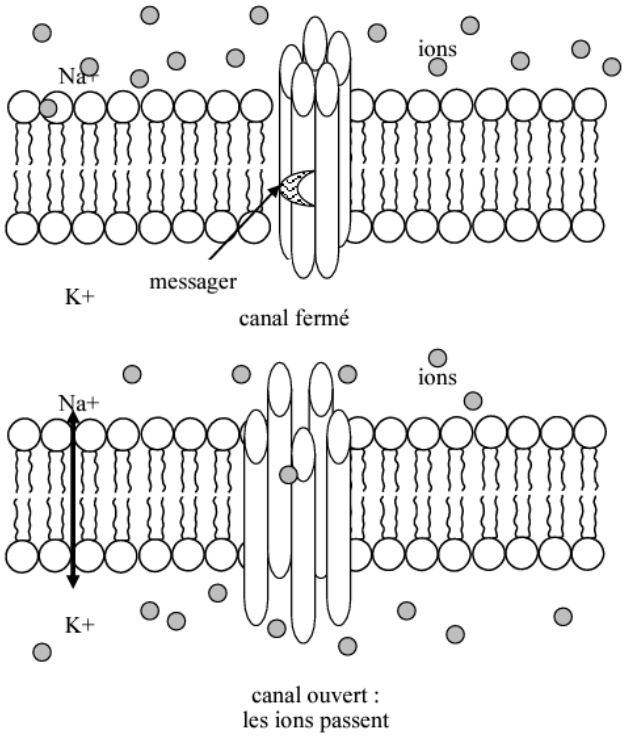
The molecules governing ion transfer are of two types: ion transporters, in this case, nicotinic and acethylcholine receptors and receptors regulating ion channels, allowing the selective passage of ions, we distinguish, we distinguish, cation channels for Na+, K^{+}, Ca^{2+} ions which generally open for excitation purposes.

The receptors that regulate ion channels are located somewhere on one of the five protein structures that the said channel is made of. Such receptors are said to cause the ion channel to open as a result of ligand attachment. This type of channel contains various glycoproteins that cross the plasma membrane from one side to the other.

When a ligand attaches to a receptor, the receptor changes its conformation, which has the effect of giving a strong impulse to the entire protein complex, causing the ion channel to open.

Example of cation channel receptors: 5-HT3 receptors.

Example of anion channel receptors: GABAA



- ***Structure and function of 4-TM ion channel receptors***

Among the receptors of the 4-TM ion channels are the nicotinic acetylcholine receptor, the serotonin receptor (5-HT3), the glycine receptor and the GABA receptor. The ion channel that is under the control of the nicotinic acetylcholine receptor comprises four different types of subunits (2* α, β, γ and δ) on the other hand the ion channel that is controlled by the glycine receptor consists of only two different types (3* α, 2*β).

- ***Structure and function of 3-TM ion channel receptors***

The ion channels that function under the control of such receptors are also made up of five protein units. Calcium channels are examples of this type of ion channel and are of particular importance in memory and learning processes.

- ***Structure and function of 2-TM ion channel receptors***

Type 2-TM ion channels consist of five protein subunits, each containing two transmembrane segments. The N-terminal and C-terminal chains are both located inside

the cell. The protein is positioned outside the cell and includes a hydrophobic region that is buried in the outer part of the plasma membrane. Such a channel is controlled by adenosine triphosphate ATP.

c) Intracellular receptors

Their location is the cytoplasm or cell nucleus. To reach them, chemical messengers must cross the plasma membrane.

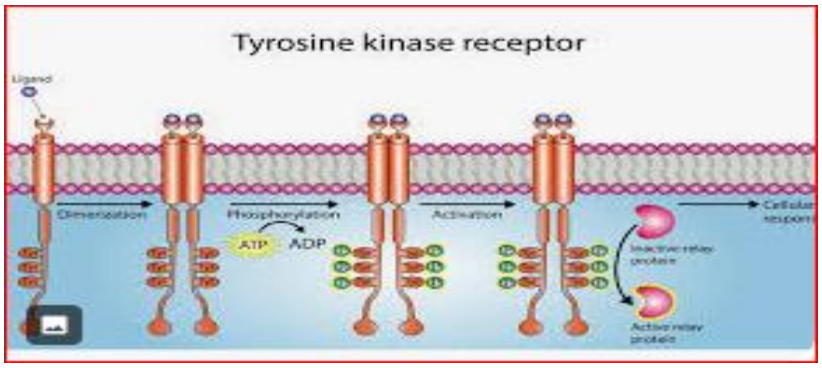
Exp: Steroid hormone receptors

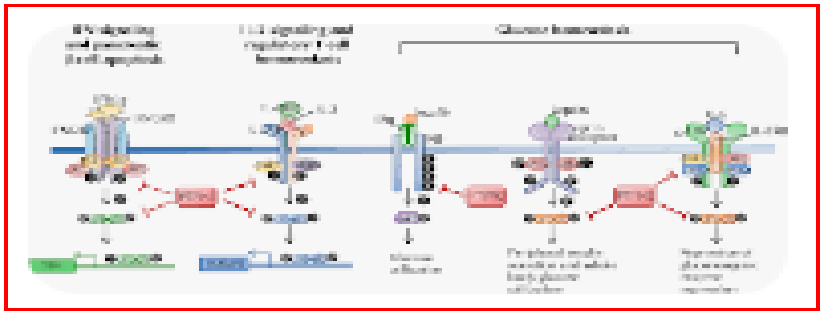
Steroids: hydrophobic molecules capable of crossing the membrane to reach their receptors in the cytoplasm. These receptors consist of a simple protein presenting, at the C-terminus, and a binding site for DNA in its central part containing two loops, each made of about 15 amino acid residues; tied together by cysteine residues surrounding a zinc atom. When a steroid combines with its receptor, the receptor changes its conformation, causing the steroid-receptor complex to diemerize. The dimer then travels to the nuclear membrane through which it passes and within the nucleus attaches to an acceptor site adjacent to the cellular DNA. This binding triggers the transcription and synthesis of mRNA which will use code for the synthesis of new receptors and other enzymes.

Example: Estrogen receptors: an intracellular steroid receptor that serves as a target for an anti-cancer drug: Tamoxifen (Nolvadex), used in breast cancer.

d) Receptor-enzymes

They are usually monomeric and have a single transmembrane helix. The receptor includes a site with enzymatic activity, such as a tyrosine kinase or tyrosine phosphatase activity as schematized below:





III.5. Mechanism of action of medicinal products. Drug-receptor interactions.

III.5.1. Mechanisms of action of medicinal products

❖ ***Drug/target complementarity***

To obtain a good therapeutic drug effect, two characteristics are necessary:

- ✓ Structural complementarity
- ✓ Electrostatic complementarity

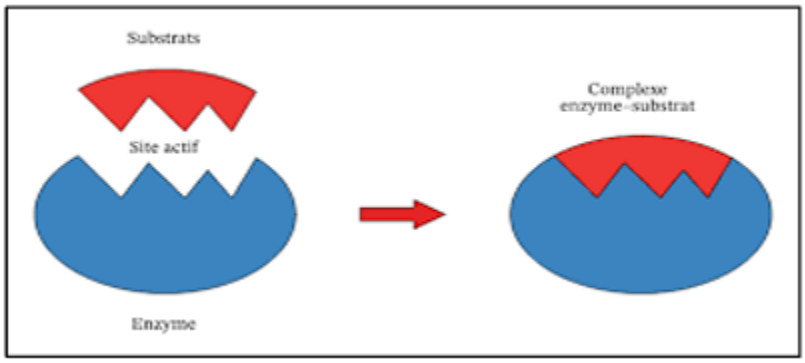
Two fundamental concepts are important: the concept of nucleophilic-electrophilic reactions and that of key-lock.

In molecular chemistry, molecules are compact and the various functional groups establish covalent bonds with each other.

On the contrary, in supramolecules, the receptor/substrate bond is not covalent, but involves several kinds of interactions.

In order for molecules to recognize each other, they must adjust like a key and lock.

The living world and the action of drugs are based on this concept, as shown in the figure below:



III.5.2 Drug/Target Binding

When a drug hits a target, strong (covalent) or weak (Van Der Waals interactions) bonds can take place.

The formation of chemical bonds is the basis of drug/receptor interactions.

- **Simple covalent bonds**: rarely formed between L and R, are strong interactions with an energy of the order of -150 to -400 kJ/mol; they are irreversible.
- **Ionic or electrostatic interactions**: have formation energies of the order of -20 to -50 kJ/mol. These bonds remain effective at relatively greater distances than for covalent bonds.
- **The ion-dipole and dipole-dipole** interactions: have formation energies of the order of -5 to -30 kJ/mol. They are established between charges of well-aligned opposing signs.
- **Hydrogen bonds**: in the range of -15 to -25 kJ/mol, are dipole-dipole interactions between a hydrogen atom and another Y atom with a lone pair.

They are particularly present in DNA, where they contribute to the formation of the helix-like structure.

- **Charge transfer forces**: have forming energies of the order of -5 to -30 kJ/mol. These interactions are established between an electro-donor molecule or group and an electro-acceptor group.
- **Hydrophobic interactions**: these are the forces that result from the interactions of non-polar fragments of a drug and a receptor.
- **The Van-der-Waals interactions**: have formation energies of the order of -3 kJ/mol.

If a temporary action is desired, a drug with a weak binding to its receptor is desired.

Example: an antidepressant or an analgesic.

If, on the other hand, a longer-term action is desired, the chosen ligand must form an irreversible complex.

Example: a chemotherapeutic agent used against a tumor must be able to act for a long time.

III.6. Quantitative aspect of the drug-receptor interaction

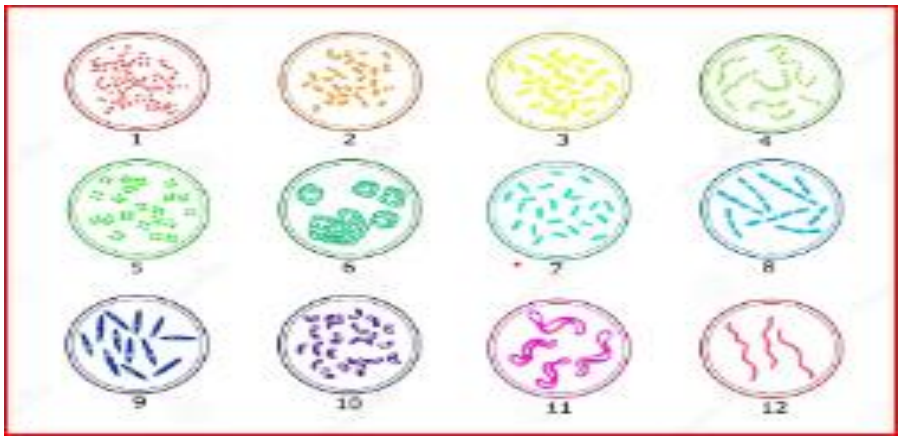
The quantitative evaluation of therapeutic effects is based on two main characteristics:

- **Affinity**: this is the power of physico-chemical interaction between the drug and its target giving rise to the formation of a lower energy complex.
- **Selectivity**: no drug is specific to a biological target: this is the binding competition between a drug and different receptors.

IV.1. ANTIBIOTICS

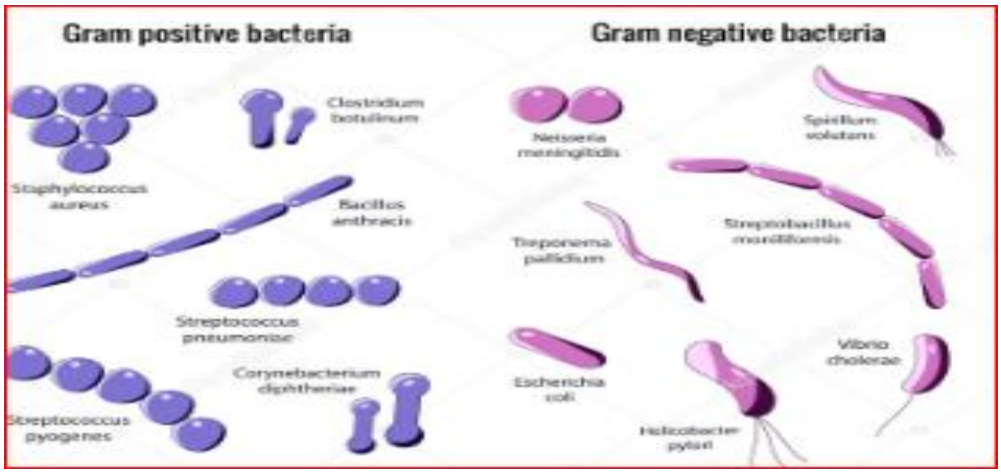
IV.1.1. Definition

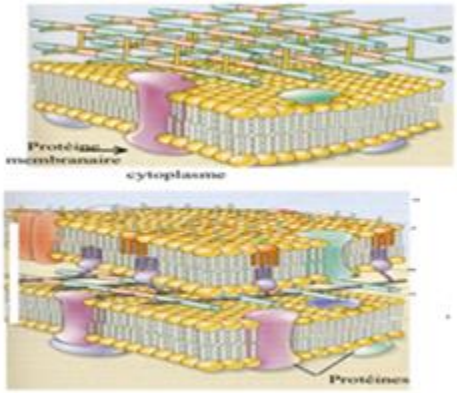
The bacteria schematized in the figure:



are single-celled organisms measuring between 1 and 10 microns (µm). They have a ***nuclear apparatus*** formed of DNA in a double helix, coiled in the ***cytoplasm*** thanks to the action of topoisomerases, which support heredity: ***chromosome*** about 1 mm long and 3 to 5 nanometers wide and plasmids (DNA, and extra-chromosomes), a ***cytoplasmic membrane,*** and a wall of rigid structure and polymeric nature constituting the outer envelope of bacteria.

