Lecture (1): Drugs Distributions (I)

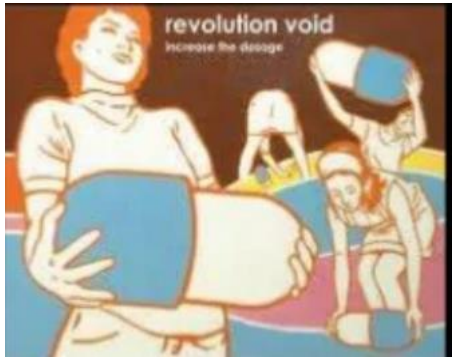
The transfer of drug from sit of administration to blood by **absorption, and** the removal of this drug from blood to sit of action (receptors) is called **distribution**.

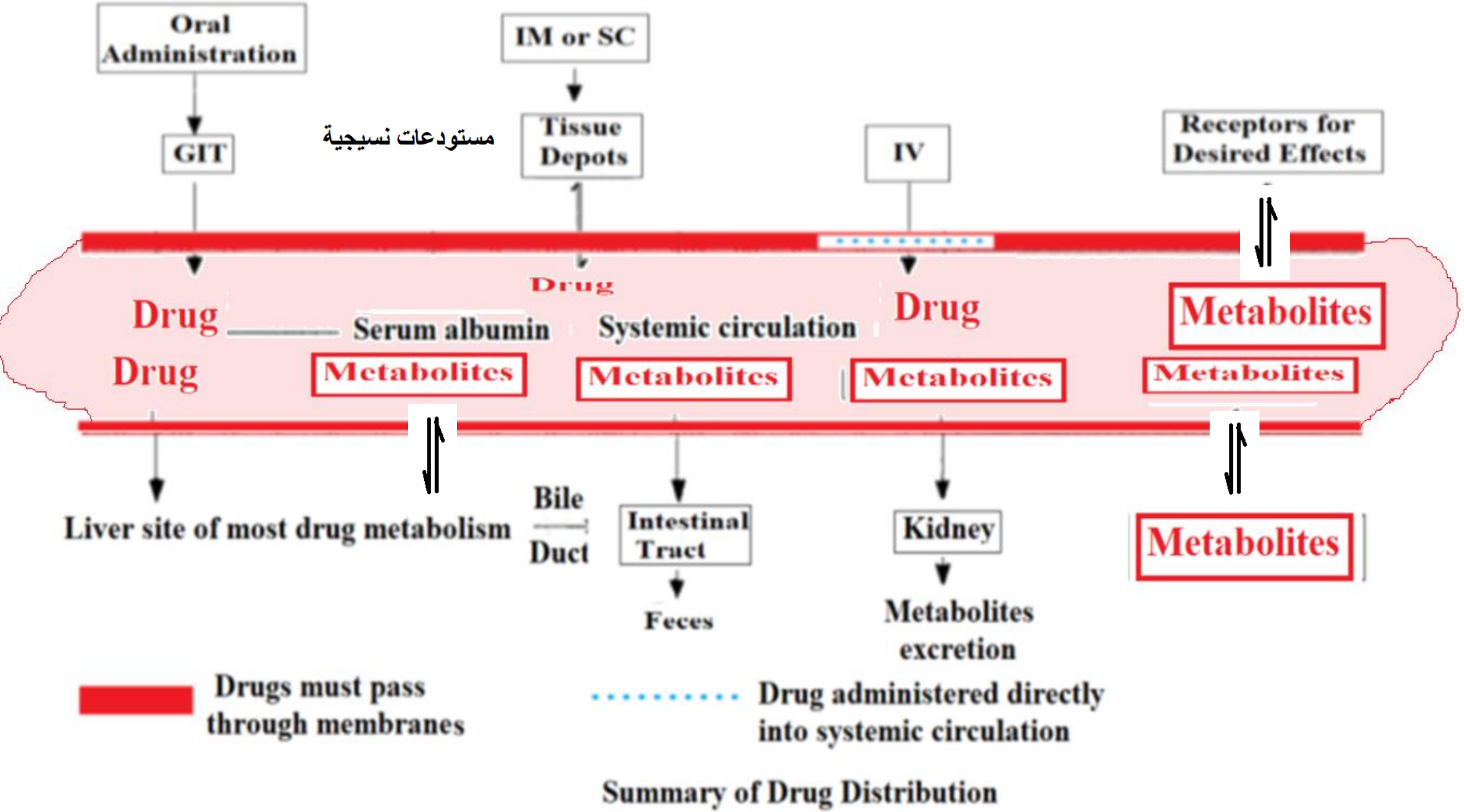
1.Drug distribution refers to the movement of a drug to and from the blood and various tissues of the body (for example, fat, muscle, and brain tissue) and the relative proportions of drug in the tissues.

2.After a drug is absorbed into the bloodstream, it rapidly circulates through the body. The average circulation time of blood is 1 minute. As the blood recirculates,

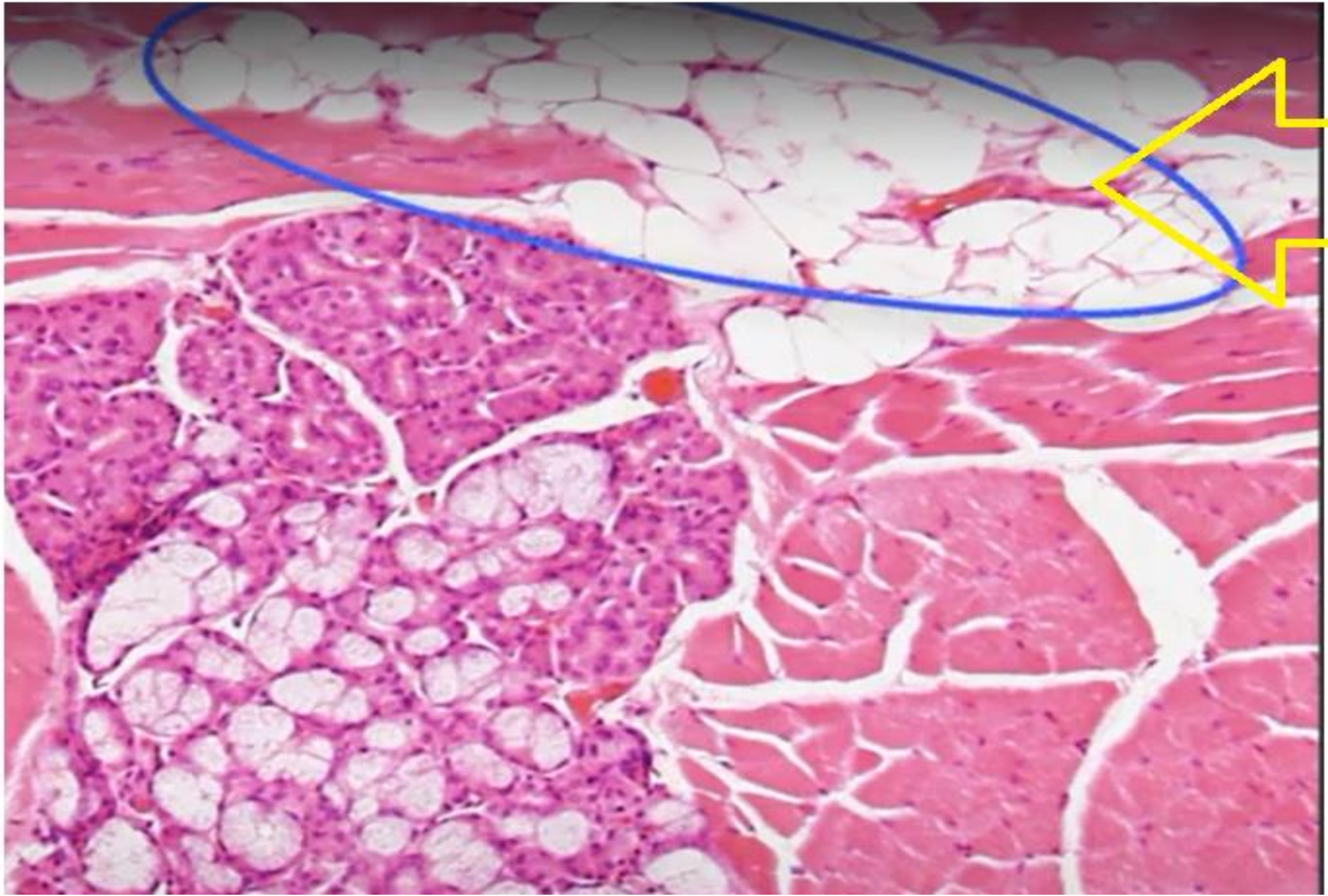
the drug moves from the bloodstream into the body's tissues.

e.g. Edrophonium Chloride[USP] (Tensilon), is a reversible anticholinesterase agent. It is a specific anticurare agent and acts within 1 minute .





Summary of Drug Distribution


Depots

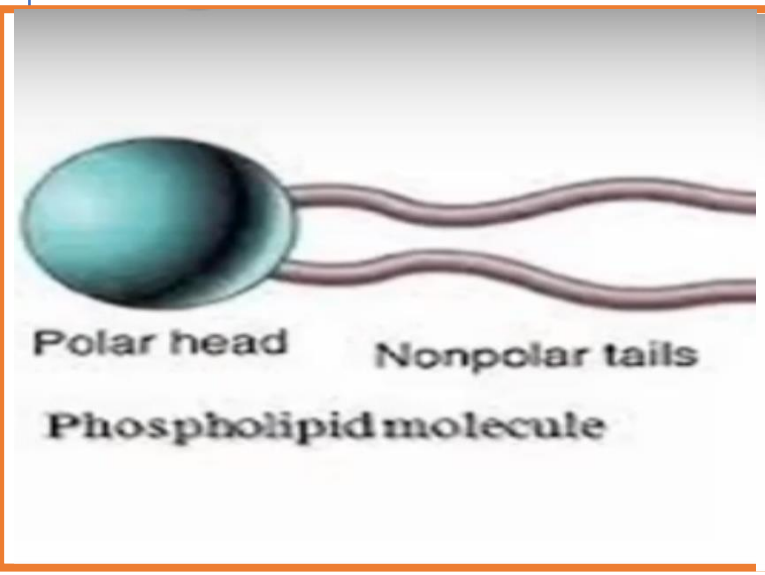
2.Once absorbed, most drugs do not spread

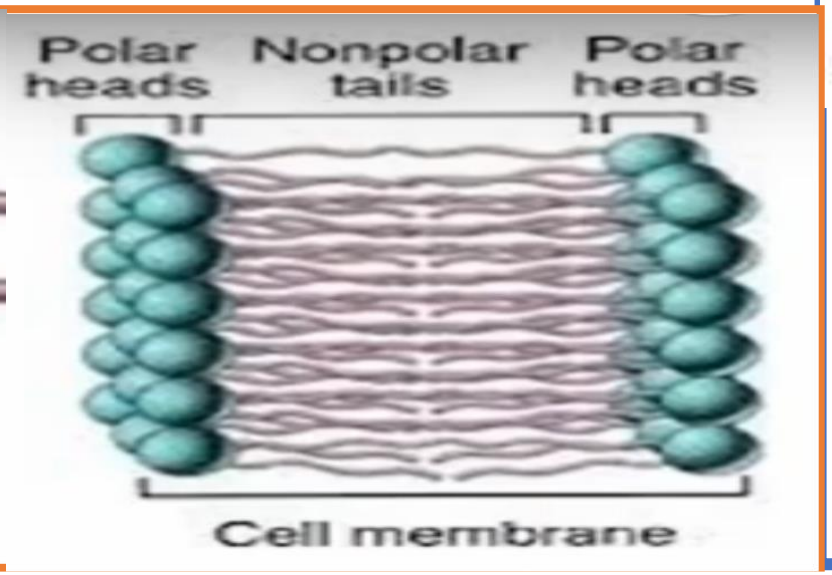
لا تنتشر بنفس الشكل evenly throughout the body

3.Water-soluble drugs such as the antihypertensive drug Atenolol, tend to stay within the blood and the fluid that surrounds cells (interstitial)

(inter. Este . Eshyal .) spaces.

4.Fat-soluble drugs, such as the antianxiety drug clorazepate, tend to concentrate in fatty tissues.



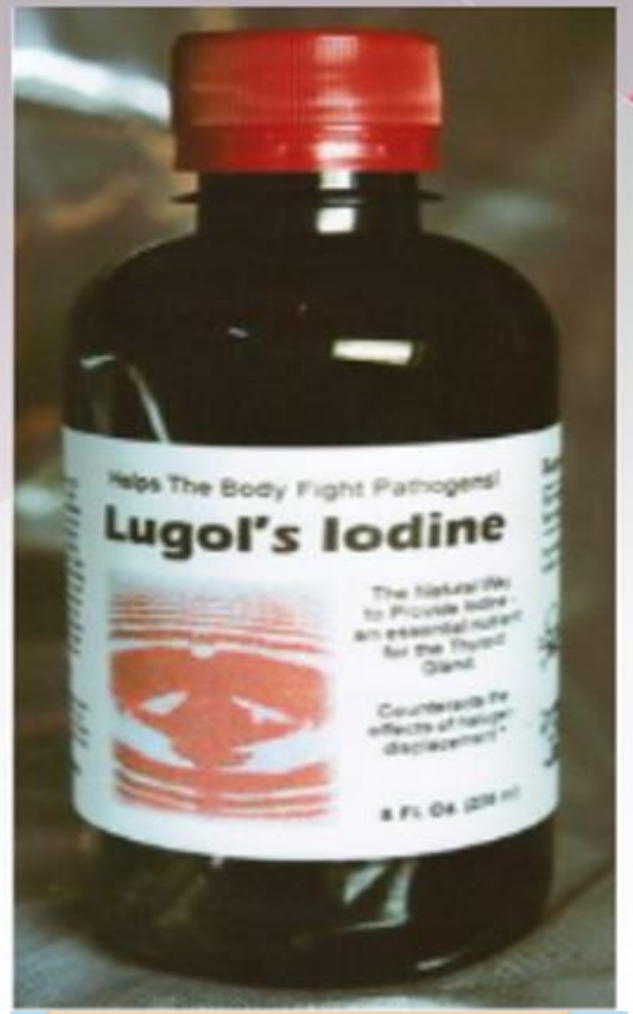


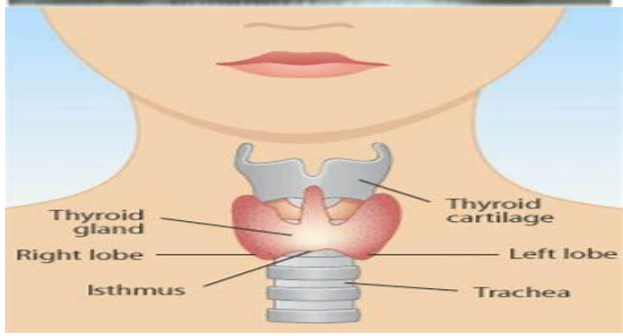
5.Other drugs concentrate mainly in only one small part of the body (for example, iodine concentrates mainly in the thyroid gland) because the tissues there have a special attraction for (affinityالفة) and ability to retain that drug.

6.Drugs penetrate different tissues at **different** speeds, depending on the drug's ability to cross membranes.

a. For example, the antibiotic rifampin (treats several types of bacterial infections, including tuberculosis) (TB), a highly fat-soluble drug, rapidly enters the brain,

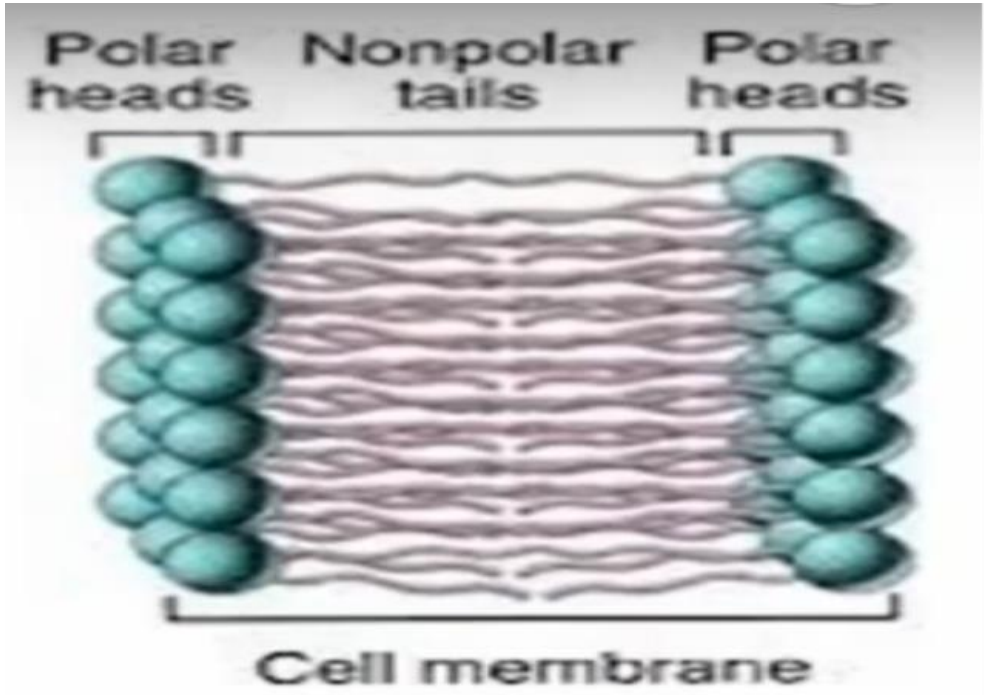
b. But the antibiotic penicillin (e.g. Penicillin G Potassium salt) a water-soluble drug, does not.



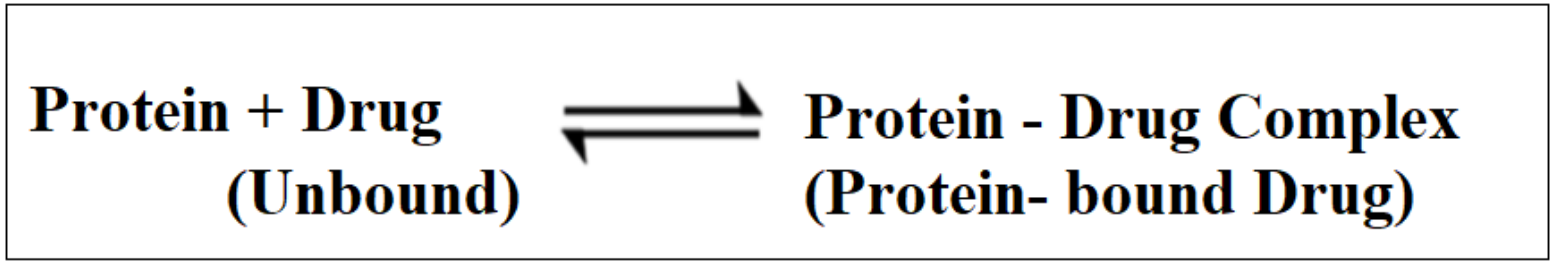


7. In general, fat-soluble drugs can cross the cell membranes more quickly than water-soluble drugs can.

For some drugs, transport mechanisms aid movement into or out of the tissues.



8. A drug in blood exists in two forms: Bound and Unbound with chemical equilibrium:



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9. i.Some drugs leave the bloodstream very slowly because they bind tightly to proteins circulating in the blood.

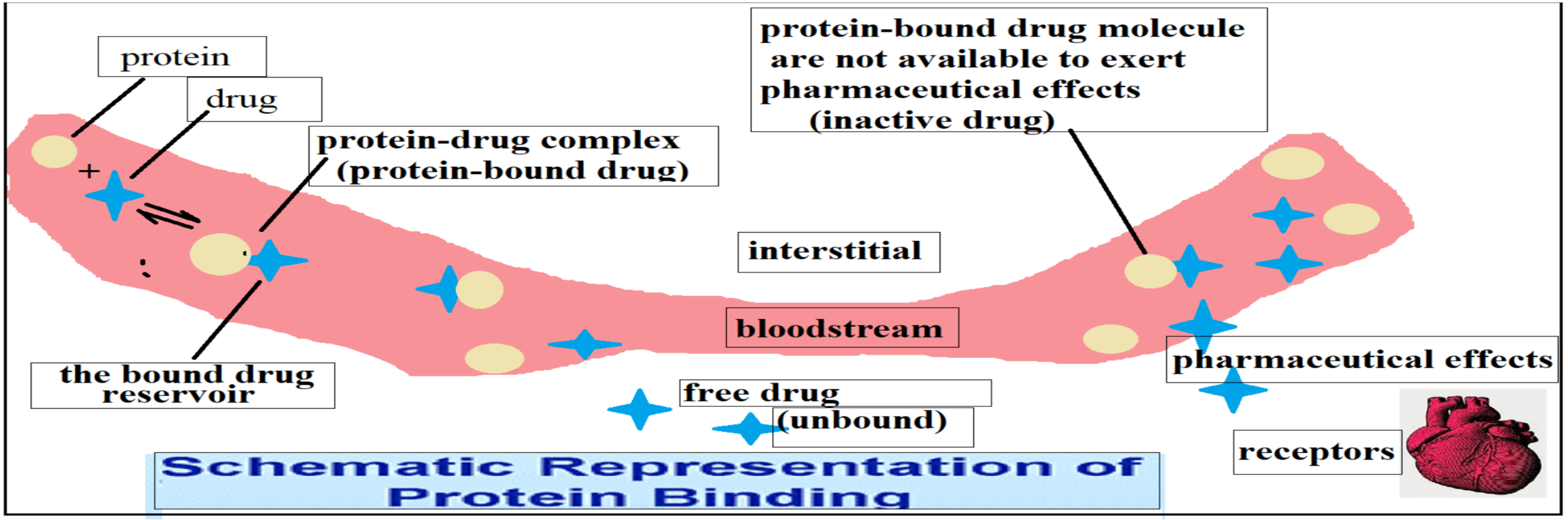
ii.Others quickly leave the bloodstream and enter other tissues because they are less tightly bound to blood proteins.

10. Some or virtually تقريبا all molecules of a drug in the blood may be bound to blood proteins.

*The protein-drug complex (protein-bound drug) is generally inactive.

10.As unbound drug is distributed to tissues and its level in the bloodstream decreases, blood proteins gradually release the drug bound to them.

Thus, the bound drug in the bloodstream may act as a reservoir خزانfor the drug



During drug distribution ,What the body does to the drug?

ADME is an abbreviation in pharmacokinetics (حركية الدواء)

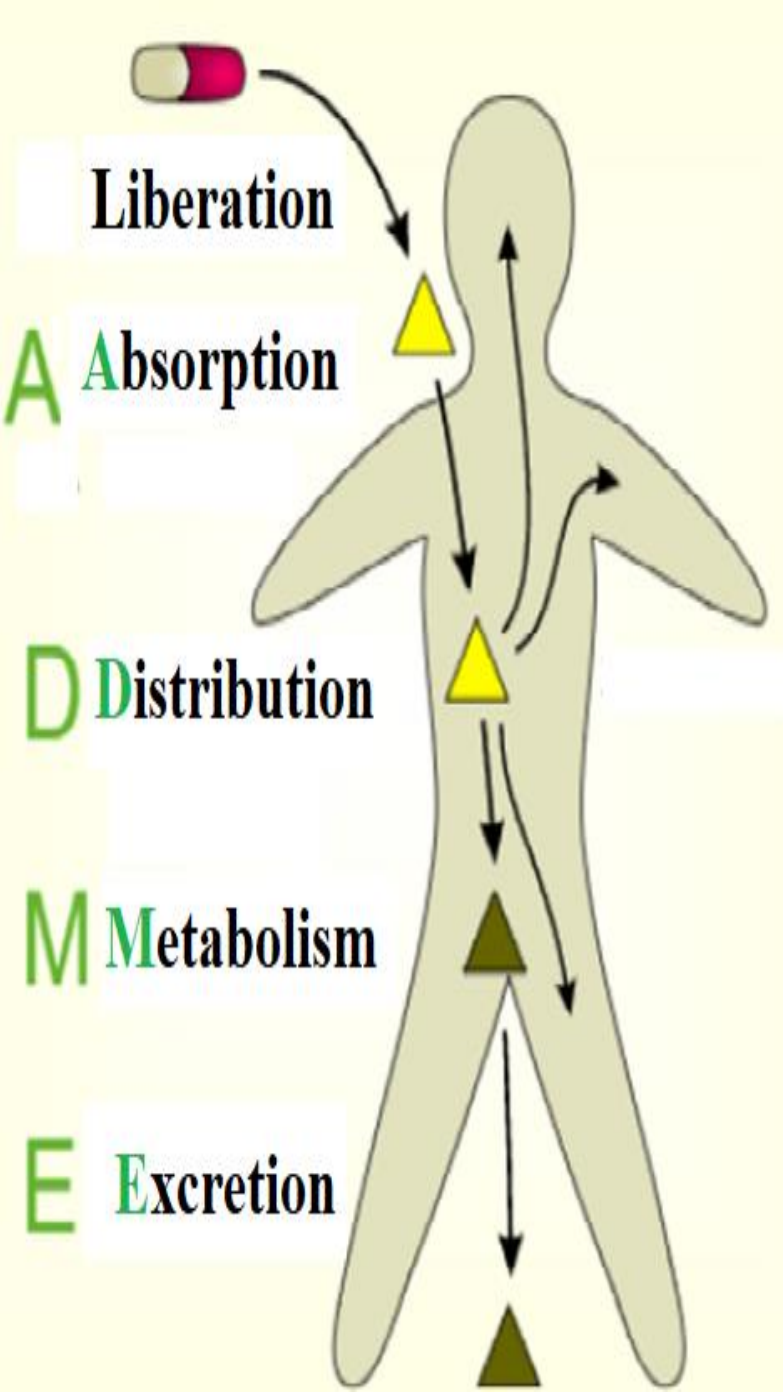
and pharmacology of what the body does to the drug:

A = Absorption ,

D = Distribution

M = Metabolism, and

E= Excretion



A drug is a chemical molecule.

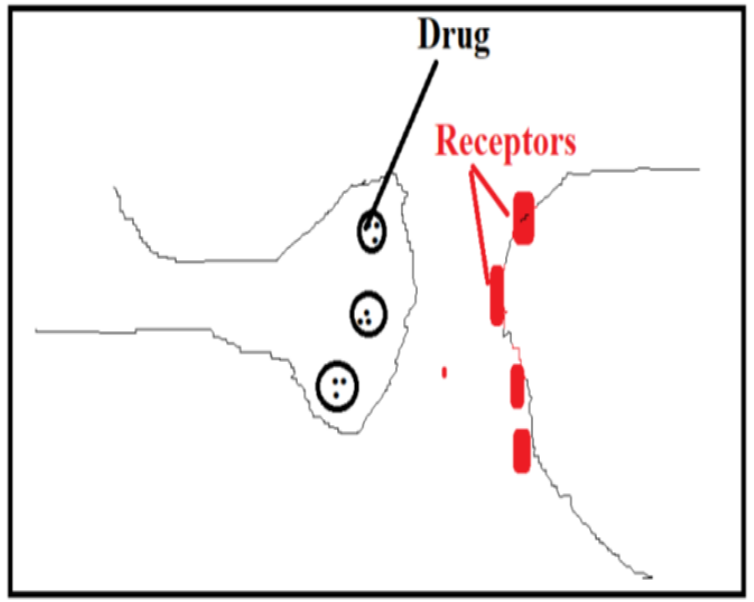
Following introduction into the body, a drug must pass through many barriers:حواجز

i. Survive alternate sites of attachment and storage.

مواقع للبقاء بديلة للارتباط والخزن

ii. Avoid significant metabolic destruction تجنب مواقع ايض كبيرة مدمرة(قبل الوصول لمواقع الفعل الدوائي وهي عادة المستقبل او الخلية)

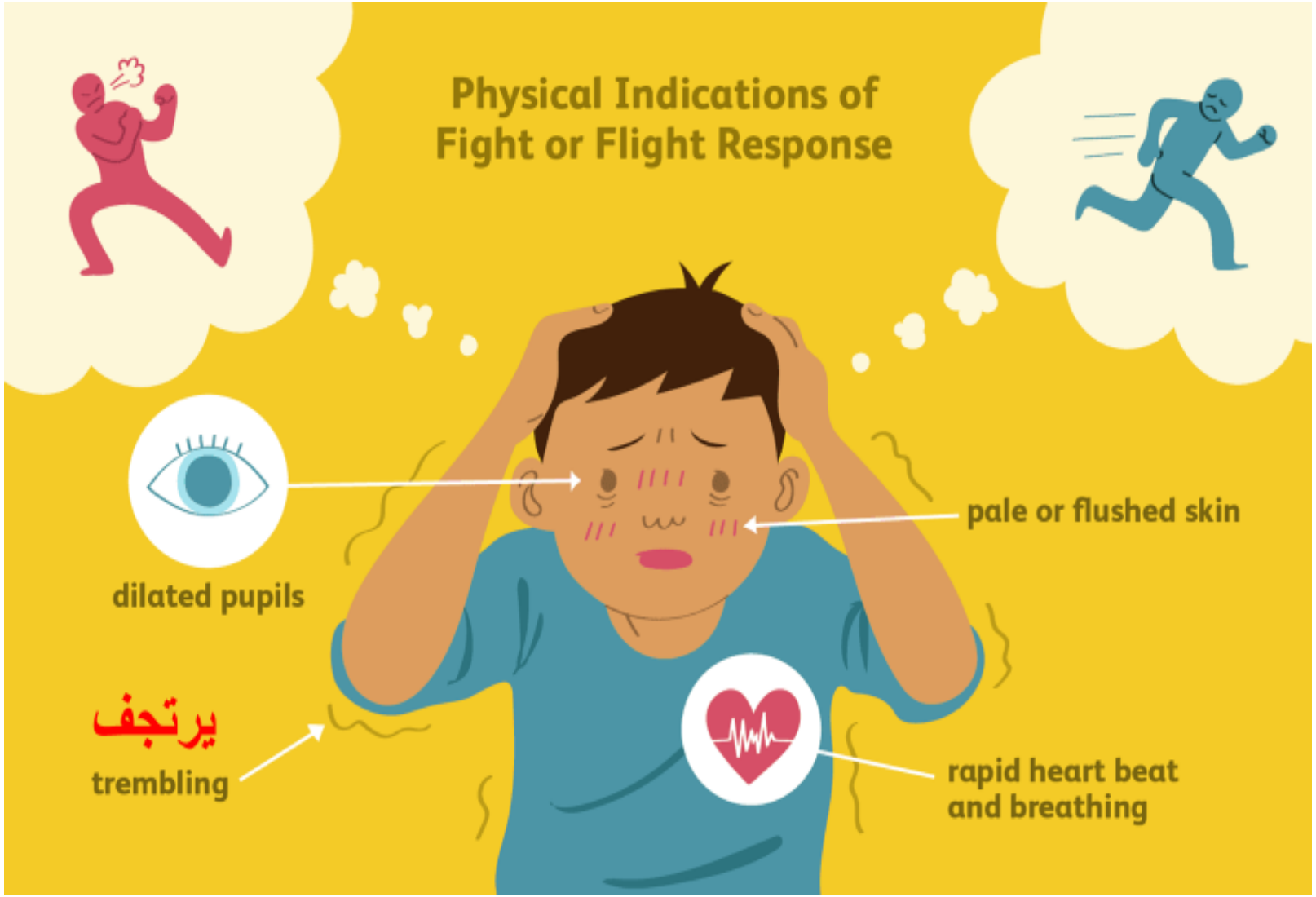
before it reaches the site of action, usually a **receptor** on or in a cell

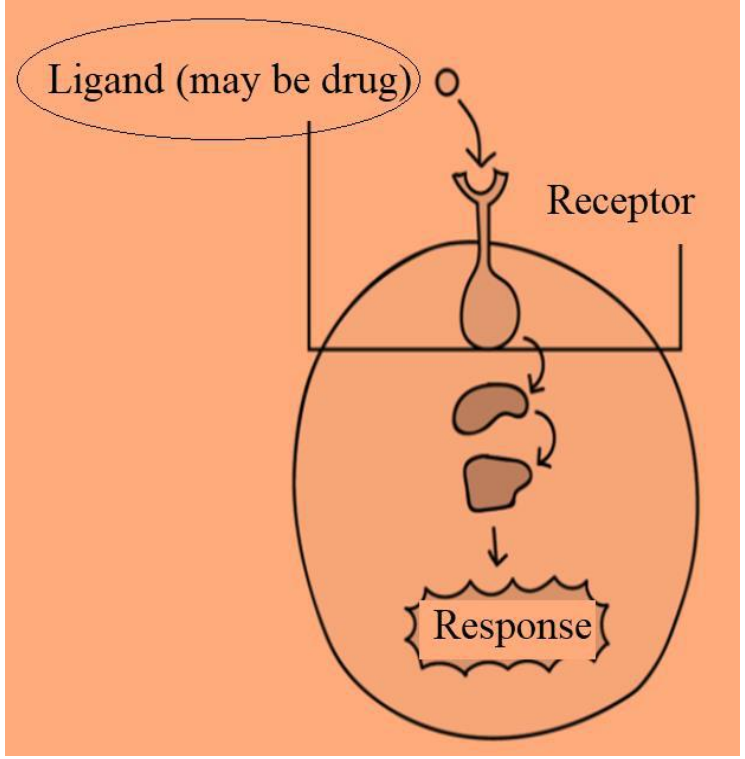


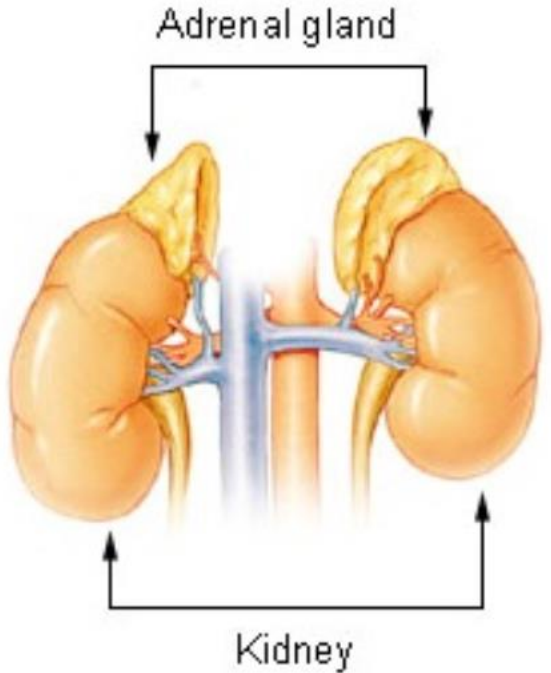
Receptor:

Macromolecule or binding site , located on the surface or inside the cell that recognize تشخص the signal molecule or drug and initiate the response.

Adrenergic receptors as examples







During fight and flight Adrenalin and Noradrenaline are release which stimulate adrenoreceptors: β1,β2,α1 and α2.This stimulate the following:

1.Heart (β1)

Increases the heart rate and force

Rate = (+**chromo**tropic)

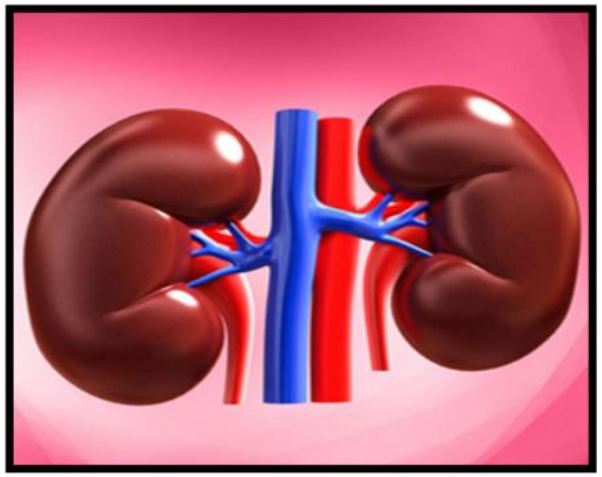
Increases heart conduction (+ **dromo**tropic)

التوصيل الكهربائي للقلب

Force = Increases myocardial contractility (+**ino**tropic) تقلصات عضلة القلب

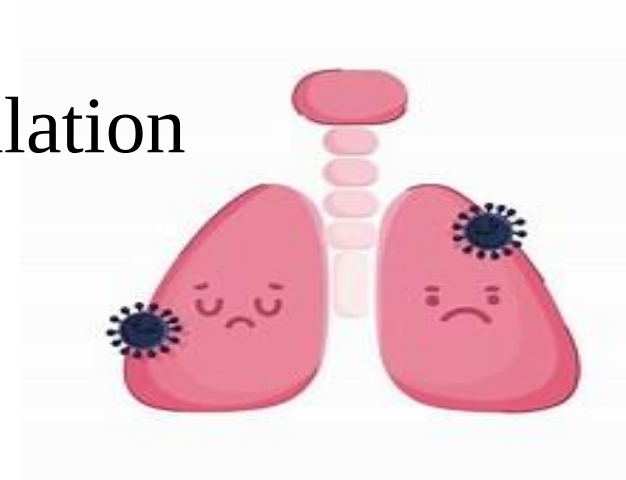
2.Kidney (β1):

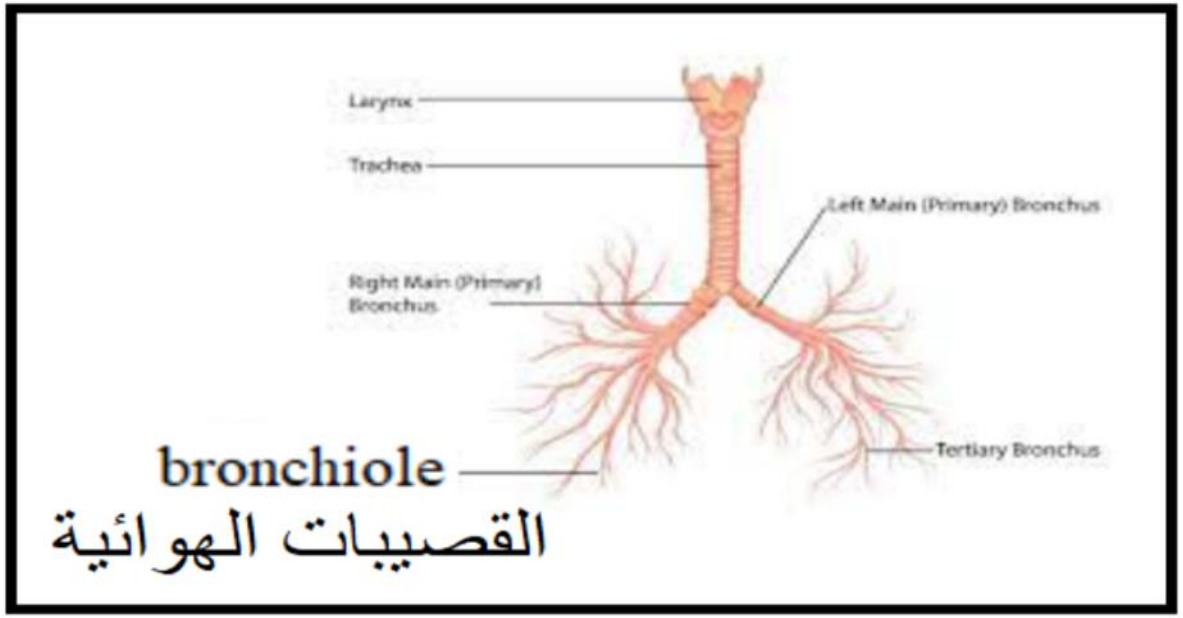
Increases renin E. (angiotensinogenase),thus increases BP



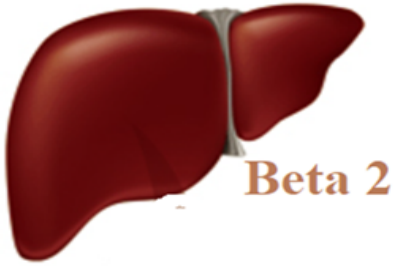
3.Lung (β2):

Produces bronchodilation



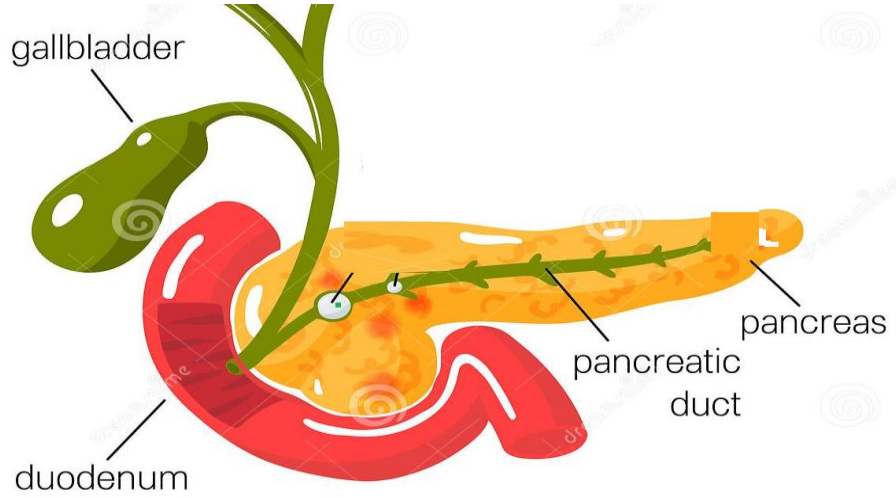


4.Liver and pancreas (β2): Increases glycogenolysis (breaking down glycogen into glucose) and in **Pancreas (β2)** increases insulin releasing and increases glucagon release.



glycogen $\xrightarrow{\text{glycogenolysis}}$ glucose

ıncreases insulin releasing



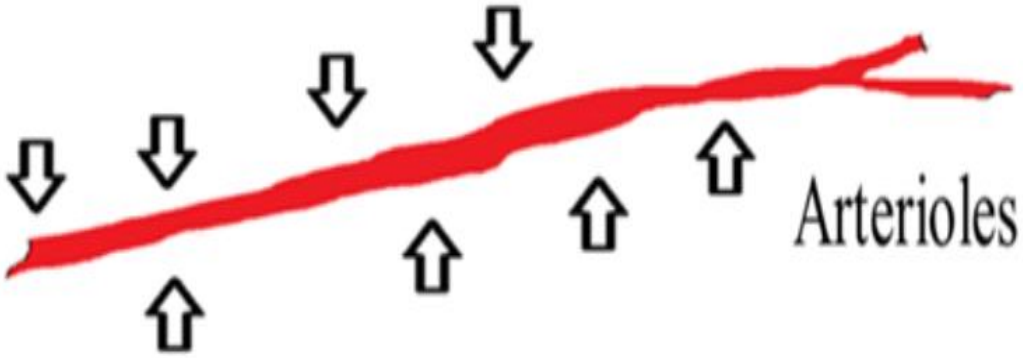
5.Uterus (β2):

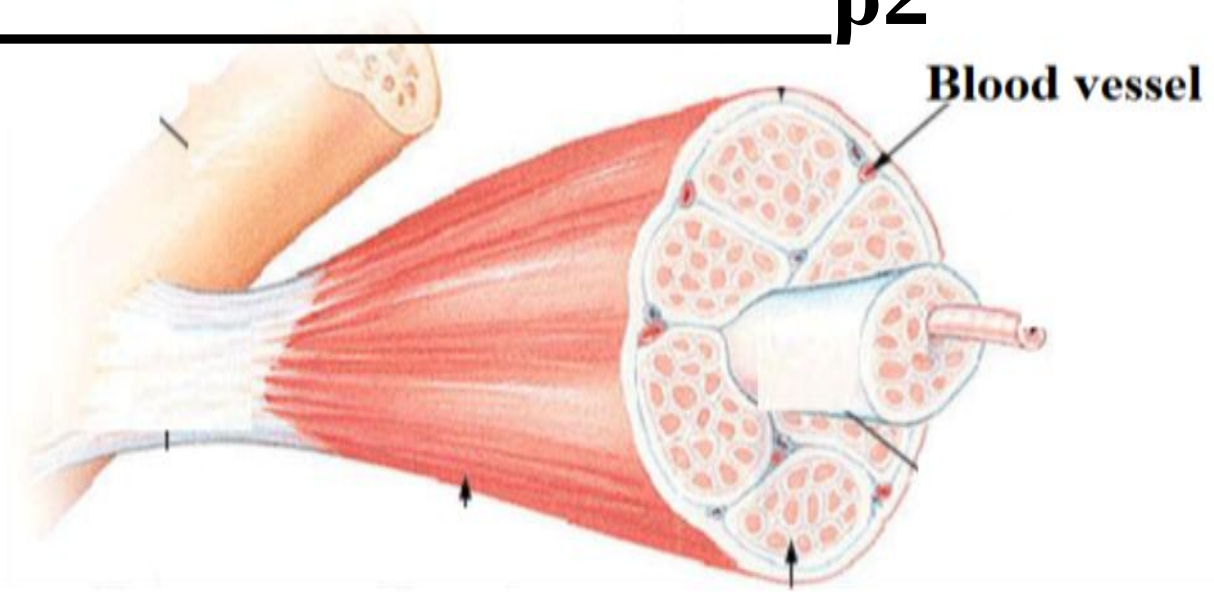
Uterus (pregnancy), Relaxation uterine smooth muscles

6.Arteries (β2 and α1):

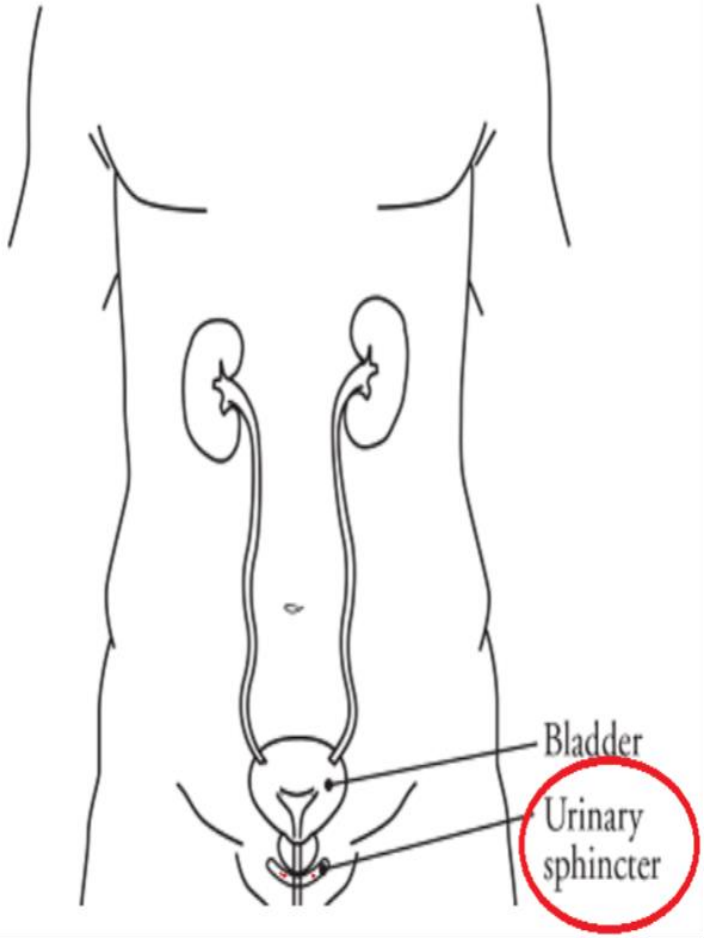
β2 decreases peripheral resistance Arterioles sketal muscles and vasodilation to supported blood to skeletal muscles. Blood vessels with α1-receptors are present in skin and during the **fight-or-flight** response, vasoconstriction results in the decreased blood flow to this organ. This accounts for an individual's skin appearing pale when frightened الخوف. This is also **reduce blood** pressure.

α1_____β2





7.Bladder (α1): increases closes the sphincter

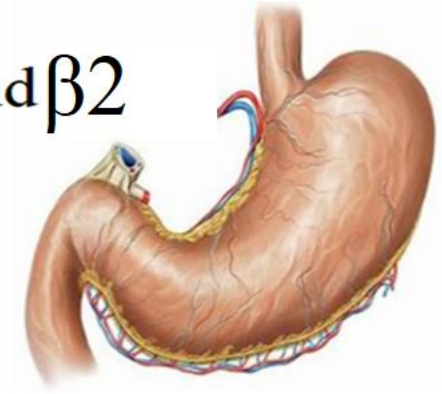


Tamsulosin is an α1 blocker of the most commonly used medicine and the first line treatment for the symptoms of BPH in men.

8. Stomach α1 & β2

α1 and β2

Decrease motility



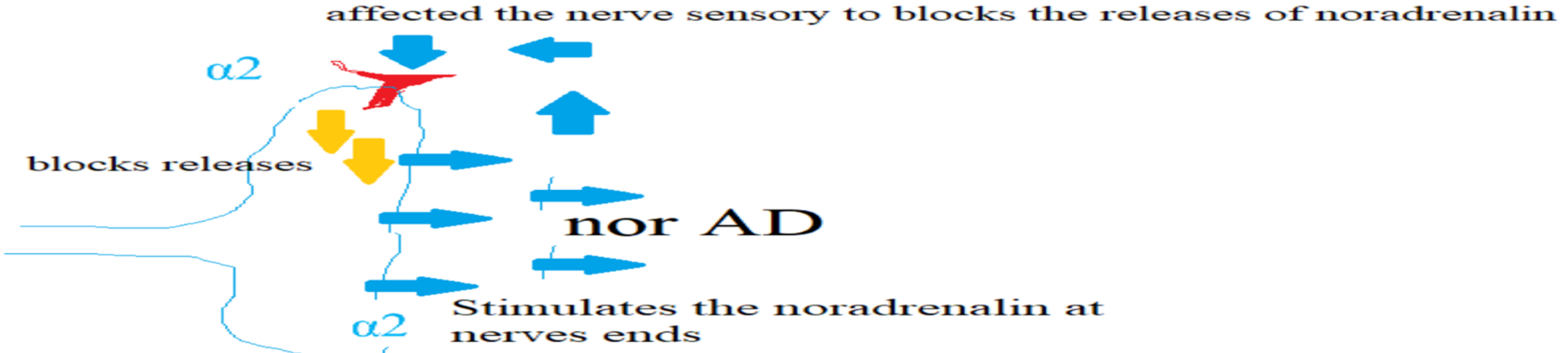
9.Eyes (α1)

Radial muscles contraction (Mydriasis)

(X myosis)

10.Nerve ends (α2)

Stimulates the noradrenalin which also affected the nerve sensory to blocks the releases of noradrenalin.



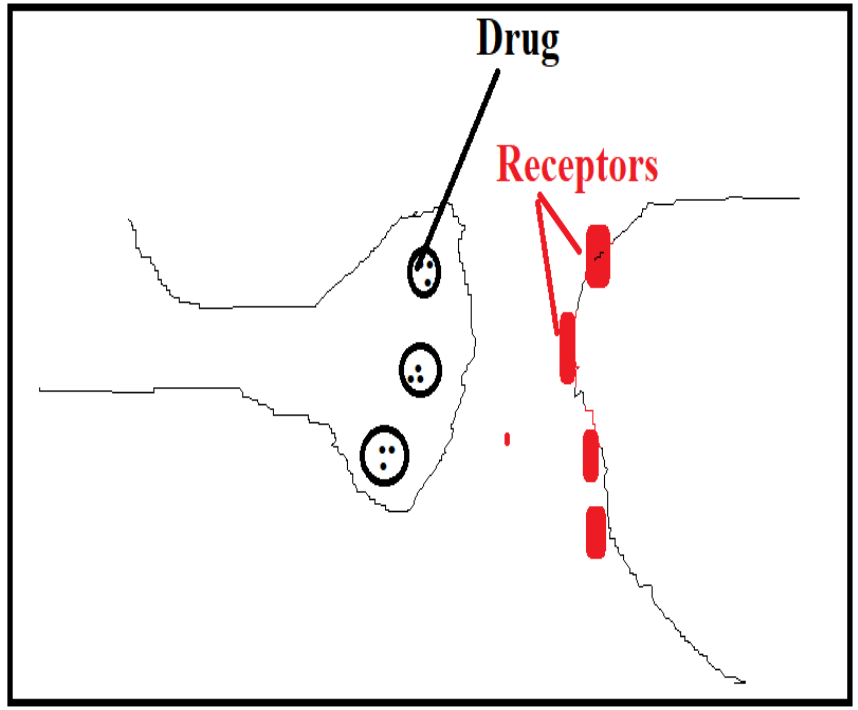
The usual use of drugs in medical treatment calls for the drug's effect to last for a finite period of time. Then, if it is to be repeated, the drug will be administered again. Q. If the patient does not tolerate* the drug well, it is even more important that the agent dissociate from the receptor and be excreted from the body, With major exceptions, include :

i. The alkylating agents used in cancer chemotherapy.

ii. A few inhibitors of the enzyme cholinesterase.

iii. Suicide inhibitors of monoamine oxidase (MAO)

v.The aromatase inhibitors like Exemestane (Aromasin) to treat breast cancer.



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*Patient Tolerate: Accept the action of a medication.

This is because these pharmacological agents form covalent bonds with the receptor, usually an enzyme's active site.

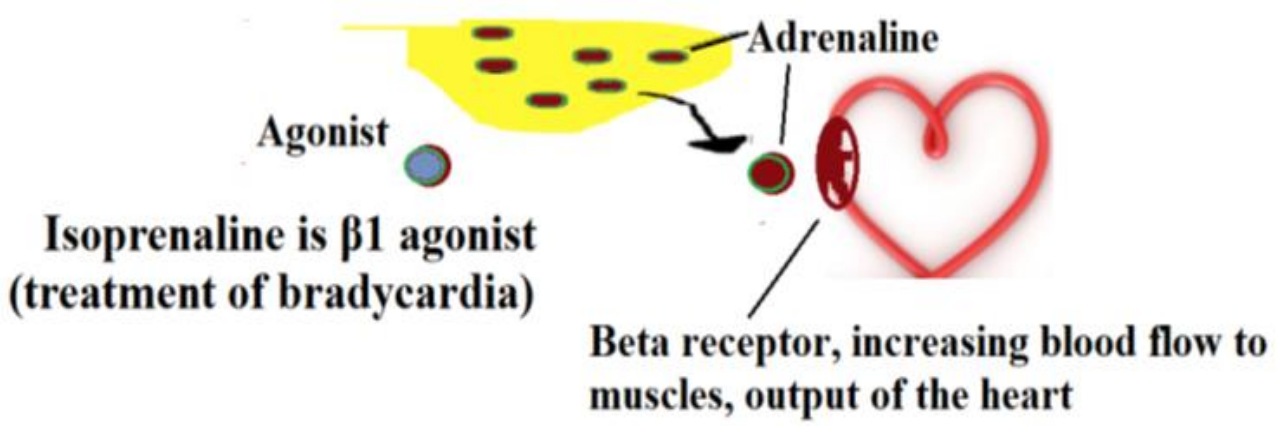
In these cases, the cell must destroy the receptor or enzyme, or, in the case of the alkylating agents, the cell would be replaced, ideally with a normal cell.

Agonist and Antagonist:

Agonist: Which activate receptor and give response as physiological signals.

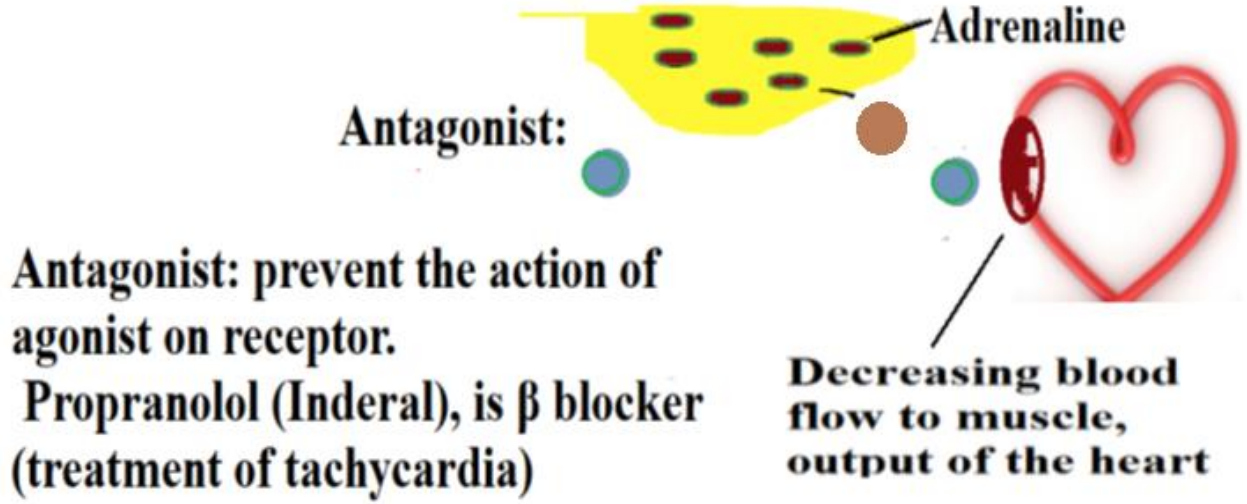
Isoprenaline is β1 agonist (treatment of bradycardia).

Antagonist: prevent the action of agonist on receptor. Propranolol (Inderal), is β blocker



Antagonist:

prevent the action of agonist on receptor.



Oral Administration:

Administration = The path by which a drug is taken into the body.

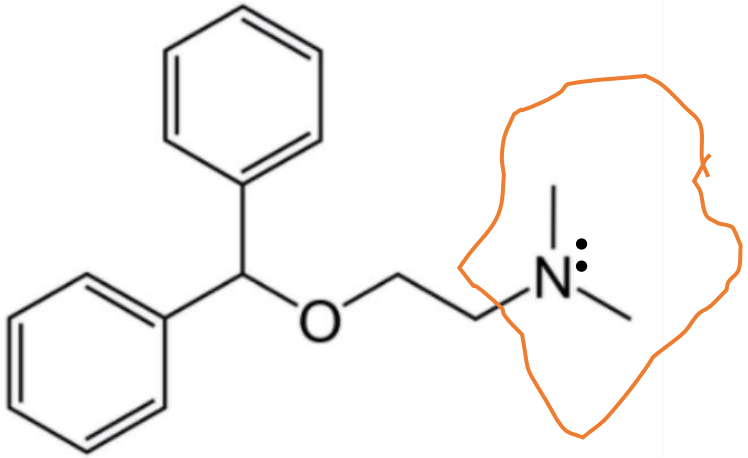
A better understanding of what is involved when the drug is administered orally, it must go into solution to pass through the GI mucosa.

*Even drugs administered as true solutions may not remain in solution as they enter the acidic stomach and then pass into the alkaline intestinal tract.

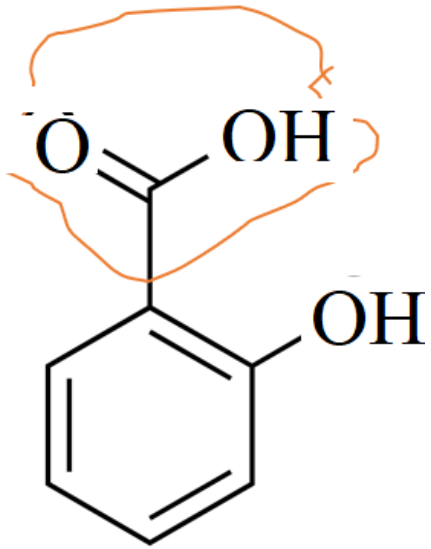
The ability of the drug to dissolve in

the body is governed by several factors, including:

i. Its chemical structure. Basic Antihistamine (Diphenhydramine) or acidic like salicylic acid

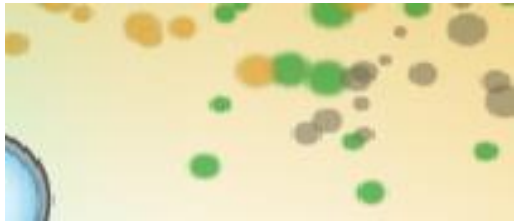


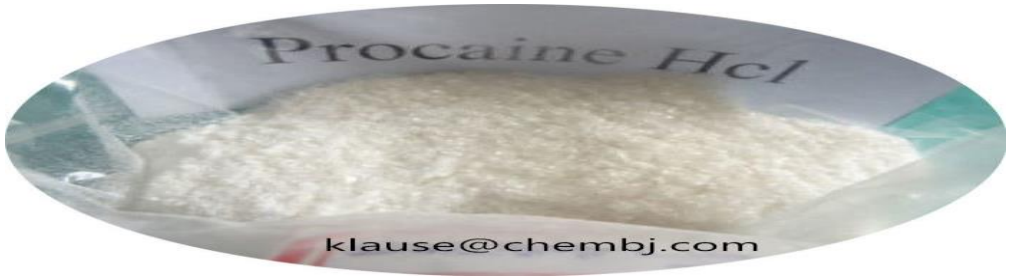
Diphenhydramine

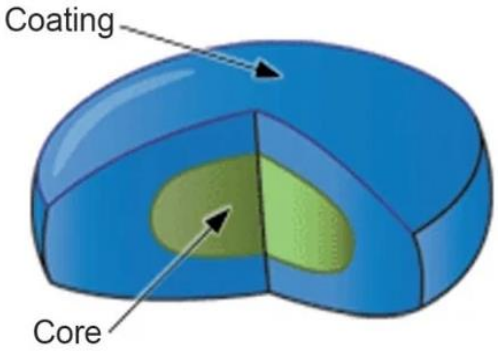


Salicylic acid

ii. Variation in particle size. iii. Variation in particle surface area.







iv. Nature of the crystal form. v. Type of tablet coating.

(e.g. sugar coated or enteric غلاف لايذوب الا بالامعاء) vi.Type of tablet matrix.

NOTES:

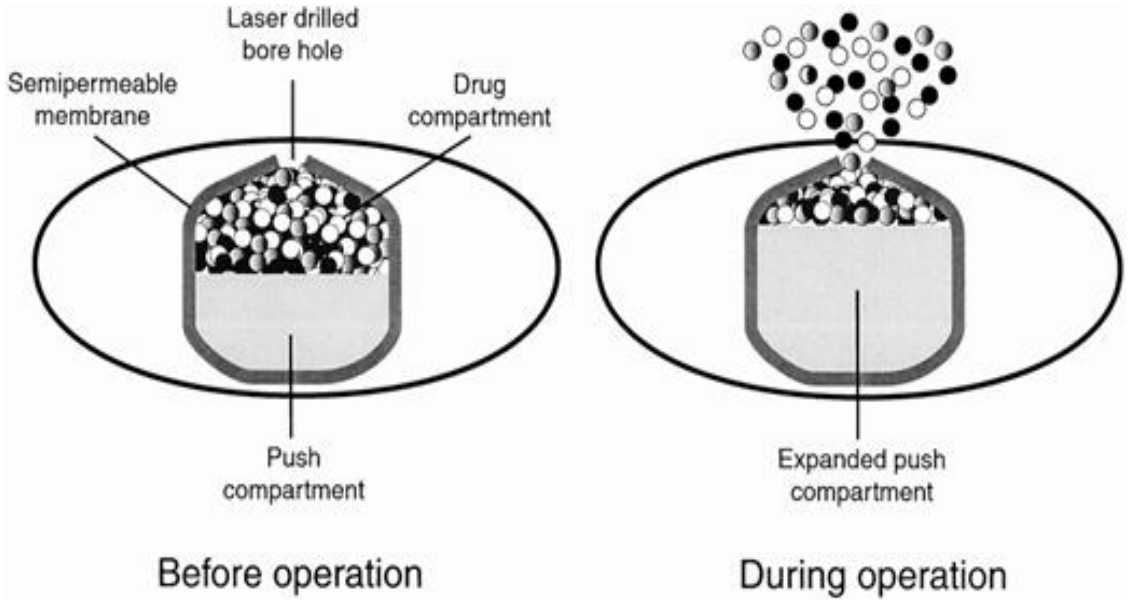
*1.By varying the dosage form and physical characteristics of the drug, it is possible to have a drug dissolve quickly or slowly.

e.g. liquid or suspension dosage form

2.*With the drug dissolve slowly being the situation for many of the **sustained** action products .الادوية التي تفرز بشكل مستدام او مستمر

e.g. oily testosterone need to be sustained released for one month

3.Orally administered sodium phenytoin , An example of variation of both the crystal form and tablet can significantly alter the bioavailability of this drug widely used in the treatment of epilepsy.



The Chemical Modifications effects on Administration :

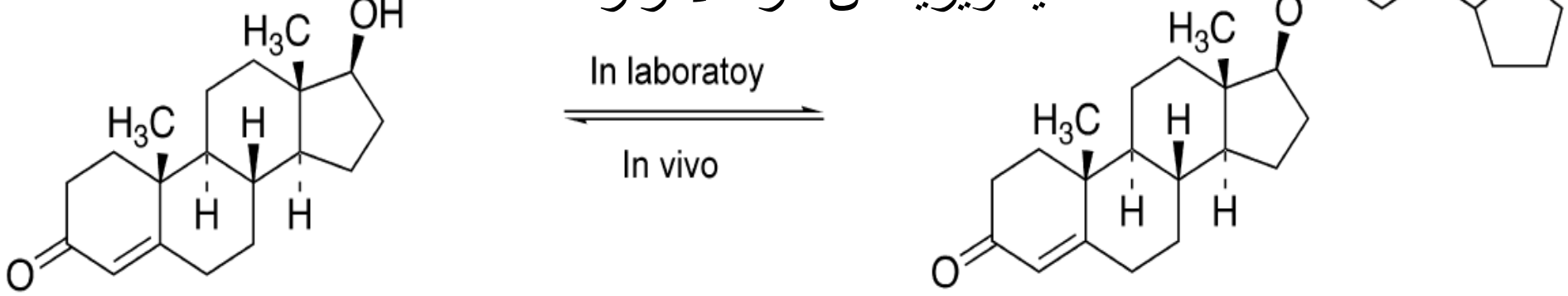
Chemical Modifications are used to a limited extent to facilitate a drug reaching its desired target (s), by many methods such as via a prodrug strategies.

Example -1-:

Q. What is the chemical modification on this drug chemical structure to solve the problem of lipid solubility and increases skin absorption?

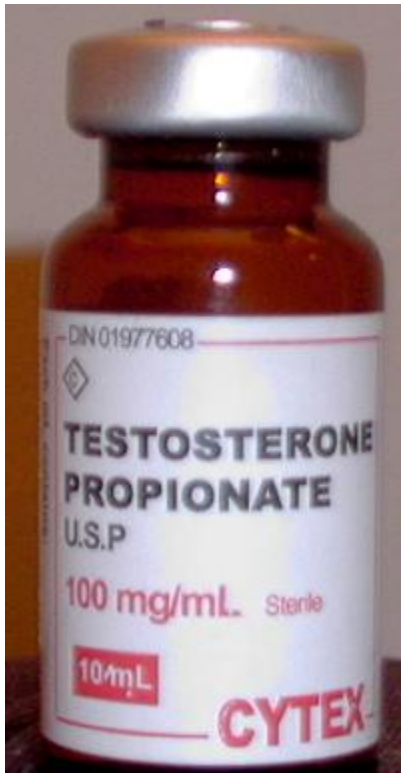
1. Increase Lipid Solubility (Slower rate of release for depot preparation; increase skin absorption)

زيادة الذوبانية بالشحوم يزيد من بقاءه بالمستودعات الشحمية ويزيد من فترة الافرازات المستدامة

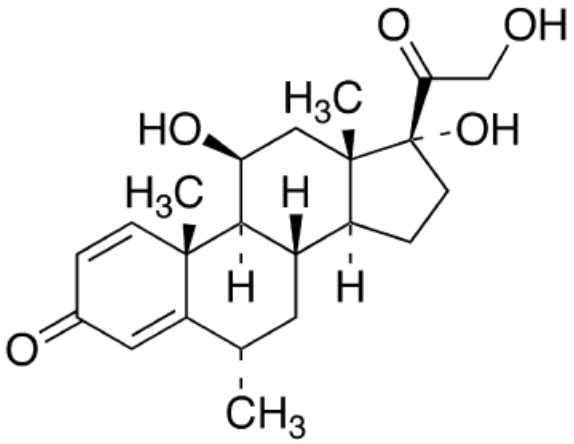


(IM dose: 10-25 mg 2-3 times/week)

Testosterone Cyclopentylpropionate*
(Testosterone cypionate; IM dose: 200-400 mg every 4 weeks)



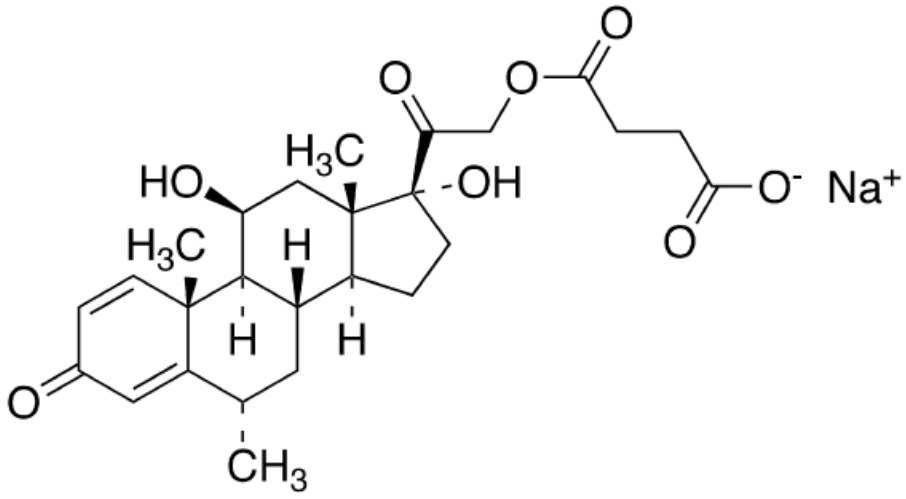
Example -2-:



Methylprednisolone
(Not water-soluble)

In laboratoy

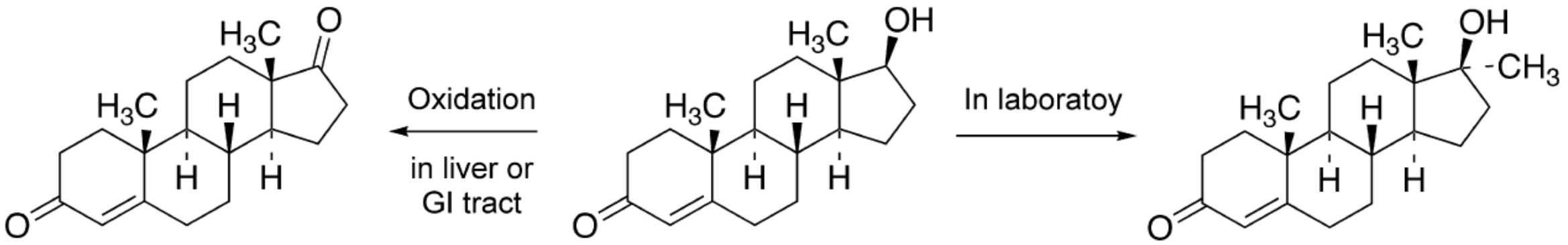
In vivo



Methylprednisolone Sodium Succinate*
(Sufficiently water-soluble for IV)

Q. What is the chemical modification on this drug chemical structure to solve the problem of water insolubility and make it sufficiently water-soluble for IV.?

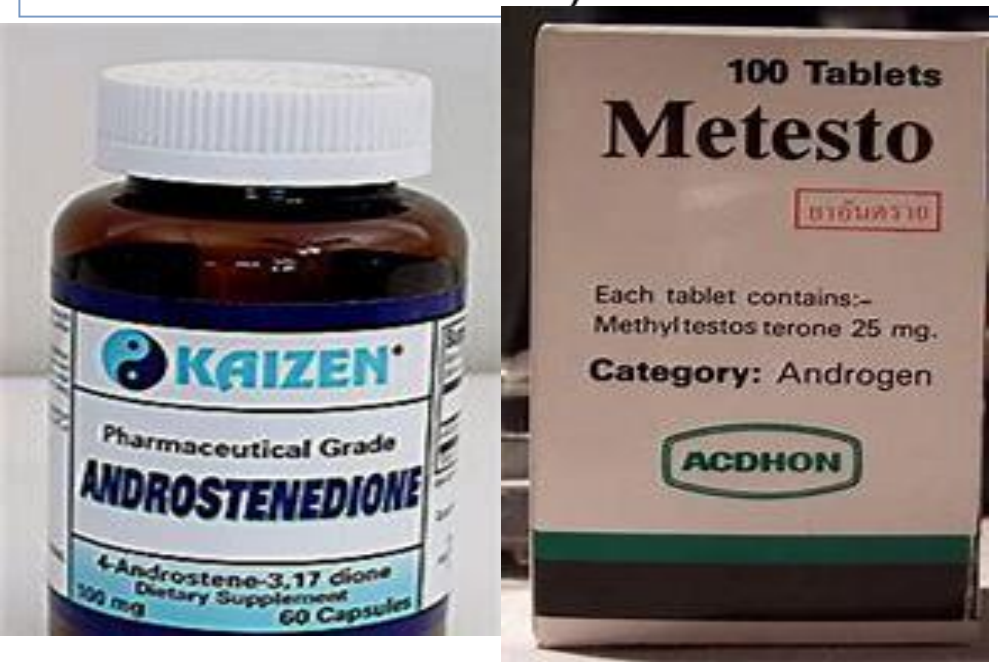
3. Decrease Inactivation



Androstenedione
(Reduced activity relative to testosterone)

Testosterone
(Not orally active)

17α-Methyltestosterone
(Orally active – 17 oxidation not possible)



Testosterone, orally inactive and its oxidation in liver to less active Androstenedione. Methylation at position17-alpha Methyltestosterone make it orally active.

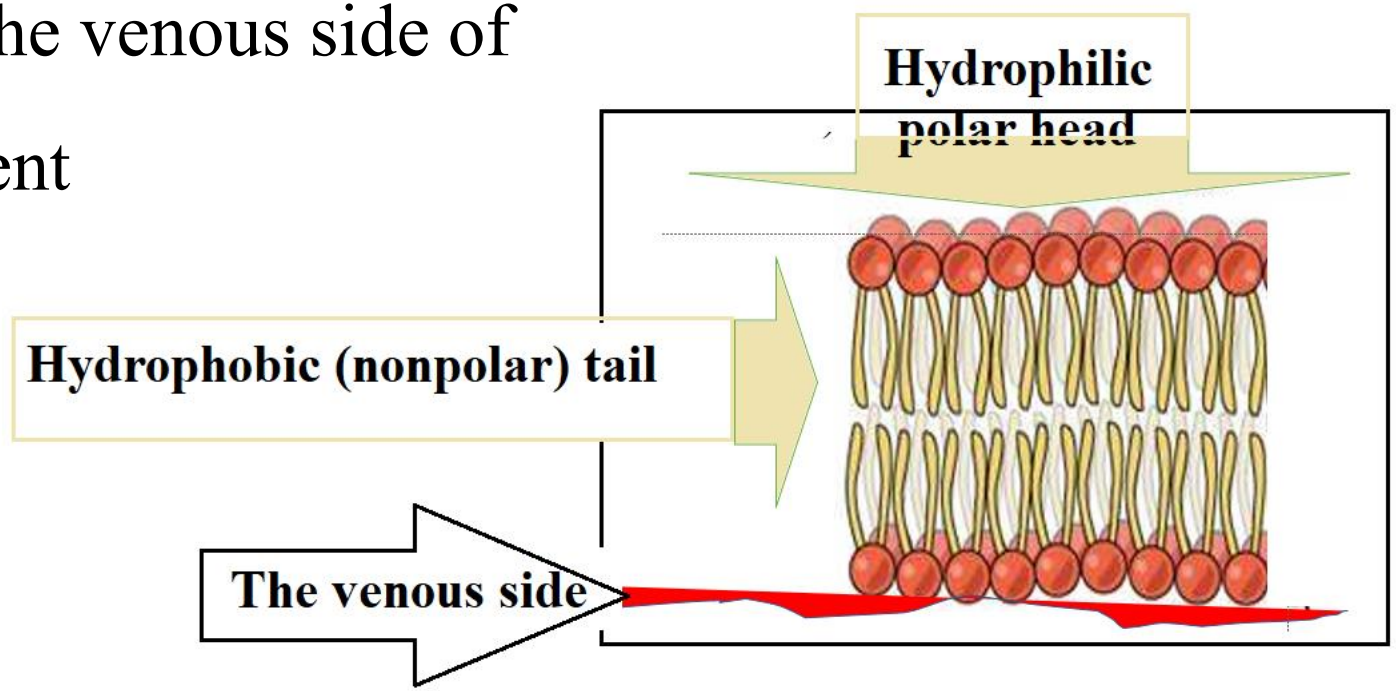
The drug’s route

The drug’s route involves *(Q.What does the drug's rout involve?)

1.Distribution or partitioning between the aqueous environment of the GIT.

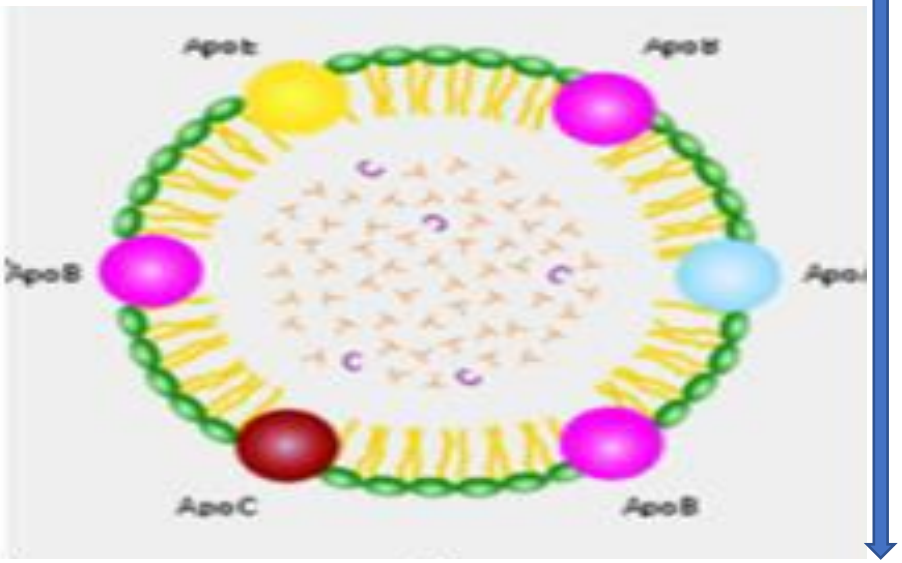
2. Distribution or partitioning between the lipid bilayer cell membrane of the mucosal cells (possibly the aqueous interior of the mucosal cells)

3.The lipid bilayer membranes on the venous side of the GIT and the aqueous environment of venous circulation.

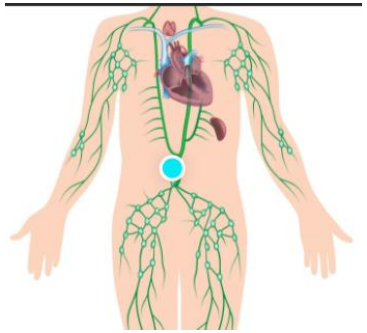


4.Some very lipid soluble drugs may follow the route of dietary lipids by becoming part of the mixed micelles(my. cells), incorporating into the Chylomicrons (kello . Microns)* in the mucosal cells into the lymph ducts, servicing تخدم فيها الامعاءthe intestines.

The mixed micelles, incorporating into the chylomicrons



5. Entering venous circulation via the thoracic صدري duct.



*** A droplet of fat present in the blood or lymph after absorption from the small intestine.**

The relationship between the right lymphatic and thoracic ducts and the venous system

Right Lymphatic Duct

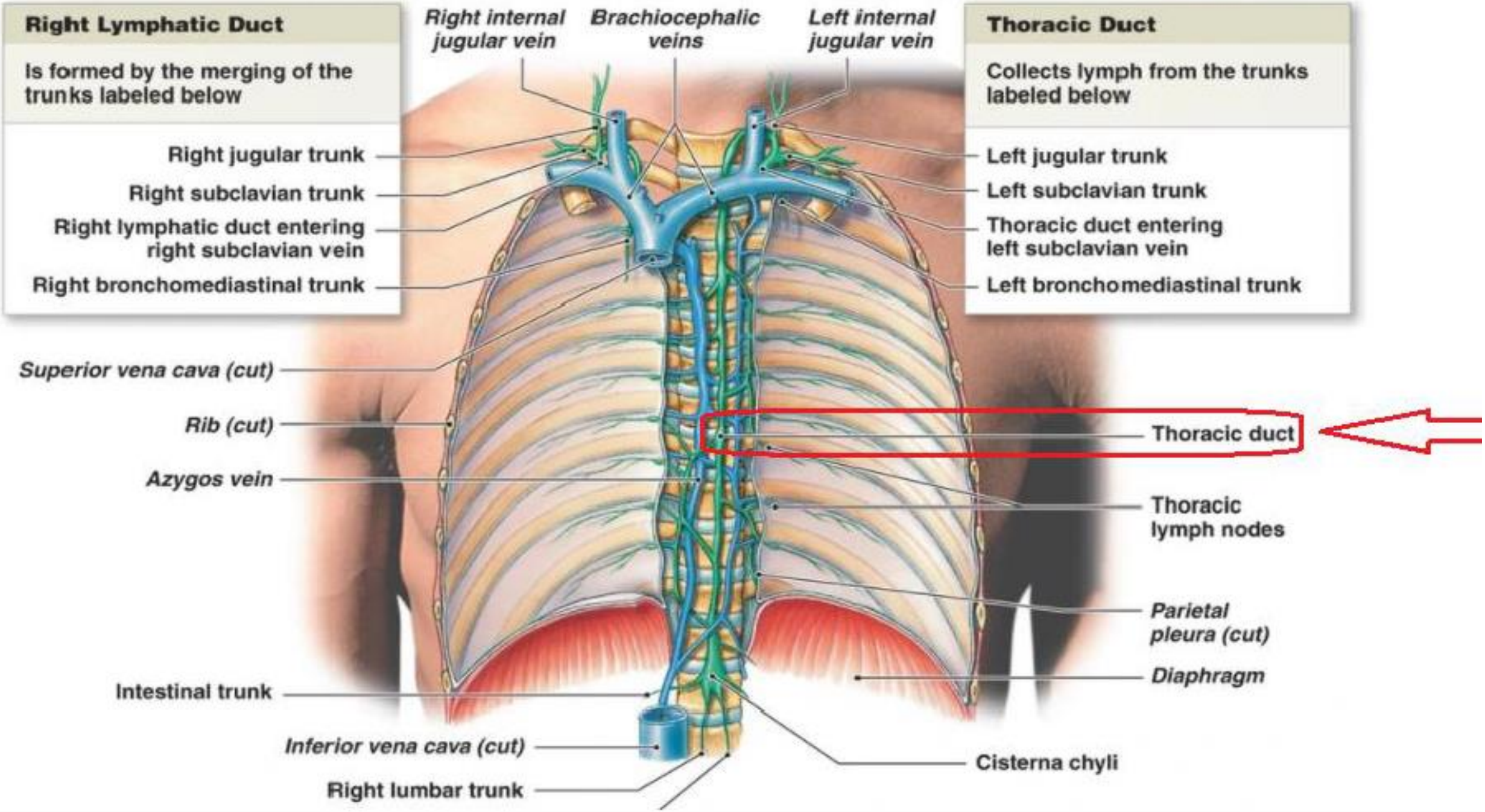
Is formed by the merging of the trunks labeled below

- Right jugular trunk
- Right subclavian trunk
- Right lymphatic duct entering right subclavian vein
- Right bronchomediastinal trunk

Thoracic Duct

Collects lymph from the trunks labeled below

- Left jugular trunk
- Left subclavian trunk
- Thoracic duct entering left subclavian vein
- Left bronchomediastinal trunk

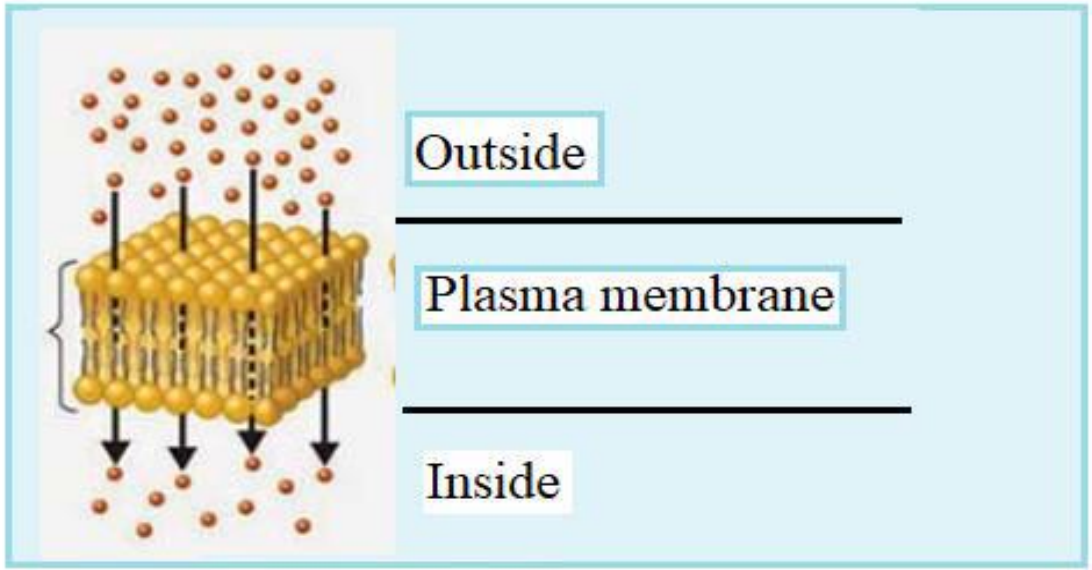


Types of drugs Transports

*The drug's passage through the mucosal cells can be two transports types:

1. Passive Transport: السلبي

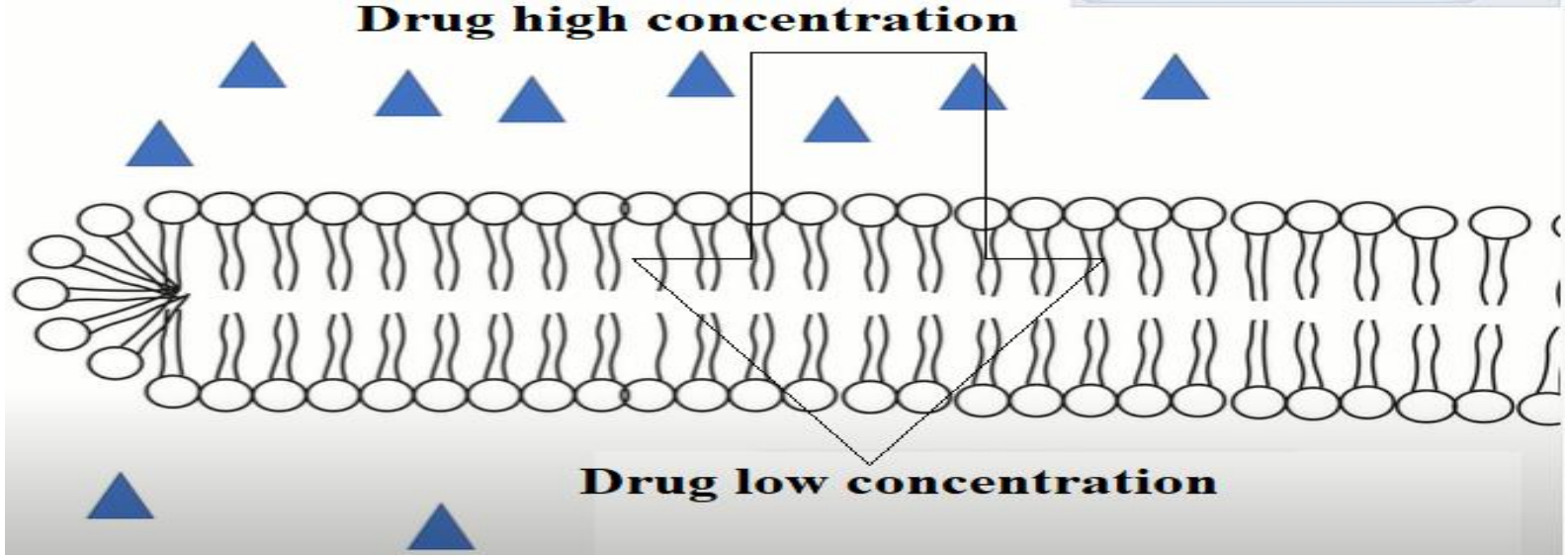
i.The most direct forms of membrane transport, which is a naturally occurring phenomenon and does not require the cell to exert any of its energy to accomplish the movement.