Bacteria are divided into two types: gram-positive and gram-negative as shown in the figure below:





Bacterial wall

IV.1.2. Definition of antibiotics

They can be natural, synthetic or semi-synthetic molecules. These are molecules capable of destroying or blocking the growth of bacteria.

Antibiotics prevent the proliferation of bacteria, they are called *bacteriostatic antibiotics*, if they destroy them completely they are *bactericidal antibiotics*.

IV.1.3. Criteria for the classification of antibiotics

- Origin;

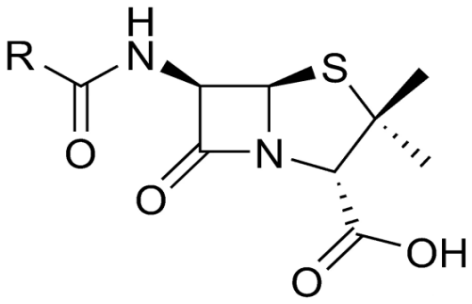
- Mode of action;
- Spectrum of activity;
- Chemical nature.

VI.1.4. Mode of action of antibiotics

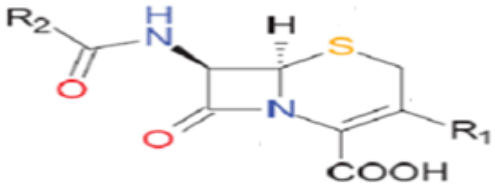
They focus on their main targets, namely; the bacterial wall, the cytoplasmic membrane by blocking their development.

IV.1.5. Main chemical structures of antibiotics

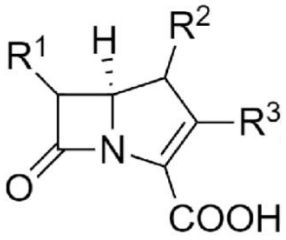
- ***Penicillins***



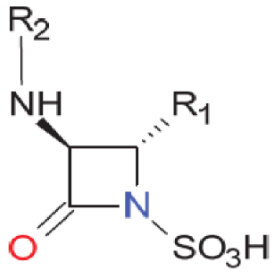
- ***Cephalosporins*** :



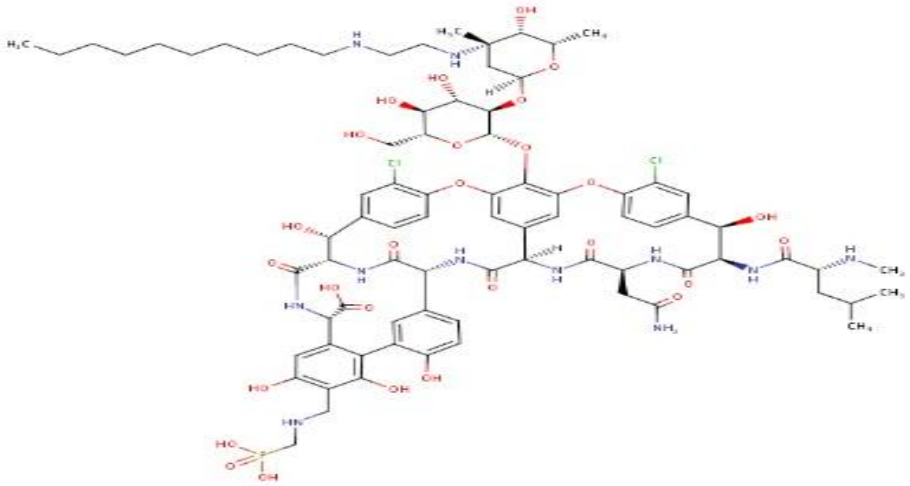
- ***Carbapenems*** :



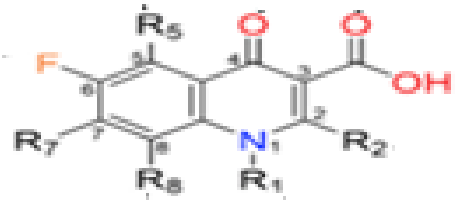
- ***Monobactams*** :



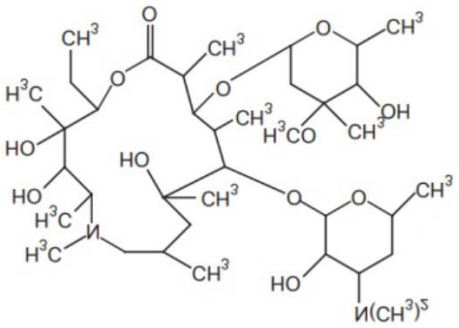
- ***Glycopeptides***:



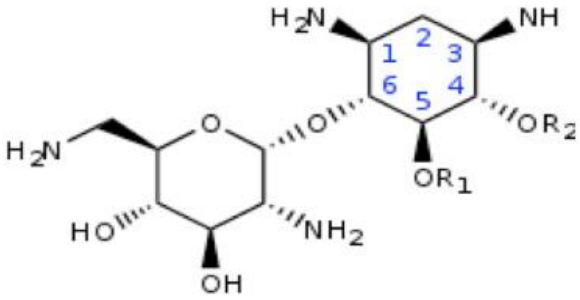
- ***Fluoroquinolones:***



- ***Macrolides:***



➢ ***Aminosides :***

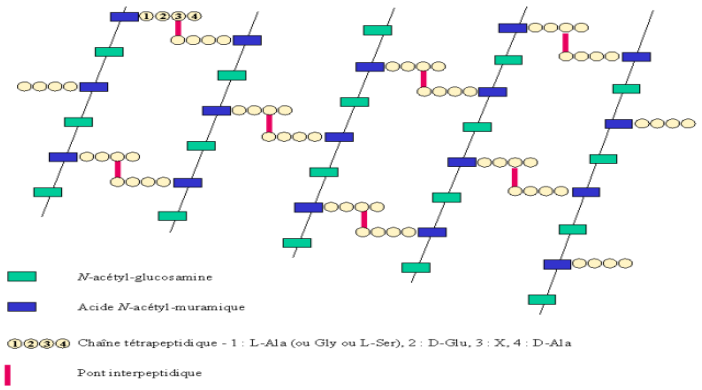


IV.1.6. Antibiotics active on the bacterial wall

A distinction is made between:

- Beta-lactam
- Les Glycopeptides
- Fosfomycin

IV.1.7.1. Construction process of this wall : built using bricks called peptidoglycans. PBPs will create a kind of cement between the bricks (peptidoglycans).

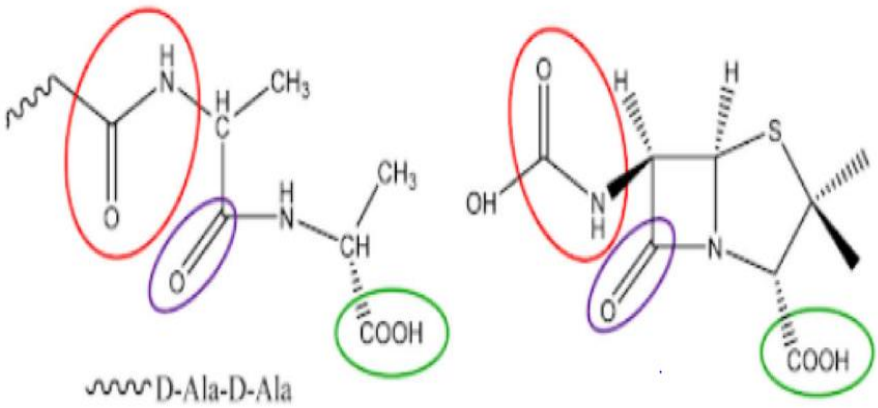


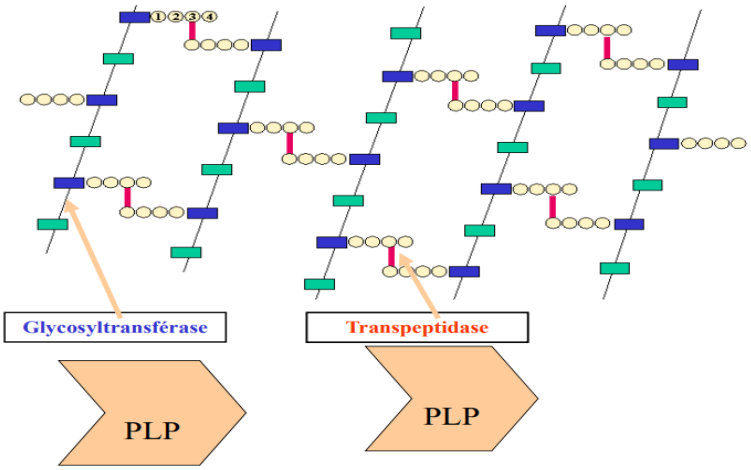
IV.1.7.2. Mode of action of beta-lactam

The target of beta-lactam at the bacterial wall is an essential constituent of the bacterium: peptidoglycan.

The mode of action of beta-lactam is based on the inhibition of cell wall synthesis. This class of drugs includes: penicillins, cephalosporins, monobactams... acts through their β-lactam nucleus.

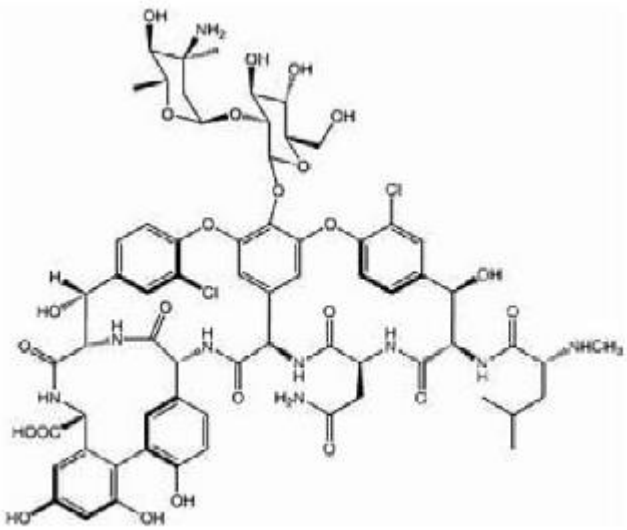
Beta-lactam bind covalently to PBPs and inhibit their function (inhibition of the formation of cyclic penta bridges responsible for the rigid structure of the wall, which causes the arrest of bacterial growth.



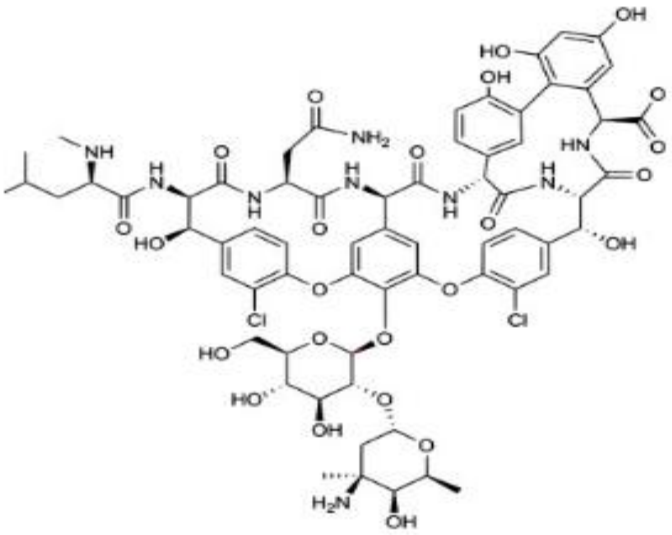


IV.1.7.3. Action on the bacterial wall

Glycopeptides such as vancomycin and teicoplanin, of chemical structures below, act as deactericids and inhibit the synthesis of the bacterial wall. They bind to the pipeptide D-Ala-D-Al, block the elongation of the peptidoglycan and thus disrupt the 1st steps of peptidoglycan synthesis.