Simple active diffusion through the lipid bilayer

ii.It is a process by which a drug ion or molecule passes through a cell via a concentration gradient (الفرق بالتركيز)from an area of high concentration to an area of low concentration) without the spending of energy.

Passive Transport:



2. Active transport الفعال

The movement of drug molecules across a cell membrane from a region of lower concentration to a region of higher concentration against the concentration gradient.

Active transport requires cellular energy to achieve this movement.

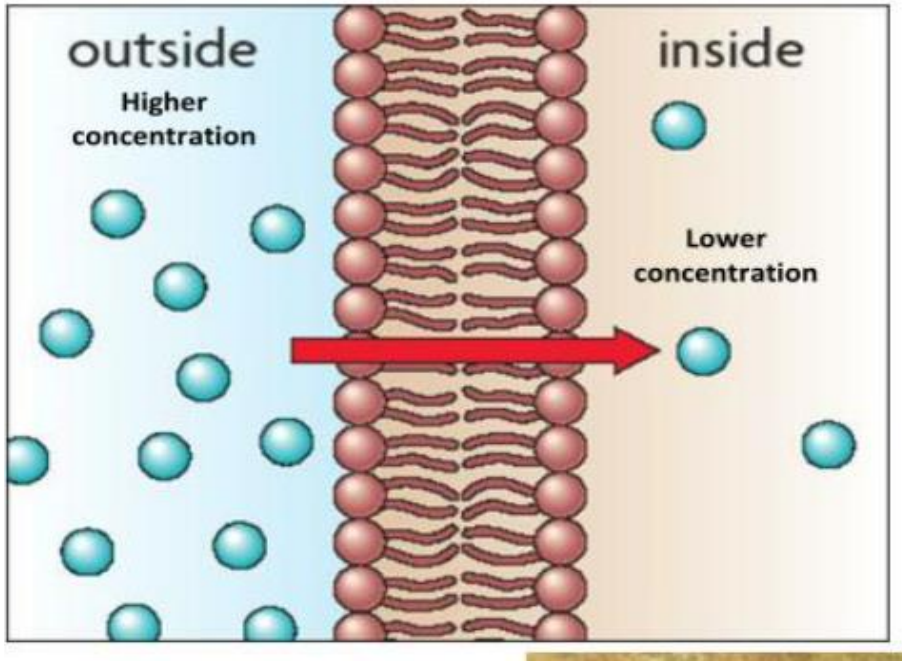
***There are two types of active transport:**

i) 1^{O} active transport that uses adenosine triphosphate ATP ,

ii)2^{O} active transport that uses an electrochemical gradient.

Note: معظم جزيئات الادوية اكبر من ان تدخل الخلية بميكانيكية النقل الفعال خلال الممرات وانما تدخل الى الدورة الدموية من خلال النقل السلبي

*Most drug molecules are too large to enter the cell by an active transport mechanism through the passages. They pass into the patient's circulatory system by passive diffusion.



Drug molecules pass into the patient's circulatory system by transport mechanism through the passive diffusion.

Pinocytosis:*

(Q. Define and discuses with drawing the Pinocytosis three steps)

The uptake of extracellular fluids and solutes, such as fat droplets, vitamins, and antigens. It is derived from the Greek word "pino," meaning "to drink," and "cyto," meaning "cell."

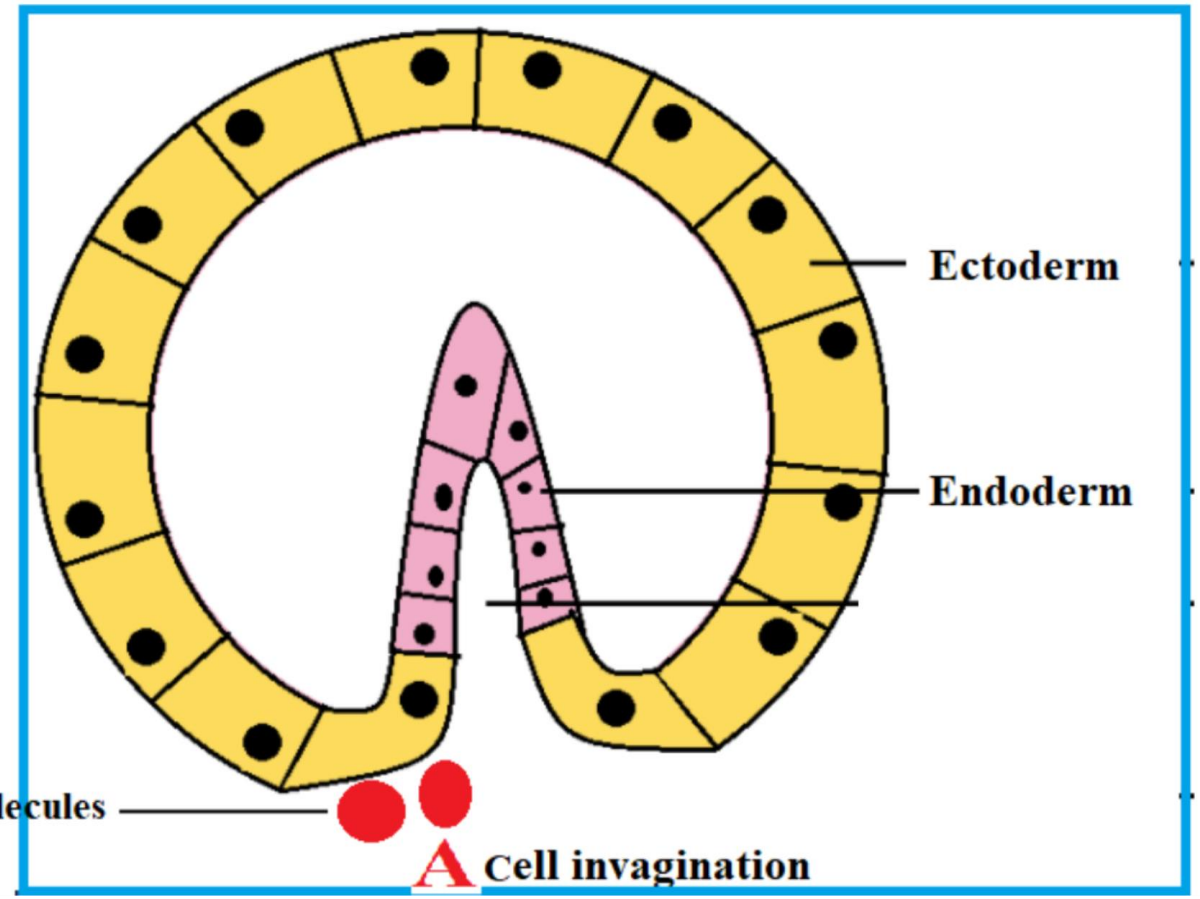
The drugs diffusing (as fluid or particles) through:

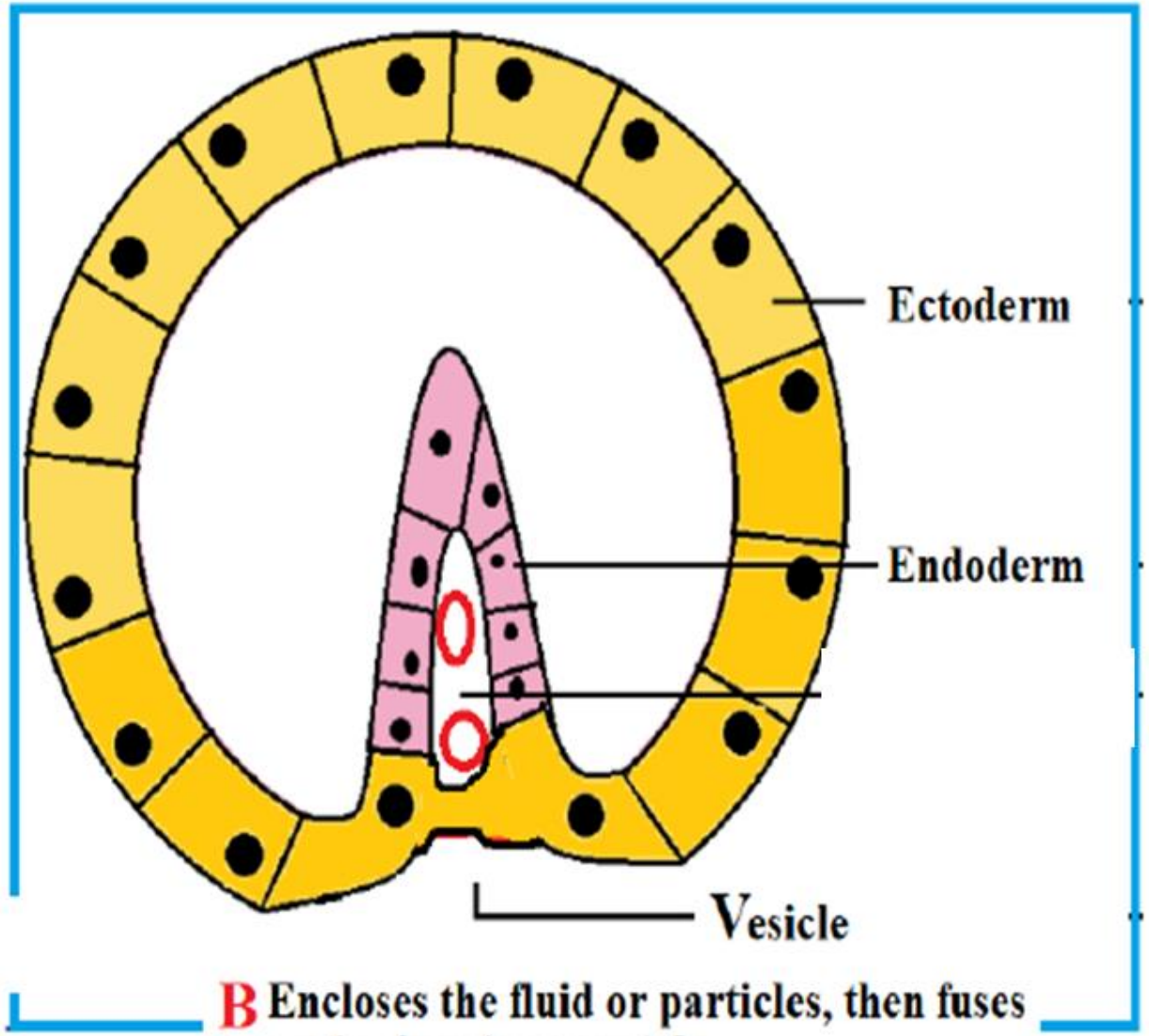
i. Surrounded invaginates(i.va.gen.ate) تتخصر للداخل and encloses وتحيط by the cell membrane then

ii. Fuses again, forming a vesicle حويصلةthat later

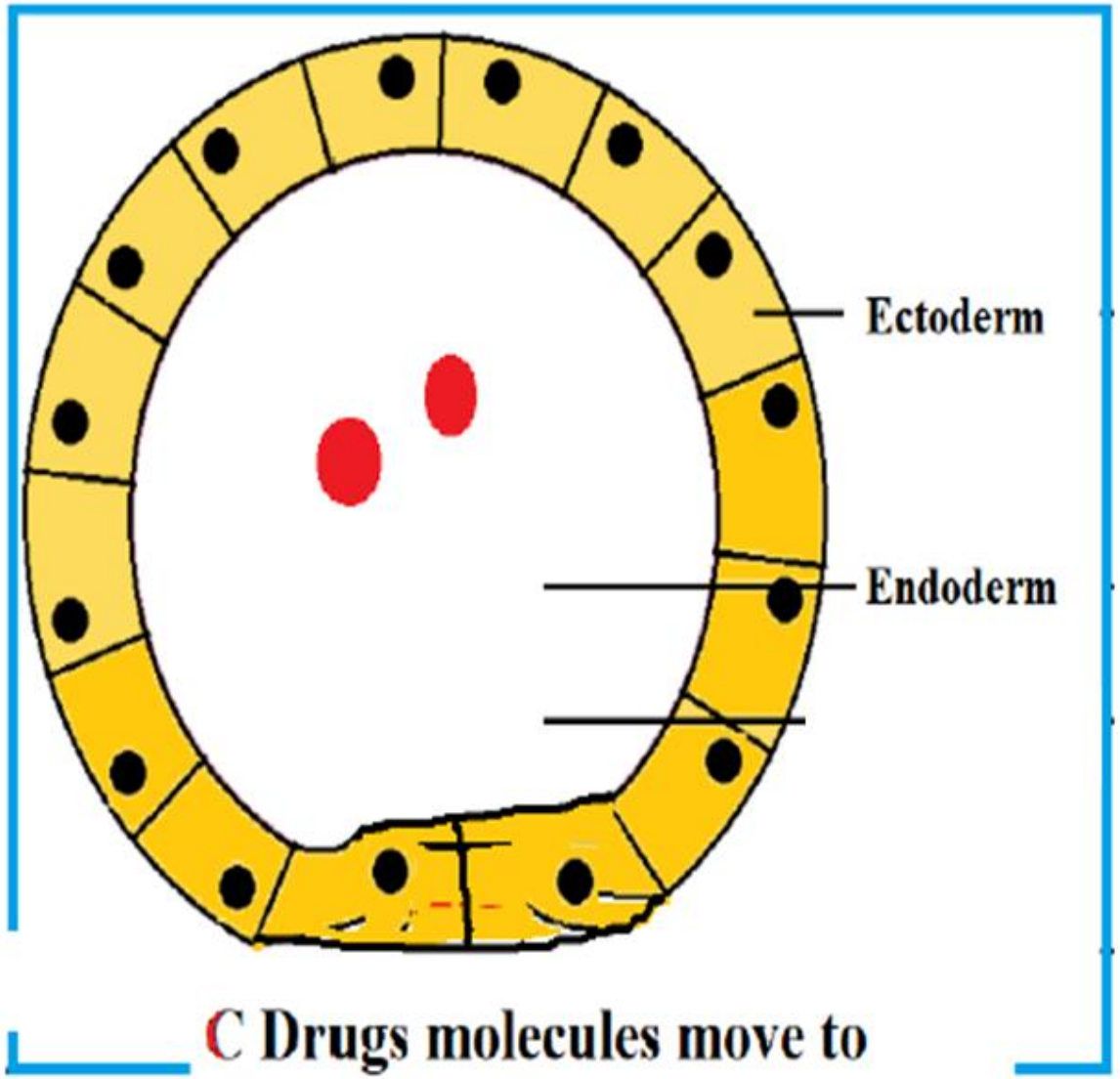
iii. Moves to the cell interior with en

*Pinocytosis probably plays a small role in drug transport, except for **protein drugs**





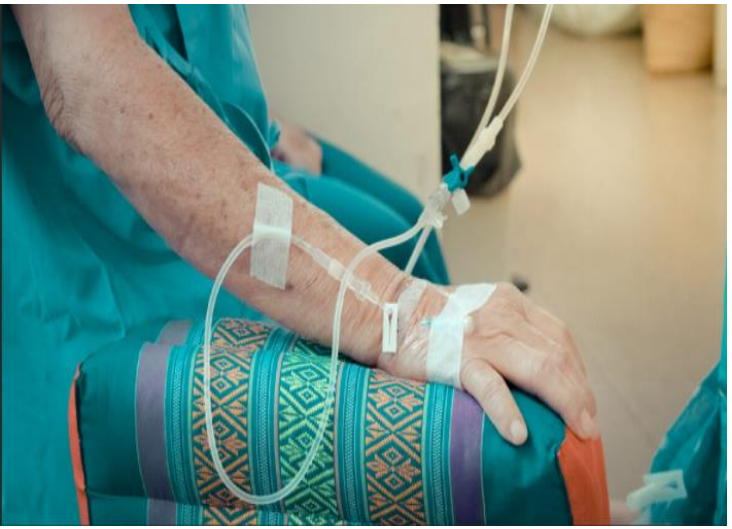
B Encloses the fluid or particles, then fuses again, forming a vesicle



C Drugs molecules move to the cell interior

Parenteral route of drug administration or Parenteral dosage forms are intended for administration of a drug as an injection or infusion.

*Parenteral Administration are Four types



The therapeutic advantages in bypassing the intestinal barrier تجاوز حاجز الامعاءby using parenteral (injectable) dosage forms:

*Q. What are the five advantages ?

i. Patients who, because of illness, cannot tolerate (incapable of accepting) drugs orally.

ii. Some drugs are so rapidly and completely metabolized to inactive products in the liver (first pass effect) that oral administration is inacceptable.

iii. (I.V.) Administration places the drug directly into the circulatory system, where it will be rapidly distributed throughout the body.

iv.*Subcutaneous (SC) and intramuscular (IM) injections slow distribution of the drug, because it must diffuse from the site of injection into systemic circulation.

v. It is possible to inject the drug directly into specific organs or areas of the body, such as (intraspinal داخل النخاع الشوكي Intracerebral داخل المخroutes) will place the drug directly into the spinal fluid or brain, respectively.

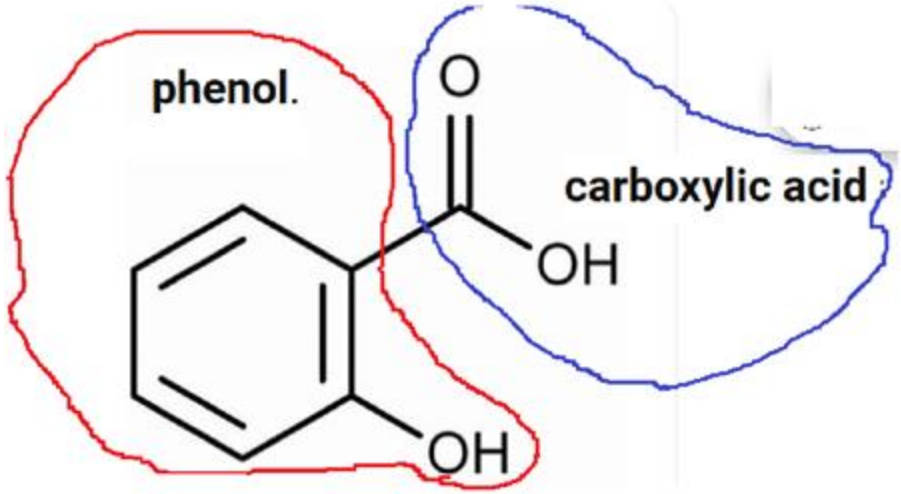
The blood brain barrier BBB, which protects the brain from exposure to a large number of metabolites and chemicals, BBB is composed of membranes of tightly joined epithelial cells lining the cerebral capillaries. الخلاية الضهارية المبطنة للشعيرات الدموية الدماغية

*The net result is that the brain is not exposed to the same variety of compounds that other organs are.

Lecture 2,

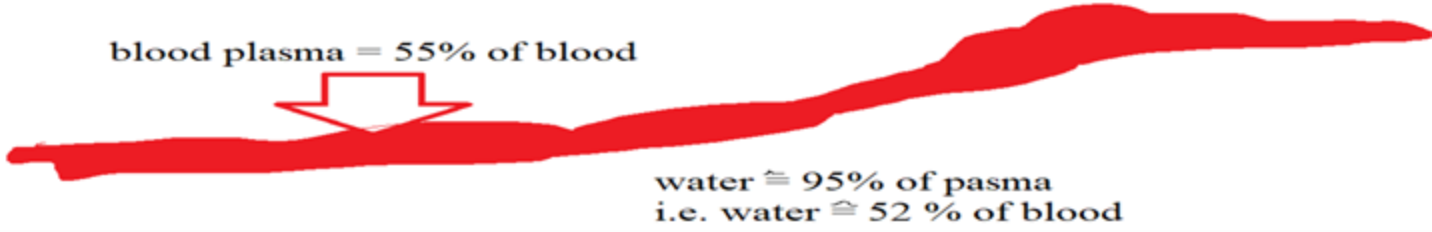
ACID BASE PROPERTIES OF DRUGS:

Organic fictional groups within a drug molecule are influence on :



Salicylic acid
(2-Hydroxybenzoic acid)

i.Water solubility ii. Lipids solubility iii. Acid-base properties iv. Partion coefficient معامل الانتشار v. Steric factors vi. Stereochemistry.

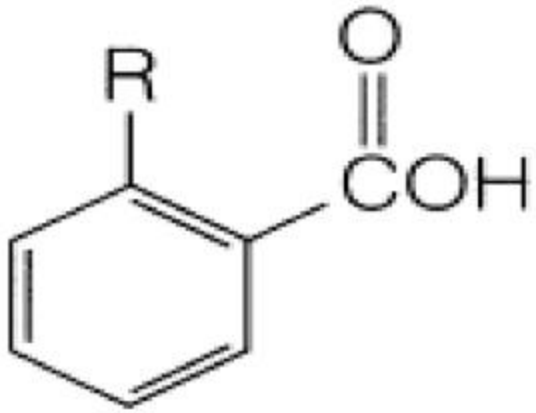


Acid-base properties help in:

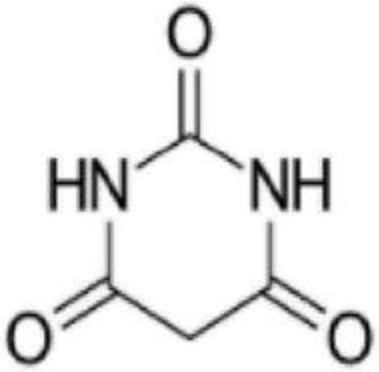
i. Absorption, un-ionized form (lipid soluble) ii. Distribution: ionized form (soluble in plasma) and iii. Excretion, Drug-receptor interaction and Drug-drug incompatibility.

Important Notes:

1.Most drugs can behave as either acids, bases or neutral as they begin their journey into the patient body in different dosage forms and end up in systemic circulation. Examples of acidic functional groups:



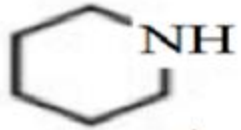
Benzoic Acid, R = H
Salicylic Acid, R = OH



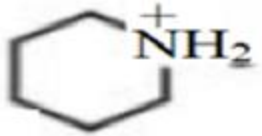
Why acid ?

Barbituric acid is the parent compound of barbiturate drugs, although barbituric acid itself is not pharmacologically active.

Examples of Acid or Basic functional groups

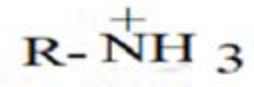


Cyclic alkyl amine
pKa (10-11)

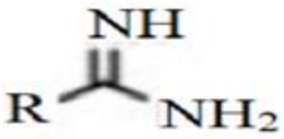


Cyclic alkyl ammonium
Conjucated acid

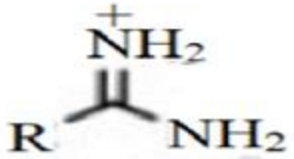
Alkylamine
pKa(9-10)



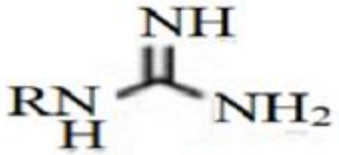
Alkylammonium
Conjucated acid



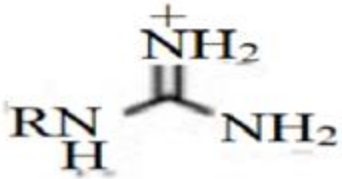
Amidine
pKa (10-11)



Amidinium
Conjucated acid



Guanidine
pKa(12-13)



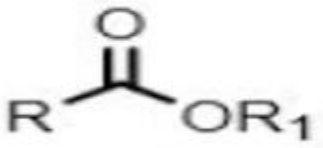
Guanidinium
Conjucated acid

Examples of neutral functional groups

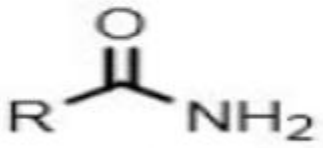
alkyl alcohol

ether

nitrile

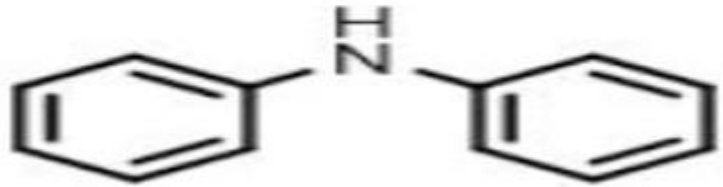


ester



amide

ketone &
aldehyde



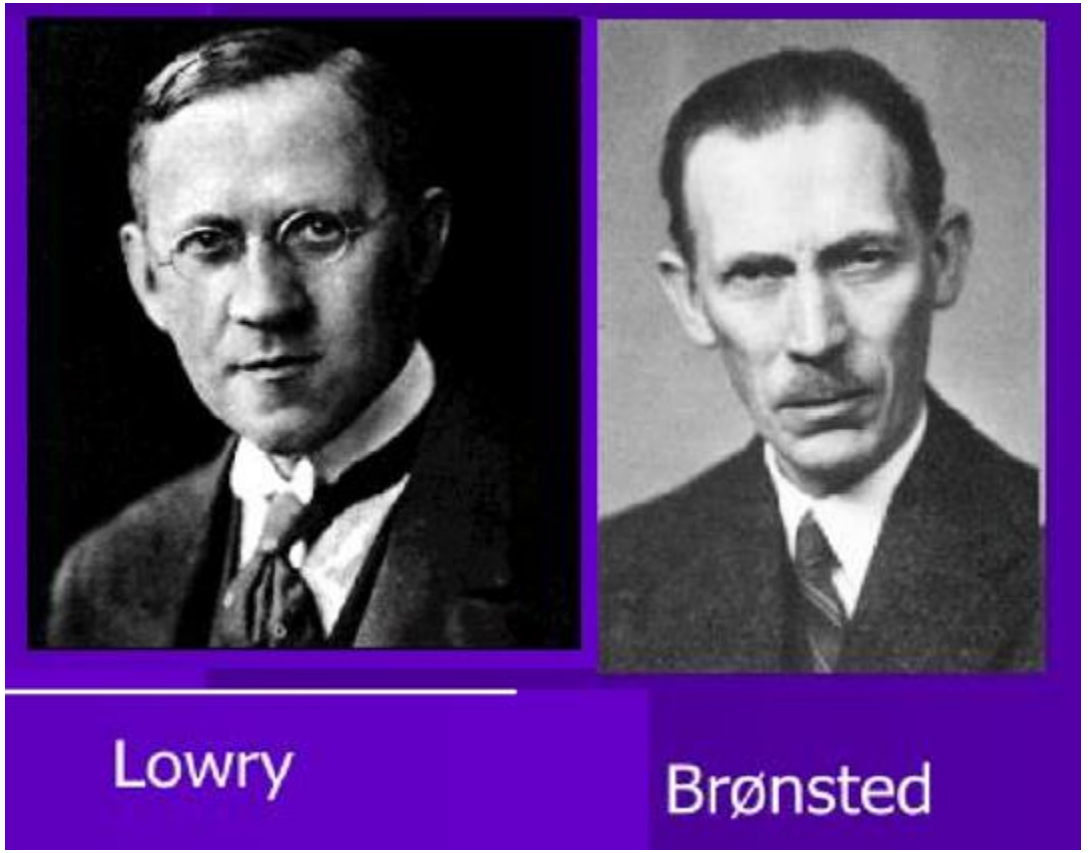
diarylamine

2.Drug's biodistribution and partitioning characteristics can greatly influence by its acid-base properties.

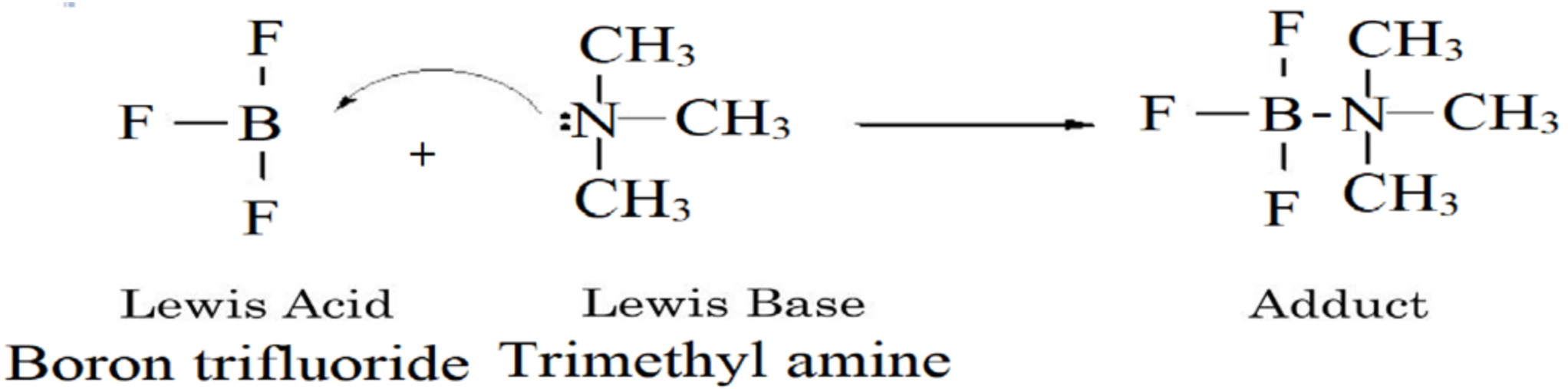
3.Acid and base major definitions model commonly used in pharmacy and biochemistry were developed by Lowry and Brønsted.

In their definition:

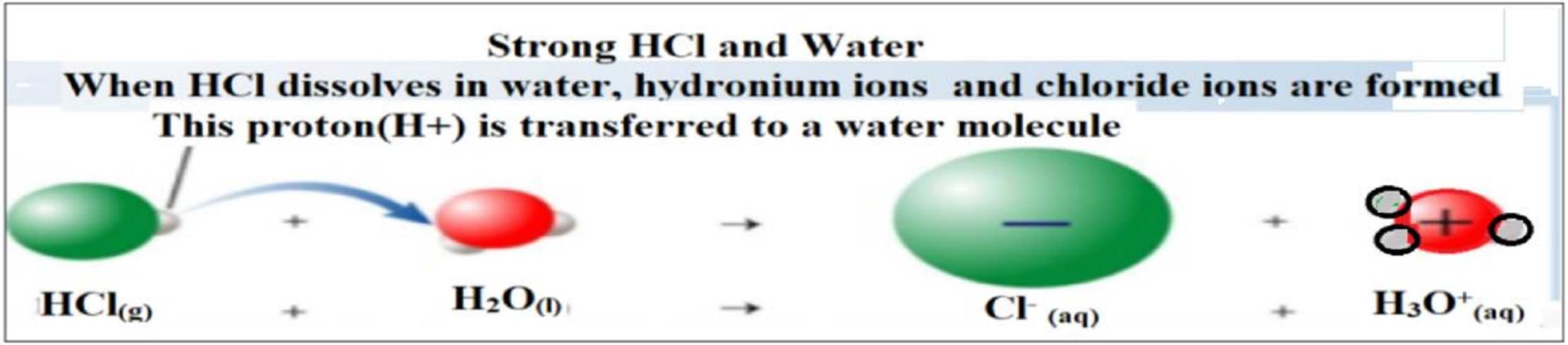
An acid is defined as a proton donor and a base is defined as a proton acceptor.



Lewis acids and bases are described by the Lewis theory of acid-base reactions as electron-pair acceptors and electron pair donors respectively. Therefore, a Lewis base can donate a pair of electrons to a Lewis acid to form a product containing a coordinate covalent bond.



Notice that for a base, *there is no mention of the hydroxide ion*. In the Brønsted-Lowry and Brønsted model, the acid plus base reaction can be expressed as:



Acid Base conjugate base conjugate acid

Notes:

i. The removal of H^+ from the HCl produces the chloride ion, Cl^-, the conjugate base of the acid.

ii. The addition of H^+ to the H_2O (acting as a base) forms the hydronium ion, H_3O^+ , (also oxonium ion) the conjugate acid of the base.

Water is Amphoteric*: That is, it can acts as both an acid and a base.

***Greek amphoteric = "each or both of two"**

All acids have a conjugate base.

All bases have a conjugate acid.

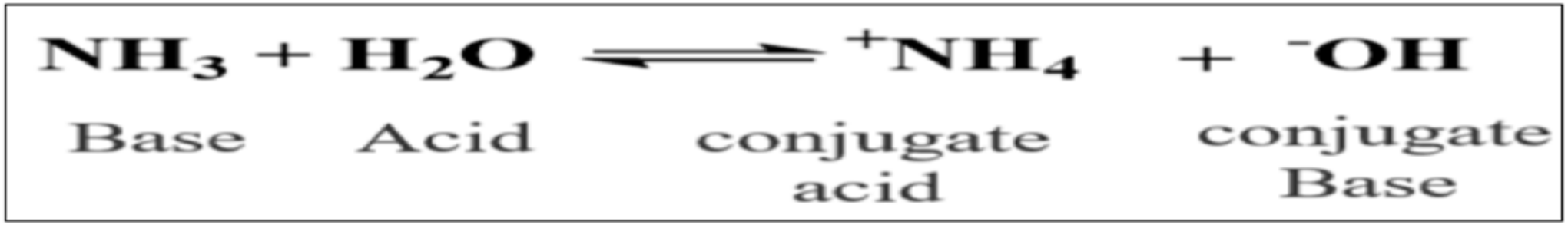
Acids "donate" H^+ when they react.

This is most easily seen when they dissociate in water:

In this example, sulfuric acid is an acid because it "donates" H^+ to the water. It becomes the hydrogen sulfite ion (HSO^-_4) which is the conjugate base of sulfuric acid.

The same idea applies to a base:

Ammonia (NH_3) is a base because is "accepts H^+ from water to come its conjugate acid, the ammonium ion ($^+NH_4$)



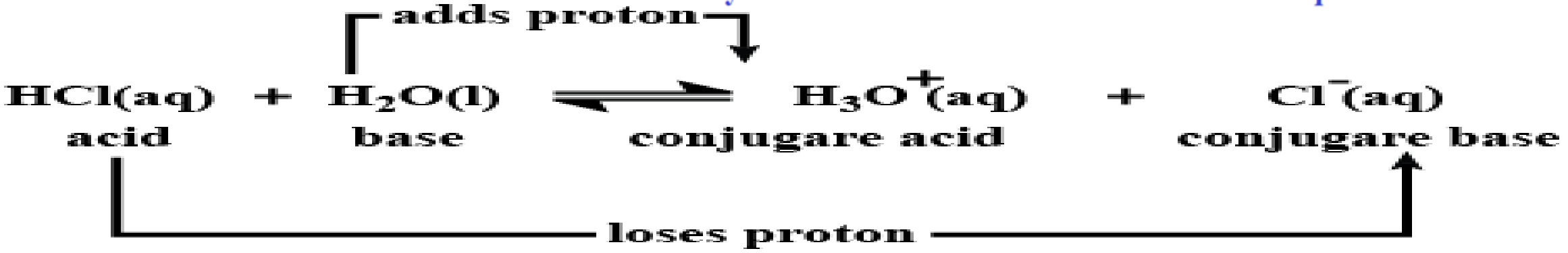
*Give equations showing the amphoteric characters of water

Example-1-

Water and its amphoteric characters

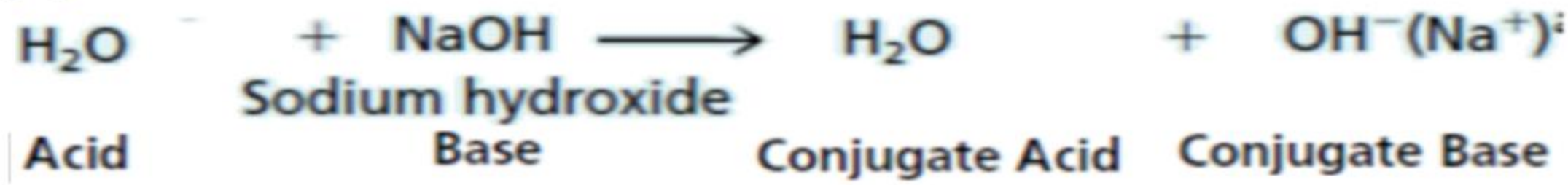
Any acid–base reaction can be written as an equilibrium reaction

a)



Cl^-, is such a weak base that it essentially does not function as a proton acceptor, and there is little reverse reaction involving water donating a proton to the hydroxide anion of ^-OH

(b)



water is such a weak conjugate acid that there is little reverse reaction involving water donating a proton to the hydroxide anion of ^-OH

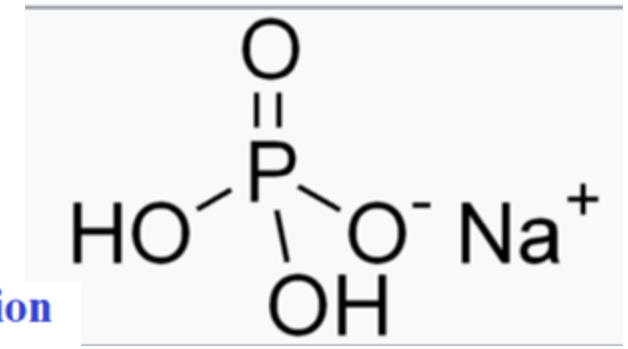
قوة هيدروكسيد الصوديوم كقاعدة حتى لو اكتسبت بروتون من الماء فانه سيصبح ايون الهيدروكسيد السالب الذي سيتحد مع ايون الصوديوم الموجب وترجع المواد كما هي

Drugs examples:

Example-2-

Sodium dihydrogen phosphate and its conjugated base monhydrogen phosphate

It is added in animal feed, toothpaste, and evaporated milk. It is used as a thickening agent and emulsifier.



Any acid–base reaction can be written as an equilibrium reaction

(c) $H_2PO_4^-(Na^+)$ + H_2O ⇌ H_3O^+ + $HPO_4^{2-}(Na^+)$

(d) H_2O + $HPO_4^{2-}(2Na^+)$ ⇌ $H_2PO_4^{2-}(Na^+)$ + $OH^-(Na^+)$

Acid + Base ⇌ Conjugate Acid + Conjugate Base

Example -3-:

Acetic acid and it's conjugated base, acetate:

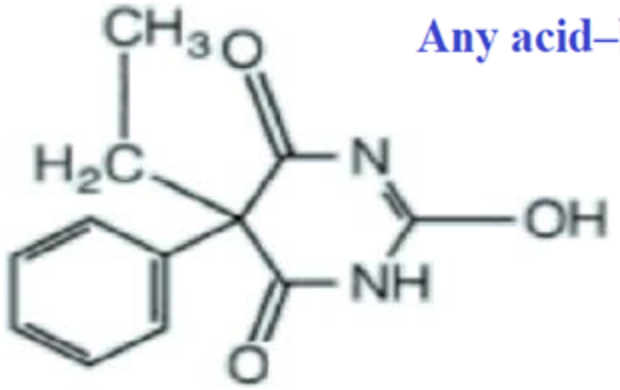
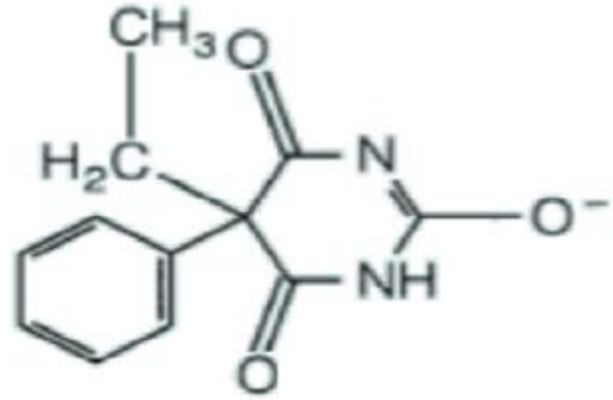
Any acid–base reaction can be written as an equilibrium reaction

Example -4- :

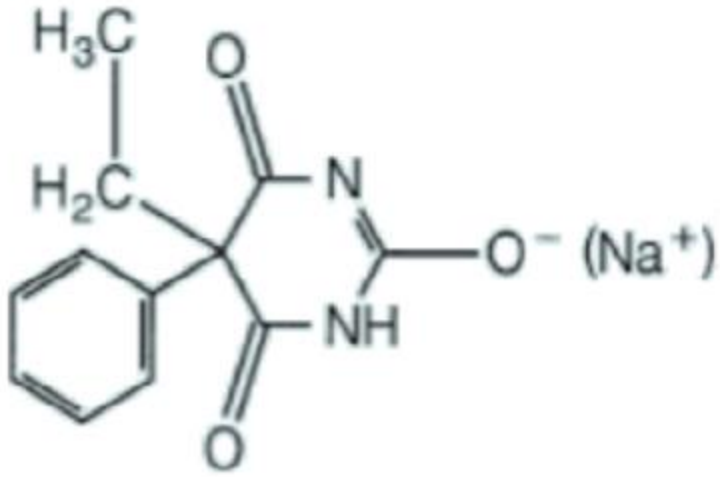
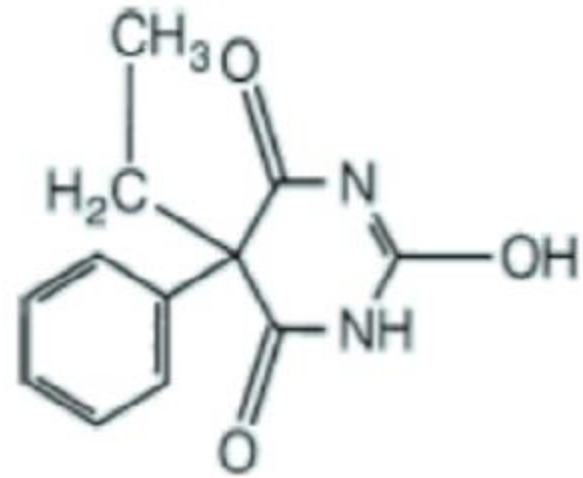
Phenobarbital and its conjugated base phenobarbital sodium:

Phenobarbital belongs to a class of drugs known as barbiturate anticonvulsants/hypnotics. It works by controlling the abnormal electrical activity in the brain that occurs during a seizure. This medication is also used for a short time (usually no more than 2 weeks) to help calm (KA. LM) or sleep during periods of anxiety.

Any acid–base reaction can be written as an equilibrium reaction

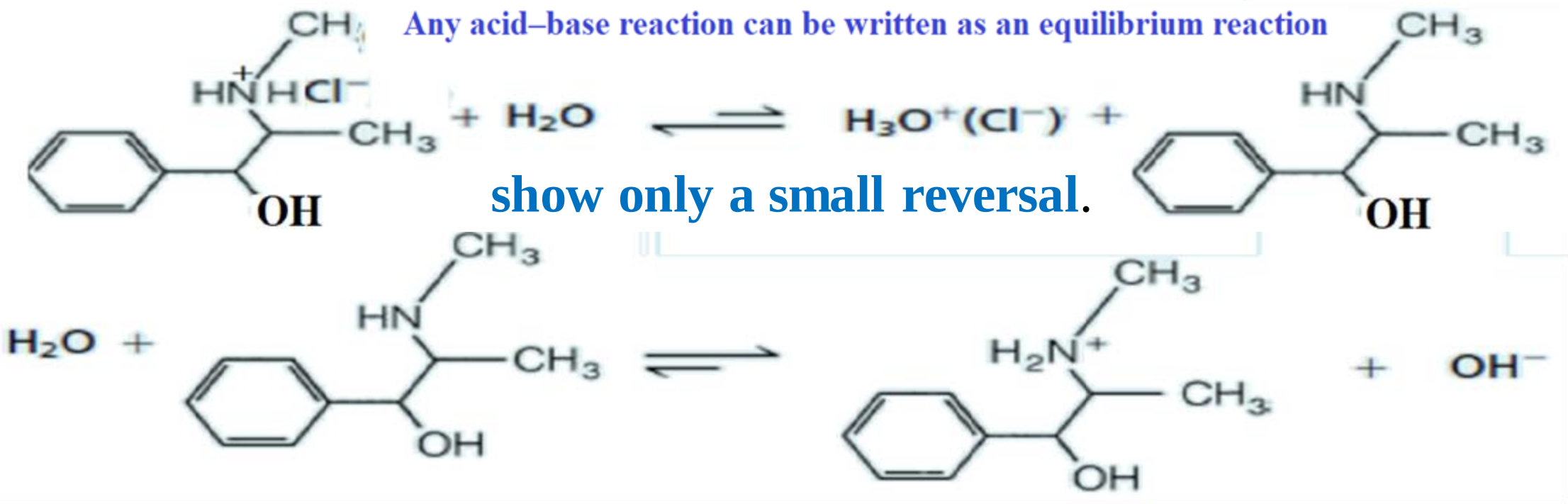
(i)  + H_2O ⇌ H_3O^+ + 

Acid **Base** **conjugated acid** **conjugated base**

(j) H_2O +  ⇌  + $OH^-(Na^+)$

Example -5-:

Epinephrine hydrochloride and it's conjugated base epinephrine:



Ephedrine is a prescription medicine used to treat the symptoms of low blood pressure during anaesthesia (Hypotension).

Draw acid-base equations showing how the water undergo an amphoteric characters with the following drugs:

1. **Drug used to treat the symptoms of low blood pressure during anaesthesia (Hypotension).**
2. **Anti- convulsant /hypnotics drug**
3. **Sodium dihydrogen phosphate**

Acid Strength

While any acid–base reaction can be written as an equilibrium reaction, an attempt has been made in the previous examples to indicate which sequences are unidirectional احادي الاتجاهor show only a small reversal.

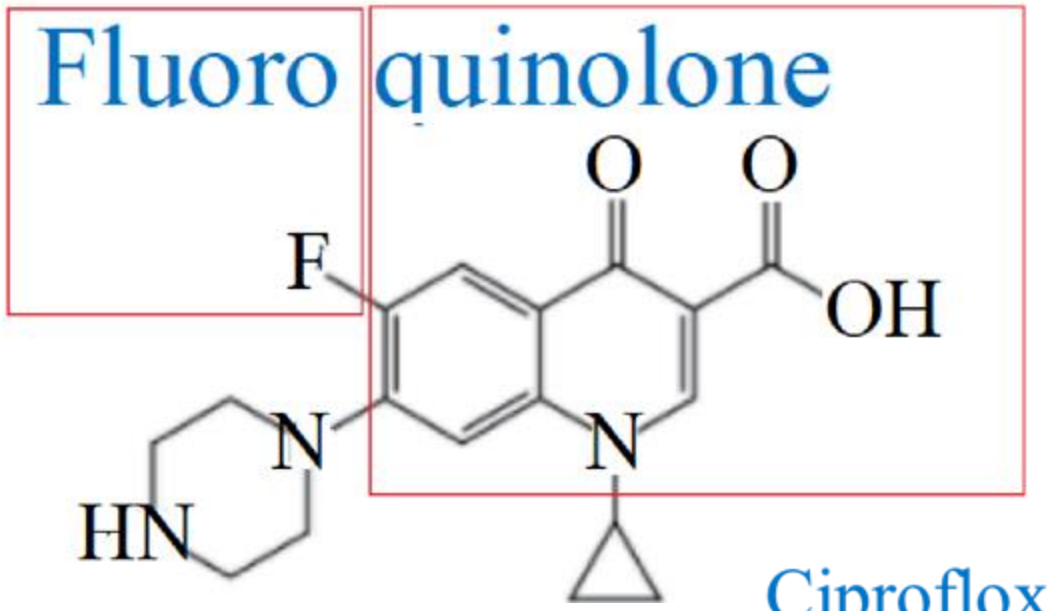
1.For hydrochloric acid **(reaction a),** the conjugate base, Cl^-, is such a weak base that it essentially does not function as a proton acceptor.

2.In a similar manner, water is such a weak conjugate acid that there is little reverse reaction involving water donating a proton to the hydroxide anion of OH^- **(reaction b).**

Effects of acid-base properties, chemical functional groups and sites of distribution on absorption of Ciprofloxacin (which is fluoroquinolone) antibiotic used to treat a number of bacterial infections, this includes bone and joint infections, intra abdominal infections, certain type of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections:

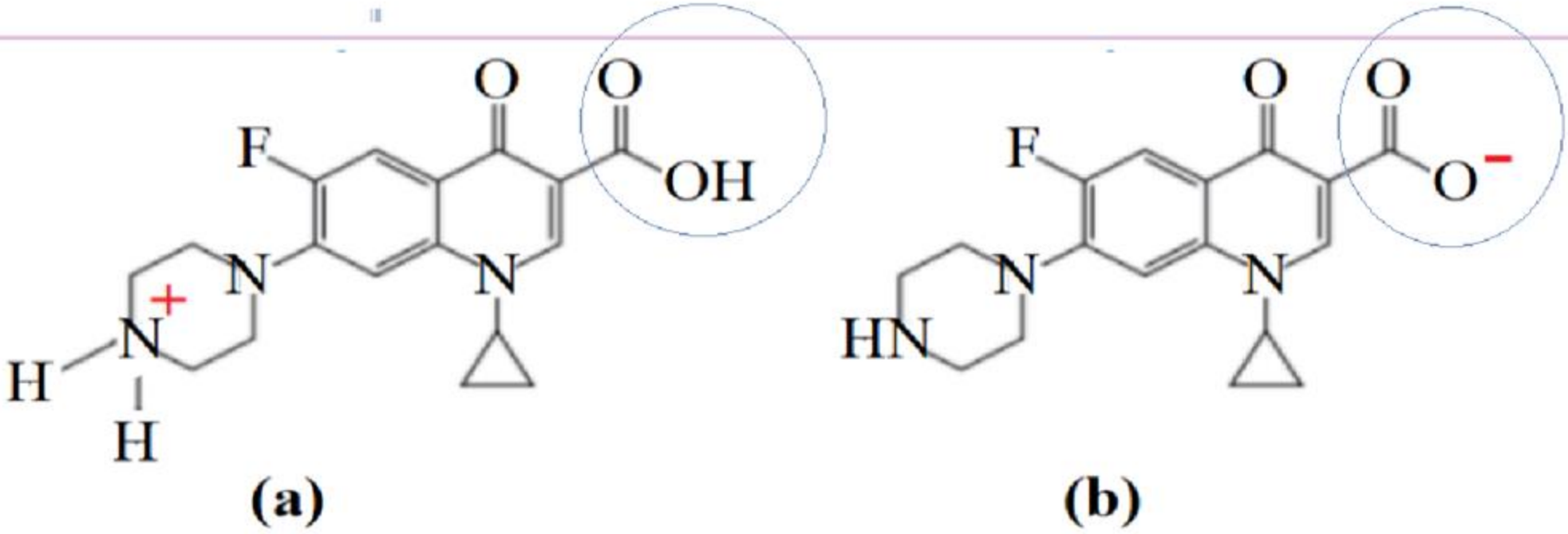
Q. What does Ciprofloxacin use for, draw its chemical structure and give the name of its class , where does it's important group is ionized.

مهم جدا



Ciprofloxacin

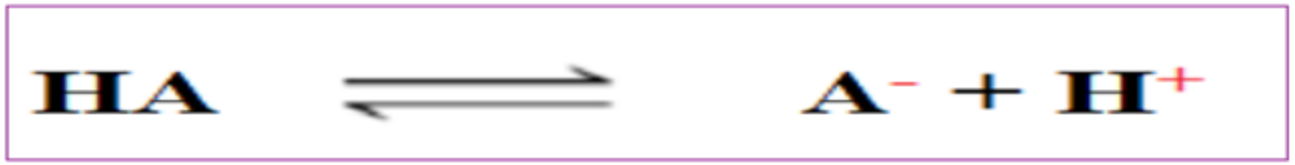
At acidity of stomach **(pH=1- 3.5)** carboxylate group is unionized fig (a)while this important group is ionized at colon of **(pH(5.6-7)**, fig (b), as shown in the following diagram:



a. At acidity of stomach **(pH=1- 3.5)** carboxylate group is unionized
b.While this important group is ionized at colon of **(pH(5.6-7).**

Derivation of Henderson-Hasselbalch equation

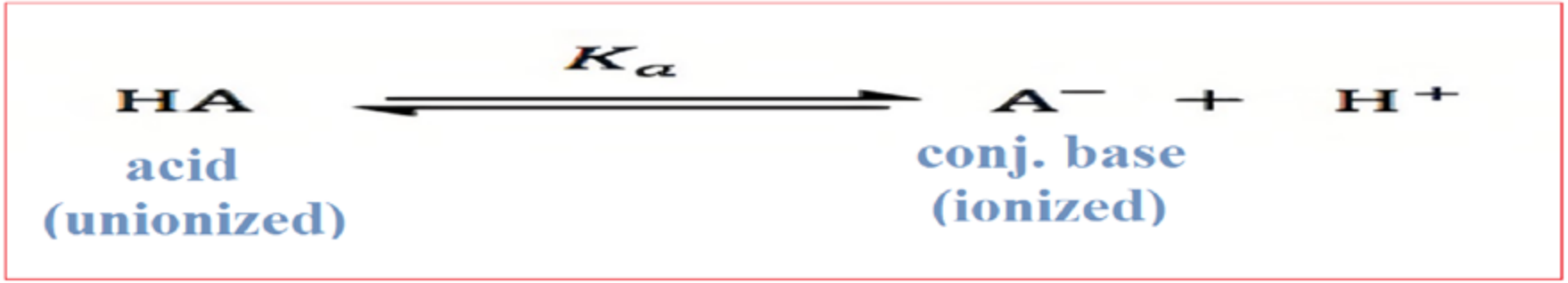
When an acid **HA** is dissociates into its conjugate base **(A^-)** and hydrogen ion **(H^+)** and the concentrations of all components will not change over time, i.e the forward and backward reactions are occurring at the same rate , thus the system is said to be in **equilibrium.**



The equilibrium constant (which is the in chemistry, biochemistry, and pharmacology) is an Acid Dissociation constant (Ka).

Increases of Ka (or decreases pKa) will increase acid strength and increase the stability of conjugate base , and Base dissociation constant or Kb

مهمGive the derivation of Henderson-Hasselbalch equation



The equilibrium constant Ka is equal to the result of multiplication of the products concentrations divided over the reactant(s) concentration

$$K_a = \frac{[H^+][A^-]}{[HA]} \quad \text{or} \quad K_a = [H^+] \times \frac{[A^-]}{[HA]}$$

Take the logs of the two sides of the equation:

$$\log_{10} K_a = \log_{10} [H \quad \text{بالضرب تجمع اللوغارتمات} \quad {}_{10} \frac{[A^-]}{[HA]}$$

$\because \quad \log_{10} X = -pX$

$$\therefore \quad -pK_a = -pH + \log_{10} \frac{[A^-]}{[HA]}$$

$$pH = pK_a + \log_{10} \frac{[A^-]}{[HA]} \quad (1)$$

Henderson-Hasselbalch equation

$$pH = pKa + \log \frac{[\text{conj. base}]}{[\text{Acid}]} \quad \text{or} =$$

$$pKa + \log \frac{[\text{ionized}]}{[\text{unionized}]} \quad \text{or} =$$

$$pKa + \log \frac{[A^-]}{[HA]}$$

From this equation:

Decreases of pKa will increase acid strength and increase the stability of conjugate base.

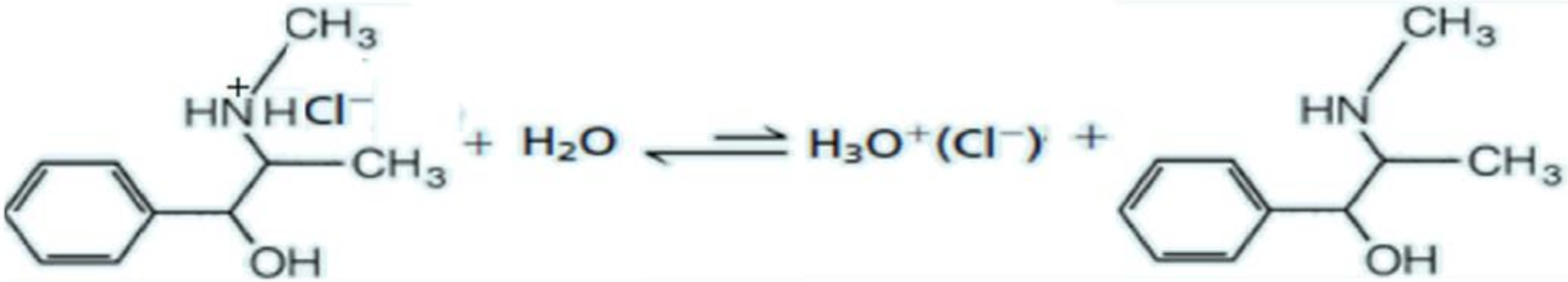
أي كلما قلت قيمة دالة ثابت الحامضية في يمين المعادلة سوف تقل قيمة دالة الحامضية في يسار المعادلة
أي زادت الحامضية

Calculations examples :

1.What is the ratio of Ephedrine to Ephedrine HCl of pKa(9.6) in the intestinal tract at pH 8? **(write the equation)**

Given that

Y	value of 10^Y
−1.5	0.06
−1.6	0.025
−1.7	0.014



Henderson-Hasselbalch equation

الماء يهمل

$$\mathbf{pH = pKa + \log \frac{[ionized]}{[unionized]}}$$

$$8 = 9.6 + \log [ionized]/[unionized]$$

$$\log [ionized]/[unionized] = -1.6 \qquad [ionized]/[unionized] = 25/1000$$

2. What is the pH of buffer contains 0.1M acetic acid of (pKa 4.8) and 0.08 sodium acetate ? **(write the equation)**

logx	x =
0.9	-0.05
0.8	-0.1
0.7	-0.15
0.6	-0.2
0.5	-0.3

$$\mathbf{pH = pKa + \log \frac{[conj.\ base]}{[Acid]}}$$

$$pH = pKa + \log \frac{[sodium\ acetate]}{[acetic\ acid]}$$

pH = 4.8 + log 0.08/0.1

4.8 + log 0.8

= 4.8-0.1= 4.7

Drug Distribution and pKa

The drug first encounter the acidic stomach

↓

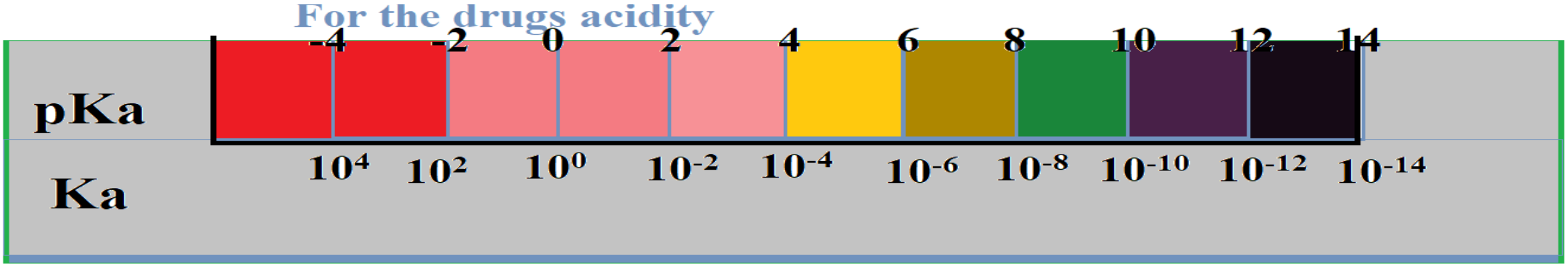
1. Amines (pKa 9–10) will be protonated (BH acids) in the acidic stomach and usually
will not be absorbed until reaching the mildly alkaline intestinal tract (pH 8).

2. HA acids with pKa's of 4 to 5 will tend to be nonionic and be absorbed partially through the gastric mucosa.

Organic Pharmaceutical Chemistry
Lecture 3 part 1
Acid base properties of drugs

∵ pKa = - log Ka

∴ The smaller the value of drug pKa the stronger the drug acidity



A general rule for determining whether a chemical is strong or weak acid or base is:

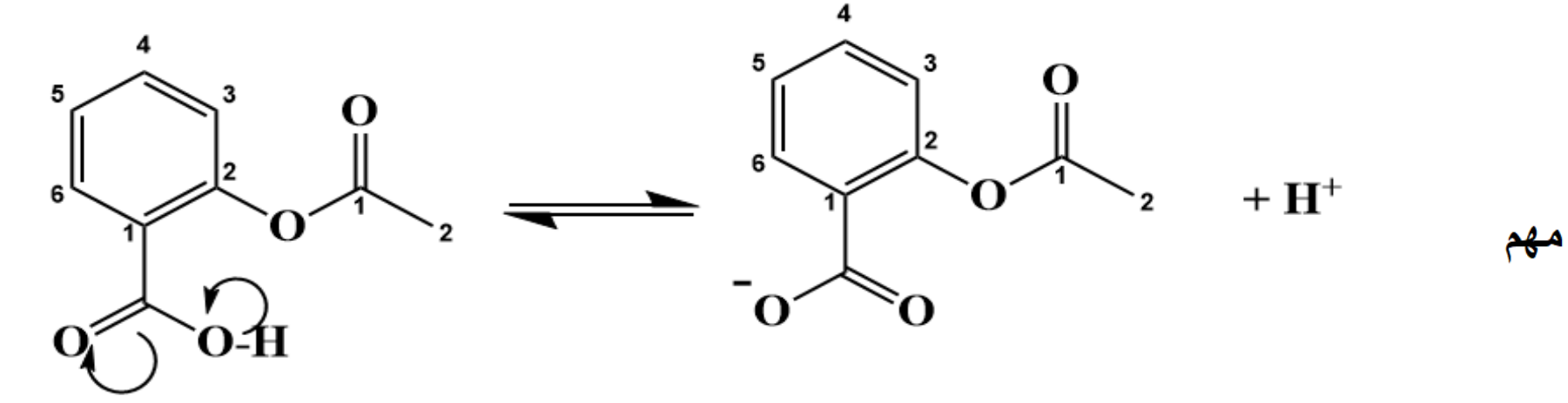
1. pKa < 2

Strong acid drug and the conjugate base has no meaningful basic properties in water.

2.pKa 4-6
Weak acid drug

i. Aspirin is a weak acid with a pKa of 3.5.

ii. When aspirin donates its proton it becomes negatively charged.



مهم

When aspirin donates its proton it becomes negatively charged

iii. Aspirin is absorbed into the blood through the cells lining the stomach and the small intestine(mucous columnar cells).

iv. Absorption of aspirin requires passage through the plasma membrane, the rate of which is determined by the polarity of the molecule: charged and highly polar molecules pass slowly, whereas neutral hydrophobic ones pass rapidly.

v. The pH of the stomach contents is about 1.5, and the pH of the contents of the small intestine is about 6.

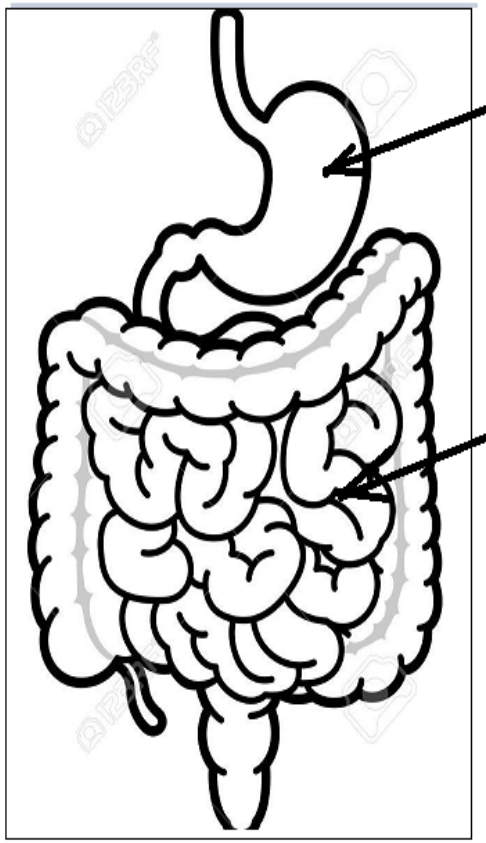
1.A drug will become lipid soluble in a solution with a pH similar to its own pH

2.A week acid drug is more lipid-soluble in acidic solution.

3.A week base drug is more lipid-soluble in alkaline solution.

4.A week acid drug is more water-soluble in alkaline solution.

5.A week base is more water-soluble in acidic solution.

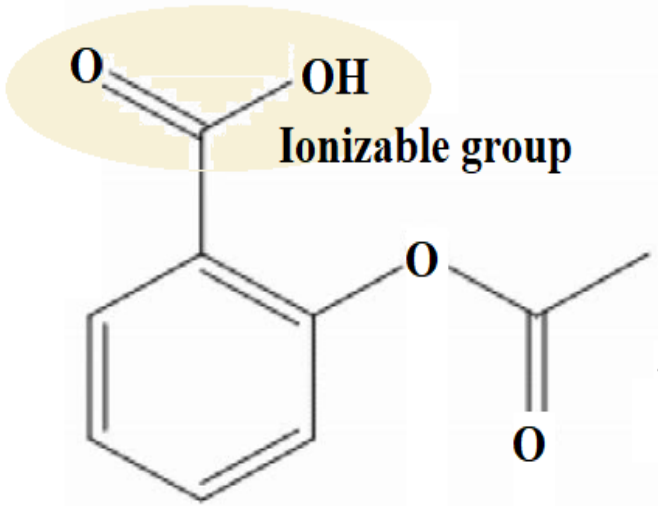


The pH of the stomach contents is about 1.5

A week acid is more lipid-soluble in stomach solution.
A week base is more water-soluble in stomach solution.

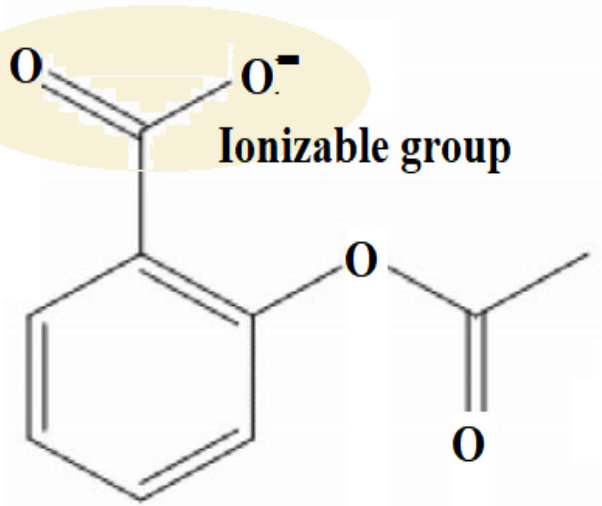
The pH of the contents of the small intestine is about 6.

A week base is more lipid-soluble in intestine solution.
A week acid is more water-soluble in intestine solution.



$-H^+$

$+H^+$



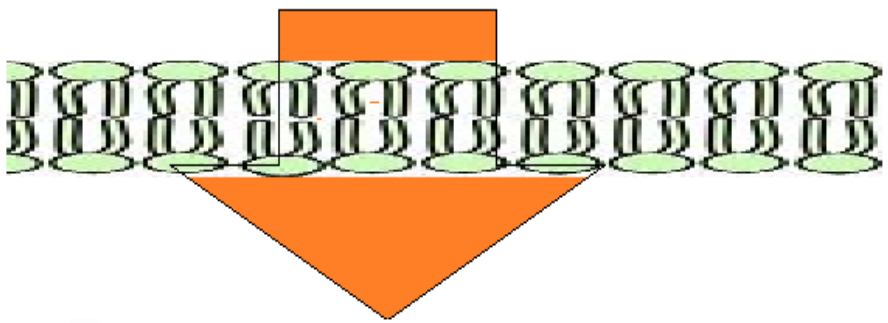
Acetylsalicylic acid (Aspirin)

pH = 1.5

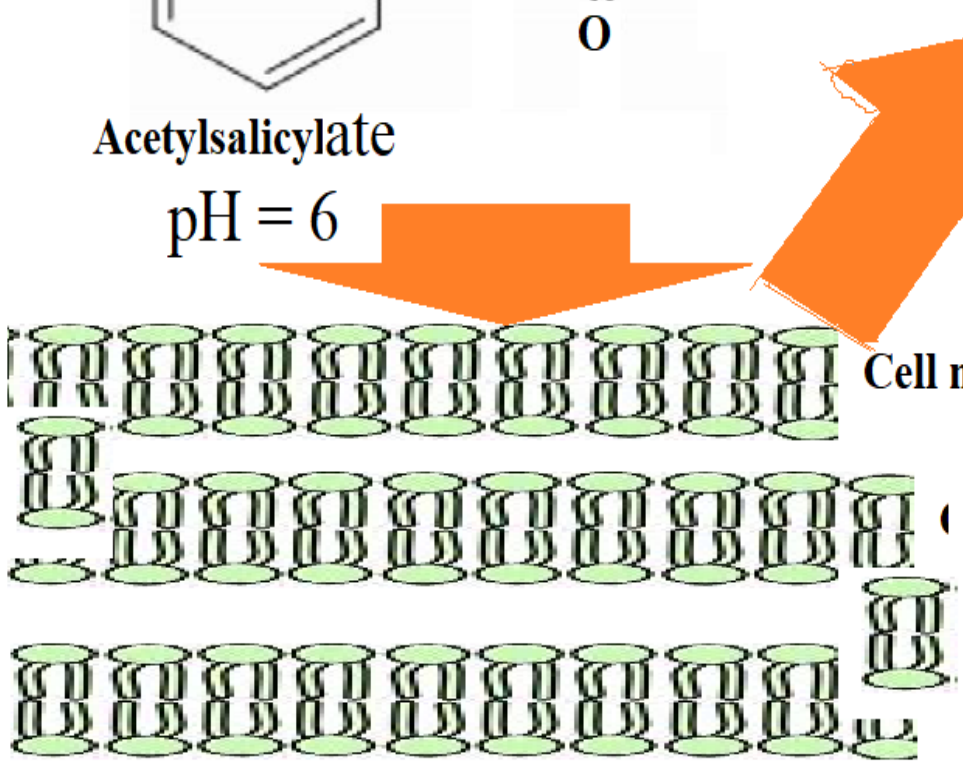
Acetylsalicylate

pH = 6

The pH of the small intestine is about 6.



Absorption of aspirin (unionized) or neutral hydrophobic pass rapidly.



Cell membrane

4.pKa >12

Essentially no acidic drug properties in water, strong conjugate base.

3.pKa 8-10

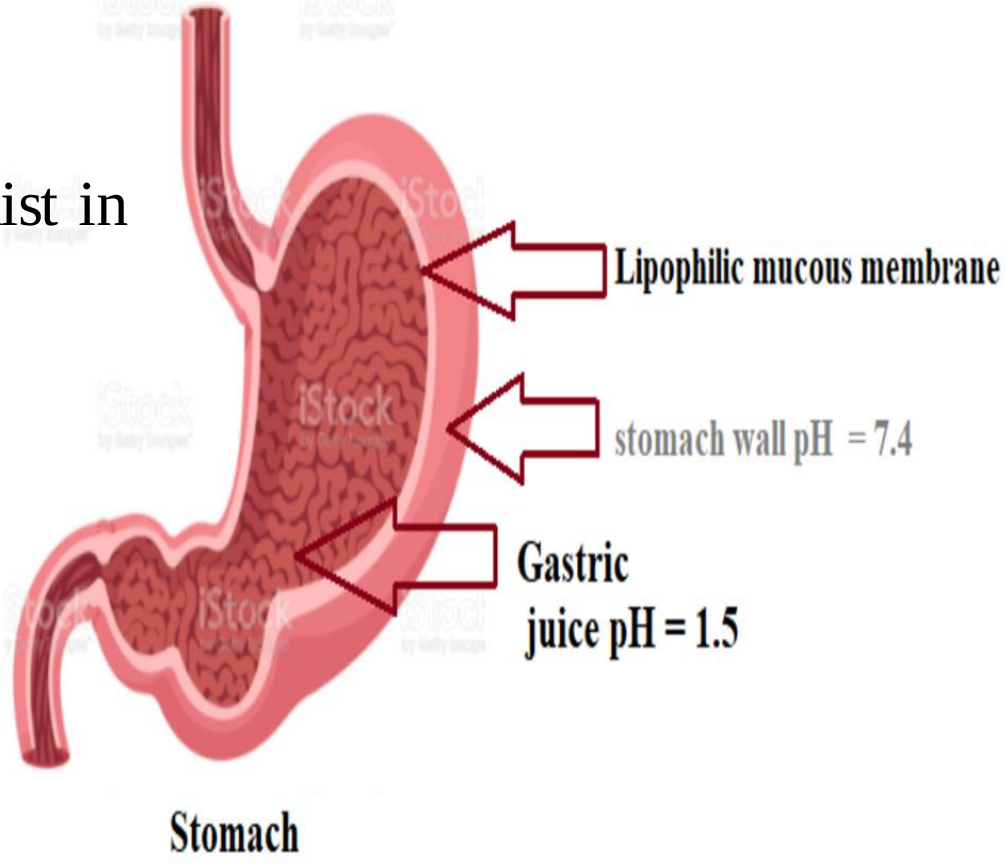
Very weak acid drug , conjugate base getting stronger

Drugs and Ionization:

1.Many drugs are weak acids or weak bases that can exist in both ionized and non-ionized forms in the body.

2.Only the non-ionized form of drugs is absorbed.

3.The ratio of the ionized form to the non-ionized form of these drugs can be calculated using the **Henderson-Hasselbalch equation.**



IONIZATION OF WEAK ACIDS

$$AH \rightleftharpoons A^- + H^+$$

Non- ionized	Ionized
Not charged	Charged
Lipid soluble	Water soluble

At equilibrium, the percentage of non-ionizes = 50% , and that of ionized = 50%

When you suggest that $pH = pKa$

When [ionized drug] = [non-ionized drug]

$$pH = pKa + \log \frac{[\text{ionized}]}{[\text{unionized}]}$$

$$pH = pKa + \log 1$$

$$\because \log 1 = 0$$

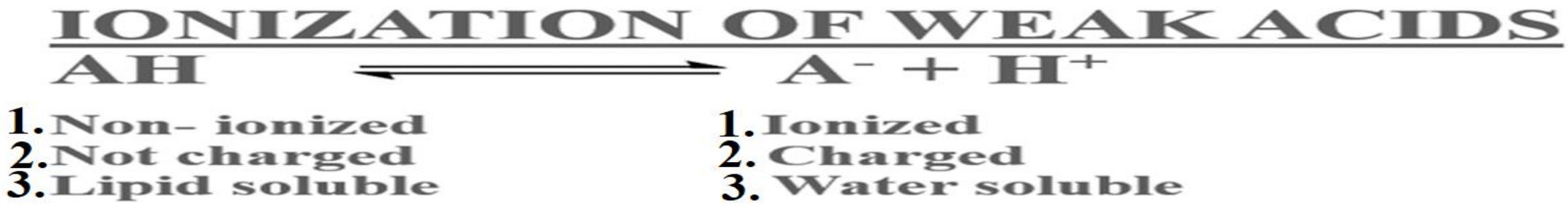
$$\therefore pH = pKa$$

- The **pKa** of a weak acid or weak base is the **pH** at which 50% **Ionized form** and the 50% **nonionized form**

Q. Compare between left and rite sites of this acid dissociation according to :

1.Ionization
2.Charging
3.Solubility

The answer:



For weak acid:

مثال مهم

The Henderson-Hasselbalch equation is written as:

$pH = pK_a + \log([A^-]/[HA])$ $pH = pK_a + \log[(salt)/(acid)]$ $pH = pK_a + \log([ionized]/[unionized])$

Example: Aspirin (acetylsalicylic acid) has a pK_a of 3.5.

Calculate the ratio of ionized/unionized of the drug

i. In the stomach where pH is (1).

ii.In the intestine where pH is 6.

III.Based on these calculations- where is aspirin absorbed within the body?

i.

$$pH = pKa + \log \frac{[ionized]}{[unionized]}$$

$1 = 3.5 + \log [A^-] / [AH]$

$\log [A^-] / [AH] = -2.5$

Thus, [ionized]/[unionized] = Antilog (-2.5) ≈ 0.003 i.e = 3/1000

From the above value it means that for every 1000 unionized aspirin molecules in the stomach there are only three molecules ionized , suggesting that aspirin is largely unionized in the stomach i.e. ionized = 3/1000 = 0.03% and unionized = (100-0.03)% = 99.7% unionized).i.e absorbed

ii. pH of the intestine = pK_a of aspirin + log[ionized]/[unionized]

6 = 3.5 + log [ionized]/[unionized]

log [ionized]/[unionized]= 6 – 3.5 = 2.5

[ionized]/[unionized] = Antilog (2.5)

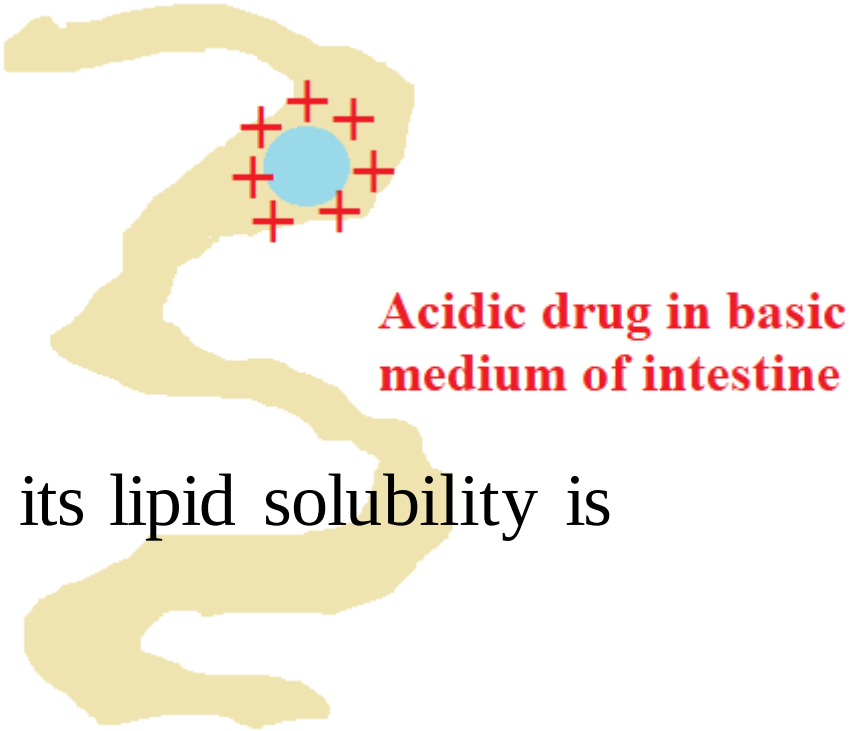
[ionized]/[unionized] ≈ 300 = 300/1

From the above value, it means that for 300 ionized molecules of aspirin in the intestine there is only 1 unionized molecule = 1/300 ≈ 0.3% and (ionized molecules = 100-0.3= 99.7) suggesting that aspirin is largely ionized in the intestine . **Aspirin is more unionized in the stomach than in the intestine.**

Thus majority of the aspirin is absorbed via the stomach under acidic pH.

Ion trapping

Ion trapping occurs with weak acid drug or weak base drugs in ionized and un-ionized forms and the % of each one varies with pH of solution can calculate with Henderson- Hasselbach equation.



Abstract:

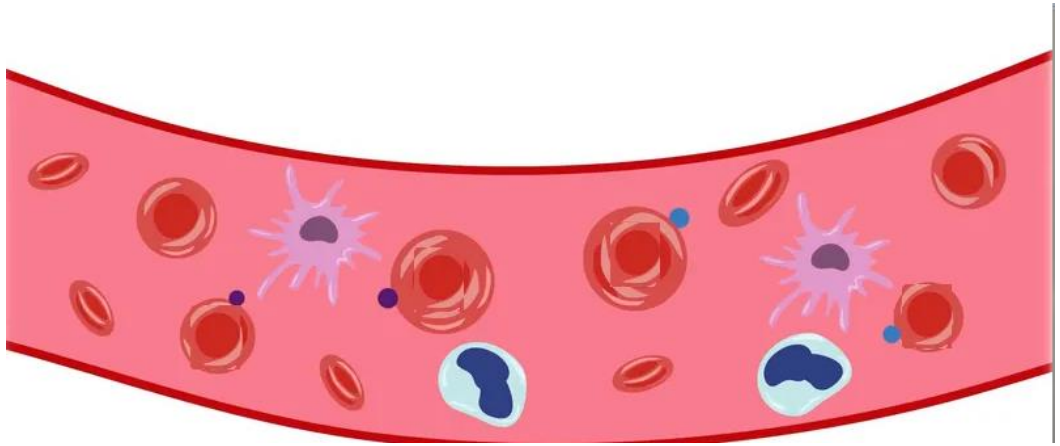
When acidic drug is putting in acidic medium (or any medium of pH, less than its pH), it stay unionized and its lipid solubility is increased, (example 1)

but when it put in basic medium (or any medium of pH, more than its pH) it surrounds its molecules by water and becomes more ionic and its lipid solubility is decreased.