Chemical structure of Vancomycin

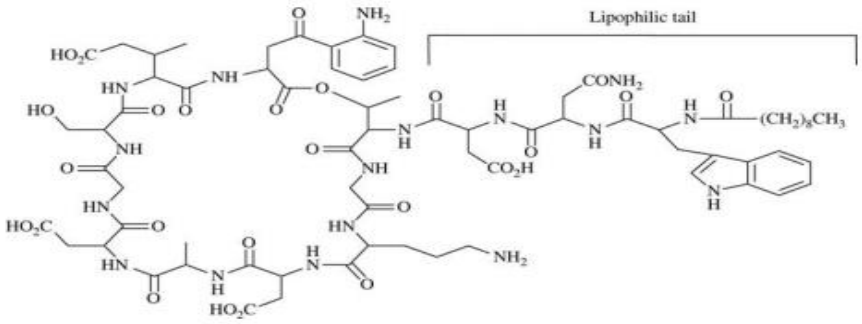


Chemical structure of Teicoplanin

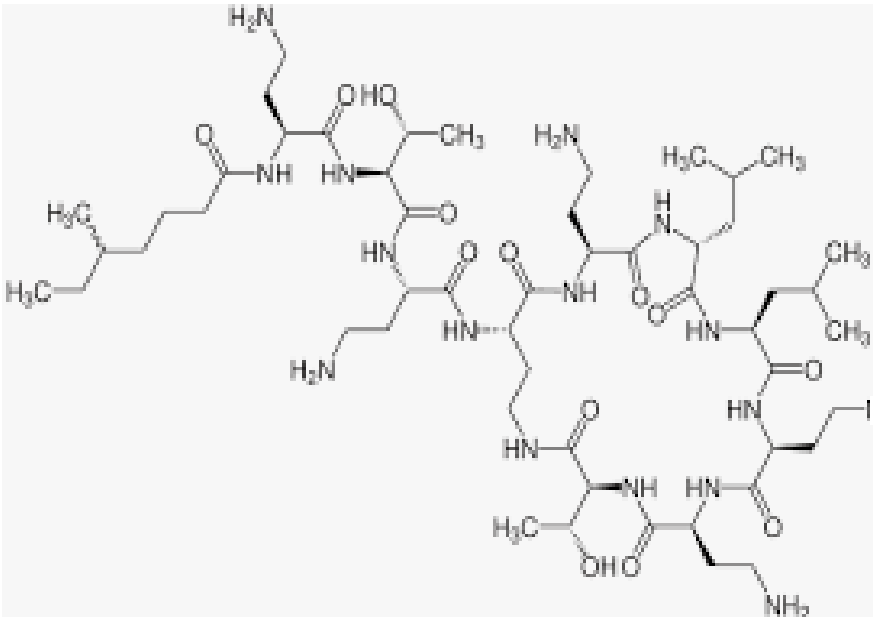
IV.1.8. Antibiotics active on cell membranes

Antibiotics acting on the cell membrane: polypeptides (such as polymyxins: polymexin B or colistin) are narrow-spectrum bactericides. They have a hydrophobic end, through which they reach the membrane. They represent a kind of axe that will shred the outer and plasma membrane, causing the death of the cell. A distinction is made between:

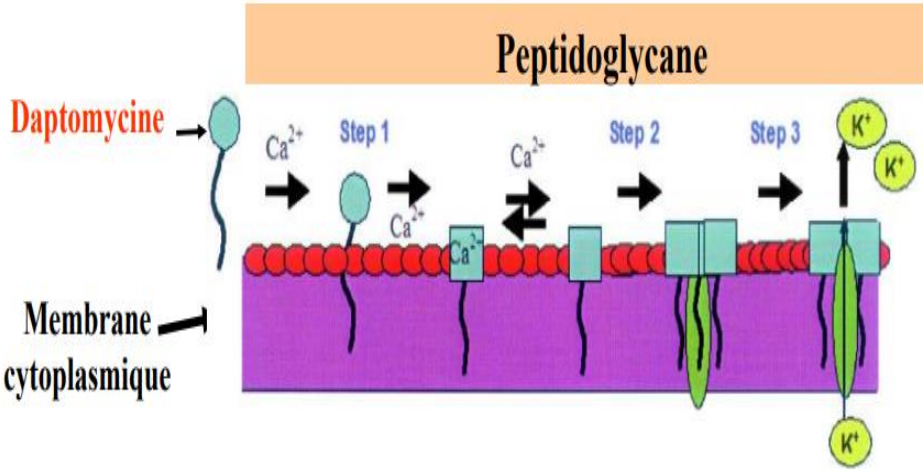
Lipopeptides such as daptomycin and collistin, of chemical structures below, have a mechanism analogous to that of cationic surfactants, they bind to the cytoplasmic membrane by cation exchange, leading to dysfunction of macromolecular synthesis pathways.



Chemical structure of Damtomycin



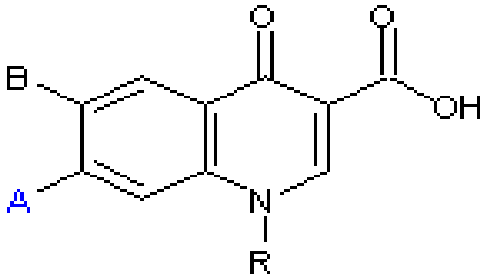
Chemical Structure of Collistin



Mechanism of action of Daptomycin

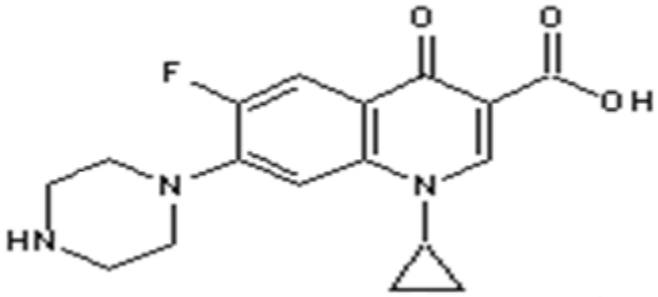
IV.1.9. Antibiotics active on nucleic acid synthesis

This class includes Quinolones and fluoroquinolones, they all have in common a piperazine ring



If B is a fluorine, it is a fluoroquinolone

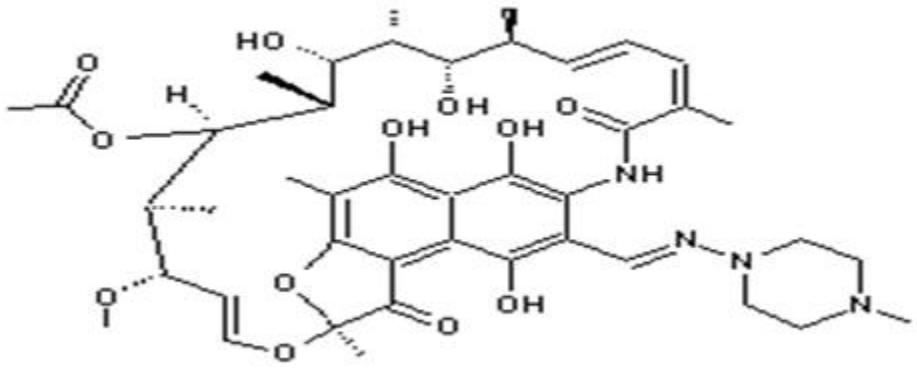
IV.1.9.1. Antibiotics acting on nucleosides by inhibiting the synthesis of nucleic acids such as fluoroquinolones (Ciprofloxacin: see chemical structure below)



<u>Mode of action</u>

Quinolones enter the cytoplasm. Their target is DNA gyrase. They inhibit DNA transcription and replication by forming a DNA-gyrase-quinolone complex, leading to the rapid death of the bacteria.

Other categories of antibiotics that act by inhibiting RNA polymerase synthesis and therefore no RNA synthesis such as rifamycins (e.g. rifampicin shown in the figure below).

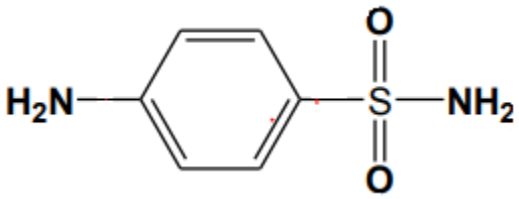


IV.1.10. Mechanism of bacterial neutralization and inhibition of metabolic pathways

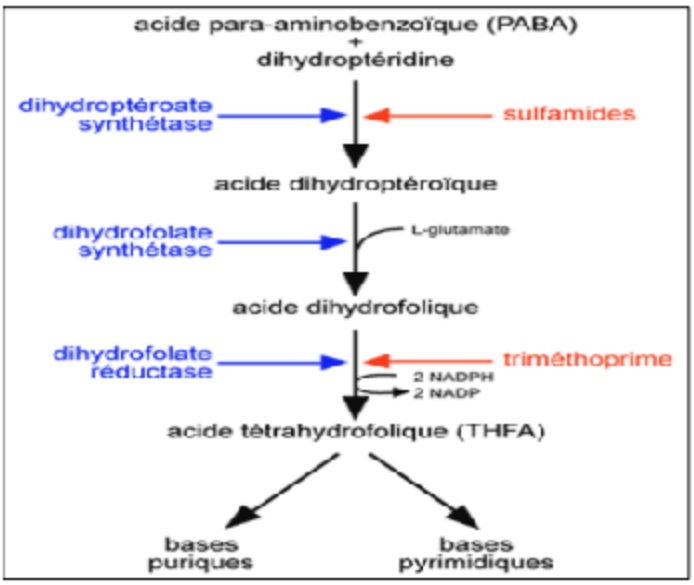
Folic acid is essential for the production of purine and pyrimidine bases. Their absence means that there are no nucleosides. However, there are antibiotics that inhibit the synthesis of folic acid such as sulfonamides and trimethroprims that inhibit the enzyme that allows the synthesis of dihydrofolic or tetrahydrofolic acid

The para Amino benzoic acid combined with dihydropteroic acid allows, thanks to a series of enzymes, the synthesis of dihydro and tetrahydrofolic acids, to give the purine and pyrimidine bases.

Sulfonamides of chemical structure:



act according to the organizational chart:



Mechanisms of action of sulfonamides

IV.1.11. Antibiotics active on protein synthesis (Action on the ribosome)

- **Aminoglycosides**

Mode of action of aminoglycosides

The bacterial ribosome is composed of two subunits, S50 and S30. These ribosomes decode the information in the RNA, allowing the synthesis of protein amino acids. Some ATBs will act by inhibiting protein synthesis by acting either on 30S subunits such as aminoglycosides which are bacteriocideal.

The aminoglycosides will put themselves on the 30S and make the synthesis of amino acids erroneous, so there will be a lot of error during the production of amino acids. The amino acids that normally allow the construction of the plasma membrane will be damaged, which will make the cell membrane permeable and therefore lead to its death.

Tetracyclines will have a bacteriostatic effect, they directly block the 30S subunit and will stop the formation of amino acids.

Other antibiotics act on 50S such as macrolides, lincosamides and chlorophhenicols, they have a bacteriostatic effect because they block the 50S subunit and therefore no amino acid formation.

IV.2. ANTIVIRALS

IV.2.1. Introduction

Viruses are intracellular parasites composed of genetic material (nucleic acid) enveloped in a protein capsid, often surrounded by a double layer of phospholipids containing proteins that are inserted. Lacking their own metabolism, they replicate only through infected host cells.

Viruses use the cellular machinery to reproduce, which means that antivirals must target and block viral multiplication without interfering with the synthesis of healthy cell components.

IV.2.2. Viral multiplication

Viral multiplication involves several steps:

1. Attachment of the virus to the target cell**;**

2. Penetration inside the cell;

3. Disruption of cellular metabolism through the capsid and genetic material of the virus;

4.

has. Nucleic acid synthesis by DNA and RNA reproduction;

b. Use of viral enzymes in the multiplication of the virus;

5. Maturation by release of daughter viruses.

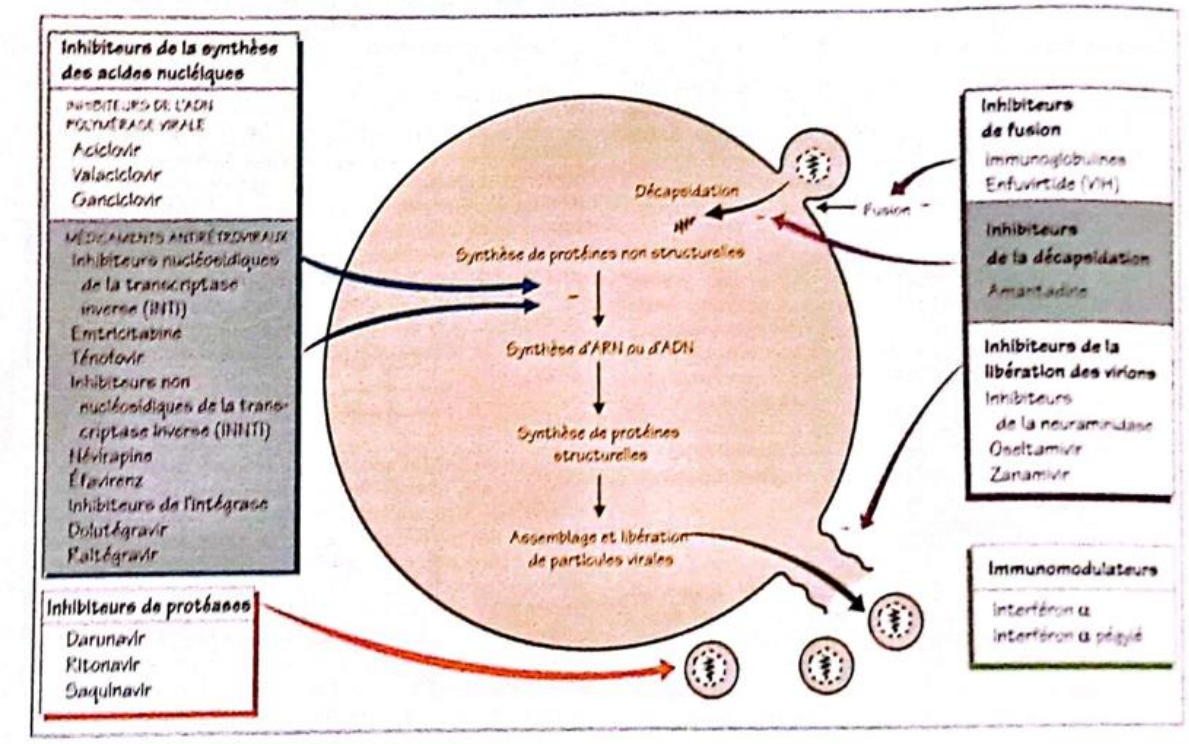
IV.2.3. Classification of antivirals

Antivirals are classified according to their therapeutic target, distinguishing:

- Antivirals against the Herpes group virus;
- Antivirals against the hepatitis virus;
- Antivirals against influenza viruses;
- Antivirals against the HIV virus (antiretrovirals).

IV.2.4. Modes of action of antivirals

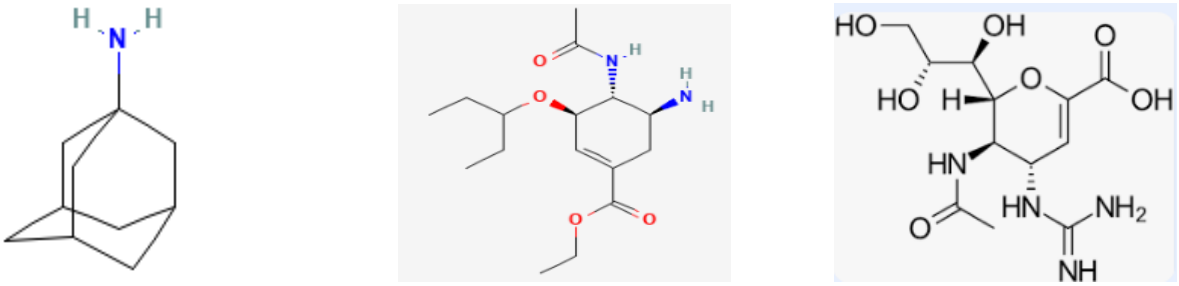
The multiplication phases of the viruses targeted by antivirals are: penetration and replication.



Antiviral drugs

❖ **<u>Action at the penetration level</u>**

Amantadine, an antiviral used to fight the influenza A virus**,** inhibits the proton pump and prevents the decapsidation of virions, thus blocking the entry of the viral genome into the cell. **<u>Oseltamivir</u>** and **<u>zanamivir</u>** mimic the effect of **<u>neuraminic acid</u>**, and act as selective inhibitors of neuraminidases, surface glycoproteins found on virions. The virus enters uninfected cells through an enzymatic reaction, and spreads and releases viral particles. Inhibition of this enzyme reduces the replication of influenza A and B viruses.



Chemical structure of Amantidine, oseltamivir and zanamivir

❖ **Action at the replication level**

Antivirals (nucleoside and nucleotic analogues) acting on herpes viruses, HBV and HIV inhibit the action of viral DNA polymerases in different ways: by competing with the natural substrate of the enzyme, by blocking the active site by steric crowding, by integrating the antiviral into the DNA chain being formed, or by preventing the elongation of this chain.

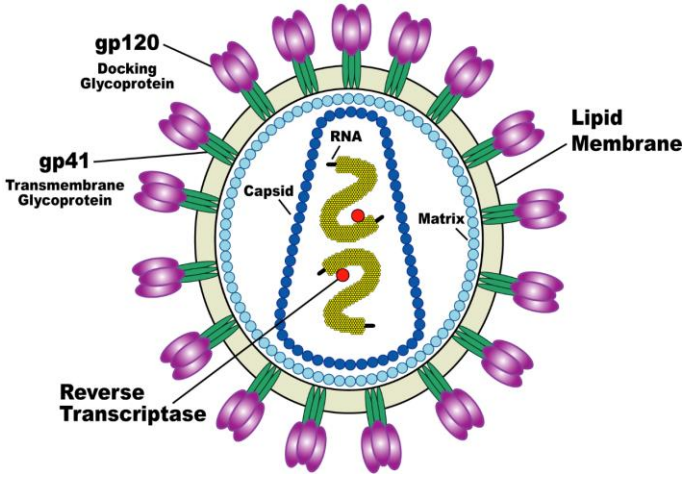
Exp: Aciclovir and Ganciclovir, nucleoside analogues of guanosine, active against herpes viruses.

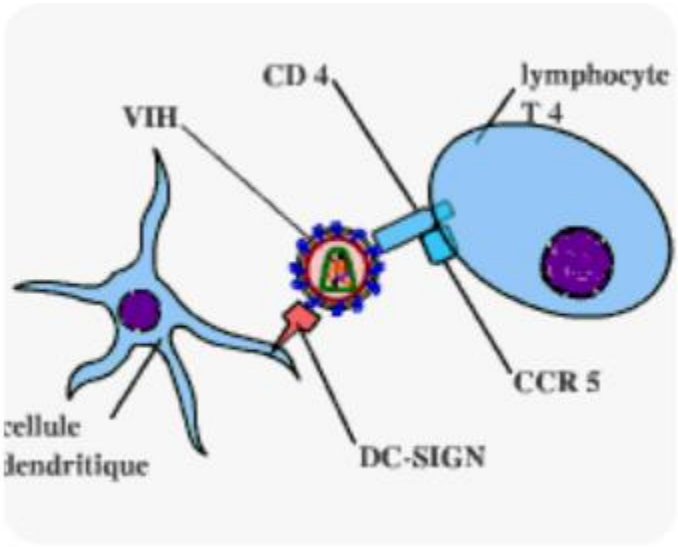
IV.2.5. Antivirals

IV.2.5.1. Antiretrovirals

HIV is the human immunodeficiency virus because it causes the infected person to have a deficiency in their immunity, and they become unable to defend themselves well against infectious agents.

This virus has a lipid envelope, a matrix and a capsid. On its envelope, there are important viral proteins, which will be the targets of drugs gp120 and gp41. Its genetic material consists of RNA with the important enzyme that will also be the target of drugs "reverse transcriptase"

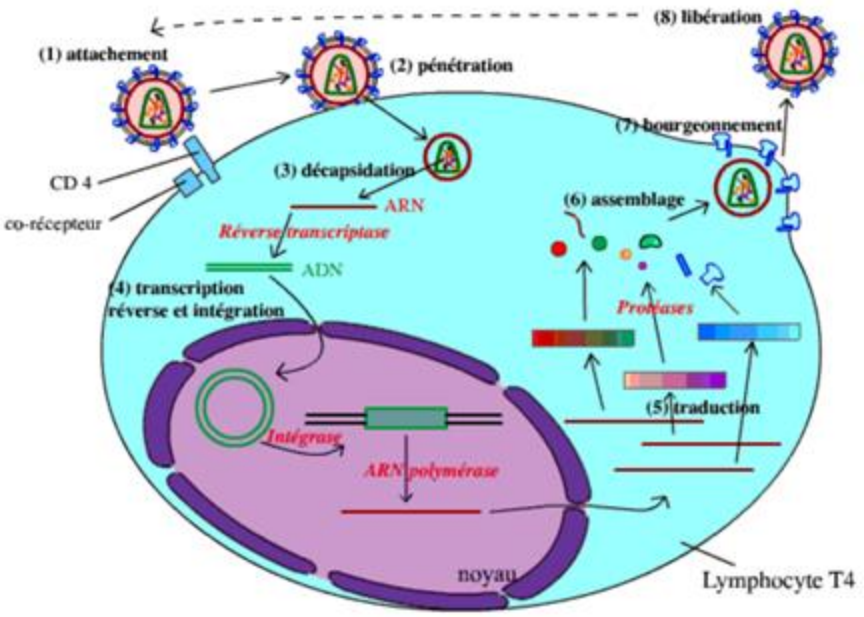




- ***HIV viral cycle***

HIV begins its penetration by attaching to the target cell (CD4 receptor) through its viral protein gp120, which undergoes a conformational change, allowing it to attach to the membrane co-receptor CCR5 or CXCR4. The viral membranes fuse thanks to the gp41 envelope protein.

HIV releases RNA, the genetic material of the virus, into the host cell and replicates, by converting its RNA into DNA. This process is made possible by an enzyme called "reverse transcriptase" produced by the virus itself.



The HIV cycle

Antivirals used in the treatment of HIV infections target various aspects of the virus's life cycle to block its replication. These treatments are designed to intervene at different stages of the viral cycle, thus hindering the ability of HIV to multiply and spread in the body.

- **Fusion inhibitors**: as *ENFUVIRTIDE* inhibits the fusion of the virus in

The target cell by binding to the GP 41 protein, so the virus cannot initiate its penetration into the host cell.

MARAVIROC inhibits the CCR5 co-receptor and blocks the entry of the virus (anti-CCR5 inhibitor)

- **Nucleoside and nucleotide inhibitors**: target the enzyme transcriptase

reverse by competing with the nucleotides to be incorporated into the DNA and block the reverse transcriptase by a chain terminator effect, which stops replication.

- **Nucleoside inhibitors** : *EMTRICITABINE, ZIDOVUDINE, STAXUDINE*
- **Nucleotide inhibitors** : *TENOFOVIR*
- **Integrase inhibitors**

By blocking this enzyme, they prevent the integration of HIV genetic material into that of the host cell to prevent the production of new viral particles. These inhibitors all have the suffix TEGRAVIR

- **Protease inhibitors**

In HIV, mRNAs are translated into inert polyproteins. These are then converted into essential mature proteins such as reverse transcriptase, thanks to a specific viral protease. HIV protease inhibitors prevent the maturation of virions, resulting in the production of non-infectious particles. These inhibitors are used in combination with other medications

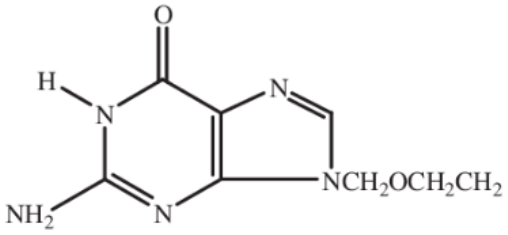
Exp: *RITONAVIR, DARUNAVIR* and *LOPINAVIR.*

IV.2.5.2. ANTIVIRALS ACTING ON THE HERPES GROUP VIRUS

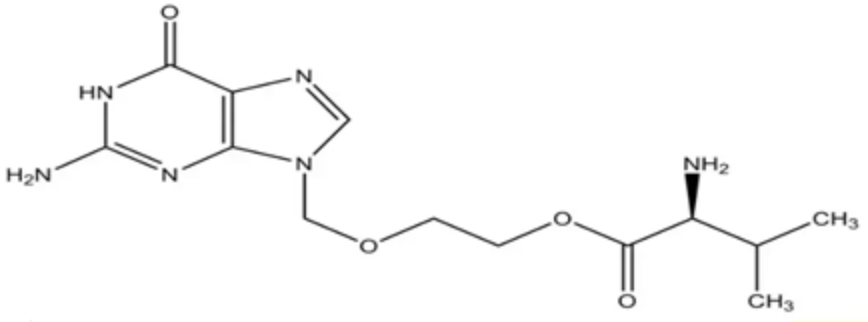
Leader: Aciclovir

It is a nucleoside derived from guanine, more precisely analogous to open-ring guanosine. Because of this structural analogy, it blocks the synthesis of viral DNA, preventing viral replication. When it enters the cell, it undergoes triphosphorylation because the active form is the triphosphate form.

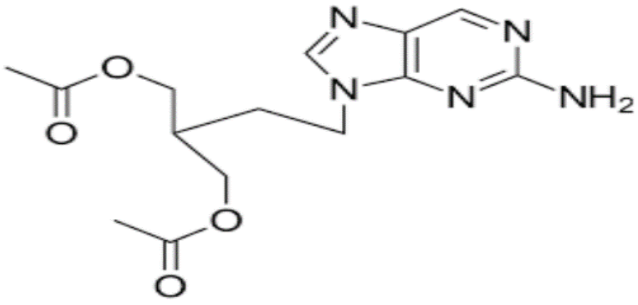
The 1st phosphorylation depends on the viral thymidine kinase, an enzyme provided by the virus. The other two phosphorylations are carried out by the host's cellular enzymes, in which case the active triphosphorus ACICLOVIR is obtained. Once active, ACICLOVIR inhibits viral DNA polymerase to interrupt synthesis and replication. Its affinity for viral DNA polymerase is 100 times greater than that of the cellular host.



VALACICLOVIR: is a prodrug of ACICLOVIR. It arrives in the body in this esterified form of ACICLOVIR, its mechanism of action is the same as that of ACICLOVIR.

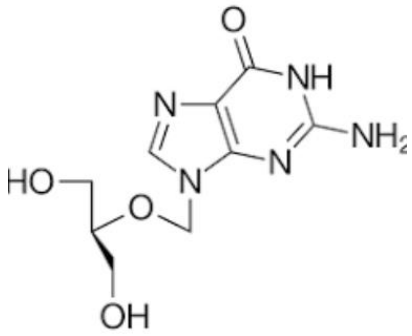


FAMCICLOVIR: is metabolized to the active PENICICLOVIR, a structural analogue of ACICLOVIR. It therefore has the same mechanism as ACICLOVIR.

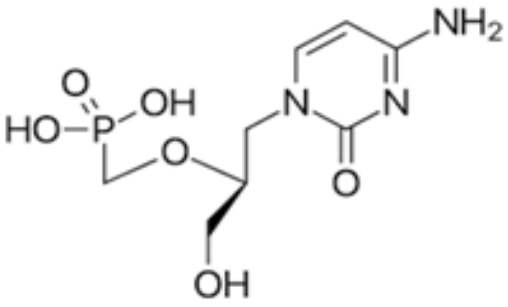


GANCICLOVIR: is like ACICLOVIR analogous to guanosine with an open osidic ring with the presence of an alcohol chain that differentiates them.

It requires intracellular triphosphorylation to be active with the same mechanism of action as ACICLOVIR except the 1st phosphorylation can be carried out using several enzymes and not only viral TK found in herpes and shingles viruses but also viral phosphotransferase and cellular TK.



CIDOFOVIR: is a nucleotide analogue of cytidine. It has a phosphate that requires only two intracellular phosphorylations to form the active CIDOFOVIR, which is an analogue of cytidine triphosphate. It acts by a chain terminator effect, as soon as it inserts itself into the nucleotide chain, it will cause the DNA synthesis to stop.



IV.2.5.3. ANTIVIRALS AGAINST HEPATITIS VIRUSES

They are based on 2 main principles:

- **Immunomodulation with interferon-alpha**
- **Inhibition of viral replication**

A distinction is made between:

- Nucleotide analogues
- Nucleotide analogues
- Protease inhibitors
- NS5B polymerase inhibitors
- NS5A and NS5A inhibitor

There are 5 liver viruses: A, B, C, D and E.

The first 3 antivirals act on hepatitis B, the last 3 in addition to interferon

act on hepatitis C.

IV.2.5.4. INTERFERONS

These are protective glycoproteins that our body synthesizes in response to a viral infection. Exhibiting a broad spectrum of action, they prevent viral replication, which triggers the production of enzymes that inhibit the translation of viral mRNA into viral proteins.

Interferon-alpha, a physiological molecule combines non-specific immunomodulatory antiviral properties, and is effective in many pathologies, including chronic myeloid leukemia, Kaposi's sarcoma, and chronic hepatitis B and C.