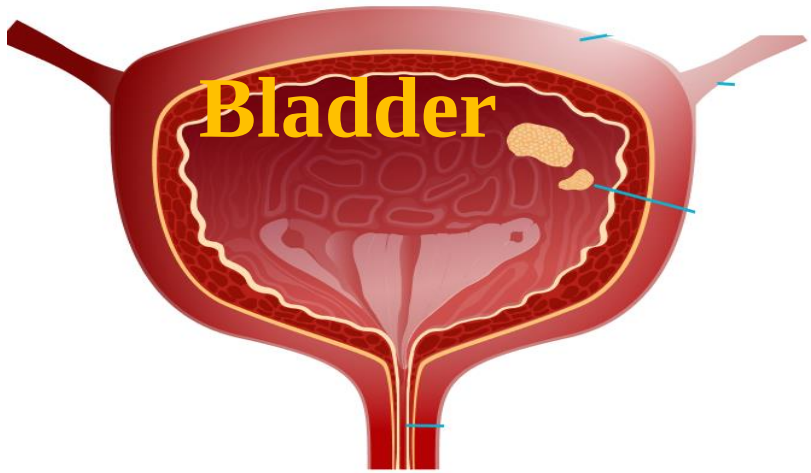
Ion Trap , occurs in the

1.Stomach cells 2.Renal 3.Breast

Ionized drug gets trapped on one side as a membrane that divides compartments (الذي تختلف مواقعه حسب الدالة الحامضية)with different pHs as: .



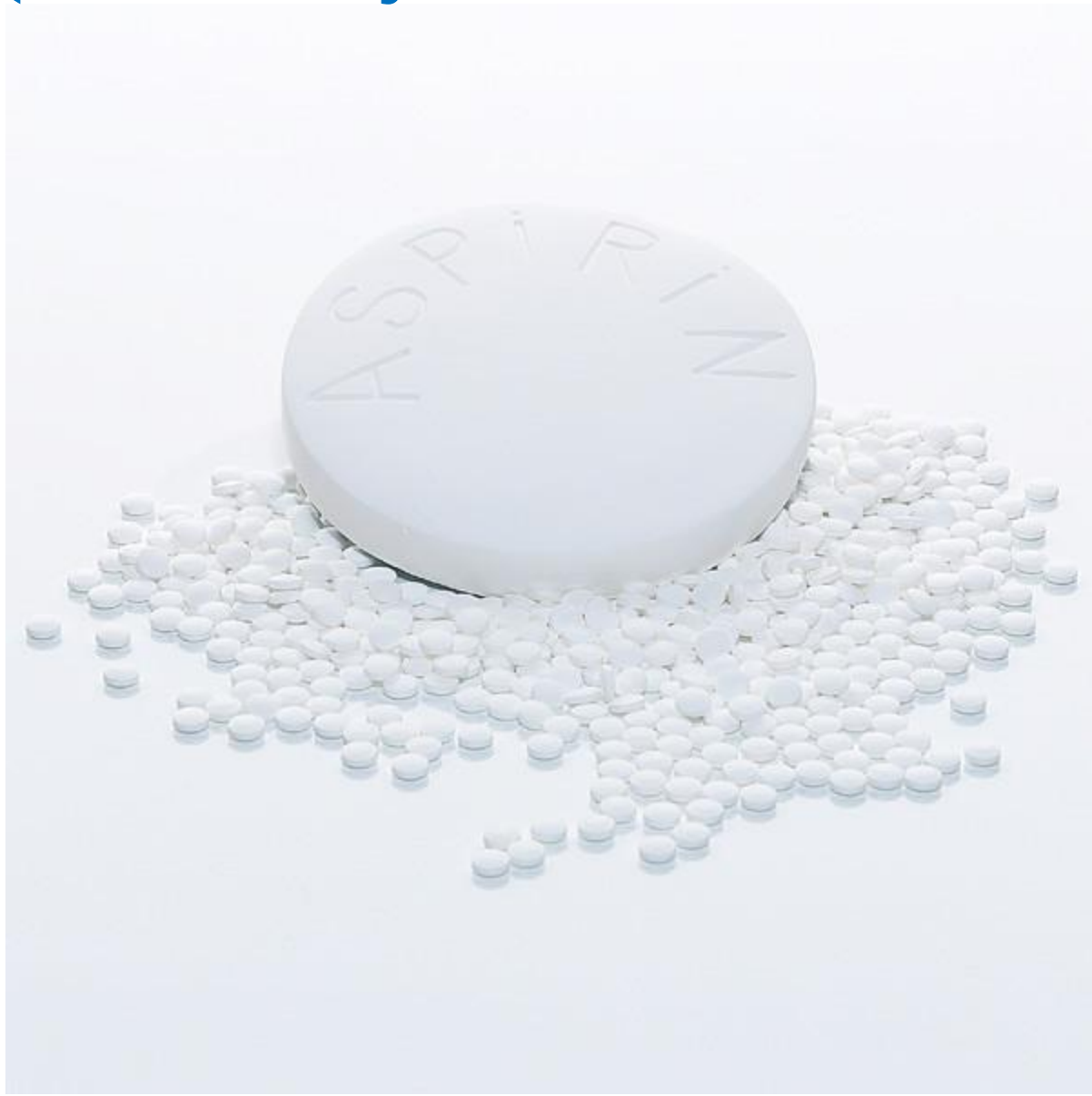
1) Blood , pH7.4



2)Urine , pH6

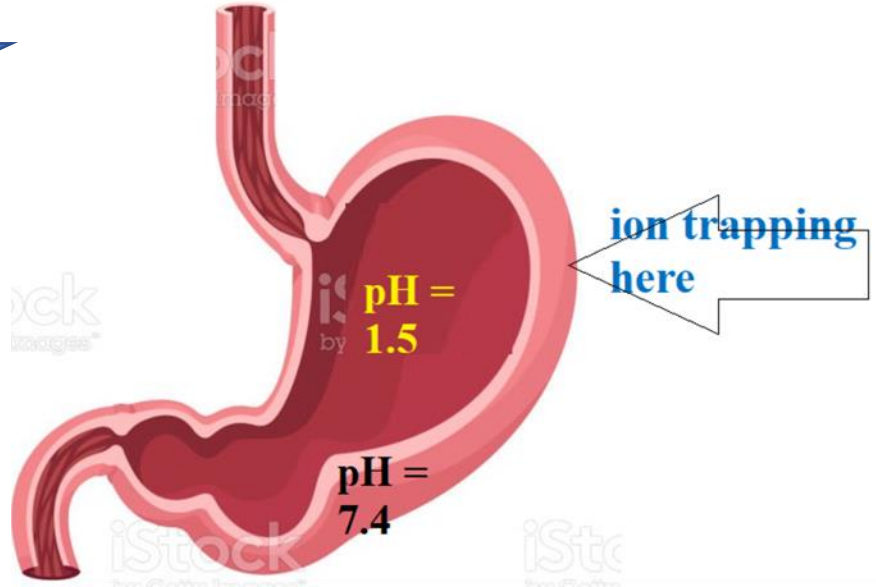
Q. Described how the Aspirin trapped in side only two the following sites: (What do you recommend patient)?

i. Stomach ii. Renal
iii. Breast



Applications of ion trapping:

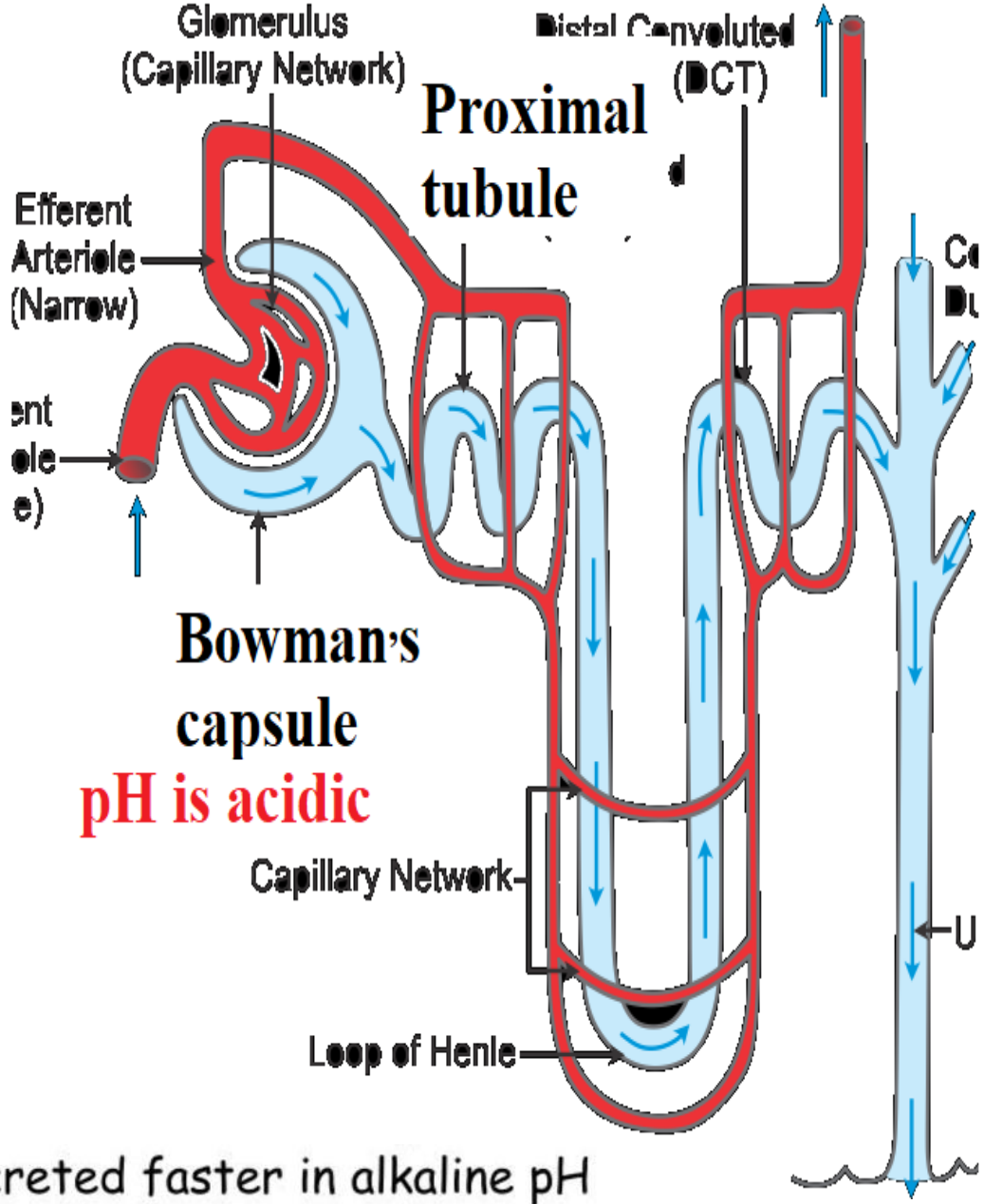
1. In stomach:



Aspirin is highly absorbed in stomach because its high acidity (1.5), but when inter the mucous membrane where the blood is pH 7.4 this high intracellular pH causes drug to trapped into this membrane and ionized thus it can not absorbed and stay their and causes ulcers. Thus we recommend patients to not taken Aspirin except it is enteric coated to not absorb in stomach and absorbed in intestine.

2. In Renal:

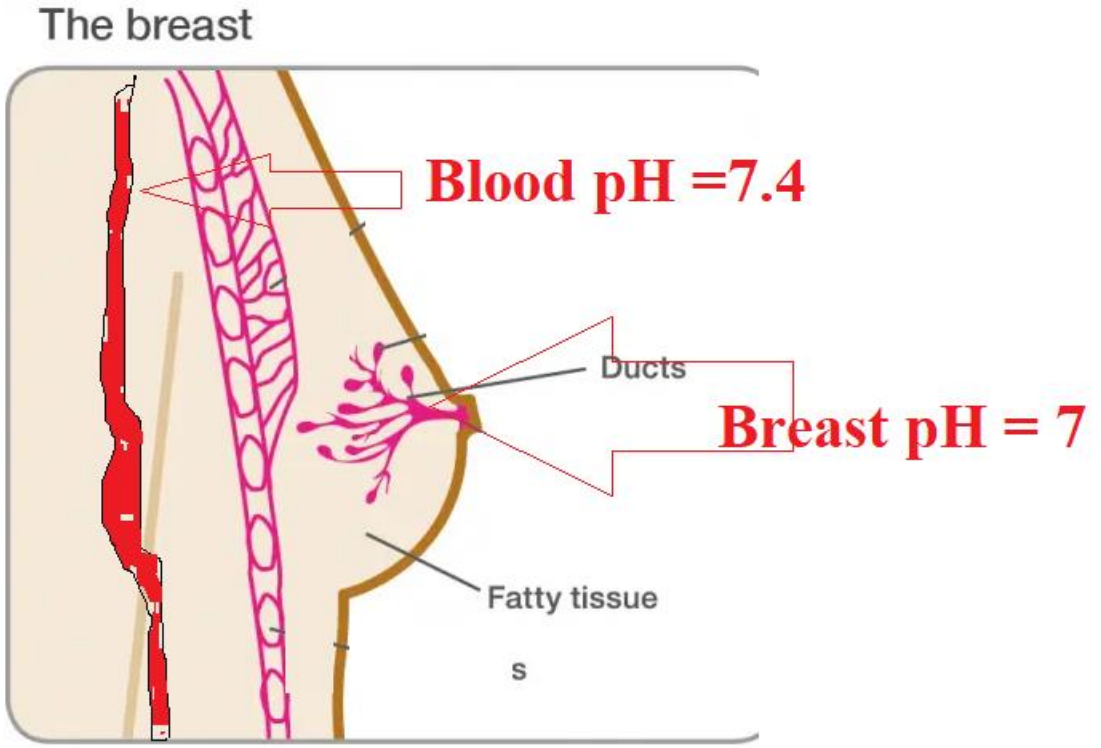
The Aspirin **overdoses** or Aspirin **toxicity** make it reach to renal system where the pH, is acidic thus it reabsorbed again to systemic cycle thus we recommended patients to take **sodium bicarbonate** to increase the pH, of the renal (**increased** the basicity) thus ionic trapping occurs and Aspirin excreted by urine.



★ Weak acids: excreted faster in alkaline pH (anion form favored)

3.In breast:

When the alkaline drug in blood plasma (of pH 7.4) reach the breast , the breast milk is slightly **acidic** as compared with plasma (its medium pH, 7.0) thus drug is surrounding its molecules by water and become more ionic and its lipid solubility is **decreased** , i.e. it is ion trapping and does not reabsorb to blood and stay in breast and reach the baby



Percent Ionization

Using the drug's pKa, the formulation or compounding Pharmacist can adjust the pH to ensure maximum water solubility (**ionic** form of the drug) or maximum solubility in nonpolar media (**un-ionic** form). This is where understanding the drug's acid–base chemistry becomes important.

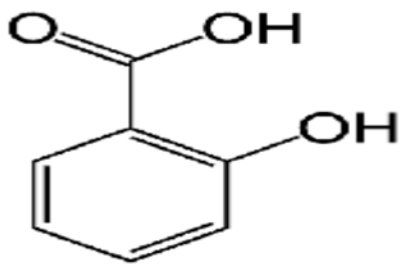
Acids can be divided into two types on the basis of its ionic form :

1. HA , which is acid go from un-ionized acid to ionized conjugate base

Acid		Base		Conj. Acid		Conj. Base
$HA_{(un\text{-}ionized)}$	+	H_2O	$\rightleftharpoons$	H_3O^+	+	$A^-_{(ionized)}$

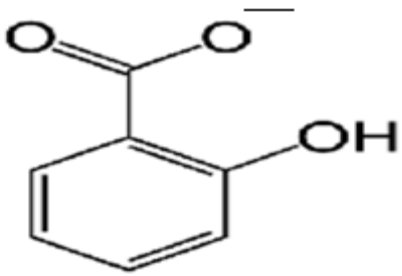
★ Examples of Pharmaceutically important HA acids include :

a. Salicylic acid:



Salicylic acid

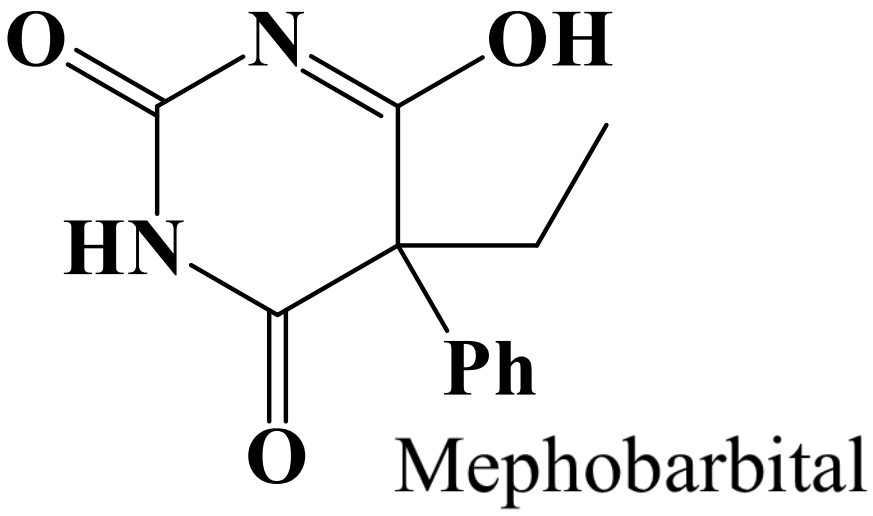
+ H_2O $\rightleftharpoons$ H_3O^+ +



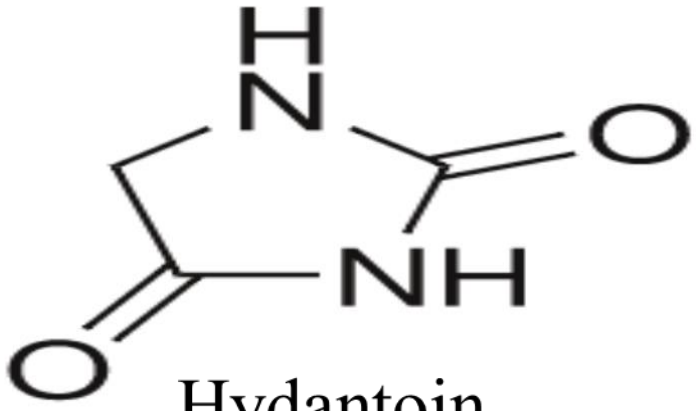
Salicylate

b. The inorganic acids (e.g., HCl)

c. Enols (e.g., a. Mephobarbital a CNS depressant, b. Hydantoin Anticonvulsants)



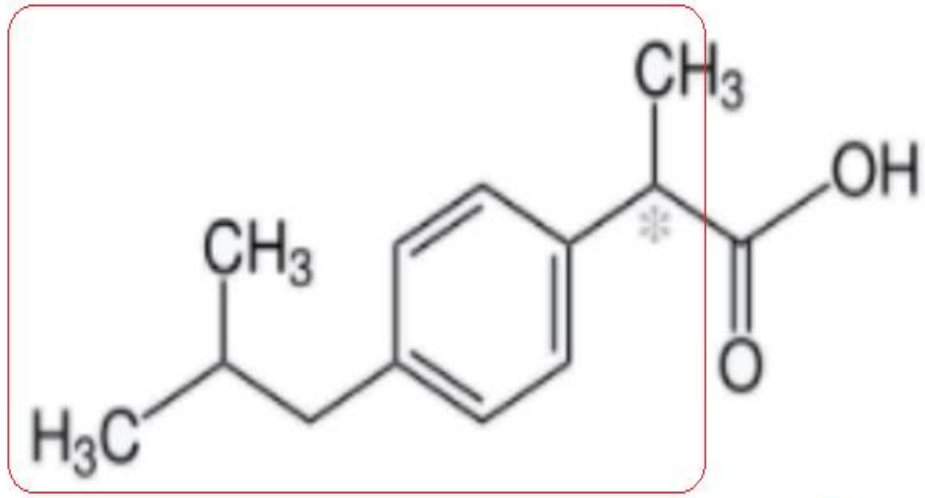
Mephobarbital



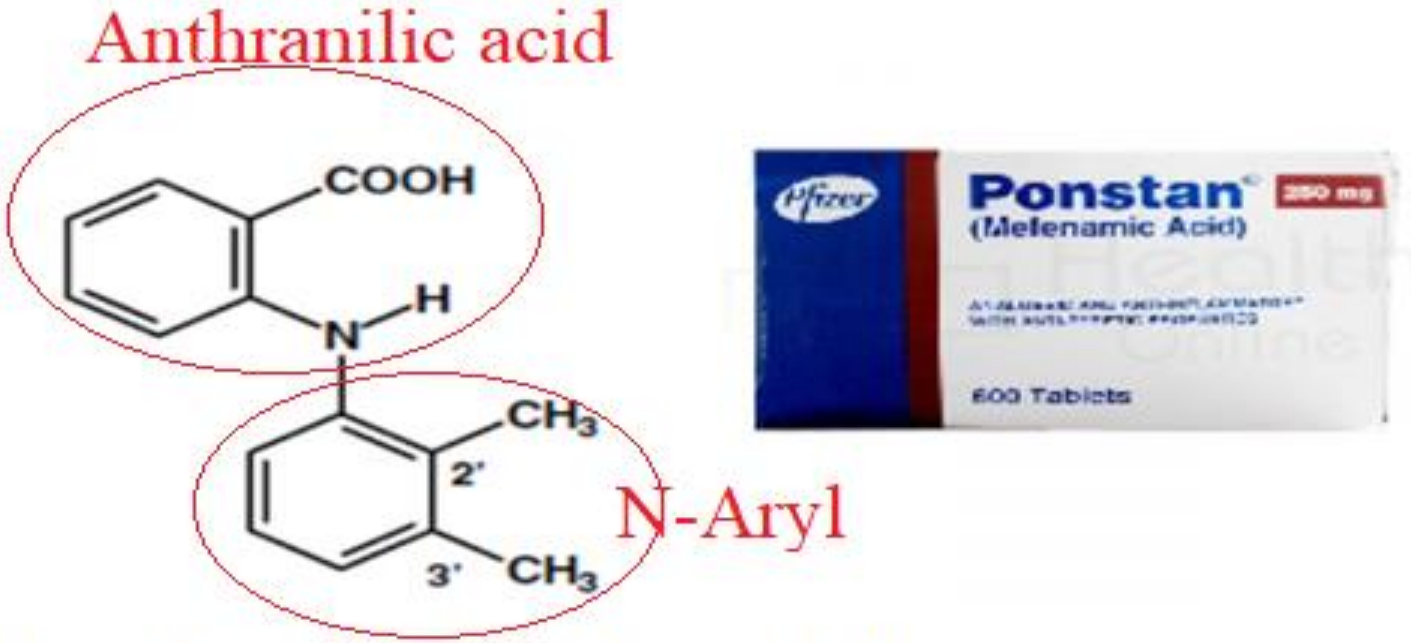
Hydantoin

d.Carboxylic acids e.g., (Low–molecular-weight organic acids),

i. Aryl acetic acids, Ibuprofen



ii. *N*-Aryl anthranilic acids

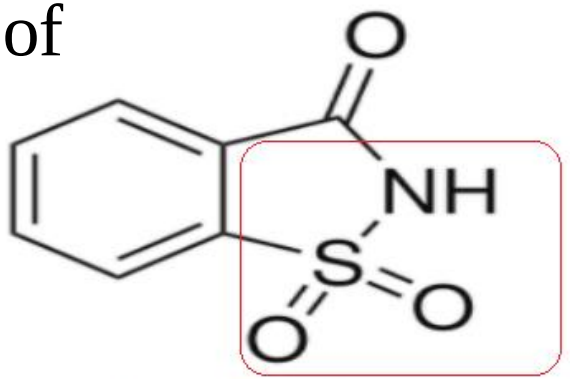


N-aryl anthranilic acids
(Mefenamic acid)
Ponstan

e. Amides and Imides (imide is a functional group consisting of two carbonyl groups bound to nitrogen,

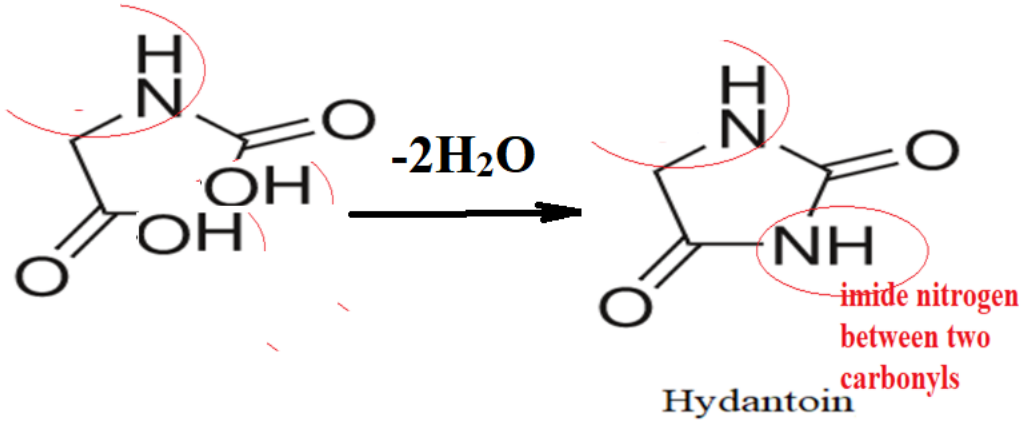
Hydanoin consists of two moites , amide and imide.

(Imides are compounds of structurally related to acid anhydrides),

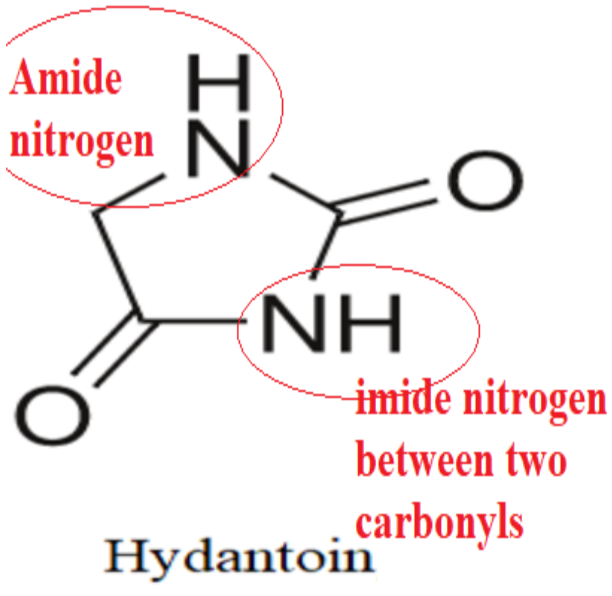


Saccharin

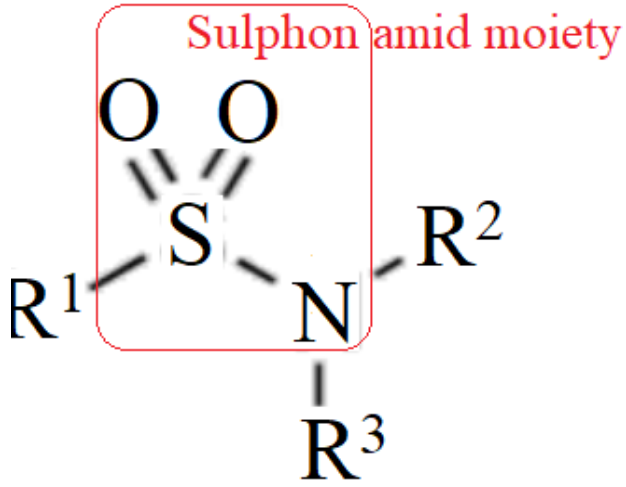
e.g., Sulphonamides and saccharin .



Hydantoin



Hydantoin



Imides are compounds of structurally related to acid anhydrides

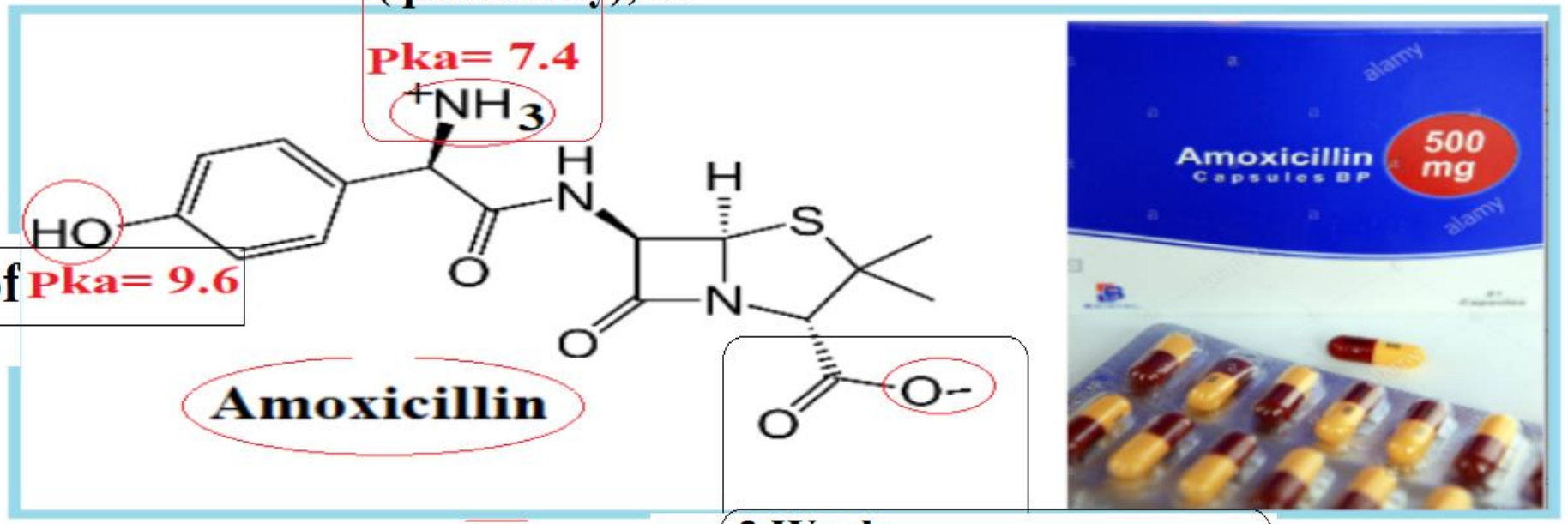
2.BH^+, which is acid go from ionized (polar) acid to un-ionized (nonpolar) conjugate base.

Acid	Base	Conj. Acid	Conj. Base
$BH^+_{(ionized)}$ +	H_2O ⇌	H_3O^+ +	$B_{(un\text{-}ionized)}$

Examples of Pharmaceutically important BH^+ acids include:

i. All protonated amines.
ii.It polyfunctional drug, which can have several pKa's (e.g., amoxicillin). The latter's ionic state is based on amoxicillin's ionic state at physiological pH 7.4.

2.Protonated amine group (quaternary), of Pka= 7.4



1.The phenolic group of Pka= 9.6

3.Weak carboxylate of Pka= 2.5

*From all these polyfunctional groups of Amoxicillin, the most acidic group is the phenolic group of pKa =9.6 (true, false)

The percent ionization of a drug is calculated by using equation 6 The following equation for HA acids:

$$\% \text{ ionization} = \frac{100}{1 + 10^{(pK_a - pH)}} \quad \text{----------eq 6}$$

and Equation 7 for BH^+ acids.

$$\% \text{ ionization} = \frac{100}{1 + 10^{(pH - pK_a)}} \quad \text{----------eq 7}$$

Drug Distribution and pKa

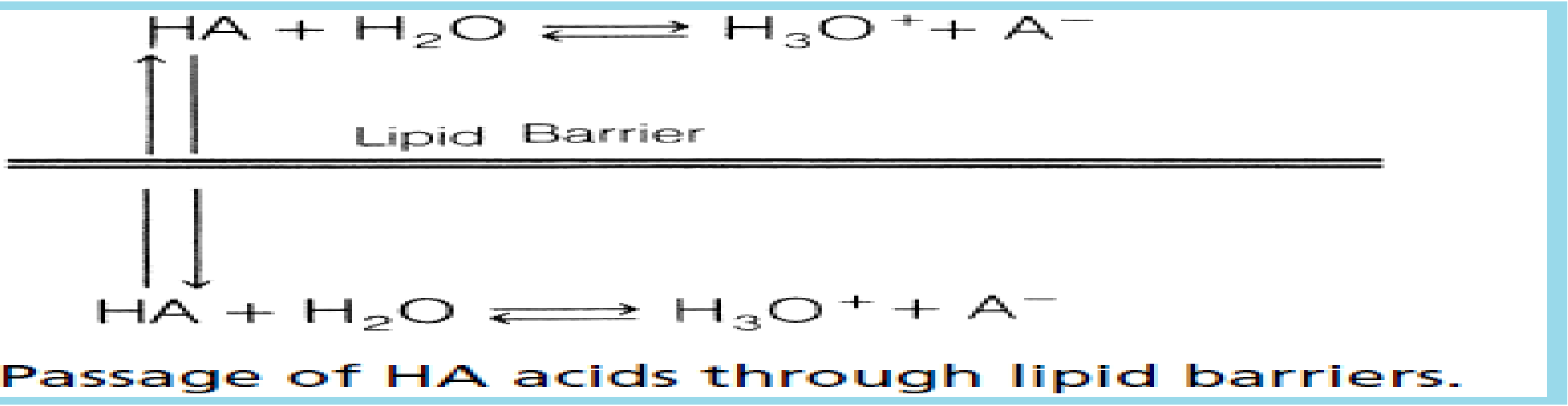
*The drugs are transported in the aqueous environment of the blood. Those drugs in ionized form will tend to distribute throughout the body more rapidly than will un-ionized (nonpolar) molecules.

With few exceptions, the drug must leave the polar environment of the plasma to reach the site of action.

In general, the un-ionized (nonpolar HA) form drugs pass through the nonpolar membranes of: مهم

i. Capillary walls ii. Cell membranes, and iii. The blood-brain barrier (BBB)

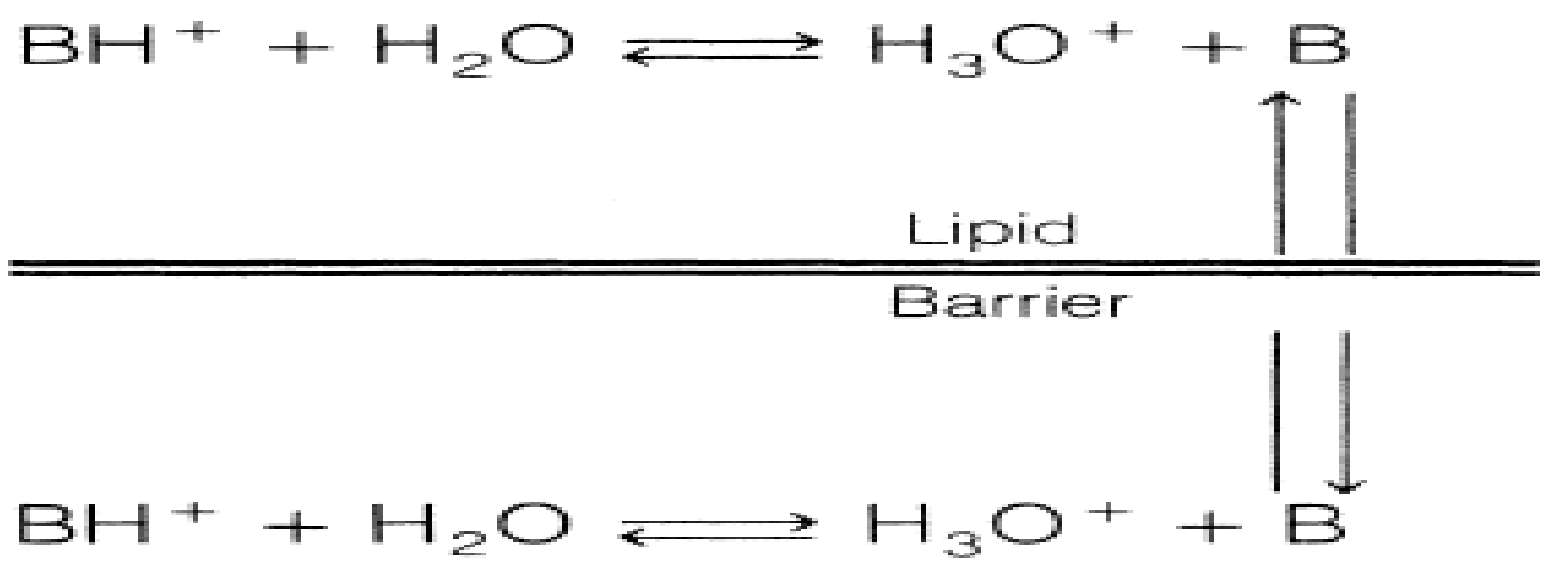
1.For un-ionized HA acids, it is the parent acid that will readily cross these non-polar membranes



Passage of HA acids through lipid barriers.

2.For ionized HB^+ acids, the situation is just the opposite,

It loses it's proton and becomes un-ionized form of conjugated base B which passes through lipid barriers .



- Passage of BH^+ acids through lipid barriers.

3.The unionized conjugate base (e.g. free amine) is the species most readily crossing the nonpolar membranes.

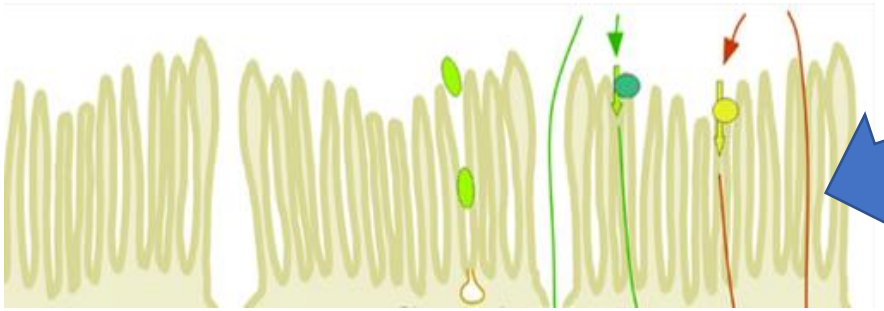
Consider the changing pH environment by the drug molecule orally administered.

The drug first encounters يلاقيthe acidic stomach, where the pH can range from 1.5 to 6 depending on the presence of food.

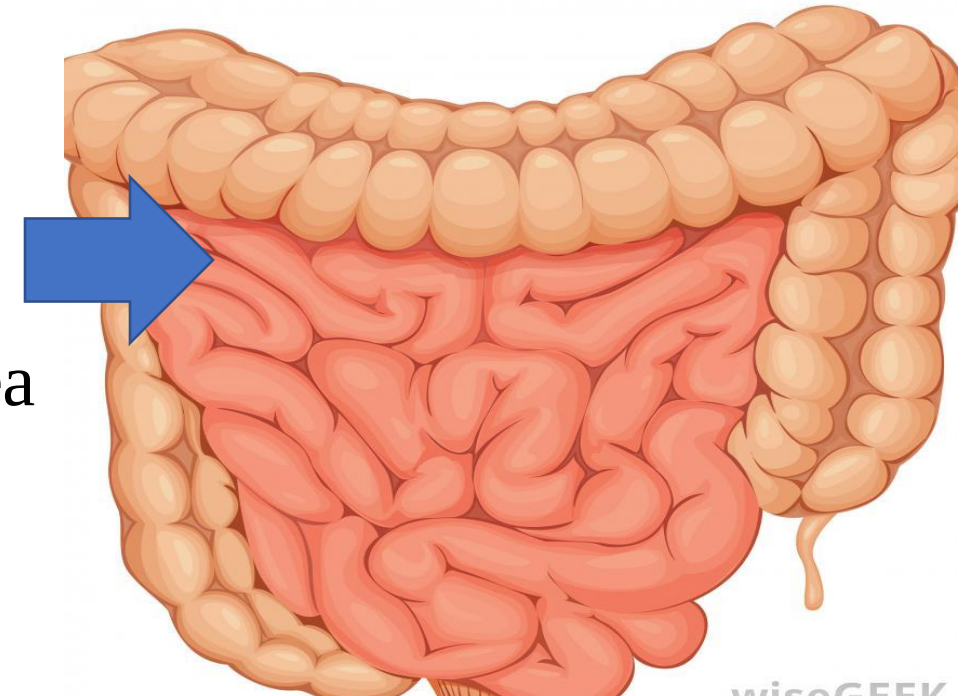
i.HA acids with pKa's of 4 to 5 will tend to be non-ionic and be absorbed partially through the gastric mucosa.

ii.The most acidic unionized drugs are absorbed from the intestinal tract rather than بدلا منthe stomach is that the microvilli of the intestinal mucosa provide a large surface area relative to that found in the gastric mucosa of the stomach.

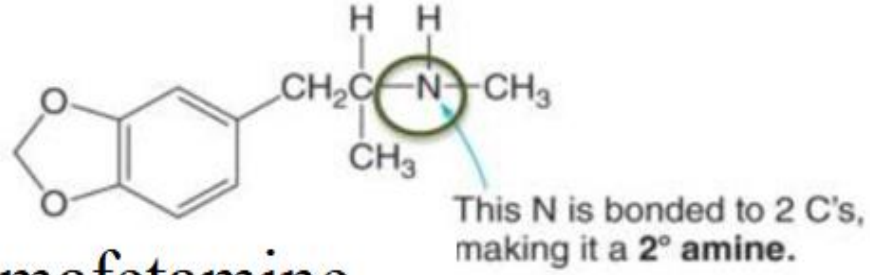
مايكروفيلايي



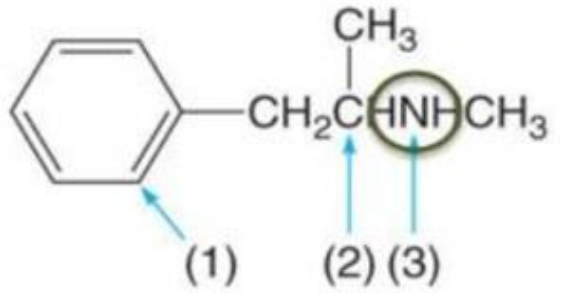
a large surface area



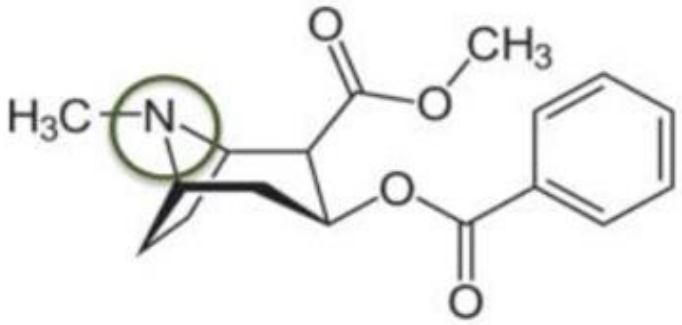
*3.Amines (pKa 9–10) will be protonated in the acidic stomach and usually will not be absorbed until reaching the mildly alkaline intestinal tract (pH 8). Even here, only a portion of the amine containing drugs will be in their nonpolar conjugate base form.