IV.2.6. Inhibition of viral replication

1. **Nucleoside and nucleotide analogues**

- **Nucleosides:** LAMIVUDINE, TELBIVUDINE, ENTECAVIR, RIBAVIRIN
- **Nuleotides:** ADEFOVIR DIPIVOXIL, TENOFOVIR DISOPROXIL

Nuleoside and nucleotide inhibitors are incorporated into the viral DNA and cause the DNA chain to be terminated. They all act on HCV.

2. **Protein inhibitors**

These inhibitors inhibit the proteins of viral replication: these are NS5A inhibitors, non-structural proteins specific to HCV.

3. **NS5B polymerase inhibitors**

It is an HCV-dependent RNA polymerase. These inhibitors prevent the virus from having good viral replication and spreading.

IV.4. ANTIHISTAMINES

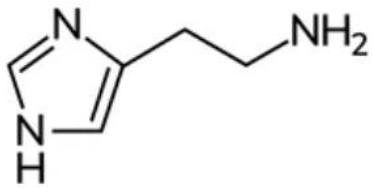
IV.4.1. Introduction

Allergy is an immunological pathology, characterized by the release of histamine.

IV.4.2. Definition of Histamine

Histamine or β-imidazol-ethylamine of chemical structure below, includes an imidazole ring that can exist in two tautomeric forms. A two-carbon chain is grafted onto imidazole, which has a α-amino group at its end. The pka of this amino group is 9.8, which means that at a plasma pH of 7.4, the histamine side chain is ionized. As for the pka of imidazole, it is equal to 5.74, it is in the non-ionized state at ph=7.4.

Histamine
$C_5H_9N_3$



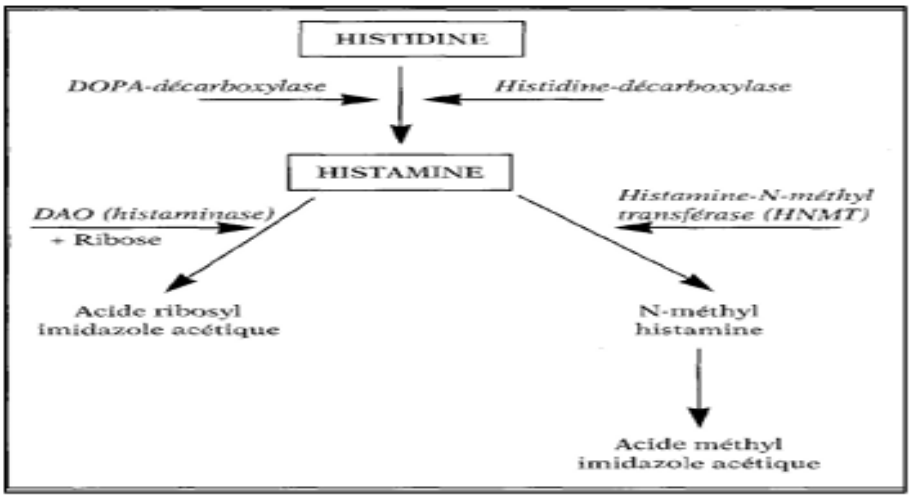
IV.4.3. Chemical structure and biosynthesis

Histamine is synthesized in the body according to the reaction test:

Histamine is widely distributed in lung tissue, skin tissue, liver tissue, in some neurons in the brain, in the gastric mucosa. It is responsible for several vascular and

glandular reactions. It stimulates the state of volence through its role as a neurotransmitter in the central nervous system. It also causes the triggering of nociceptive impulses (pain, pruritus) and in the vasodilation mechanism. It plays a mediating role in the gastric mucosa (in the control of gastric hydrochloric acid). Stored in the body, it also plays a mediating role in allergic reactions. In the lungs, it stimulates bronchial smooth muscles and triggers an asthma attack. In the intestine, it stimulates peristalism and can lead to diarrhoea. Histamine stimulates the release of NO, a vasodilator that relaxes smooth muscle, especially vascular muscle.

Histamine is inactivated according to the flowchart below:



IV.4.4. Histamine Receptors

- ***H1 receptors***

They are found in the bronchi, the intestine, the salivary glands, the adrenal medulla; They fix histamine in anti conformation (distance between the nitrogen of the primary amine function and one of the nitrogen of the imidazole ring is 0.455 nm.

- ***H2 receptors***

They are found in the heart, gastric wall, mast cells, and leukocytes. They are sensitive to histamine in the left conformation where the distance between the 2 nitrogens is 0.36 nm.

- ***H3 receptors***

They are located on neurons, coupled to proteins. They inhibit the release of different neurotransmitters. Histamine receptors are coupled to proteins.

H1 and H2 receptors are the target of many drugs.

Antihistamines have been designed to treat problems such as hay fever, erythema, insect bites, or asthma.

Mepyramine and diphenylhydramine are two well-known examples of 1st antihistamines.

The antihistamines H1 and H2 are highly selective, non-competitive histamine antagonists that may counteract the effects of the released histamine.

IV.4.5. Structure-activity of antihistamines

The so-called classic antihistamines block the H1 receptors. These are the oldest substances on the market, they derive from ethylene diamine. H2 receptors are blocked by imidazole and thiourea derivatives.

The specific agonist of H3 receptors is R-α-methylhistamine.

The H3 receptor antagonist is thioperamide.

IV.4.6. H1 and H2 antihistamines

IV.4.6.1. H1 antihistamines

H1 antihistamines antagonize the vascular and bronchial effects of histamine.

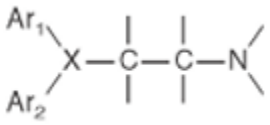
Example:

- Dexchlorpheniramine (Polaramine): a cough suppressant for allergic respiratory disorders.
- Tripolidine: a derivative of pyrrolidine, combined with paracetamol, under the name Actifed, is used in rhinitis and flu-like conditions.
- Cetirizine: a derivative of piperazine: an antihistamine in racemic form marketed in Zyrtec.

These substances do not have a sedative action.

IV.4.6.2. Chemical structure of H1 antihistamines

Most H1 antagonists contain a substituted ethylamine half and a tertiary amine group linked to two aromatic groups, through an aliphatic chain, their general formula:

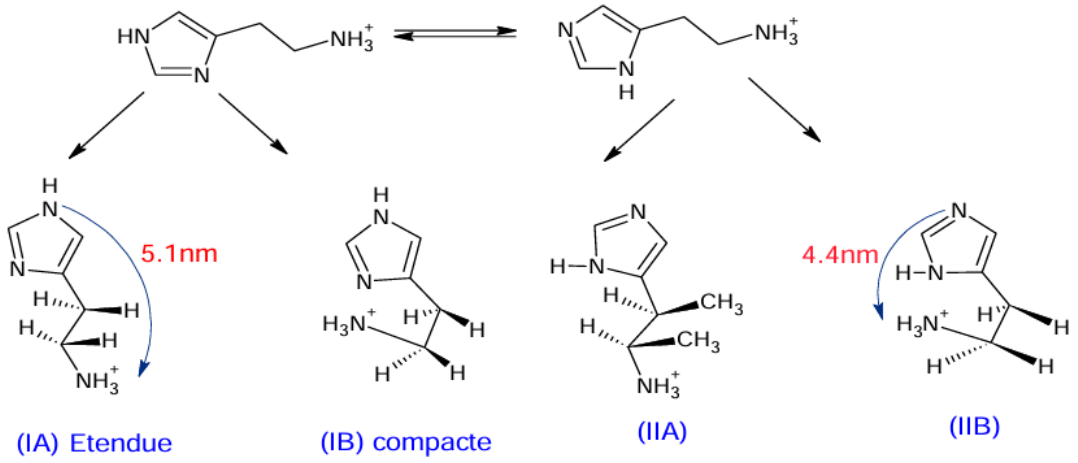


Where Ar is an aryl group.

IV.4.6.3. Structure-activity relationship

For these molecules to bind to these receptors, various requirements are necessary:

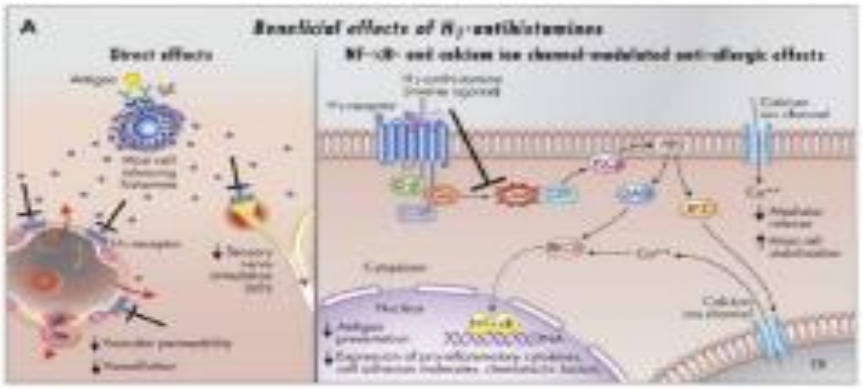
- The side chain must have a positively charged nitrogen atom (reaction balance below) and carrying at least one hydrogen. Ammonium salts give rise to extremely low activity.
- The existence of a flexible chain between the positive center and a heteroatomic cycle is indispensable.



The antagonist binds to the H1 receptor in a form (IA), as for the H2 receptor, ligand binding requires the compact form (IIB)

IV.4.6.4. Mode of action and pharmacological properties of H1

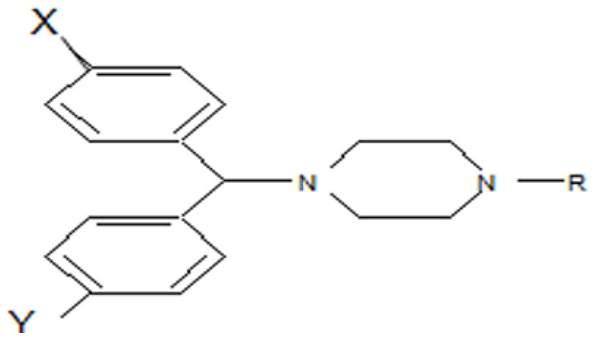
H1 blockers are inverse agonists of H1 receptors. They block the activation of H1 by histamine in the skin, vessels and conjunctival, nasal, bronchial and intestinal mucous membranes. They therefore reduce vasodilation and capillary permeability responsible for edematous reactions. First-generation H1 blockers often lack selectivity, they act as competitive antagonists of muscarinic acetylcholine receptors.



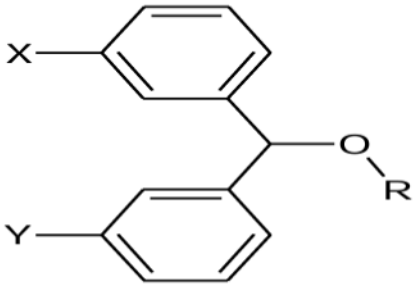
IV.4.6.5. Classification of H1 blockers

These are the 1st and 2nd generation series:

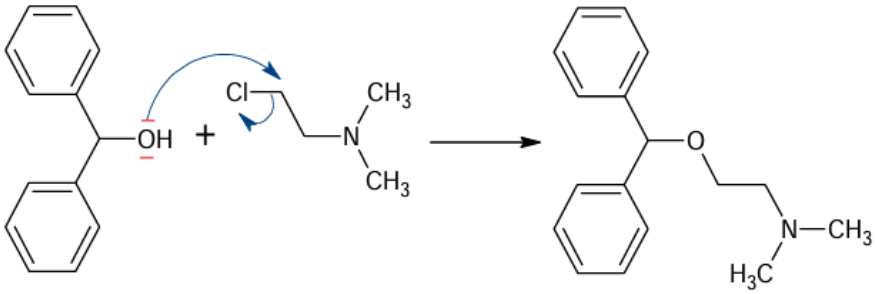
A/ Cyclizine series or piperazine derivatives



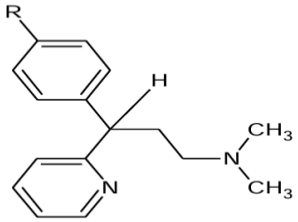
B / Benzhydrol or ether series



Summarized as follows:

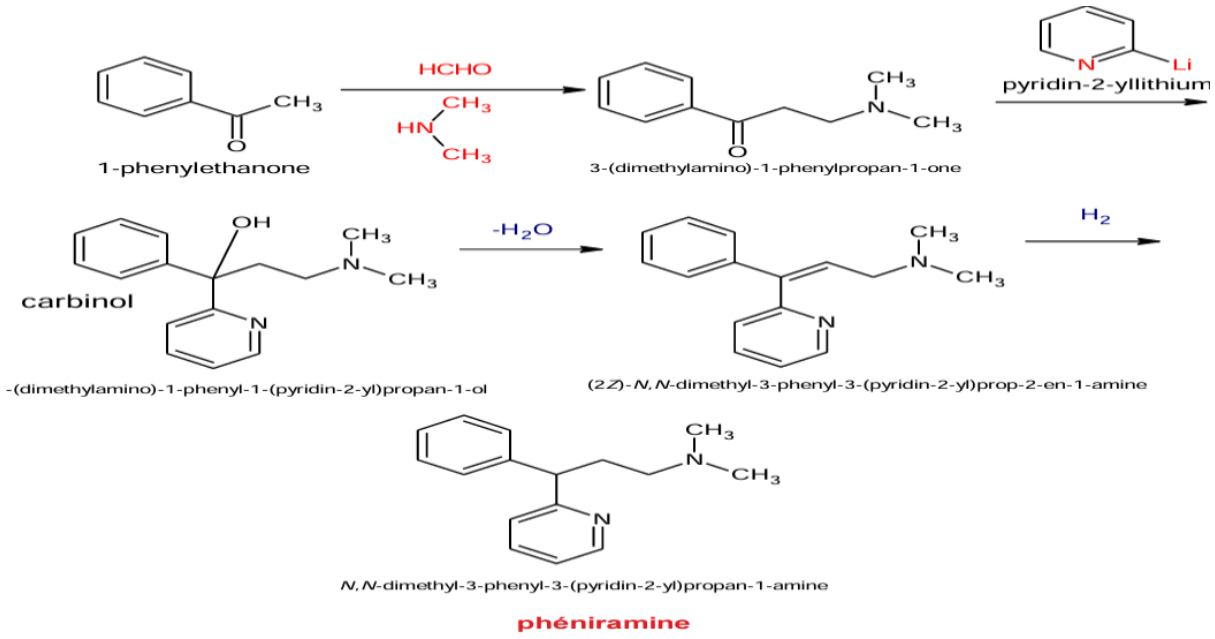


C/. Pheniramine series



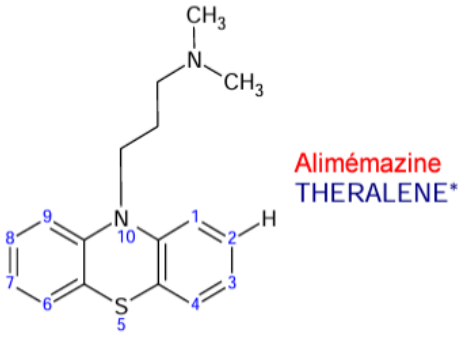
Preparation of the amine phenir

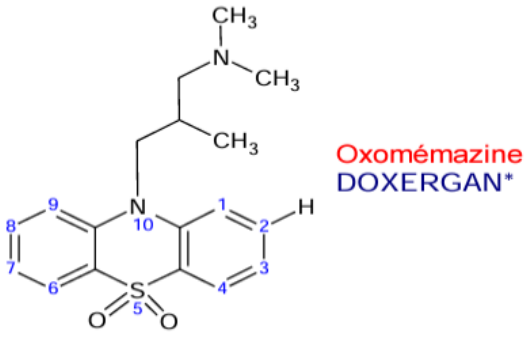
It is prepared by the Mannich reaction which gives rise to the formation of aminoketone. Its condensation in the presence of pyridinyl lithium provides carbinol, which by dehydration followed by hydrogenation forms "Pheniramine"



Phenothiazin series

A. Dimethylaminopropyl chain phenothiazines





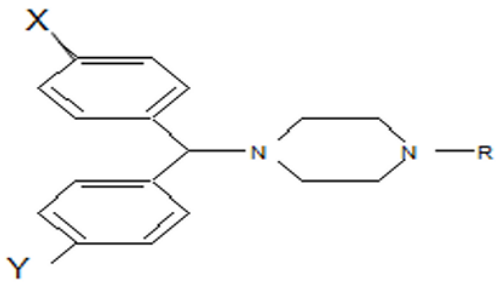
They are rarely prescribed for their multiple side effects, such as drowsiness, dry mouth, constipation, risk of urinary retention, risk of glaucoma, etc.

Second-generation H1 blockers, non-anticholinergic:

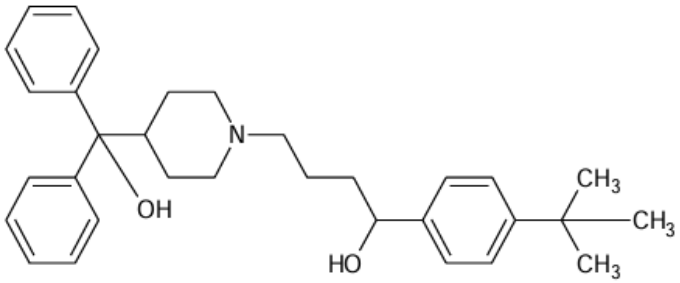
They are frequently prescribed because of their effectiveness and less significant side effects. A distinction is made between:

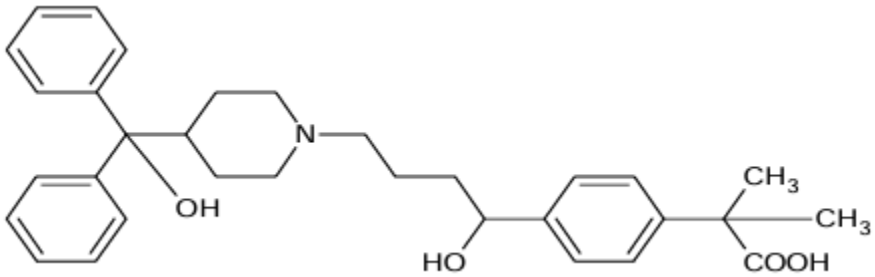
- loratadine and cetirizine: second-generation histamine H1 receptor antagonists:

- Piperazine derivatives with a chemical structure:



- Piperidine derivatives: such as terfenadine and fexofenadine of the following chemical structures:





,HCl

IV.4.6.6. H2 antihistamines

H2 blockers are reversible antagonists of H2 receptors. They oppose the stimulating effects of histidine on gastric secretion. The first drugs representing this group are cimetidine and ranitidine

IV.4.6.7. Structure-activity relationship

The essential requirements are similar to those for H1 receptors, except that the cycle must contain an entity (HN-CH-N :)

The terminal α-amino group is involved in an ionic or hydrogen bridge interaction, regardless of the type of histamine receptor. As for the nitrogen atoms of the heteroatomic ring, they would interact by hydrogen bridge.

IV.4.6.8. Mode of action of H2 blockers

H2 blockers are molecules with a heterocyclic nucleus extended by an aliphatic side chain. They have a chemical structure close enough to that of histamine to be recognized by the binding site but different enough not to be recognized by the activating site.

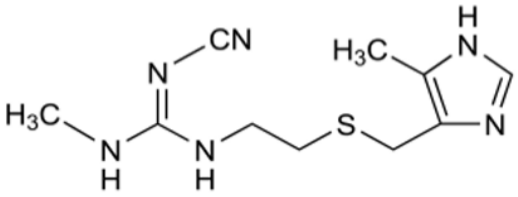
The imidazole nucleus of histamine is considered necessary for biological activity.

Ranitidine has a furan nucleus whereas famotidine and nizatidine have a thiazole nucleus in their structure. This cyclic part is probably decisive for the link. It is the changes made to his level that have made it possible to considerably improve the power of inhibition.

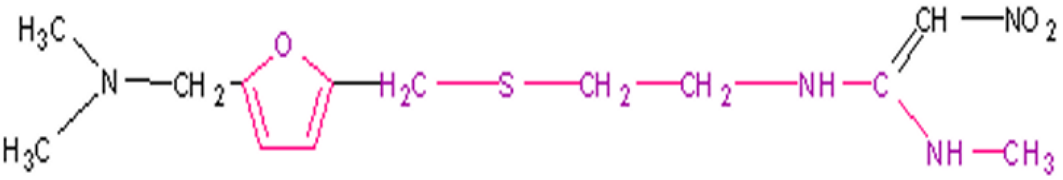
H2 blockers are antagonists, which have the effect of blocking H2 membrane receptors by inducing the reduction of acid secretion. These are highly recommended oral medications in the treatment of ulcers

Some chemical structures and indications of H2 antihistamines

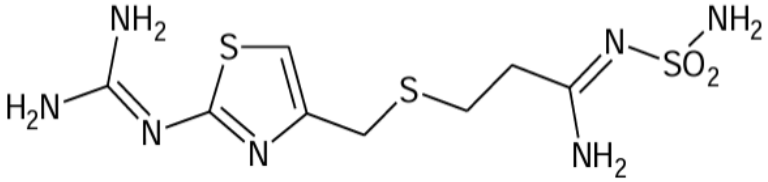
- **Cimetidine**



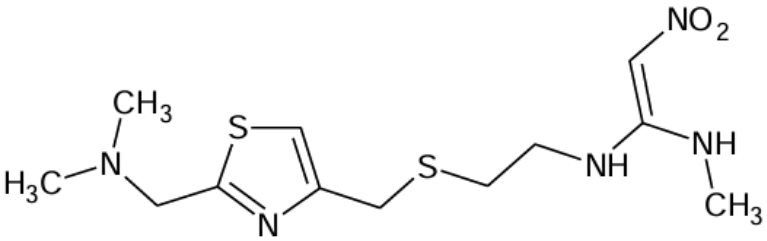
- **Ranitidine**



- **Famotidine**



- **Nizatidine**



IV.5. ANTIDIABETICS

IV.5.1. Definition of diabetes

Diabetes is a serious condition, resulting from when the body cannot produce insulin, or cannot produce enough or cannot effectively use the insulin it produces. It is therefore characterized by hyperglycemia linked to either a disorder of insulin secretion, or a disorder of insulin action, or both.

Insulin is a hormone produced by the pancreas. It is the only hormone with a hypoglycemic action.

IV.5.2. Main Types of Diabetes

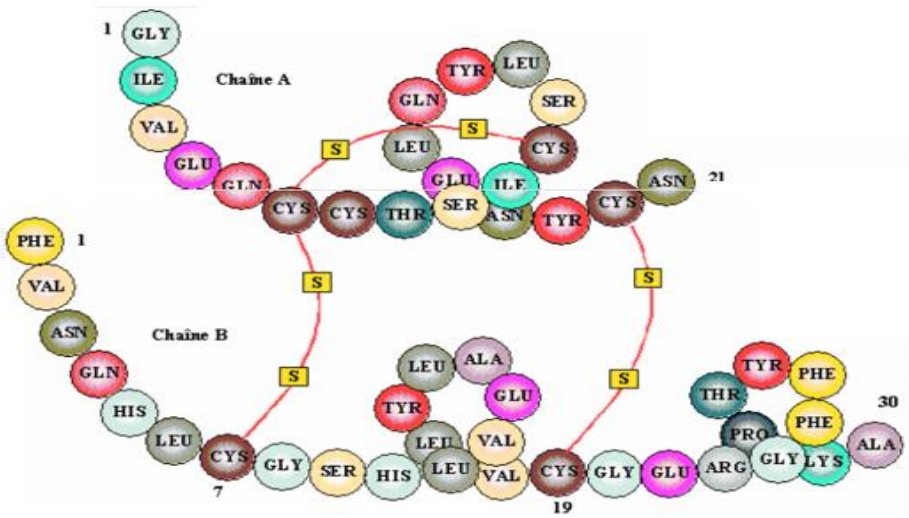
- **Type 1 diabetes**
- **Type 2 diabetes**

It comes when pancreatic β cells and adipic tissues secrete and resist the action of insulin.

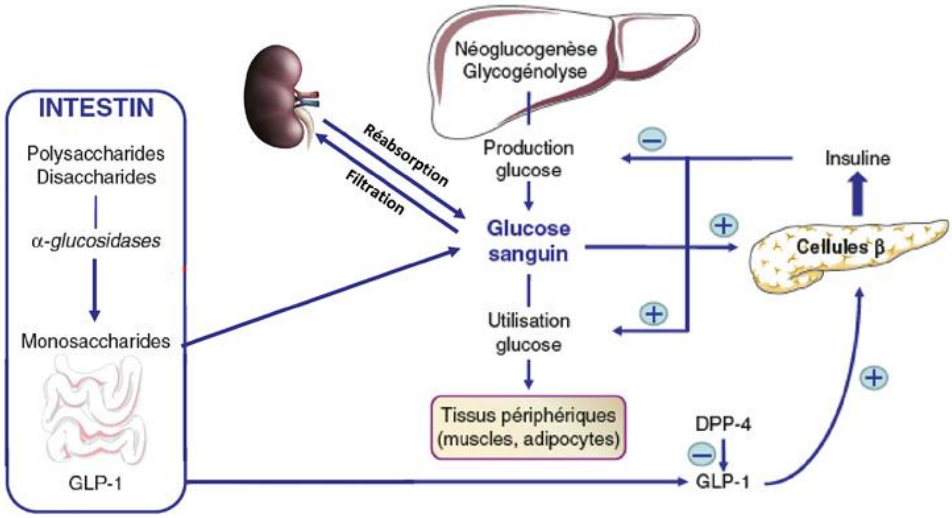
IV.5.3. Definition of insulin

Insulin is a fairly large peptide-lowering hormone made up of AA. It cannot be absorbed orally,

It is a key that allows glucose to enter the cells. The figures below represent the constitution and regulation of insulin.