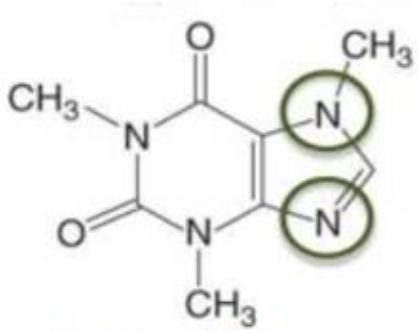
1. Midomafetamine



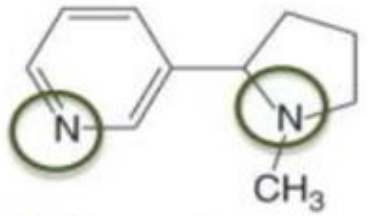
2.Methamphetamine



3. Cocain



4.Caffeine



5.Nicotine

Statistical Prediction of Pharmacological Activity II

تصميم رياضي يستخدم لوصف موديل عدة عمليات كيميائية

As mathematical modeling is used to explain the model of many chemical processes, it has been the goal of medicinal chemists to measure the effect of a structural change on a defined pharmacological response, this would meet three goals in drug design:

★ كذلك هو هدف الكيميائيون الطبيون لحساب تاثير التغيير بالشكل على الاستجابة الدوائية

Q. What are the goals in drug design to measure the effect of a structural change on a defined pharmaceutical response?

ماهي الاهداف عند تصميم الدواء لحساب التغير الشكلي على الاستجابة الدوائية المعروفة؟

1. To predict pharmaceutical activity in untested compounds.

للتنبؤ بالفعالية الدوائيه للمركبات غير المفحوصة

2. To define the structural requirements for a good fit between the drug molecule and the receptor, and

للتعريف بالمتطلبات الشكلية لتداخل جيد بين جزيئة الدواء والمستقبل

3. To design a test set of compounds to maximize the amount of information about the structural requirements for activity from a minimum number of compounds tested.

لتصميم مجموعة فحوصات لمركبات للوصول الى اعلى كمية معلومات حول المتطلبات الشكلية حول الفعالية من اقل عدد من المركبات المفحوصة

This aspect of medicinal chemistry is commonly referred to as quantitative structure–activity relationships (QSAR).

Crum Brown and Fraser, 1838 to 1922 who showed that :*the gradual chemical modification in the molecular structure of a series of poisons produced some important differences in their action.

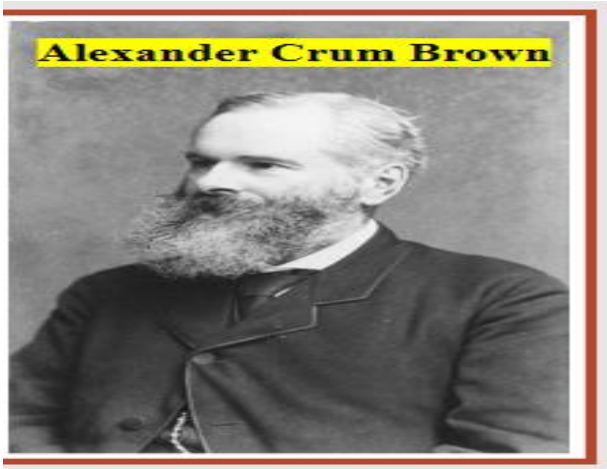
They postulated that the **physiological action of a molecule fhi *(Φ)* is a function of its chemical constitution, C.**

This can be expressed in Equation (1)

$$\Phi = f(C).....Eq.1$$

Fhi = ef of C

(f) حرف يدل في الرياضيات والفيزياء والكيمياء على الدالة بينما *(Φ)* يدل على التأثير الفسيولوجي للدواء حرف لاتيني ينطق فاي



Q. Expressed the Crum Brown and Fraser equation, give example.

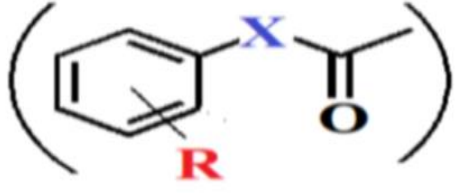
They postulated that the physiological action of a molecule fhi *(Φ)* is a function of its chemical constitution, C.

This can be expressed in Equation (1)

$$\Phi = f(C) \ldots\ldots\ldots\ldots Eq.1$$

example

Φ NSAIDs = f (or Analgesic)



Where :

Aspirin, R = (2-COOH) X= O

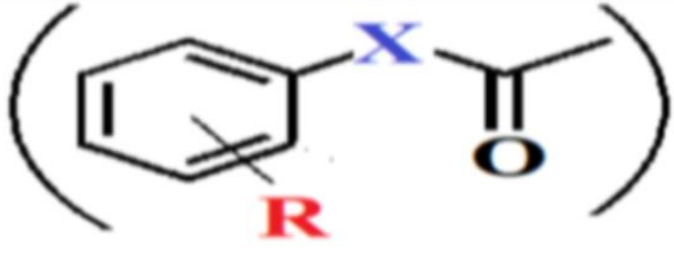
Paracetamol, R = (4-COOH) X= N

*Example-1- states that : A defined change in NSAIDs chemical structure results in a predictable change in physiological action: Change in type and positions of **R** and type of **X** gives **Aspirin** is reduced the amount of prostaglandins (Antipyral), which causes pain and inflammation in addition of controls swelling from any injured area and anticoagulant, with adverse side-effects of causing stomach ulcers. , **Acetaminophen** is also considered reduced the amount of prostaglandins(Antipyral), and as an analgesic may only work on the pain receptors and not on other things such as inflammation and it is not anticoagulant, with no adverse side-effects of causing stomach ulcers.

Q.Write the **Crum-Brown and Fraser** equation of physiological action of a NSAIDs molecule (aspirin) or Analgesic acetaminophen) fhi *(Φ)* is a function of its chemical constitution, C. (which are types and positions of **R** and type of **X**)

مهم جدا

$$\Phi \text{ NSAIDs (or Analgesic)} = f$$



Where :

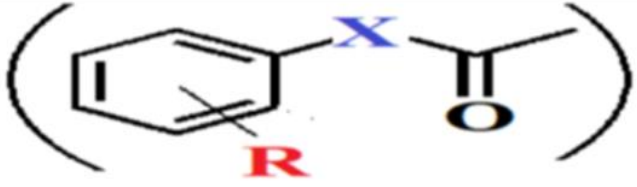
Aspirin, R = (2-COOH) X= O

Paracetamol, R = (4-COOH) X= N

This is the Crum-Brown and Fraser equation of physiological action of a NSAIDs molecule (aspirin) or Analgesic acetaminophen) fhi *(Φ)* is a function of its chemical constitution, C.
(which are types and positions of R and type of X)
Define: A,B,C and D

مهم جدا

$$\Phi_{\text{NSAIDs (or Analgesic)}} = f$$



Where :

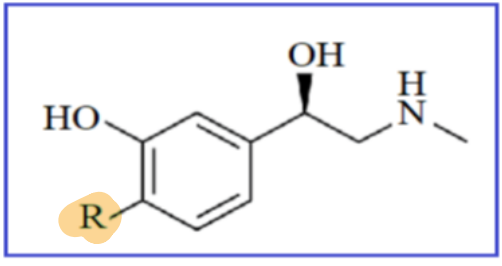
Aspirin, R = A X = B

Paracetamol, R = C X = D

Example -2- :

A defined change in Epinephrine chemical structure (replacement of R= OH to the R=H)results in a predictable change in physiological action .

حساسية احتشاء القلب



Epinephrine (adrenaline): R =OH
A medication (or hormone), it is used to treat a number of conditions, including anaphylaxis cardiac arrest, asthma, and superficial bleeding.

Phenylephrine: R = H
A medication primarily used as a decongestant, to dilate the pupil, to increase blood pressure, and to relieve hemorrhoids

Q. (Enumerate the five physicochemical properties affected biological response)

مهم جدا

1. Vapor pressure of volatile drugs.
2. Water solubility.
3. Electronic parameters
4. Steric hinderance
5. Partition coefficients

(Physicochemical properties affected Biological response)

The biological response can be predicted from physicochemical properties such as:

1. Vapor pressure of volatile drugs

هو ميل الجسيمات للهروب من السائل (أو الصلبة)

Is the tendency of particles to escape from the liquid (or a solid).

A substance with a high vapor pressure at normal temperatures is often referred to as volatile.

Example:

Volatile Methyl amphetamine, a potent (CNS) stimulant use as Nasal inhaler decongestant

Absorption of inhaled drug is dependent upon the physical characteristics of the drug which include:

I .Particle size 2.Lipid solubility, and 3. Volatility.

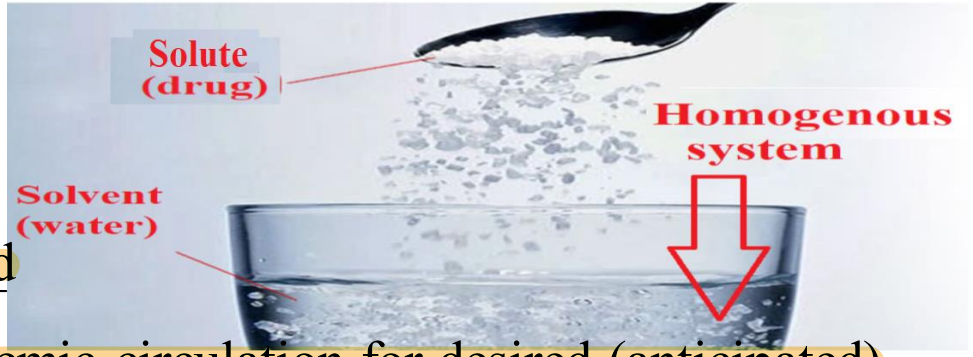
Clearly, a drug's volatility would play an important role in determining its inhalation potential.

Drug volatility is determined by many factors:

1. Boiling point 2.Melting point, and 3.Vapor pressure.

2. Water solubility.

1. Solubility, the phenomenon of dissolution انحلال of solute in solvent to give a homogenous system.

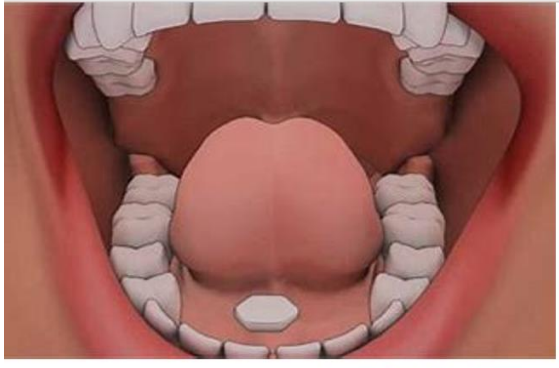


2. *It is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response.

3. Low aqueous solubility is the major problem and it is a major challenge for formulation scientist.

انخفاض الذوبان المائي هو المشكلة الرئيسية وهو كبير تحدي لعالم الصياغة.

*4.Any drug to be absorbed must be present in the form of solution at the site of absorption.



Any drug to be absorbed must be present in the form of solution at the site of absorption

Q. Enumerate The physical and chemical modifications techniques that are used for the enhancement of the solubility of poorly soluble drugs :

i. Particle size reduction ii. Crystal engineering iii. Salt formation

iv. Solid dispersion* v. Use of surfactant vi. Complexation

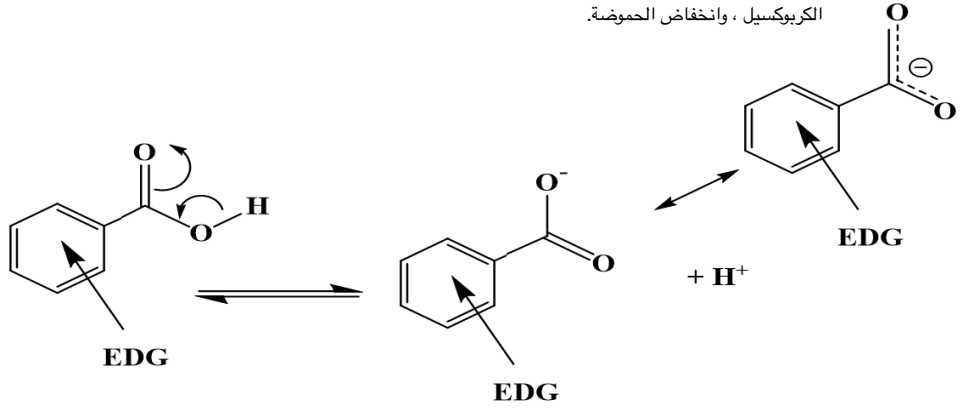
Insoluble drug are dispersed in soluble drug without physiological inert carrier and soluble drug itself act as carrier for solubility.

3.Electronic parameters (e.g. effects on acidity):

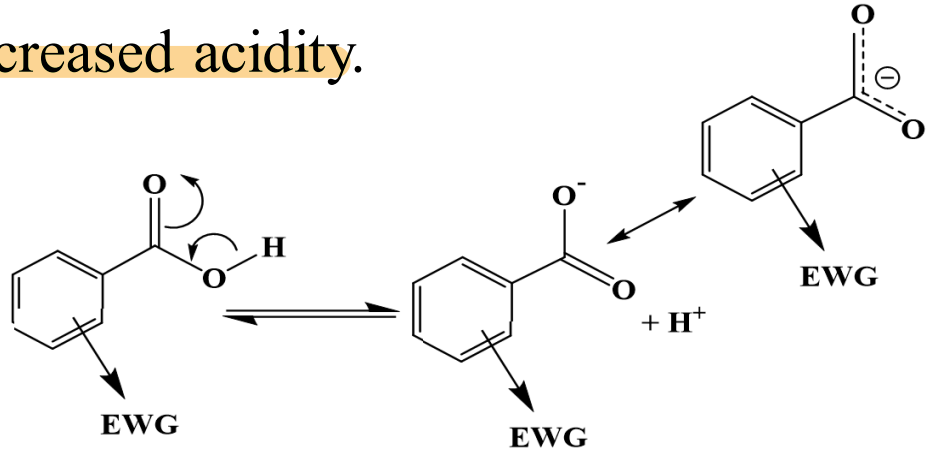
The equilibrium position depending on the type of substituent:

a)) Electron donating group (EDG) increased the carboxylate negative charge, thus destabilize the carboxylate anion , decreased acidity.

زادت مجموعة التبرع بالإلكترون (EDG) الشحنة السالبة للكربوكسيل ، وبالتالي زعزعة استقرار أنيون الكربوكسيل ، وانخفاض الحموضة.



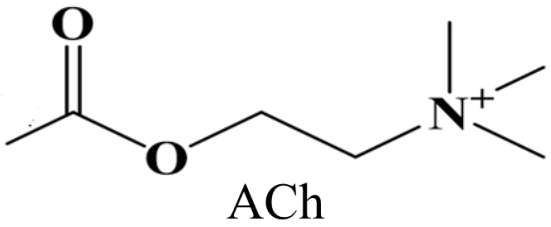
b)) Electron withdrawing group(EWG) decreased the carboxylate negative charge, thus stabilize the carboxylate anion , increased acidity.



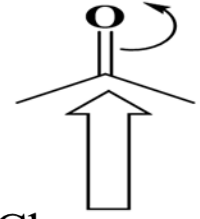
Acetic acid, CH3 COOH, is about 10 times weaker as an acid than formic acid, HCOOH.

Example:
Electronic parameters (e.g. effects on stability in aqueous solutions)

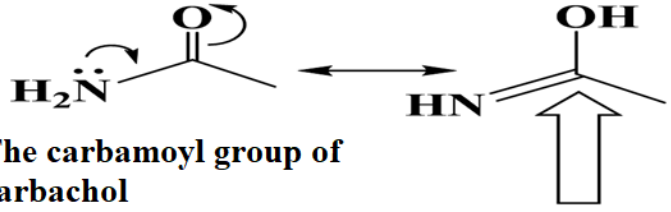
Carbachol differs chemically from ACh in its stability to hydrolysis. The carbamoyl group of carbachol decreases the electrophilicity of the carbonyl and, thus, can form resonance structures more easily than ACh can. The result is that carbachol is less susceptible (sus.ek.table) to hydrolysis in aqueous sol. and, therefore, more stable in aqueous sols.



ACh



poor center
electrophilic
susceptible to hydrolysis

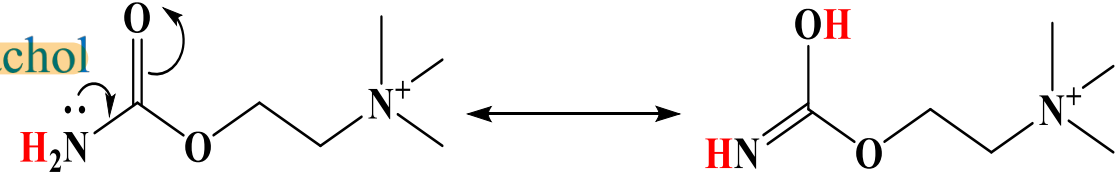


The carbamoyl group of carbachol

Carbachol

decreases electrophilicity
form resonance
less susceptible to hydrolysis
more stable in aqueous solutions.

Carbachol



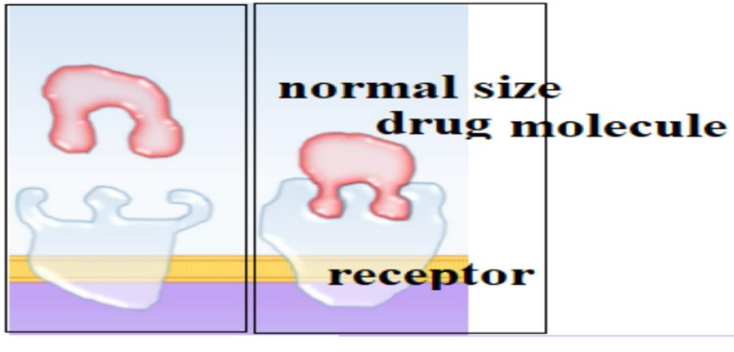
The carbamyl group of carbachol decreases the electrophilicity of the carbonyl and, thus, can form resonance structures more easily than ACh can. The result is that carbachol is less susceptible to hydrolysis and, therefore, more stable in aqueous solutions.

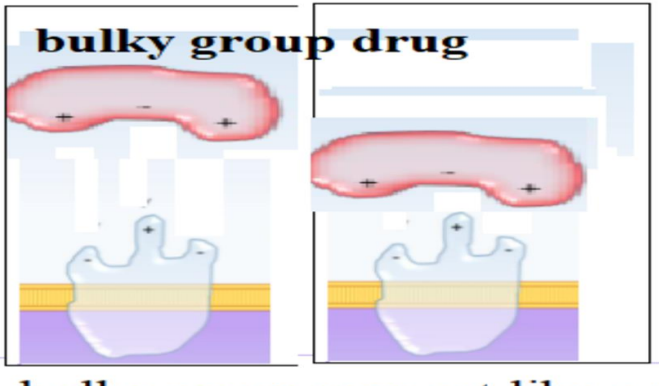
سيؤثر حجم جزيء الدواء وحجمه وشكله على مدى سهولة الاقتراب والتفاعل مع موقع الارتباط (الموقع النشط) للمستقبل. جماعة ضخمة قد تتصرف كدرع عرد وتمنع قيعت التفاعل المثالي.

4.Steric hinderance الاعاقة بالفراغ

The bulk, size and shape of a drug molecule will influence how easily it can approach and interact with a binding site (active site) of receptor.

A bulky group may act like a shield درع and hinder تعيقthe ideal interaction .

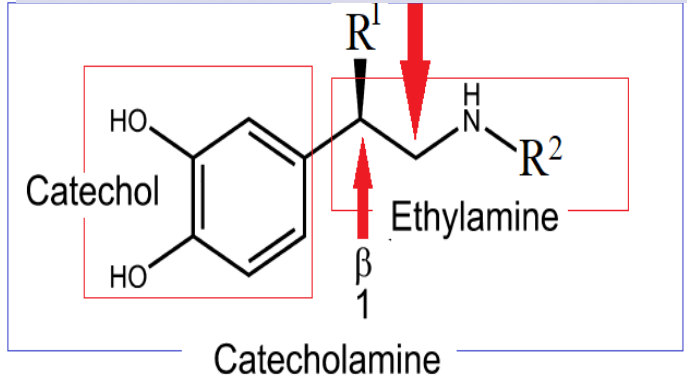




A bulky group may act like a shield and hinders the ideal interaction

Substitution by small alkyl group (e.g., CH_3- or C_2H_5-) slows metabolism by MAO* but has little overall effect on DOA of catechols because they remain substrates for COMT**. *However, the resistance to MAO activity is more important in noncatechol indirect-acting phenylethylamines.

ولكن لها تأثير عام ضئيل على DOA لمضادات الاكسدة لأنها تظل ركائز لـ COMT **. * ومع ذلك ، فإن مقاومة نشاط MAO أكثر أهمية في فينيل إيثيل أمين غير المباشر المفعول غير الكاتيكول.



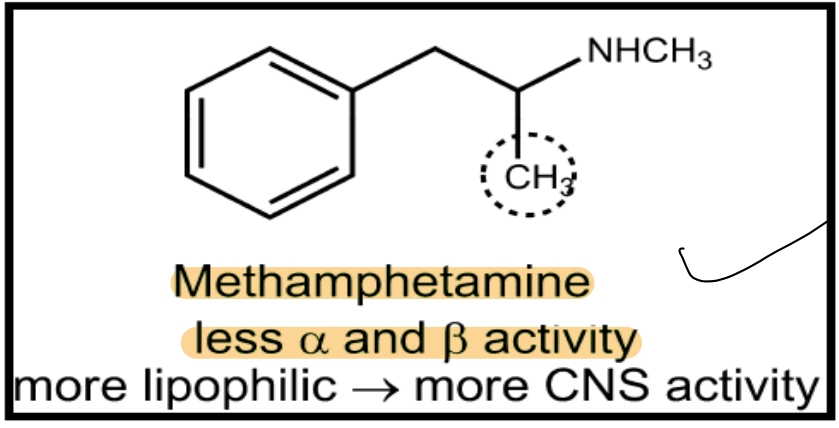
$R^1 = OH$, $R^2 = CH_3$- Epinephrine (E)

$R^1 = R^2 = H$ Dopamine (DA)

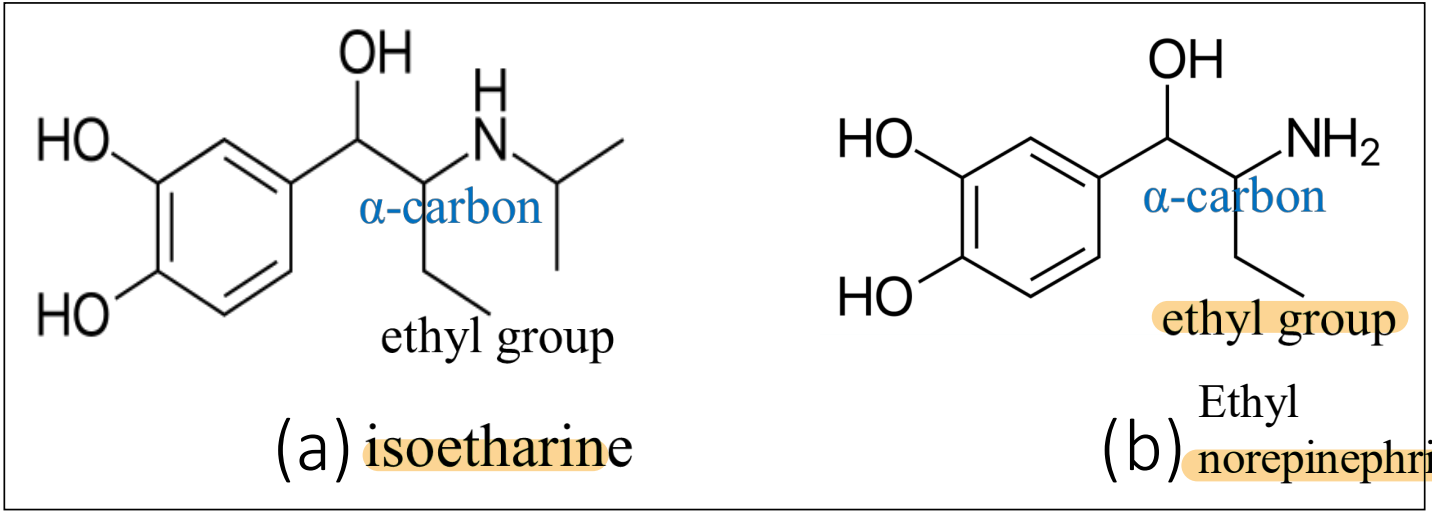
* MAO, Monoamine oxidase E. is involved in removing the neurotransmitters norepinephrine, serotonin and dopamine from the brain.

**COMT, Catechol-*O*-methyltransferase is E involved in the inactivation of the catecholamine neurotransmitters (dopamine, epinephrine, and norepinephrine).

Example1: Methyl or ethyl substitution on the α-carbon of the ethylamine side chain reduces direct agonist activity at both α- and β-receptors.



Example2: An ethyl group in on the α-carbon position diminishes α-activity far more than β-activity, affording compounds with β-selectivity (e.g., Isoetharine (a) and ethyl norepinephrine(b).

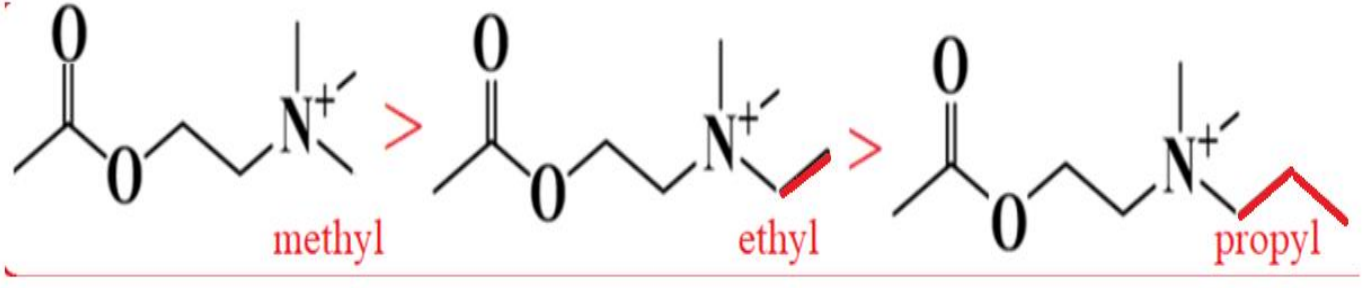


Ethyl group diminished α-activity far more than β-activity,

تقلل مجموعة الإيثيل الموجودة في موضع α-carbon نشاط α أكثر بكثير من نشاط β ، مما يمنح المركبات ذات انتقائية β (على سبيل المثال ، Isoetharine (a) و ethyl norepinephrine (b).

Example-3-: استیل کولین

Another example is the substitution of one of the methyl groups of acetylcholine with higher alkyl groups like ethyl or propyl make the molecules less active than acetylcholine.



Less active molecules than acetylcholine

5.Partition coefficients معامل التوزيع P.C .

*

The movement of molecules from one phase to another is called partitioning.

- If two immiscible phases are placed adjacent to each other, the solute will distribute itself between two immiscible phases until equilibrium is attained; therefore no further transfer of solute occurs.

In the Chemical and Pharmaceutical Sciences a partition coefficient is the ratio of concentrations of a compound in the two phases of a mixture of two immiscible liquids at equilibrium.

This compound is unionized

Partition coefficient (P) =

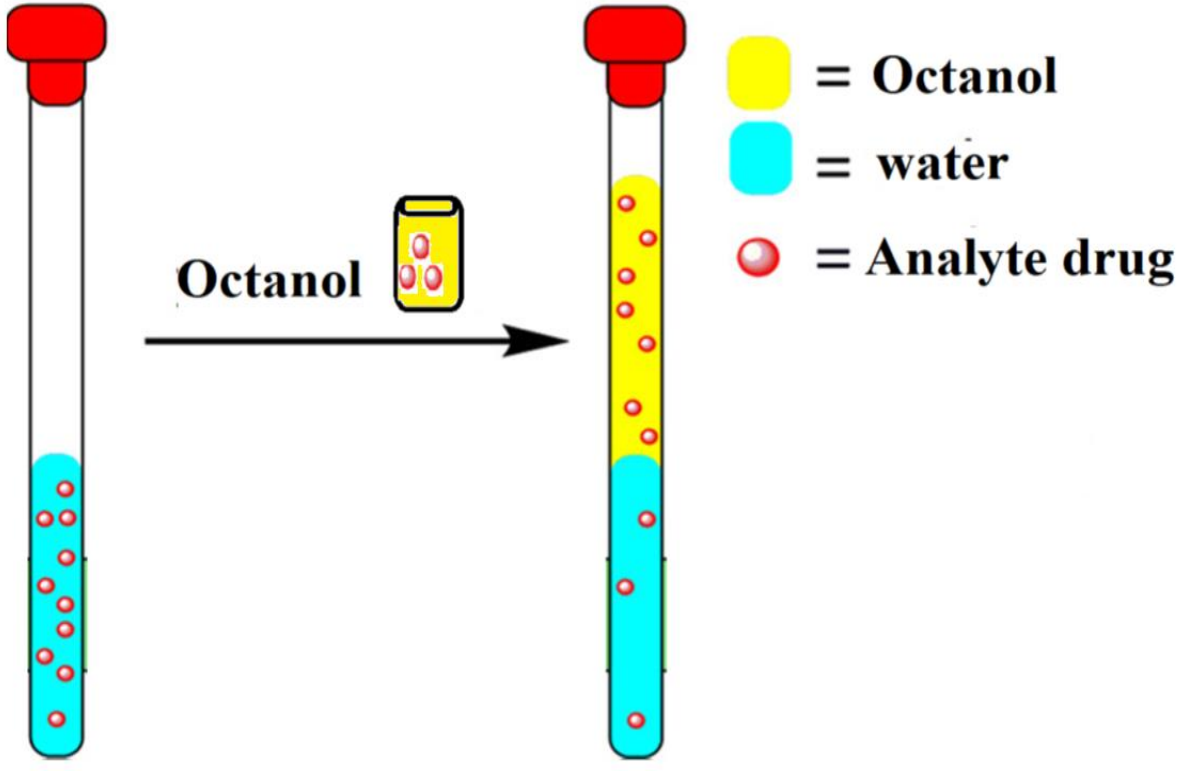
Conc. of unionized Drug in organic phase / Conc. of Drug in aqueous phase

Octa = 8 (October)

For example, in an octanol-water system:

Taking the logarithm of the two sides of equation:

$$\log P_{oct/wat} = \log \left(\frac{[solute]^{un-ionized}_{octanol}}{[solute]^{un-ionized}_{water}} \right)$$


Octanol
= Octanol
= water
= Analyte drug

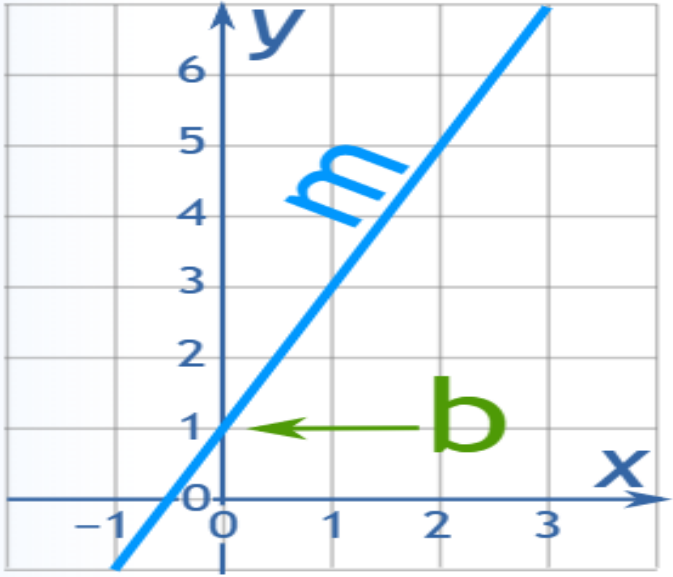
ملاحظات مهمه

1. The partition coefficient measures how hydrophilic ("water-loving") or hydrophobic ("water-fearing") a drug is.
2. Partition coefficients are useful in estimating the distribution of drugs within the body. Hydrophobic drugs with high octanol-water partition coefficients are mainly distributed to hydrophobic areas such as lipid bilayers of cells

معاملات التقسيم مفيدة في تقدير توزيع الأدوية داخل الجسم. عقاقير كارهة للماء مع قسم عالي من الأوكتانول والماء
يتم توزيع المعامِلات بشكل أساسي على مناطق كارهة للماء مثل الدهون طبقات الخلايا

3. Conversely, hydrophilic drugs with low octanol/water partition coefficients are found primarily in aqueous regions such as blood serum.

* Today, the partition coefficient has become the single most important physical chemical measurement for QSAR studies. Note that the equation for a straight line :



$$y = mx + b$$

y = how far up

x = how far along

m = Slope

b = value of **y** when **x=0**

the physical chemical property equals zero

Also, this is equation for a straight line:

$$y = mx + b$$

log BR = a (physico-chemical property) + *c* .....Eq. 2

*Where BR a defined pharmacological (Biological) Response usually expressed in millimoles such as:

مهمه

ثابت الشبيط

i. The inhibitory constant *Ki*

ii. The effective dose in 50% of the subjects (ED50)

iii. The lethal dose in 50% of the subjects (LD50), or

iv. The minimum inhibitory concentration (MIC)

It is common to express the biological response as a reciprocal مقلوب. Physio-chemical property 1/BR and 1/C .

$$y = mx + b$$

a is the regression coefficient or (slope) of the straight line.

b = value of **y** when **x=0**

c the intercept term on the *y* axis (when the physical chemical property equals zero)

1. The inhibitory constant *Ki*, the concentration of the inhibitor that is required in order to decrease the maximum rate of the reaction by half.

*Therefore, the smaller the Ki, the smaller amount of medication needed in order to inhibit the activity of that enzyme

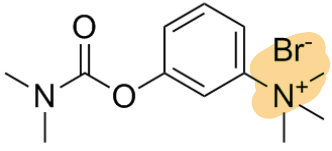
Acetylcholine esterase enzyme AChE inhibitors, such as neostigmine bromide has Ki < of that of Neostigmine in the treatment of myasthenia gravis, i. e this bromide salt is more potent.

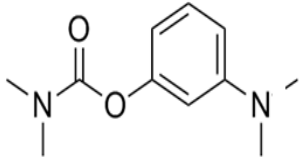
كمية تركيز المثبط المطلوب لتقليل معدل تفاعل الدواء الى النصف وكلما قلت Ki قلت كمية الدواء المطلوبة للتثبيط اي ان الدواء اكثر فعالية

ماي سينيا

Myasthenia gravis

الوهن العضلي الوبيل





Neostigmine Bromide **Ki<** Neostigmine

* **The effective dose (ED),** is a dose of a drug that produces a pharmacological response.

It is used when measurements are taken in vivo, while the term:

***The effective concentration** is used when the measurements are taken in vitro.

The effective dose fifty (ED_{50})

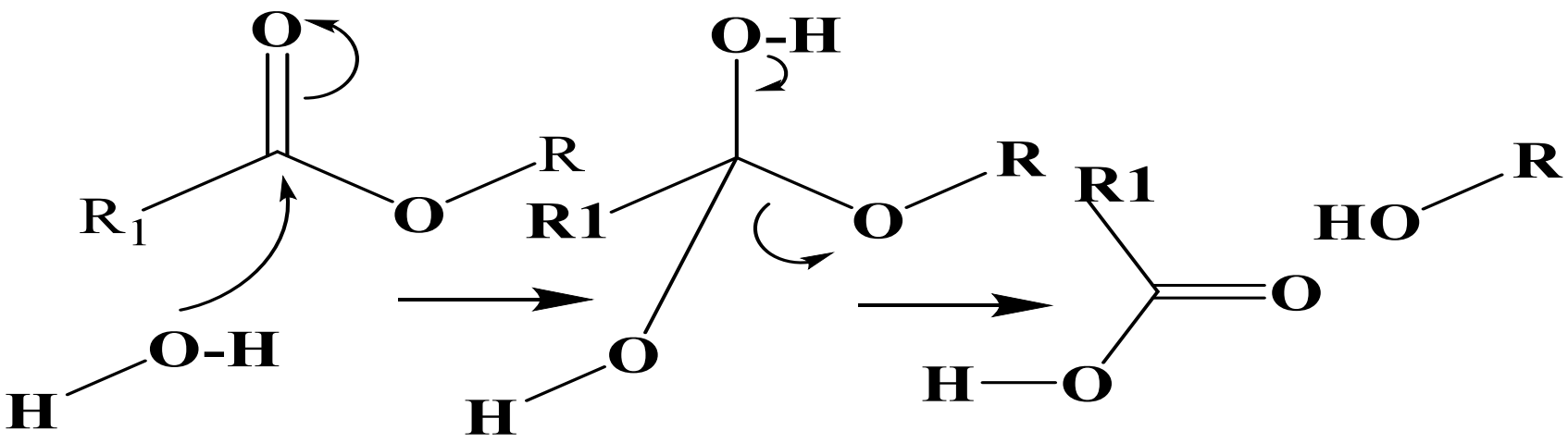
A dose of a drug needed to obtain the defined pharmacological response in 50% of the test subjects.

FORCE INVOLVED WITH

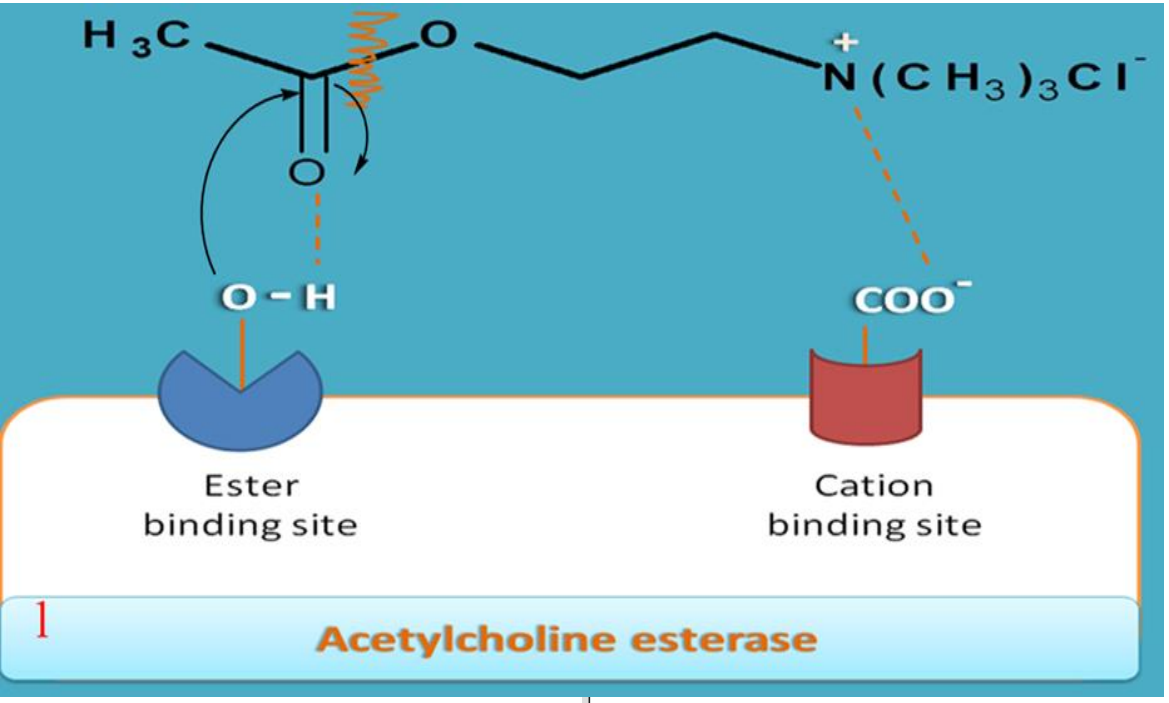
DRUG-RECEPTOR INTERACTIONS

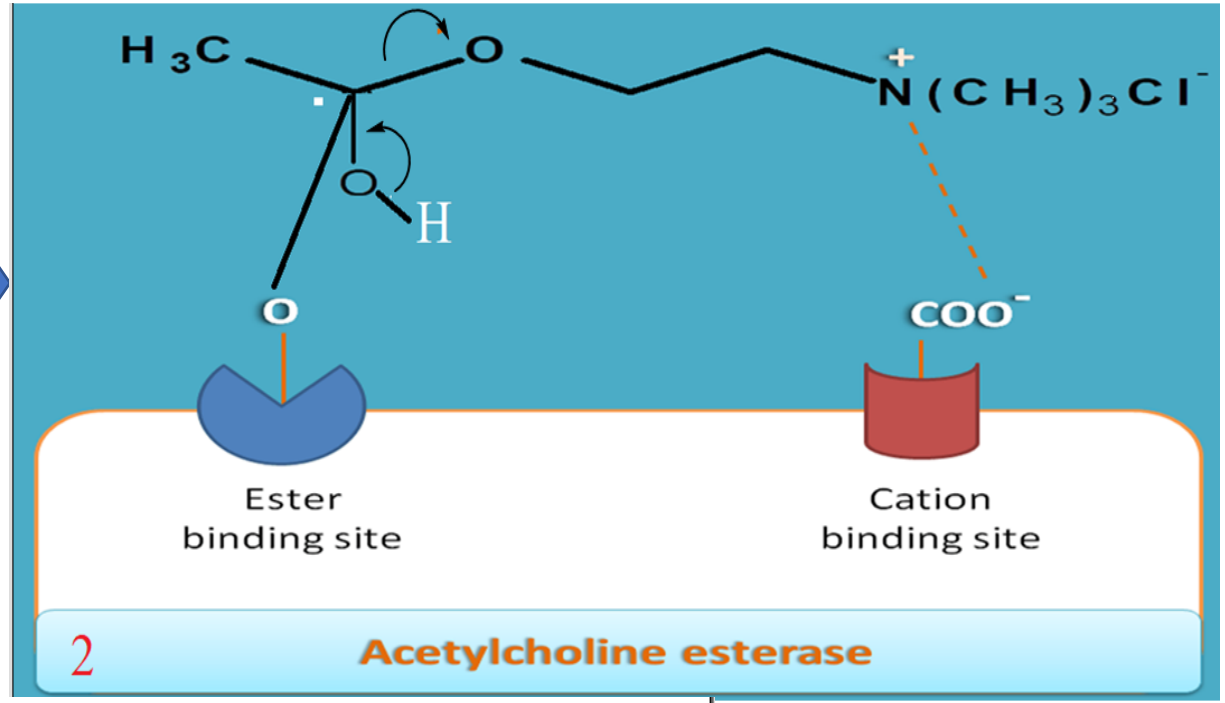
Biological response is produced by the interaction of a drug with a functional groups of molecules. This interaction would be expected to take place by using the same bonding forces as are involved when simple molecules interact.