Insulin constitution



Blood sugar regulation

IV.5.4. Principle of operation of insulin

- Arrival of sugar in the digestive tract
- Absorption into the blood
- Insulin secretion
- Absorption of this glucose by muscle cells for use by liver and fat cells

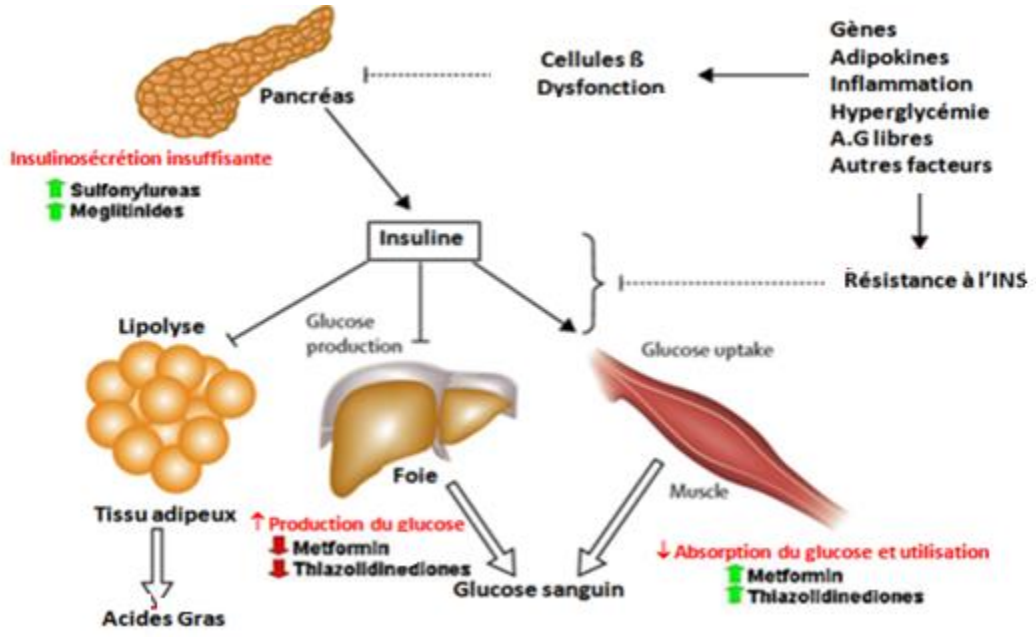
IV.5.5. Treatment of Type 2 Diabetes

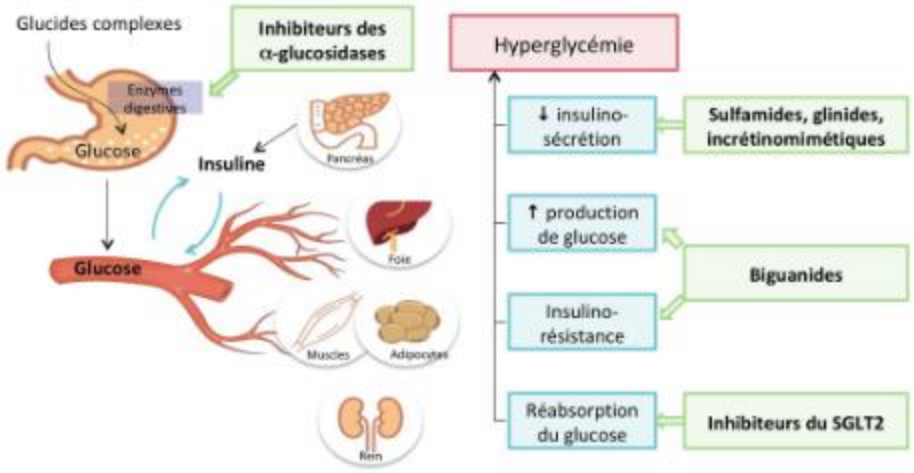
IV.5.5.1. Oral antidiabetic drugs

Antidiabetic drugs are divided into four groups:

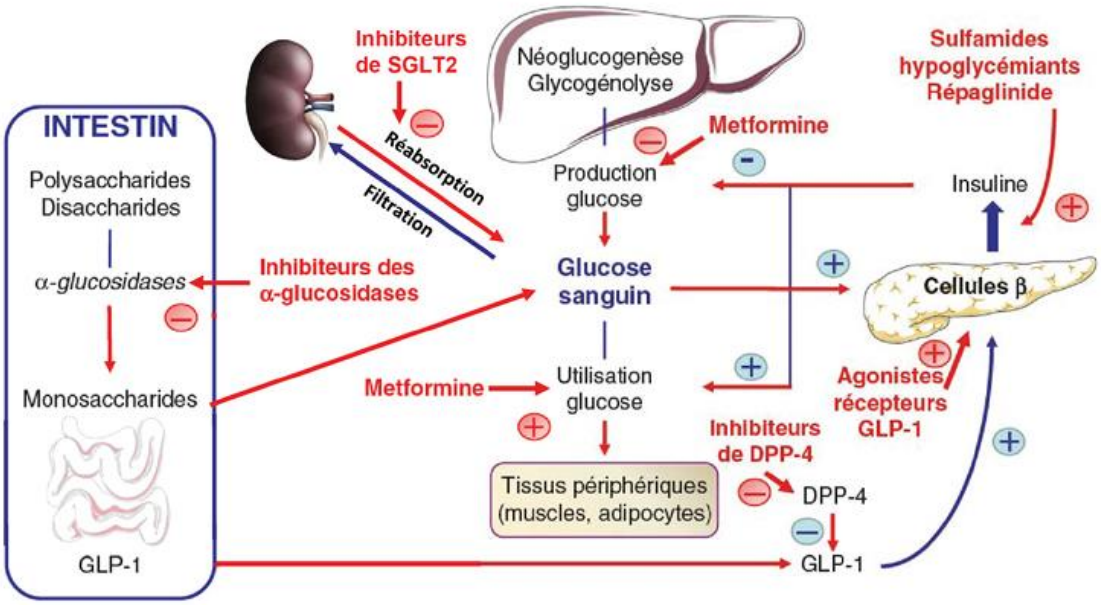
- The Biguanids
- Insulin secretors
- α-glucosidase inhibitors.

The class and mechanism of action of oral antidiabetic drugs are shown in the figures below:





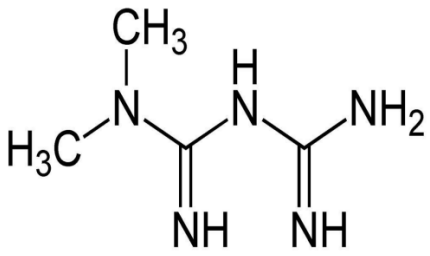
Class of oral antidiabetic drugs



Mechanism of action of oral antidiabetic drugs

1. The Biguanids

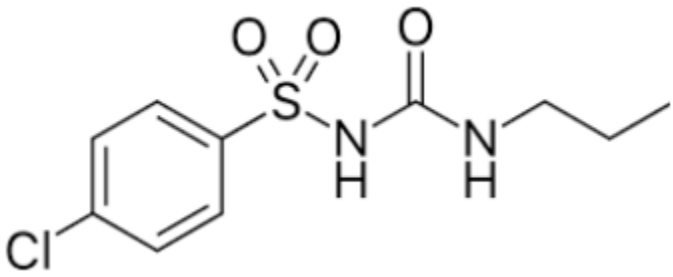
The metformin of the chemical structure below has an anti-hyperglycemic action according to a very complex and poorly understood mechanism. Its main action is at the hepatic level by increasing the hepatic sensitivity of insulin.



2. **Glucose-lowering sulfonamides such as Glicolazide, Glimepiride, Glibenclamide**

Mechanism of action

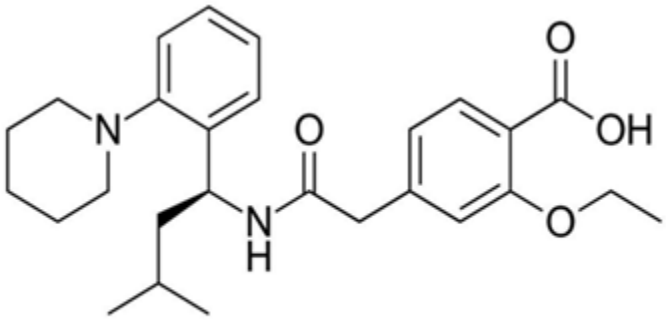
Sulfonamides bind to the SUR (Sulfonylurea Receptor) receptor of ATP-gated potassium channels, thus causing these channels to close. This closure leads to depolarization of the β cells, which triggers the release of insulin.



Chemical structure of sulfonamides

3. **Non-sulfonamide insulin secretors: glinides**

   Like repaglinide; its mechanism of action results in its binding to SUR, thus leading to the closure of ATP-dependent potassium channels of the β cell membrane.



Repaglidin

4. **GLP-1 Receptor Agonists**

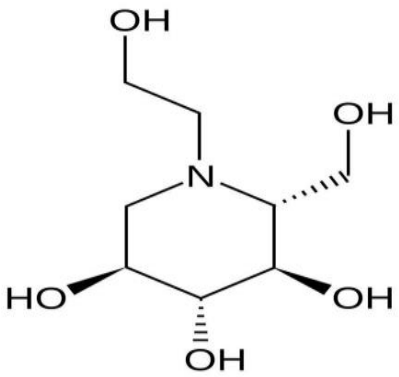
They are synthetic peptides with an amino acid sequence similar to that of **(Glucagon Free Peptide 1).** Their mechanism of action lies in the activation of the GLP-1 receptor in pancreatic β cells.

5. **DPP-4 inhibitors (gliptins)**

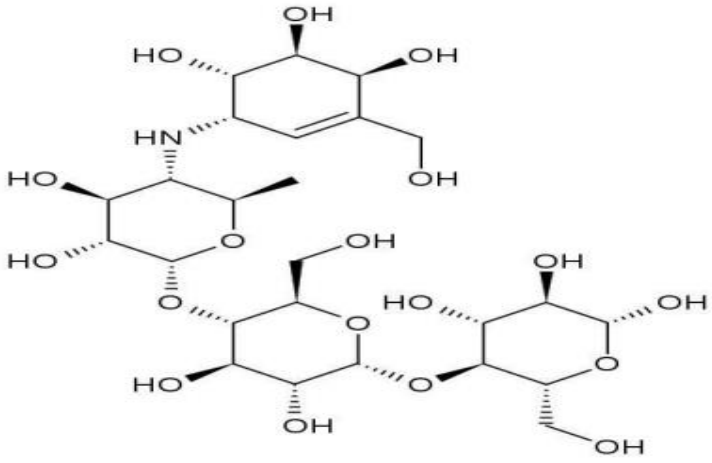
Gliptins inhibit an enzyme (DPP4), which renders GLP-1 inactive and insulin secretion is increased.

6. **α-glucosidase inhibitors**

A distinction is made between acarbose and miglitol, competitive inhibitors of intestinal α-glucosidase.



Miglitol



Acarbose

IV.6. ANTIDEPRESSANTS

IV.6.1. Definition

Depression is a profound disturbance of mood. It manifests itself in symptoms, such as sadness or loss of interest and pleasure, anorexia, feelings of guilt and unworthiness, despair, agitation or psychomotor slowdown, disruption of thought and concentration processes, disturbances in sleep or appetite, difficulty concentrating or suicidal thoughts.

IV.6.2. Treatment

Different classes of antidepressants are marketed to combat depressive illness. These drugs are capable of improving the patient's condition and relieving his or her moral suffering.

IV.6.3. Symptoms of depression

- Depressed mood
- Loss of interest
- Suicidal ideation
- Feeling of worthlessness
- Fatigue
- Psychomotor slowing down
- Loss of appetite
- Insomnia

IV.6.4. Antidepressants

A distinction is made between thymoanaleptics that stimulate depressed mood such as imipramine, a tricyclic amine, and mood-boosting thyme, such as iproniazid, a monoaminooxidase inhibitor.

IV.6.5. Classification of antidepressants

DPAs are categorized into:

- ❖ SSRIs
- ❖ RNSRI
- ❖ Tricyclic TDAs
- ❖ MAOI
- ❖ Other antidepressants

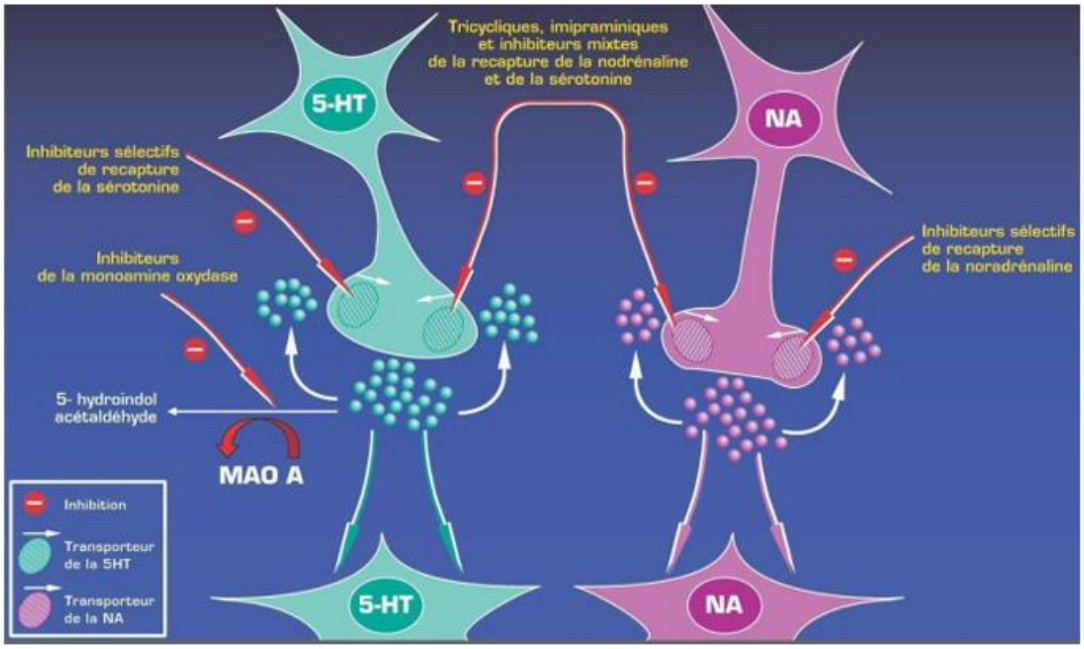
The first DPAs discovered:

Imipramine (see structure below), is a tricyclic compound derived from imino-dibenzyl, tested for its antihistamine and antipsychotic activity

iproniazid of the following chemical structure, is an irreversible inhibitor of MAO.

Both of these drugs are able to block the reuptake of serotonin and norepinephrine. They therefore have the pharmacological effect of increasing the concentration of neuromediators in the synaptic cleft.