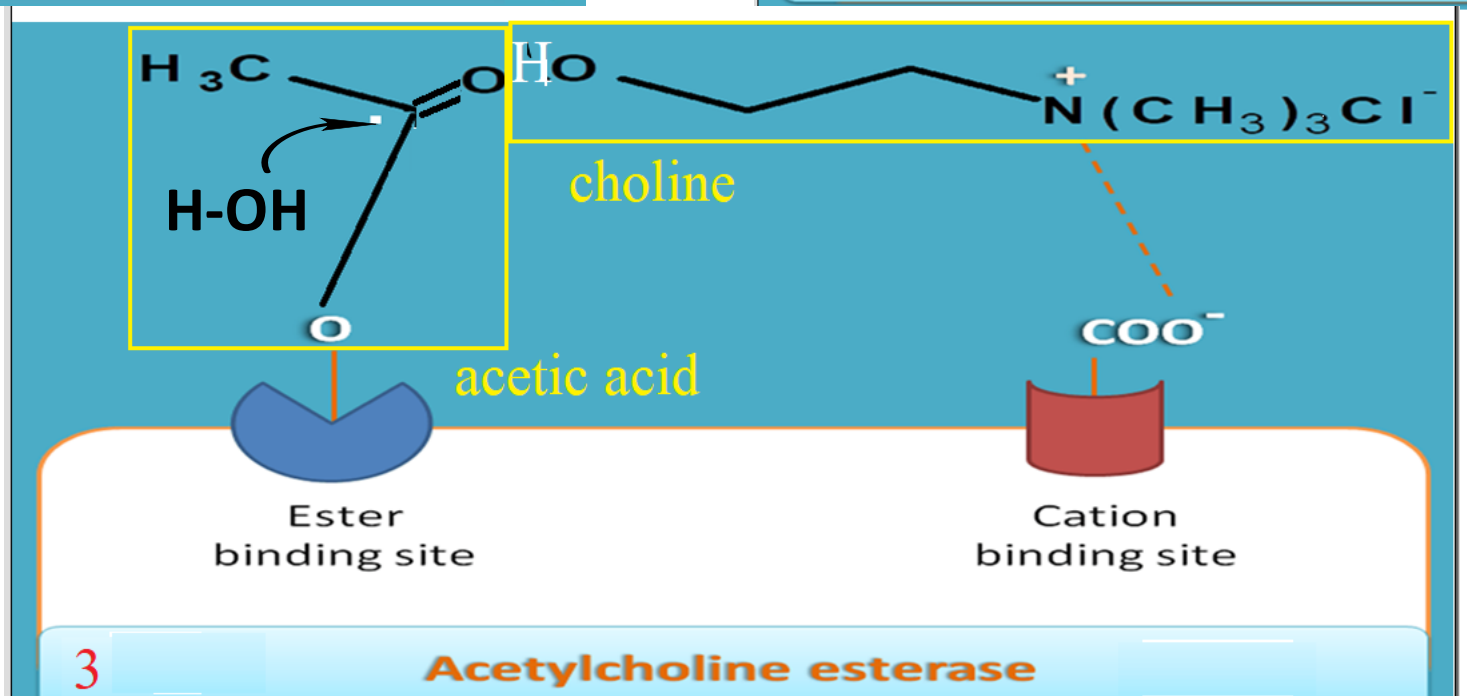
Examples: carbonyl, amine, ester or double bonds. **e.g. water hydrolysis of ester and acetyl choline hydrolysis by active site of Acetylcholine esterase**



Ach hydrolysis by Active site of Acetylcholine esterase

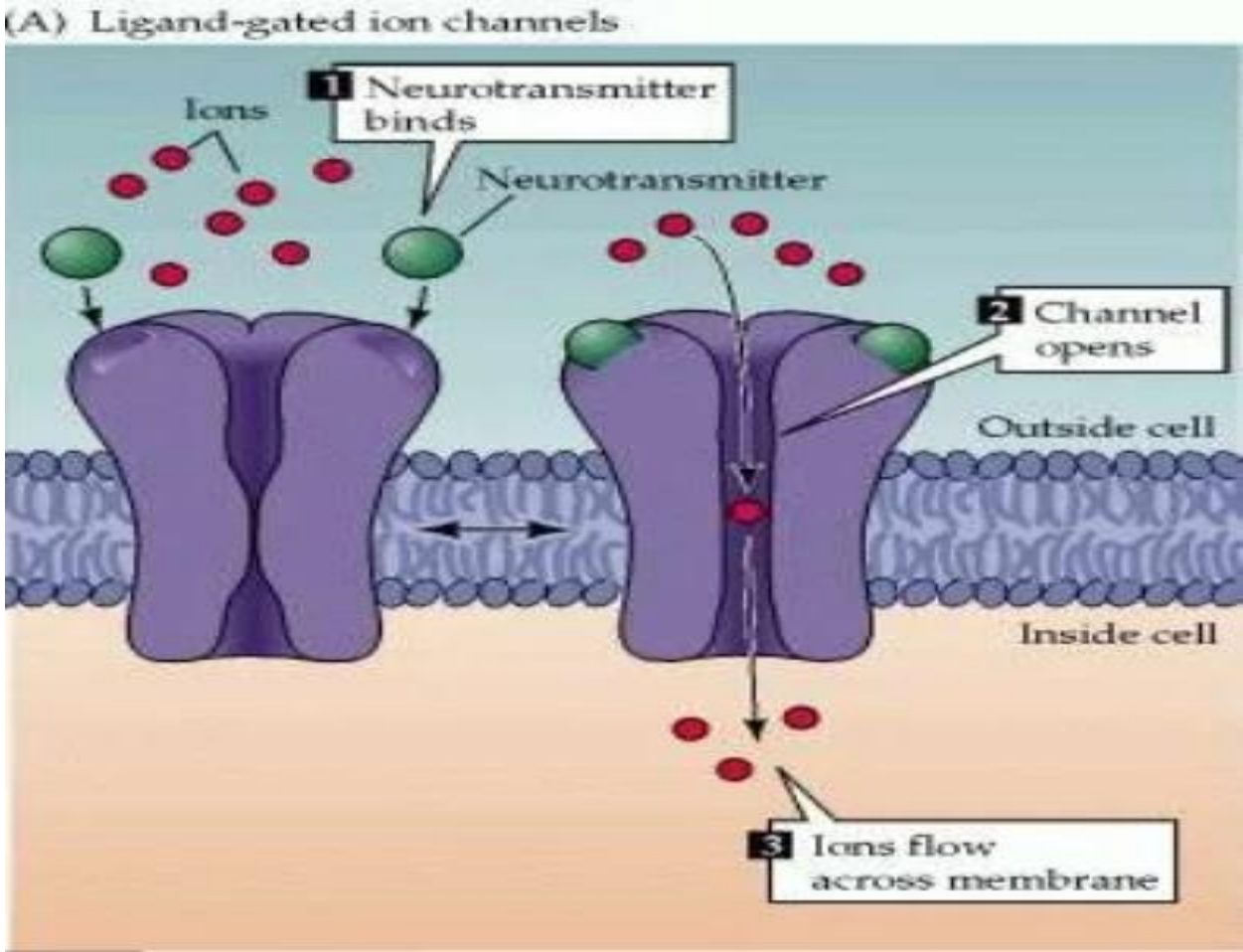






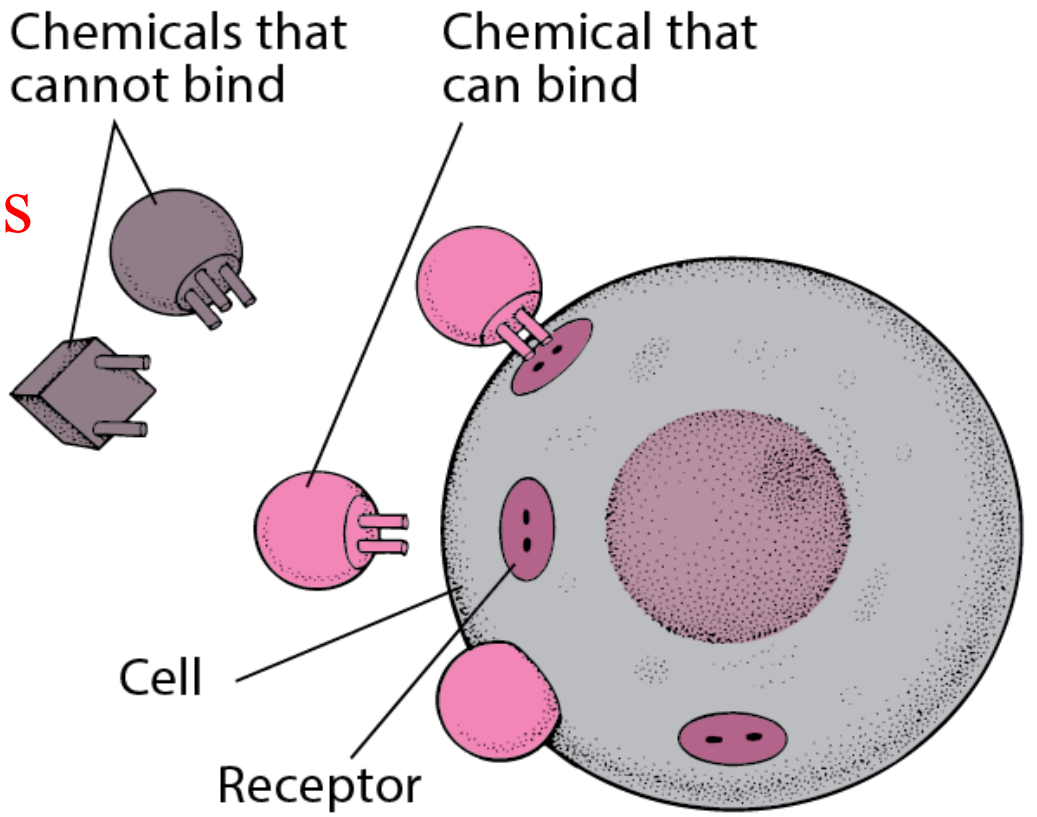
Receptors; are chemical structures, composed of protein, that receive and transduce تستقبل وتحولsignals which may be integratedتتكامل into biological systems. These signals are typically chemical messengers which bind to a receptor and cause some form of cellular/tissue response,

e.g. *A change in the electrical activity of a cell.



There are receptors on the cell surface where hormones such as epinephrine or insulin bind, setting off a series of biochemical events within the cell.

The substrates

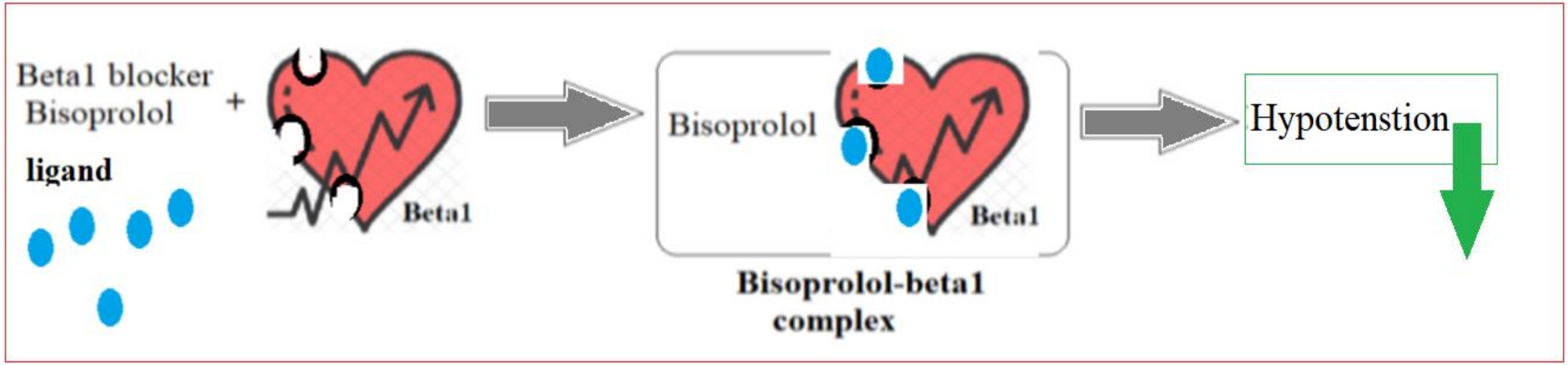


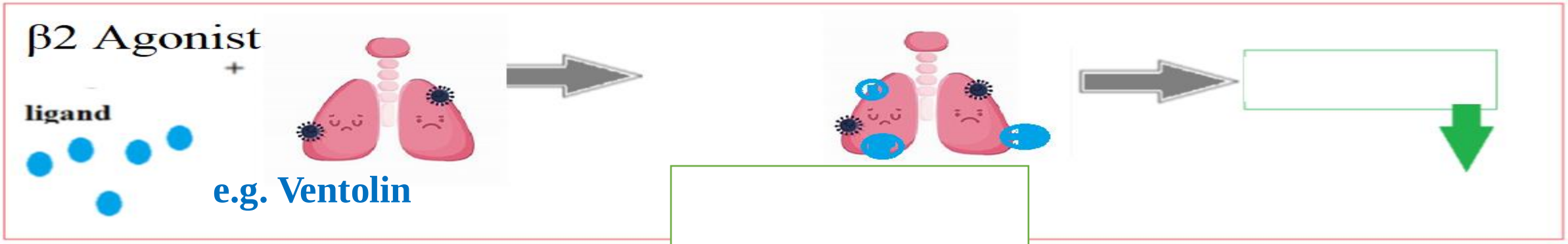
*Some of these receptors are used by viruses to gain entrance into the cells, where the virus reproduces.

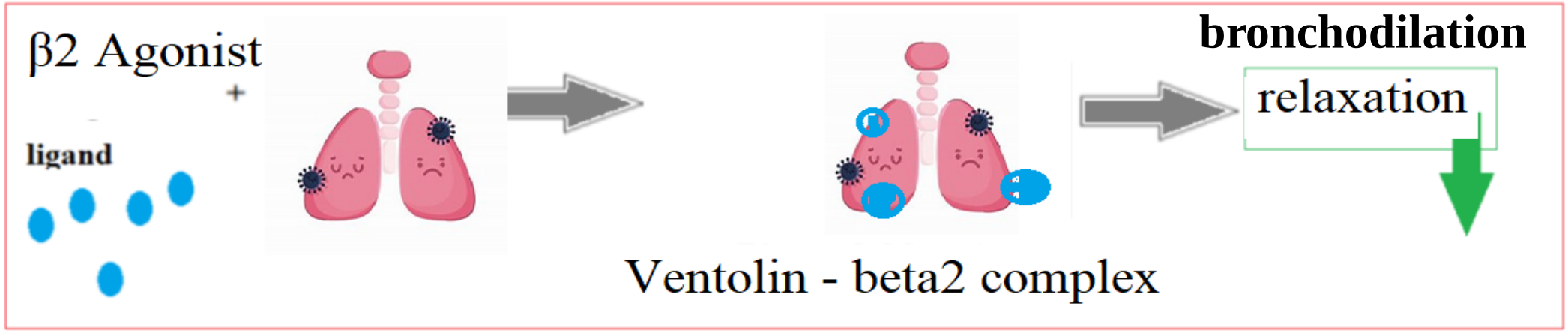
The drugs act on receptor to produce the drug–receptor complex , which give the needed response.

Drug + Receptor = Drug– Receptor complex = Pharmacological Response

Example is the heart β1 receptor and it's blocker bisoprolol

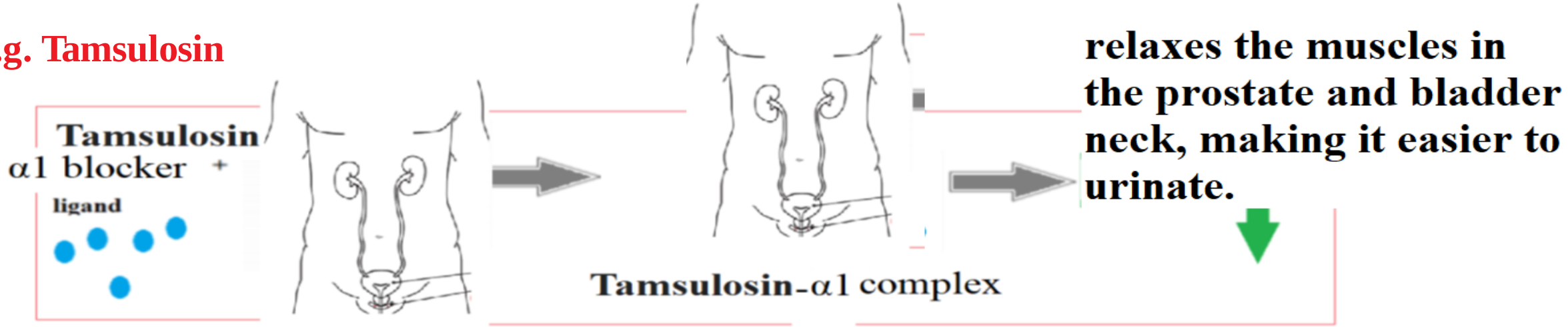






Salbutamol, (albuterol,Ventolin) opens up the medium and large airways in the lungs. It is a short-acting β2 adrenergic receptor agonist which works by causing relaxation of airway smooth muscle. It is used to treat asthma.

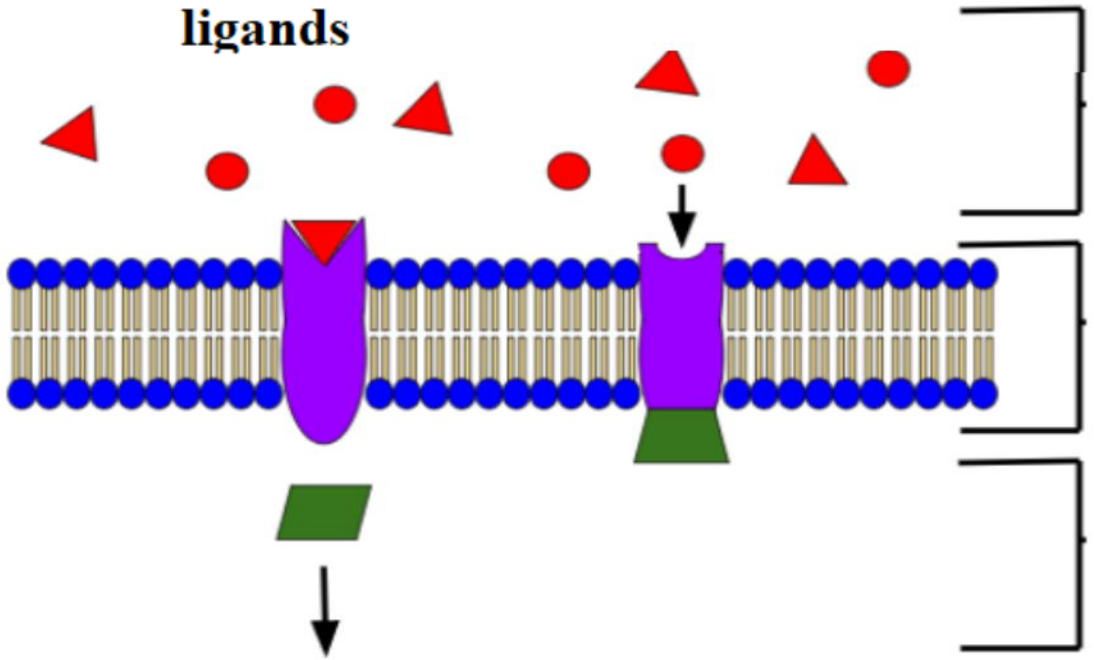
e.g. Tamsulosin



There are three main ways that the action of the receptor can be classified:

1. Relay of signal (open and close, i.e. swich)
2. Amplification تضخيم
3. Integration

Schematic example of ligands, receptor and messengers



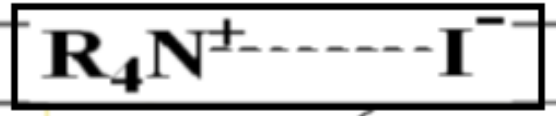
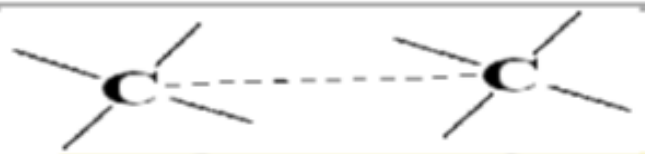
The substrate

1)Ligands, located outside the cell

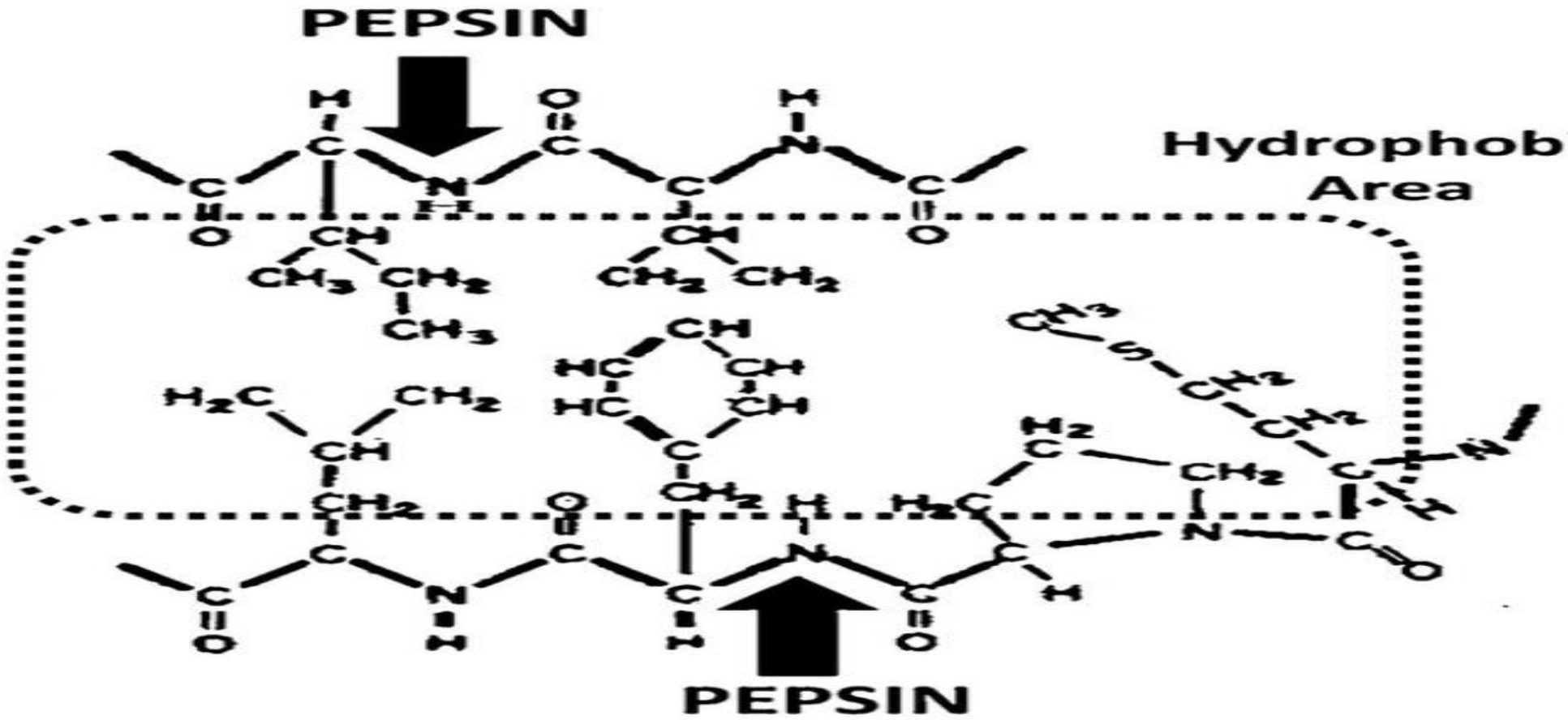
2)Ligands connect to specific receptor proteins based on the shape of the active site of the protein.

3)The receptor releases a messenger once the ligand has connected to the receptor.

Draw examples of five of the following bonds types that may formed between receptors and drugs (write the values of their strength)

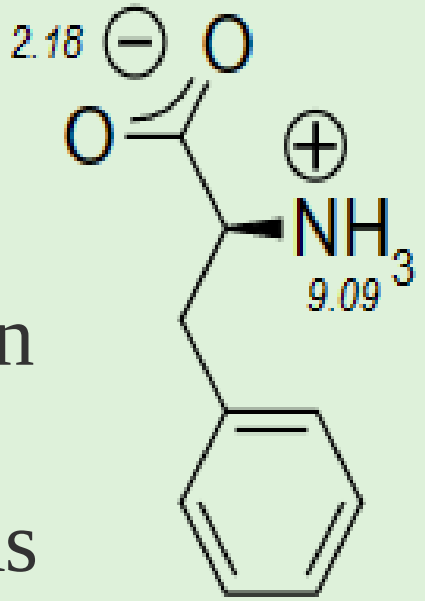
Bond types	Bond strength (kcal/mole)	Example
Covalent	40 - 140	Methanol (CH3OH)
Reinforced ionic	10	
Ionic	5	
Dipole- Dipole	1 - 7	
Van Der Waals	0.5 - 1	
Hydrophobic	1	

Decreasing of bonds strength



Phenylalanine

Phe F



Hydrophobic bonding that occurs between chains in protein where each has several aliphatic-aromatic amino acids in sequence. These amino acids each have hydrophobic ends on one chain that collaborates with the ends from a similar array on another chain.

Examples:

1.The weakest chemical bond strength is the Van der Waals bond which is 0.5-1 kcal/mole $H_4C\ldots CH_4$.

2. The bond between carbon and hydroxyl oxygen atom of the Methanol is covalent bond, it is the strongest chemical bond which is 40-140 kcal/mole.

Receptors examples

1.Cholinergic Receptors:

Receptors found in the central and peripheral nervous systems and use acetylcholine (Ach) as their neurotransmitter.

ملحظات مهمه

1.Nicotinic and muscarinic receptors are the two main types of cholinergic receptors. المستقبلات النيكوتينية تحوي النيكوتين والمسكرينية تحوي المسكارين والاثنان يثاران بالناقل العصبي الاستيل كولين ولكن كل بموقع يختلف بالاعصاب وبميكانيكية مختلفة وهما اغلفة بروتينية متكاملة.

2.They are integral membrane proteins activated by the binding of neurotransmitter acetylcholine.

3.The mechanism of action is different in each receptor(4&5)

4.The nicotinic receptors become ion channels for sodium upon binding of the acetylcholine to the receptor

5.The muscarinic receptors phosphorylate various second messengers.

6. Nicotinic receptors are also called ionotropic acetylcholine receptors while

7. Muscarinic receptors are also called metabotropic acetylcholine receptors depending on their action.

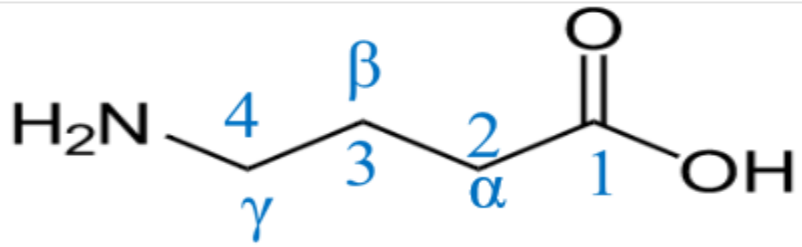
Ionotropic receptor activation, it opens a channel that allows ions such as Na+, K+, or Cl− to flow.
Metabotropic receptor activation, a series of intracellular events are initiated that can also result in opens a channel that allows ions such as Na+, K+, or Cl− to flow.

*Drugs acting on the acetylcholine system are either agonists to the receptors, stimulating the system, or antagonists, inhibiting it.

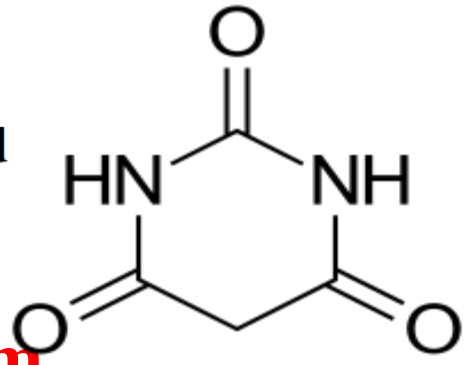
Acetylcholine receptor agonists and antagonists can either have an effect directly on the receptors or exert their effects indirectly *e.g., by affecting the enzyme acetylcholinesterase, which degrades the receptor ligand.

Agonists increase the level of receptor activation, antagonists reduce it.

2.The γ-Aminobutyric acid Neuroreceptors:



Barbituric acid chemical structure



It is reducing neuronal excitability throughout the nervous system.

Central nervous system (CNS) depressant. الكاما يقلل الاثارة العصبية وكذلك مشابهاته بزيادة ادخال ايونات الكلور السالبة

مثل مشتقات الباربيتيوريت او البنزودايابينات

a. Barbituric acid derivatives, are coupled to GABA receptors, increasing the intracellular chlorine entry, as well as the action on glutamate, reducing its activity.
b. Benzodiazepines, on the other hand, is characterized by specific binding to GABA receptors, generating a controlled entry of chlorine into the interior of the neuron, and hyper-polarization or neuronal inhibition.

Hyperpolarization is when the membrane potential becomes more negative at a particular spot on the neuron's membrane,

D**epolarization** is when the membrane potential becomes more positive.

Depolarization and hyperpolarization occur when ion channels in the membrane open or close, altering the ability of particular types of ions to enter or exit the cell.

For example:

1.The opening of channels that let positive ions flow out of the cell (or negative ions flow in) can cause hyperpolarization.

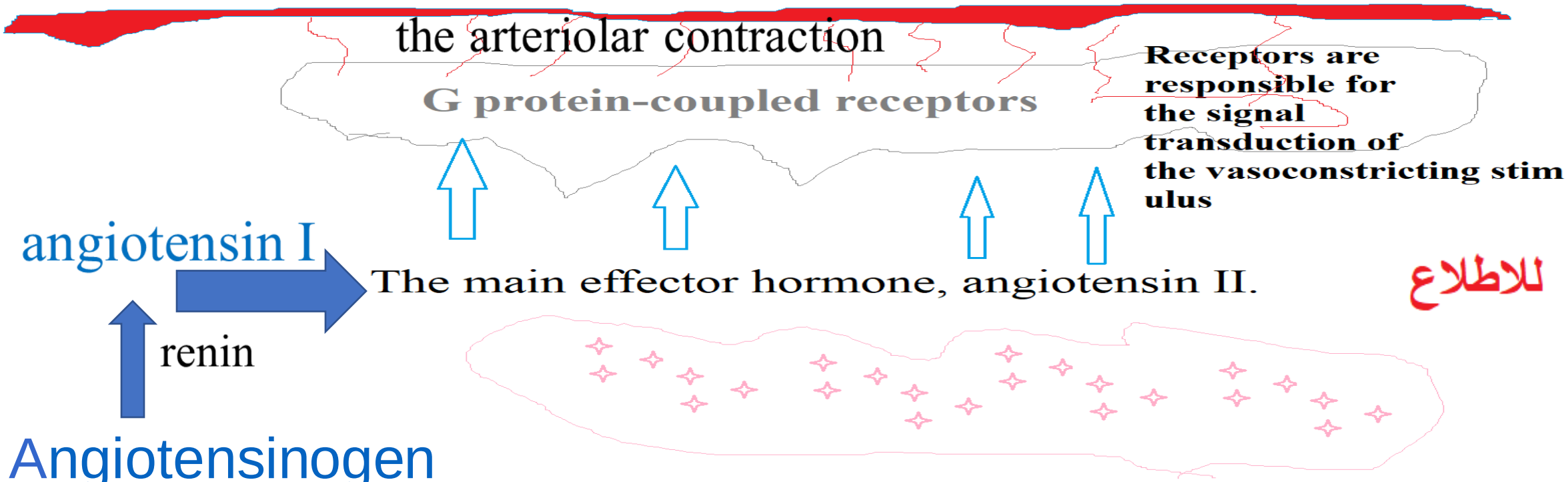
i.e. The opening of channels that let positive ions (e.g. Na^+) flow into the cell can cause depolarization.

The opening and closing of these channels may depend on the binding of signaling molecules such as neurotransmitters (ligand-gated ion channels), or on the voltage across the membrane (voltage-gated ion channels).

3.The angiotensin II receptors:

ATR I and ATR II, are a class of G protein-coupled receptors with angiotensin II as their ligands.(**Guanine nucleotide-binding proteins**)

They are important in the renin–angiotensin system: they are responsible for the signal transduction of the vasoconstricting stimulus of the main effector hormone, angiotensin II.



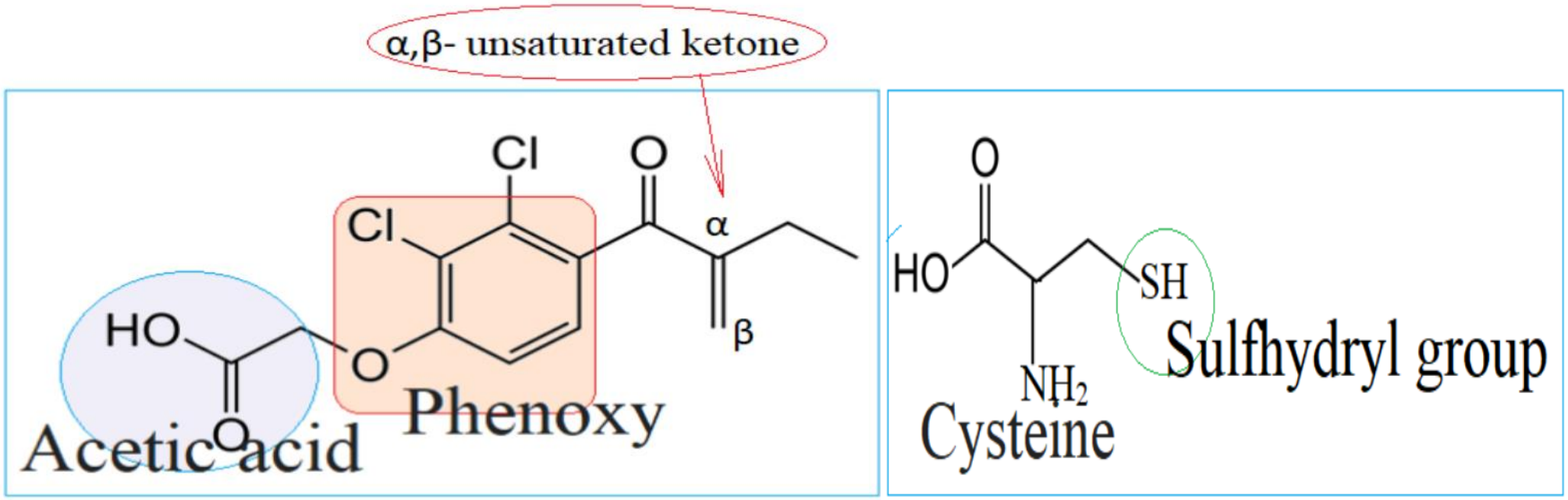
Angiotensin II receptor blockers (ARBs),or Angiotensin II receptor antagonists, are a group of pharmaceuticals that bind to and inhibit the angiotensin II receptor (ATRII) and thereby block the arteriolar contraction and sodium retention effects of renin–angiotensin system. Their main uses are in the treatment of hypertension (high blood pressure),

Covalent bond formation between drug and receptor is the basis of Baker's concept of active-site-directed irreversible inhibition.

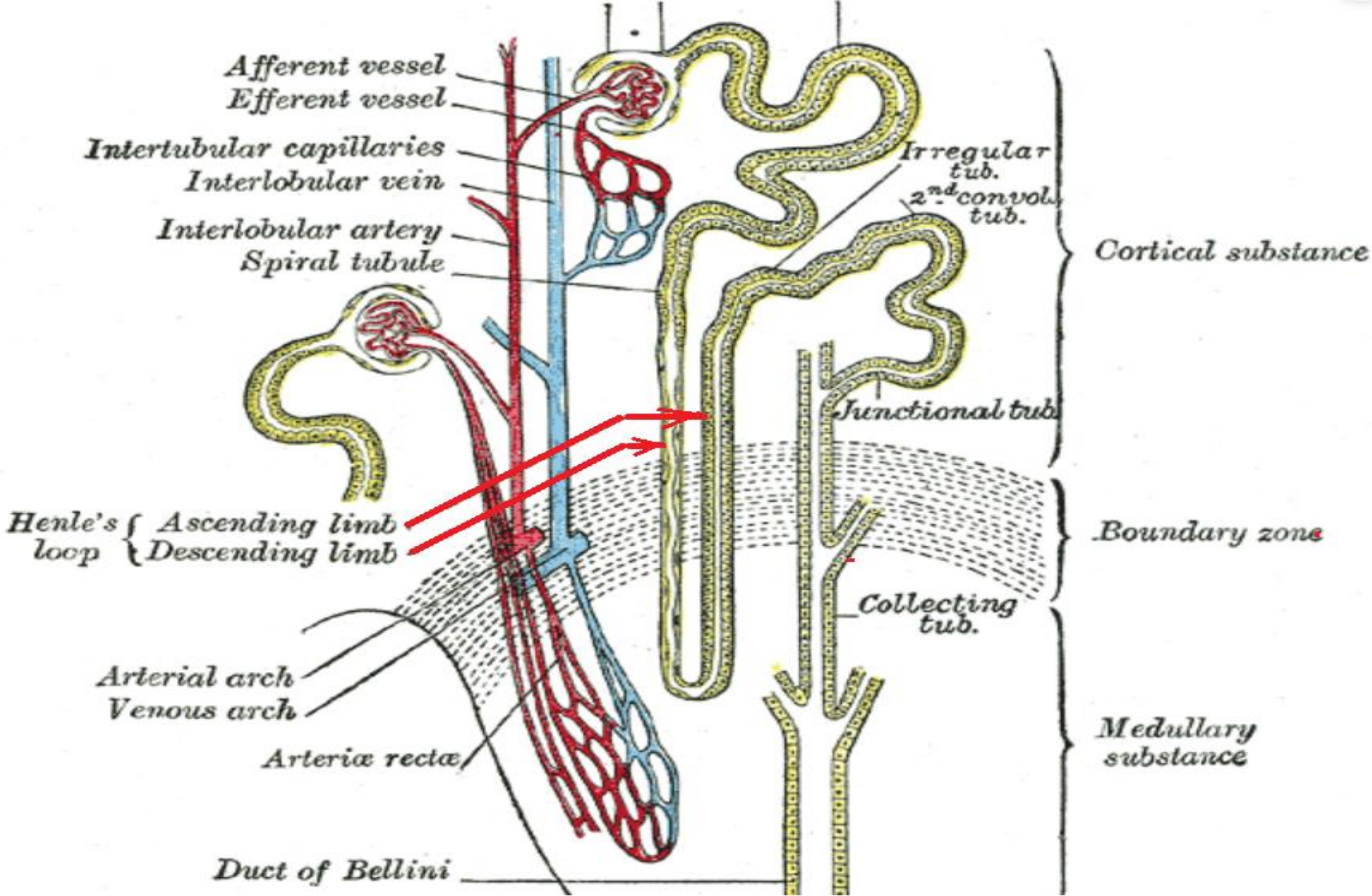
If, in addition, the compounds carry reactive groups capable of forming covalent bonds, the substrate may be irreversibly bound to the drug–receptor complex by covalent bond formation with reactive groups adjacent to the active site.

An examples of drugs act by covalent bond formation :

1.The diuretic drug Ethacrynic acid is α,β- unsaturated ketone, thought to act by covalent bond formation of methylene group with sulfhydryl group of cysteine adduct and this is the active form in the renal tubules.

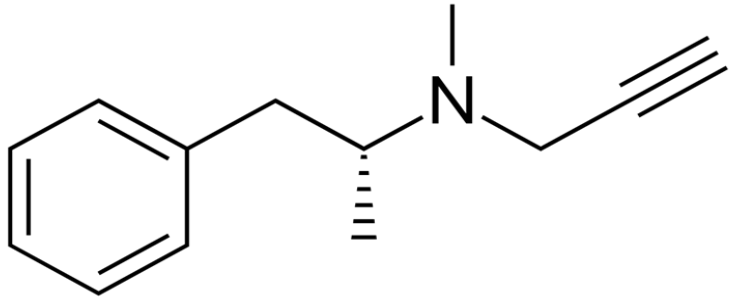


Edecrin (Ethacrynic acid trade name**)**, is a loop diuretic*(fig) used to treat high blood pressure and the swelling caused by diseases like congestive heart failure, liver failure, and kidney failure. It is a phenoxyacetic acid derivative


Afferent vessel
Efferent vessel
Intertubular capillaries
Interlobular vein
Interlobular artery
Spiral tubule
Irregular tub.
2nd convol. tub.
Cortical substance
Junctional tub.
Henle's loop
Ascending limb
Descending limb
Boundary zone
Collecting tub.
Arterial arch
Venous arch
Arteriæ rectæ
Medullary substance
Duct of Bellini

2.Selegiline:

Use for treatment of Parkinson's disease and major depressive disorder, selective inhibitor of MAO-B*, irreversibly inhibiting it by binding to it covalently. It exerts effects by blocking the breakdown of dopamine, thus increasing its activity.