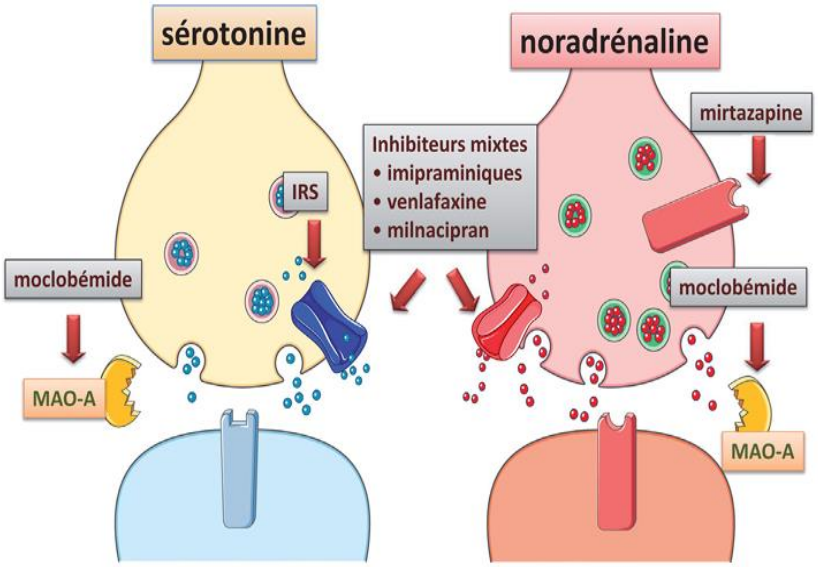
MAOIs inhibit MOA and increase its concentration.



The different classes of antidepressants and their therapeutic targets

IV.6.7. Mechanisms of action of antidepressants

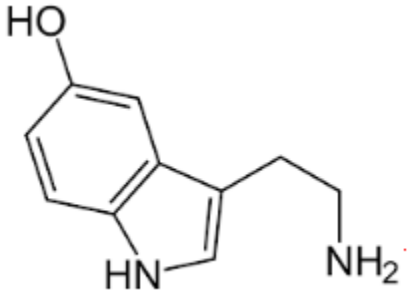
The figure below shows the mechanism of action of the different families of DPS:



Mechanism of action of antidepressants

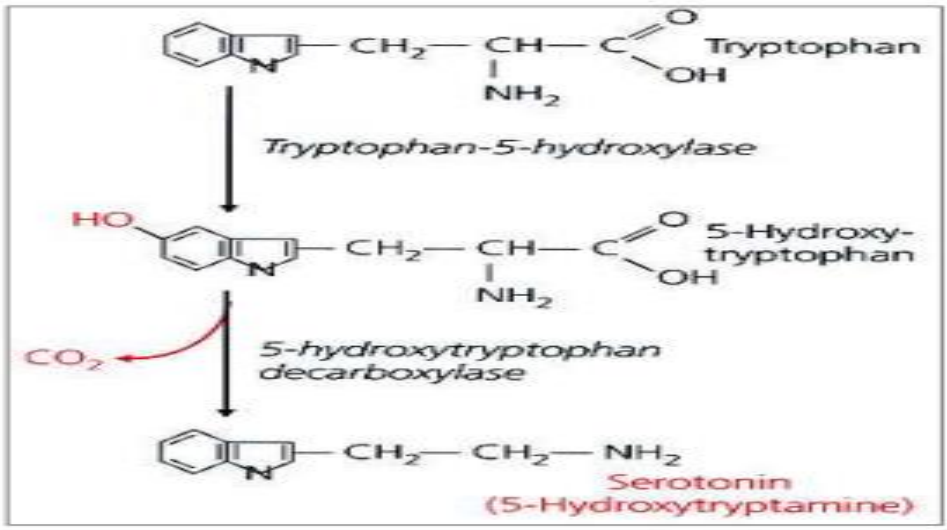
a) Selective serotonin reuptake inhibitors (SSRIs)

Serotonin, whose chemical structure is listed below, is a biogenic amine synthesized according to the diagram below, by a hydroxylation and decarboxylation reaction of an amino acid with an indole motif, tryptophan.



Chemical structure of serotonin

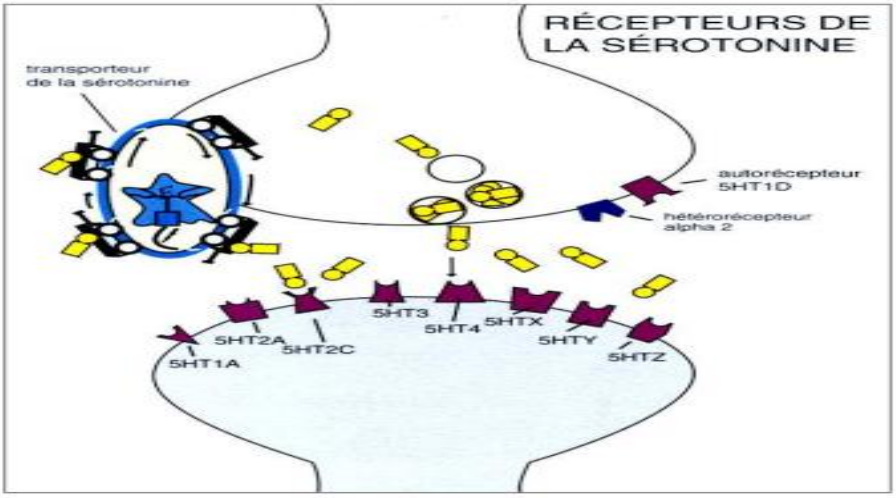
Serotonin plays the role of neurotransmitter and neurohormone in the central nervous system and in the general circulation.



Serotonin synthesis

Mechanism of action of SSRIs

They act selectively on serotonin by increasing its concentration according to the mechanism shown in the figure:



Mechanism of action of SSRIs

In the synapse, serotonin is found in the presynaptic vesicles. The post-synaptic receptors that target serotonin are the 5-HT receptors that have the role of regulator. There are the SERT transporters, responsible for the reuptake and storage of serotonin.

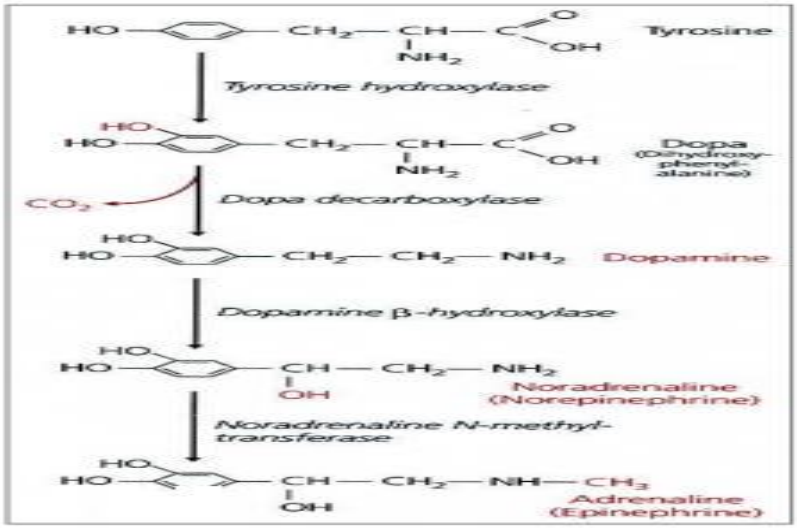
In a normal person, the precursor L-Tryptophan is converted into serotonin and then stored in the vesicles. If necessary, serotonin will be released into the synapse and its receptors will be activated. Part of it will act on the auto-receptor in order to regulate it in the synapse. The other part will be stored by SERT for possible use.

In a person with depression:

She has an insufficient stock of serotonin, which is why the SSRI prevents her reuptake

b) Serotonin reuptake inhibitors and norepinephrine reuptake inhibitors (SNRIs)

Norepinephrine is synthesized from L-tyrosine (see diagram below) by enzymatic catalysis in the presence of an enzyme, in this case tyrosine hydroxylase. This catalytic reaction gives rise to the formation of L-Dopa, which by decarboxylation, provides dopamine. The latter is then hydrolyzed into norepinephrine, a neuromediator known for its cardiovascular (blood pressure, myocardial contraction, heart rate) or bronchial effects.



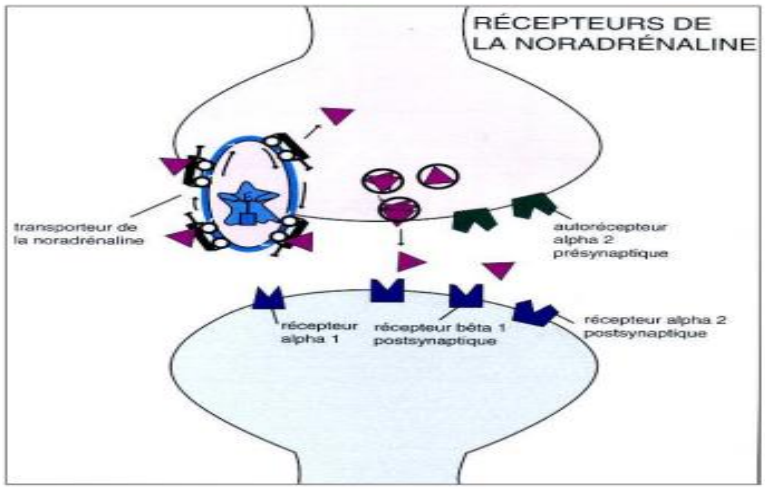
Adrenaline synthesis process

How does SNRI work

SNRIs act like SSRIs on serotonergic and noradrenergic transmission.

The SERT and NET transporters will be inhibited to increase the concentration of these two neuromediators in the synapse. The postsynaptic receptors on which norepinephrine acts are alpha-1 receptors and beta-1 receptors.

The IRSNAs will therefore have two targets, the two transporters: SERT for serotonin and NET for norepinephrine.



Mechanism of action of RNIs

Biochemical elements of norepinephrine and serotonin transmissions

- Synthesis is done from tyrosine and L-tryptophan
- Release from synaptic vesicles
- Binding to post-synaptic and pre-synaptic receptors (auto-receptors)
- Presynaptic reuptake by specific transporters
- Degradation by monoamine oxidases (MAO)

c) Tricyclic antidepressants

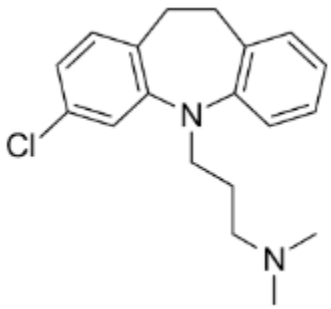
The term tricyclic drug refers to compounds that have a dibenzazepine-like cyclic structure, e.g.: imipramine or dibenzocycloheptadiene such as amitriptyline. They are basic compounds with a structure similar to that of phenothiazines. They have the characteristics of binding to both albumin and α1-glycoproteins. They exhibit the same blocking effects on muscarinic cholinergic, α-adrenergic and histaminergic receptors. Their mechanism of action is summarized in their metabolism, i.e., their hydroxylation and demethylation by CYP1A2, 2D6 and 3A4. This metabolism results in the formation of active products, capable of inhibiting the reuptake of norepinephrine and serotonin, leading to an accumulation of these neurotransmitters in the presynaptic cleft.

Tricyclic antidepressants act on serotonergic and noradrenergic transmission.

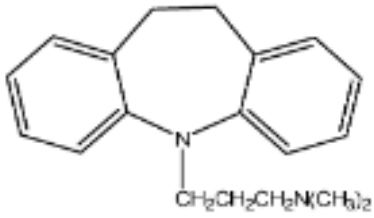
- Clomipramine: 5HT>NA
- Desipramine, maprotiline NA>5HT

These antidepressants therefore inhibit SERT and NET

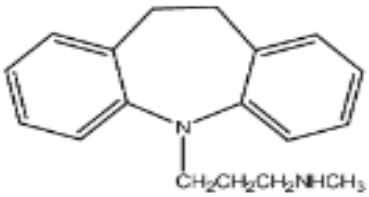
The main molecules are: Clomipramine, Imipramine, Amitriptyline, Amoxapine.



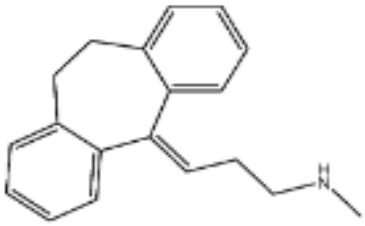
Chemical Structure of Clomipramine



Chemical Structure of Imipramine



Chemical Structure of Desipramine



Chemical Structure of Amitryptiline

d) ***The (MAOI)***

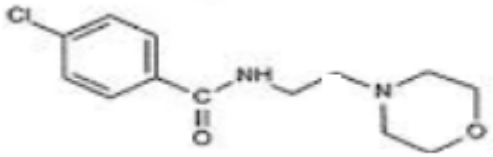
MAO is an enzyme that eliminates monoamines such as norepinephrine and serotonin, which are two examples of monoamines found on presynaptic neurons. They will act on serotonergic and noradrenergic transmission not by reuptake but **by inhibition of the monoamine oxidase enzymes present in the presynaptic neuron.** The role of this enzyme is therefore to eliminate serotonin and norepinephrine which will bind to it in order to regulate the monoamine stock. MAOIs inhibit these enzymes that prevent the breakdown of catecholamines in the brain and sympathetic system (adrenaline, norepinephrine, serotonin, phenyl-ethylamine), so that they have even more serotonin and norepinephrine stock.

MAOIs are of two types:

- Selective MAOIs such as moclobemide (reversible inhibition)

Moclobemide mode of action:

- Selective inhibition of type A monoamine oxidase that removes serotonin and norepinephrine



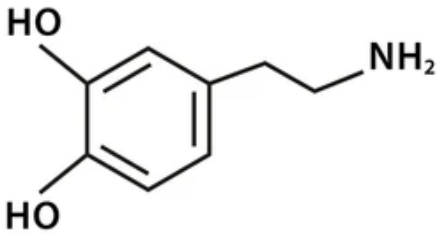
Chemical structure of Moclobemide

- Non-selective MAOIs such as iprozianide (irreversible inhibition)

How iprozianid works:

Inhibition of MAO type A and B (dopamine removal)

Inhibition is irreversible because no MAO remains available to inhibit monoamines such as dopamine.



Chemical Structure of Dopamine

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