يعمل هذا الانزيم على تحطيم الدوبامين وانتاج تثبيط للجهاز العصبي ويعمل هذا العلاج على الارتباط مع الانزيم باصرة تساهمية ويثبطها ويمنع تحطم الدوبامين وزيادة فعاليته

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*M**onoamine oxidase**) is an enzyme that breaks down monoamines, such as neurotransmitters that transmit signals between nerve cells in the brain with two types (A and B). They act by degrading serotonin, norepinephrine, and dopa.

Q. مهم Selegiline, is used for treatment of Parkinson's disease and major depressive disorder, (nonselective, selective) inhibitor of MAO-B, irreversibly inhibiting it by binding to it (coordenatingly, covalently). It exerts effects by blocking the breakdown of dopamine, thus (decreasing, increasing) its activity.

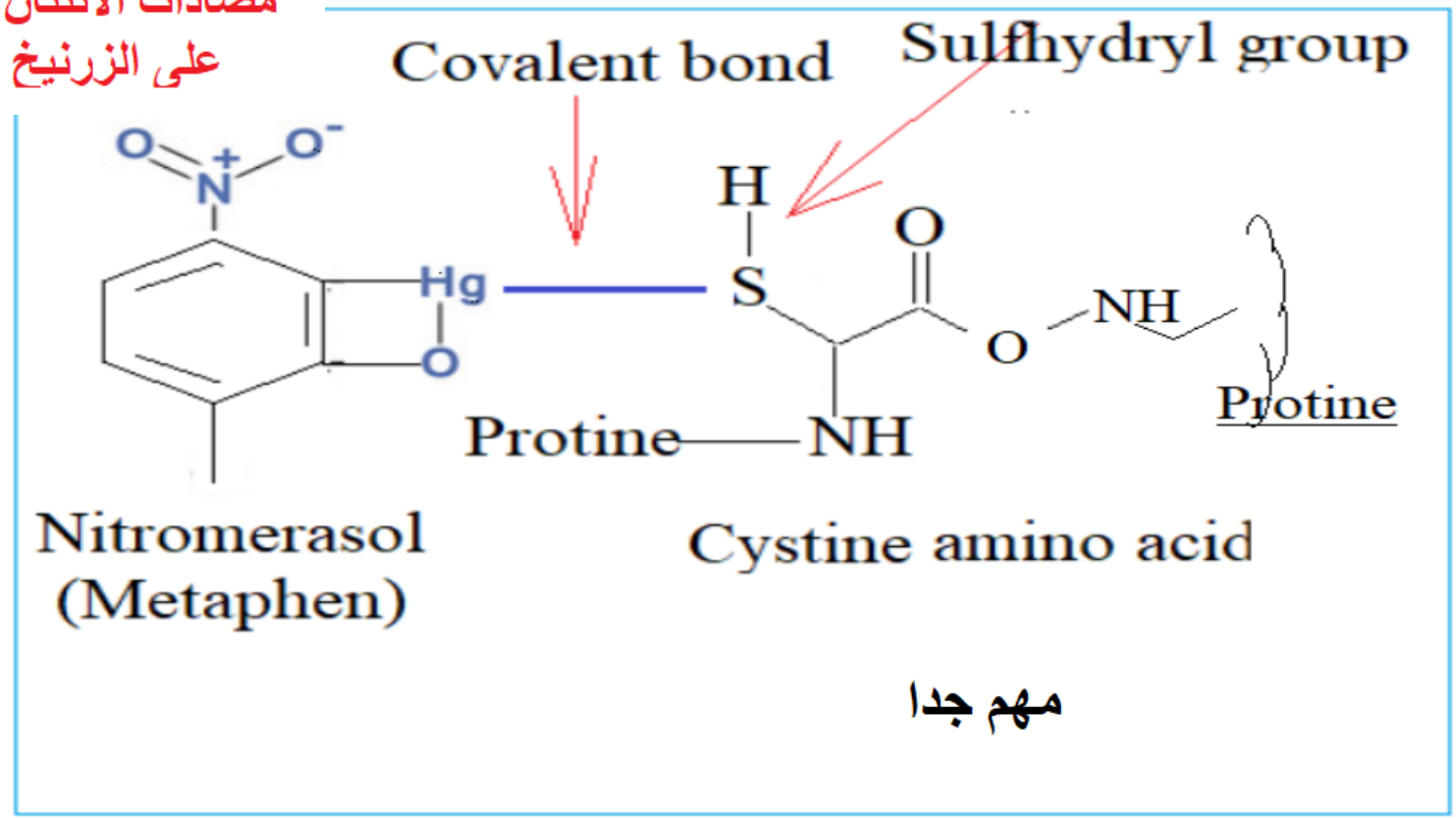
3.Arsenicals and mercurial:

مضادات الانتنان الحاوية على الزرنيخ والزئبق

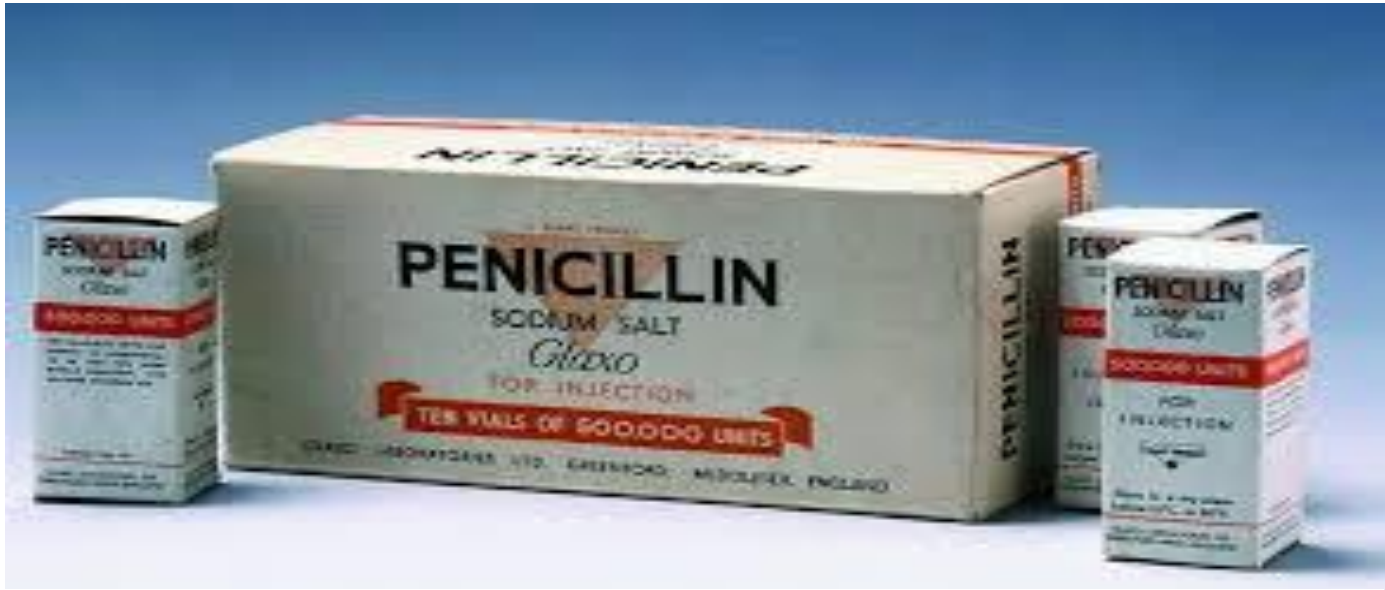
Also make covalent bond with the protein (cystine sulfhydryl group).

Draw Nitromersol (Metaphen)

Which is antiseptic for skin and ocular infections showing the covalent bond with the receptor.

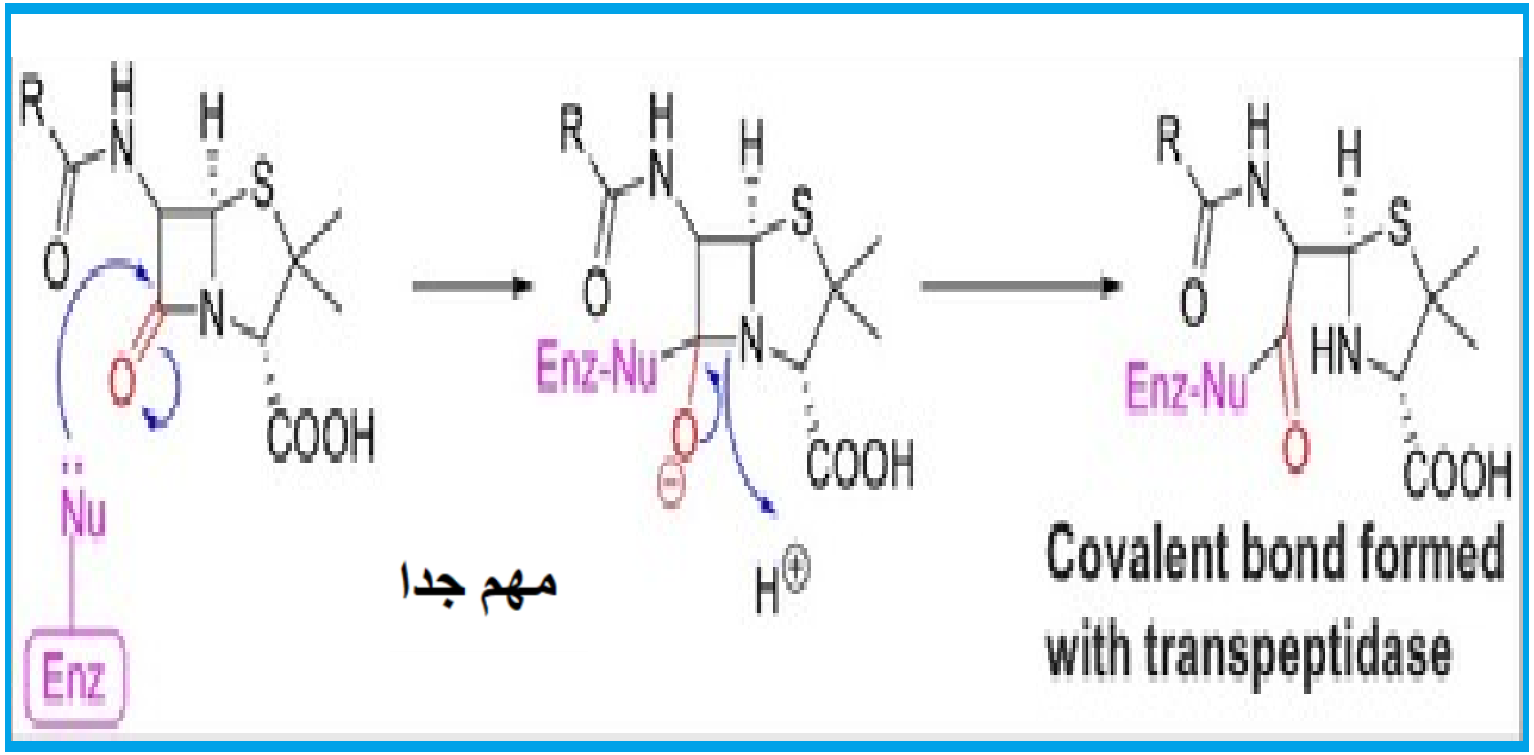


4.Penicillins:



The acylation of bacterial cell wall constituents by penicillin, and the phosphorylation.

β-lactams A.Bs. is capable of binding by covalent bond to transpeptidase enzyme and inhibit the cell wall synthesis, which result in damage the bacterial cell wall.



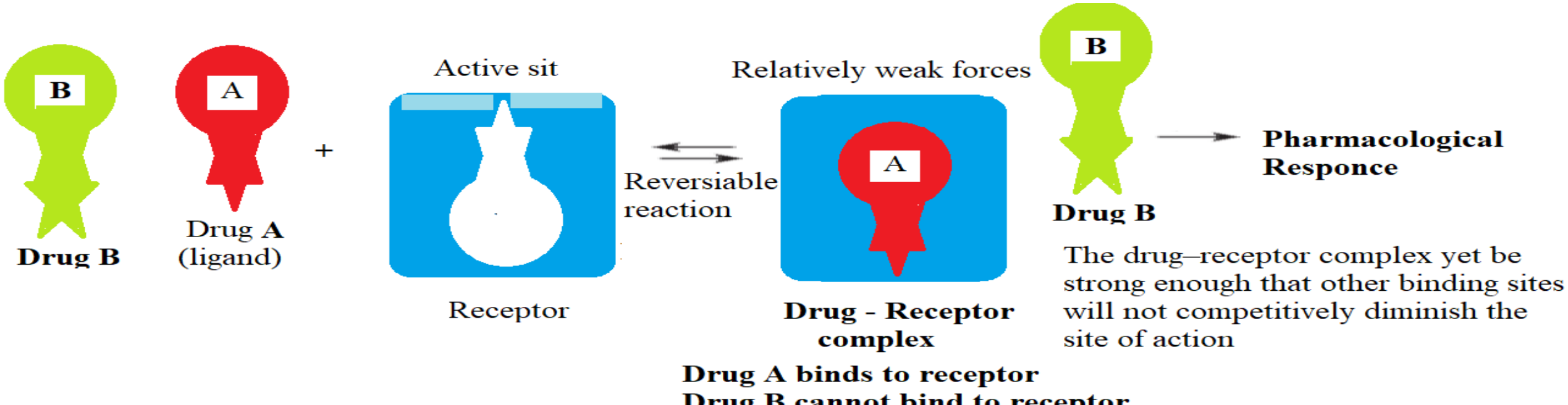
Q. Draw Penicillins showing the covalent bond with transpeptidase enzyme مهم جدا

Q. Enumerate (only) the covalent bond formation between four drugs and receptor is the basis of Baker's concept of active-site-directed irreversible inhibition. مهم جدا

في دراسة القوة التي تنطوي عليها تفاعلات المستقبل ـ
الدواء من المطلوب ان تكون معظم التاثيرات بارتباط
عكسي مثل ارتباط الدواء (A) مع المستقبل باستخدام
قوى ضعيفة نسبيا ولكن هذه القوة قوية بما يكفي بحيث لاتضعف
مواقع الاتصال وتسمح للدواء (B) بالتنافس

Note that :

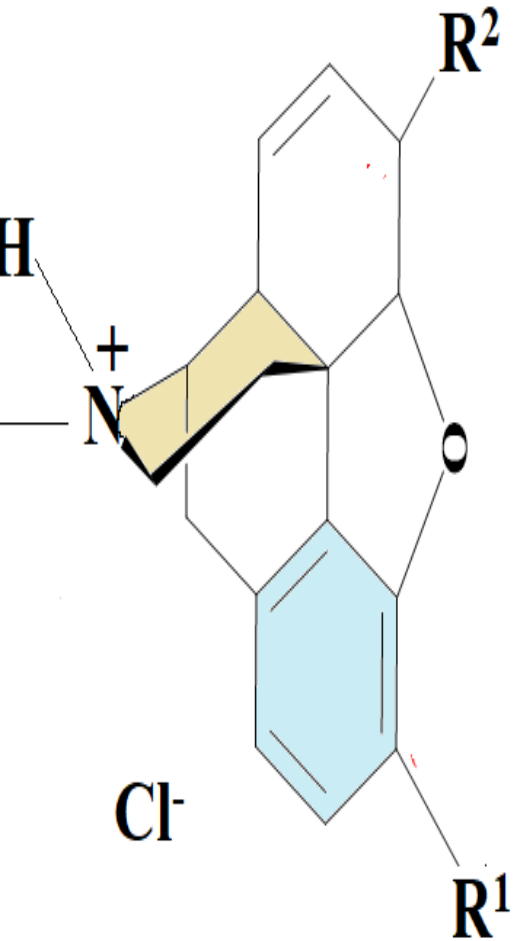
1. In the study of force involved with drug-receptor interactions, it is wanted to have most drug effects reversible, and for this to occur, relatively weak forces must be involved in the drug–receptor complex yet be strong enough that other binding sites will not competitively diminish the site of action.

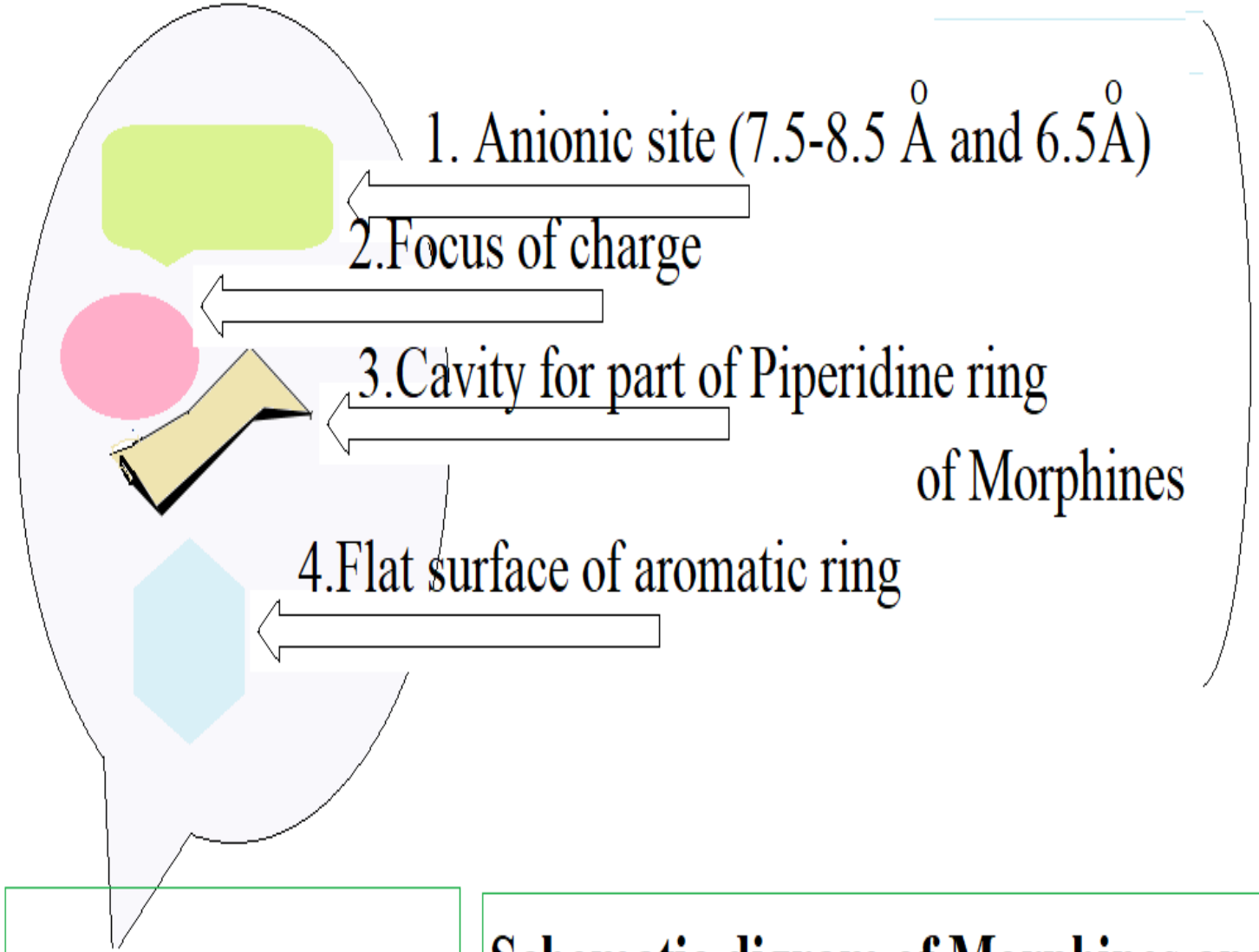


Compounds with high structural specificity (like Morphines) may orient several weakly binding groups so that the summation of their interactions with specifically oriented complementary groups on the receptor provides total bond strength sufficient for a stable combination.

المركبات ذات الشكل الكيميائي العالي الخصوصية كالمورفينات ترتب بعض مجاميعها ذات الارتباط الضعيف بحيث حاصل جمع تداخلاتها مع المجاميع الخاصة على المستقبل يوفر مجموعة قوة تاصر كافية لارتباط مستقر

Q. Draw the Morphines high structural specificity showing the orientation of its weakly binding groups which the summation of their interactions with specifically oriented complementary groups on the receptor provides total bond strength sufficient for a stable combination.





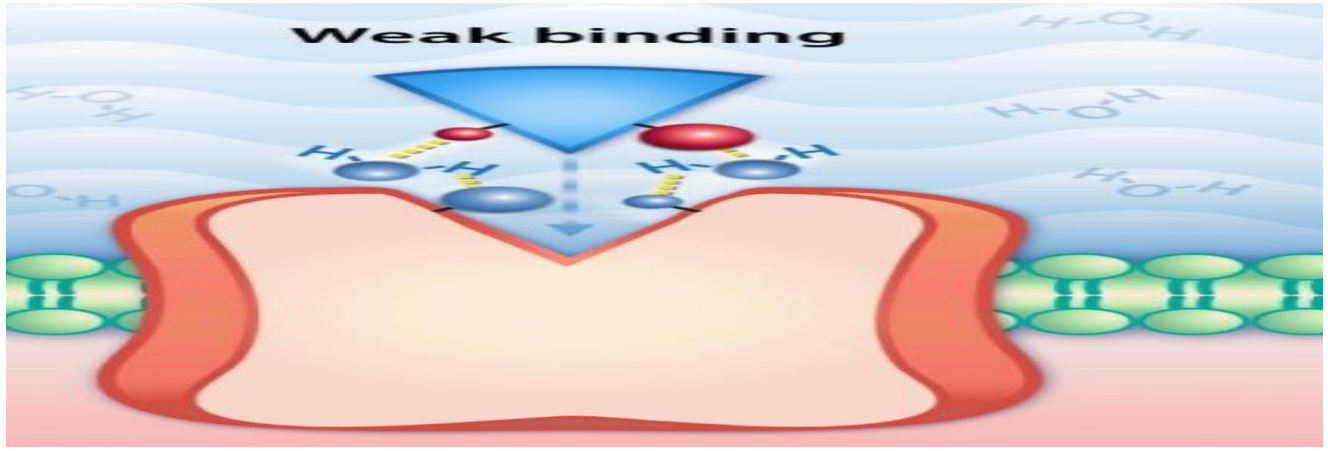
Specifically oriented complementary groups on the receptor

Morphines several weakly binding groups

Morphines(analgesic) receptor active site

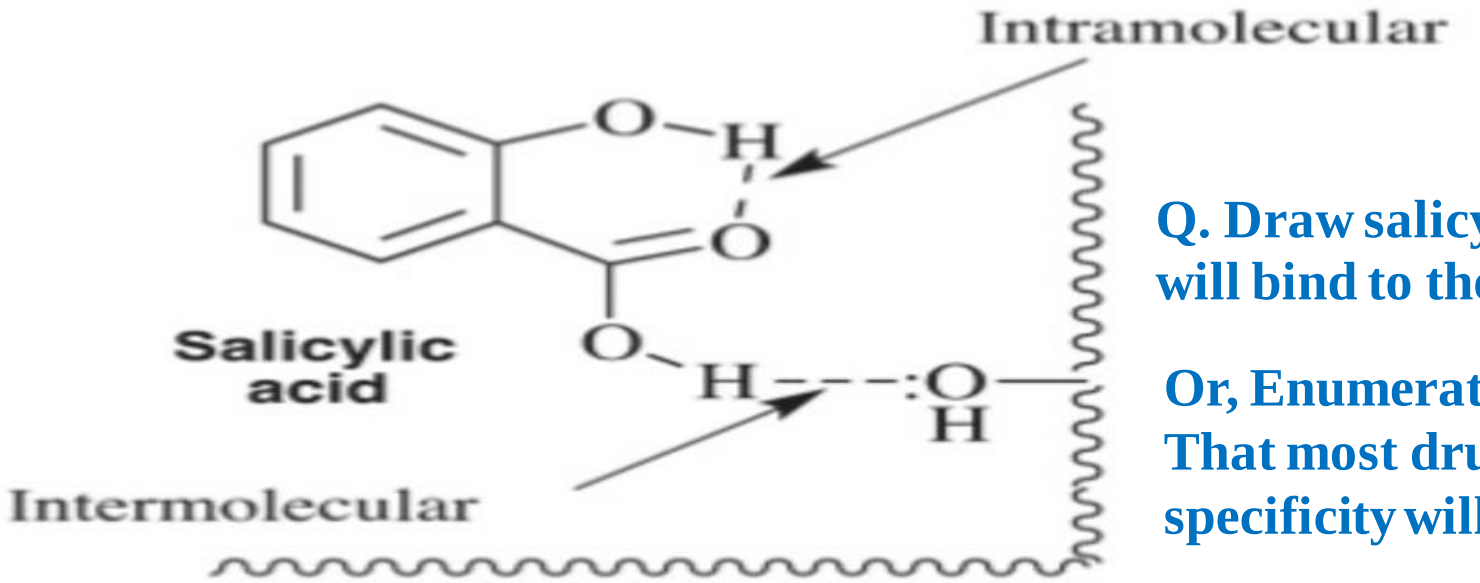
Schematic digram of Morphines analgesic functional groups and specifically oriented four complementry groups on receptors

3.Consequently, وبالتالي most drugs acting by benefit of their structural specificity will bind to the receptor site by :



i. Hydrogen bond:

e.g. Salicylic acid



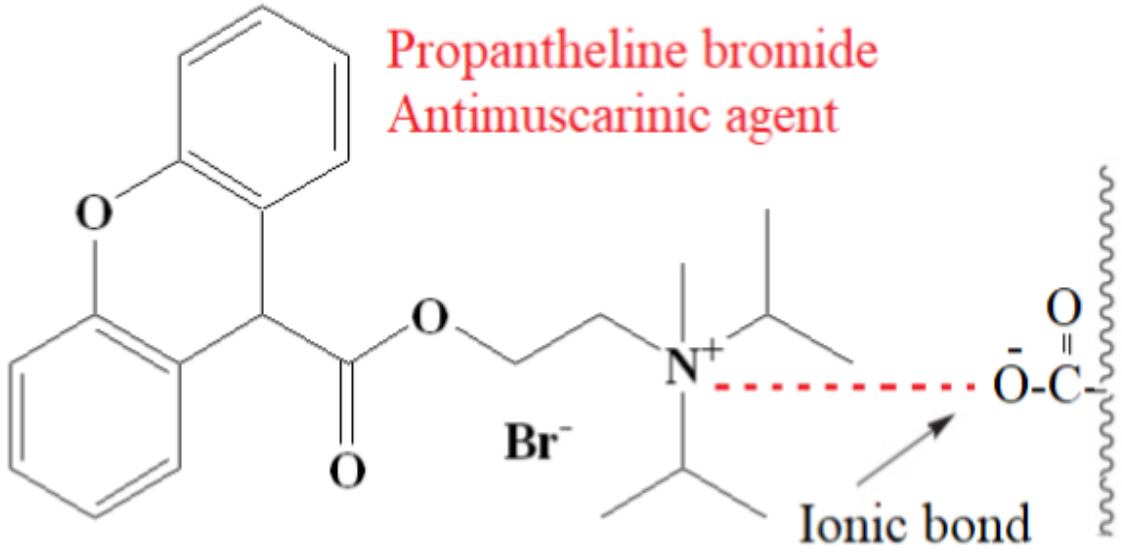
Schematic diagram of
Salicylic acid H-bonding to receptor.

Q. Draw salicylic acid showing its structural specificity will bind to the receptor site by hydrogen bonding

Or, Enumerate five bond types and give one example That most drugs acting by benefit of their structural specificity will bind to the receptor site:.

ii. Ionic bonds:

e.g. Pro- pantheline



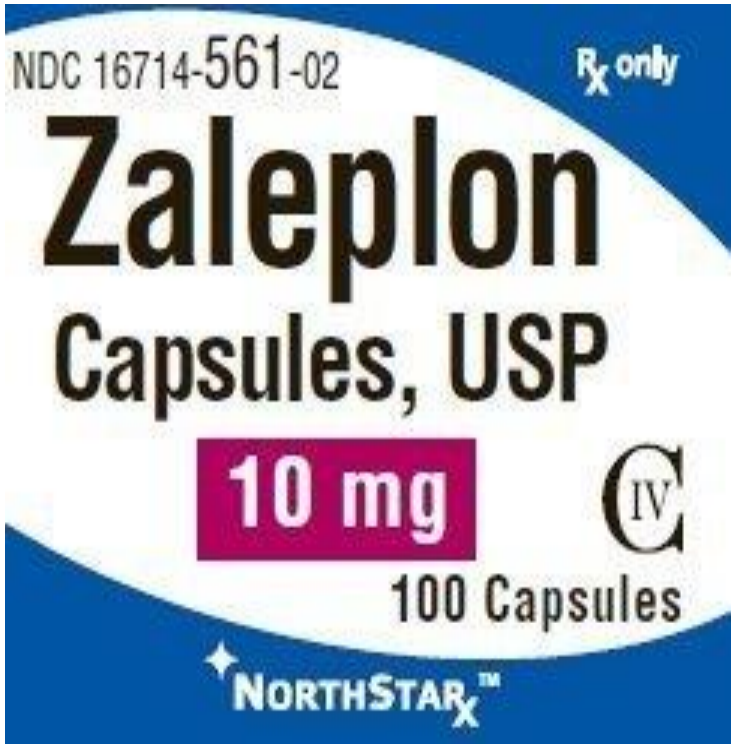
Schematic diagram of Pro- pantheline bromide ionic-bonding to receptor.

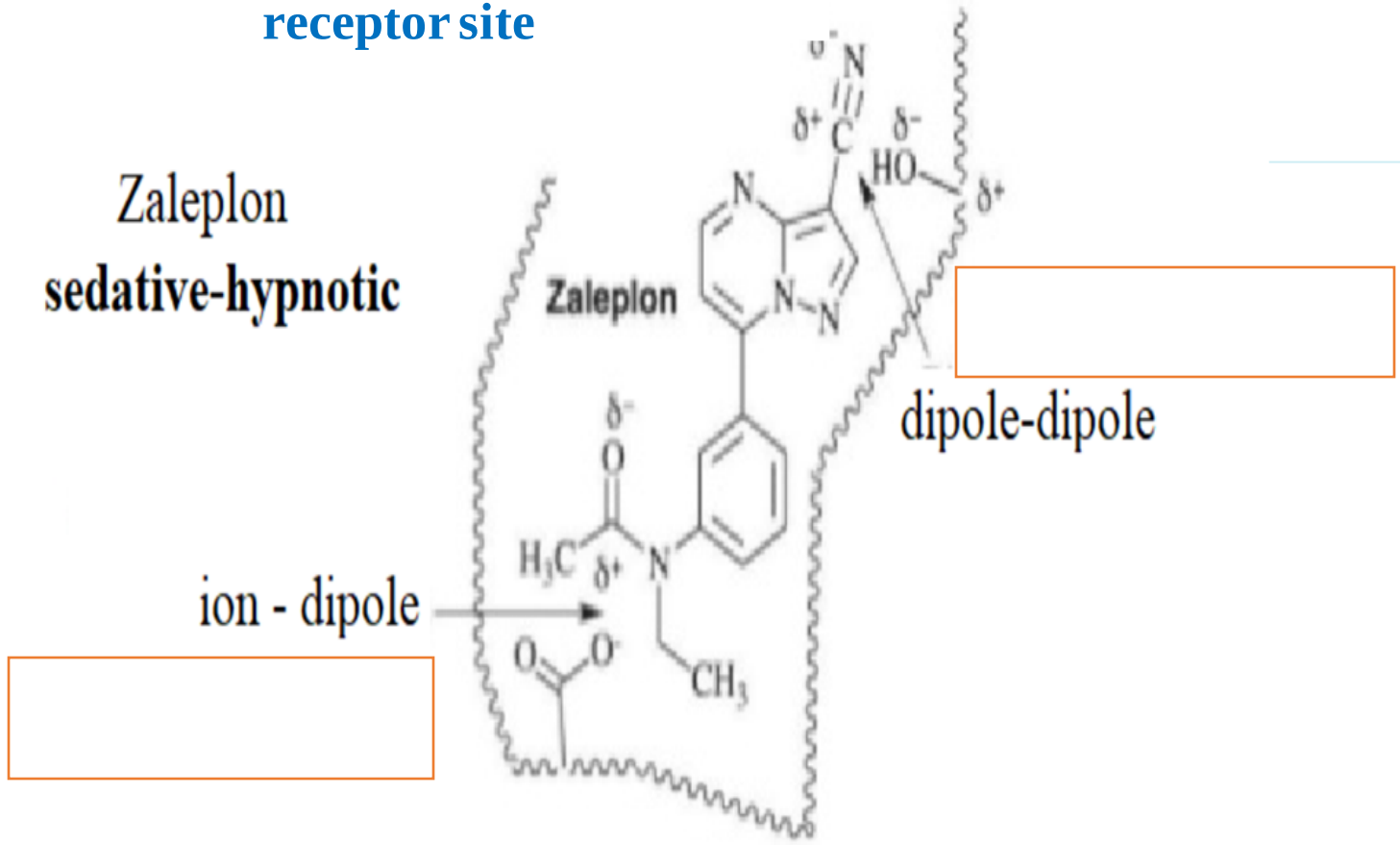
Q. Draw Pro-pantheline bromide showing its structural specificity will bind to the receptor site by ionic- bonding

iii . Ion- dipole & Dipole–dipole interactions:

e.g. Zaleplon (sedative-hypnotic)

Q. Name the bonds interaction (A and B) of Zaleplon (Sedative Hypnotic) functional groups that bind to the receptor site

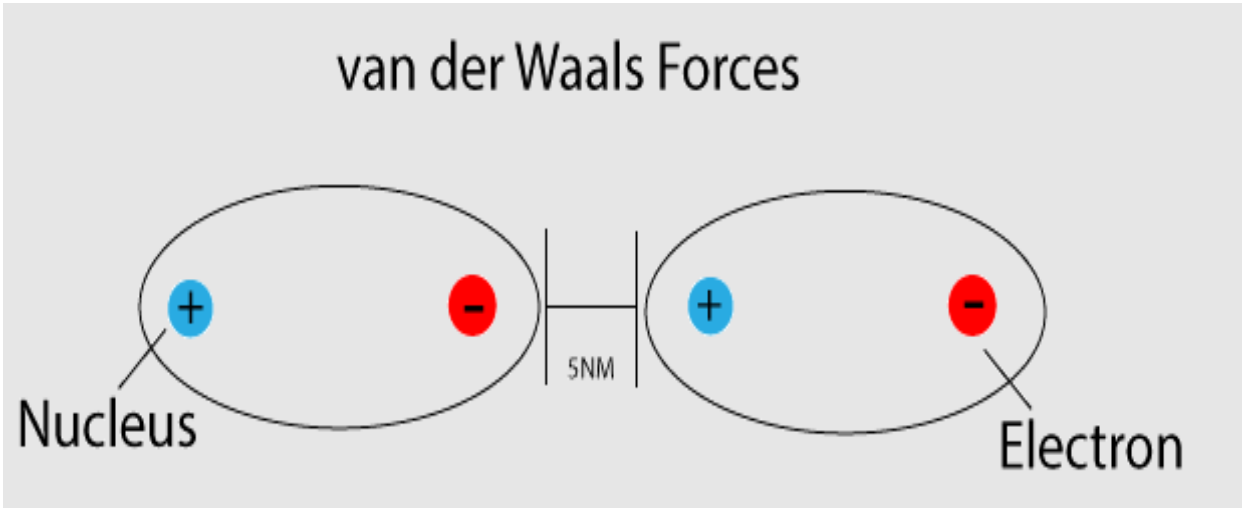




Schematic diagram of

Pro- pantheline bromide Ion-dipole & dipole-dipole interactions to receptor

iv. Van der Waals and hydrophobic forces

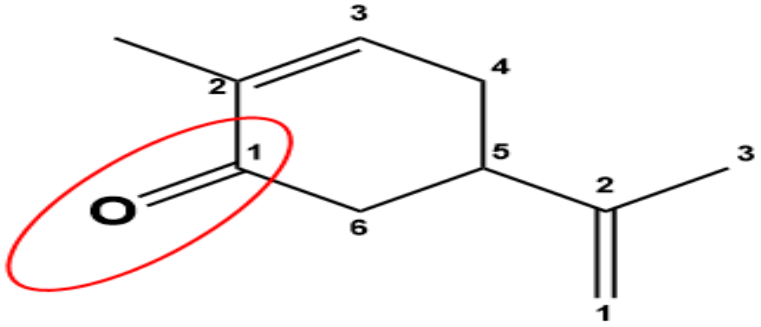


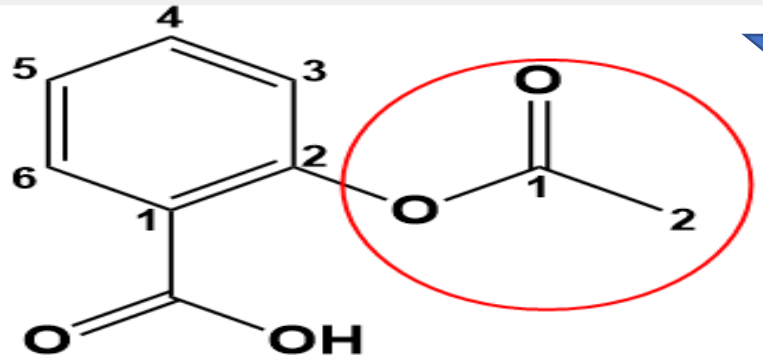
Potential ionization of active drugs at physiological pH would normally occur with:

I. The carboxyl
II. Sulfonamido
III. Aliphatic amino groups
IV. Quaternary ammonium group .

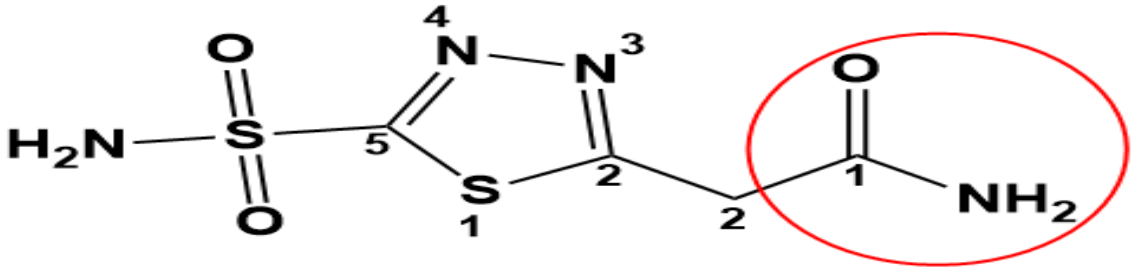
Q. With what groups will potential ionization of active drugs at physiological pH) would normally occur ?
(enumerate four only)

Differences in electronegativity between carbon and other atoms, such as oxygen and nitrogen, lead to an asymmetric distribution of electrons (dipoles) that are also capable of forming weak bonds with regions of high or low electron density, such as ions or other dipoles of :1. Carbonyl 2. Ester 3. Amide 4. Ether v. Nitrile

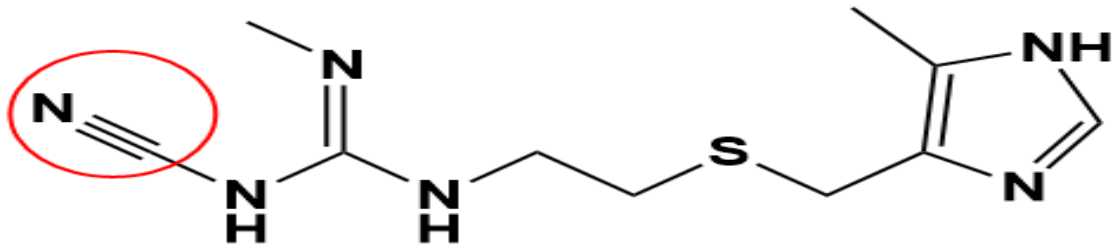




1.Carvone (Spearmint oil) 2.Aspirin (o-Acetoxybenzoic acid)

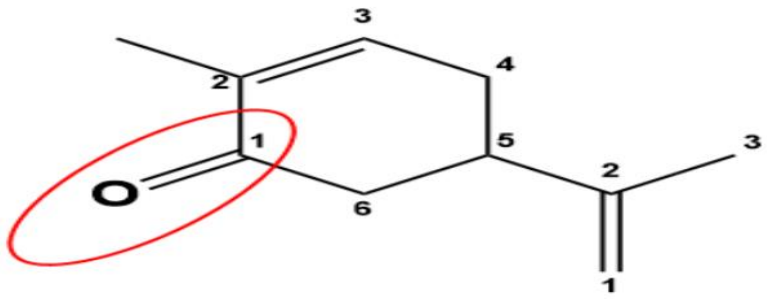


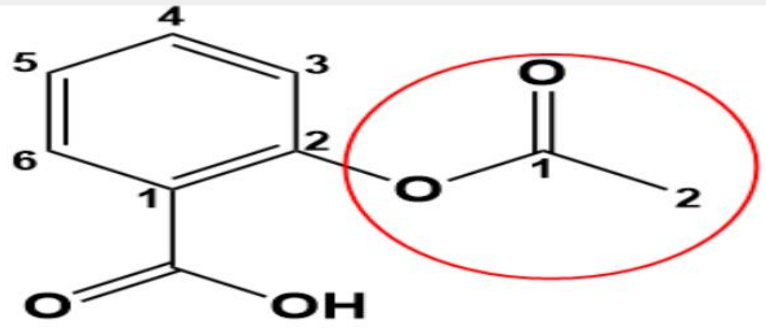
3.Acetazolamide (Diamox)



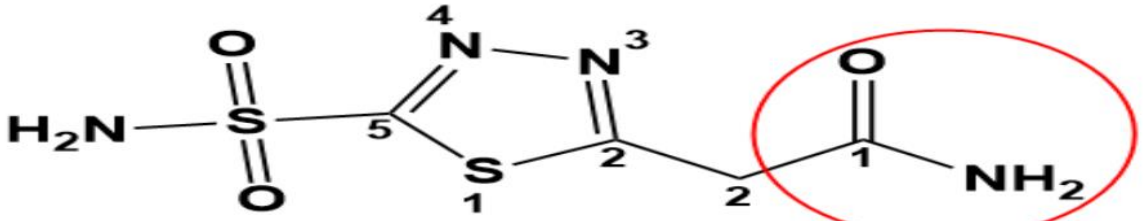
4. Cimetidine (Tagamet)

Q. Differences in electronegativity between carbon and other atoms, such as oxygen and nitrogen, lead to an asymmetric distribution of electrons (dipoles) that are also capable of forming weak bonds with regions of high or low electron density, such as ions or other dipoles, Name the functional groups or organic chemical classes of the following circled :

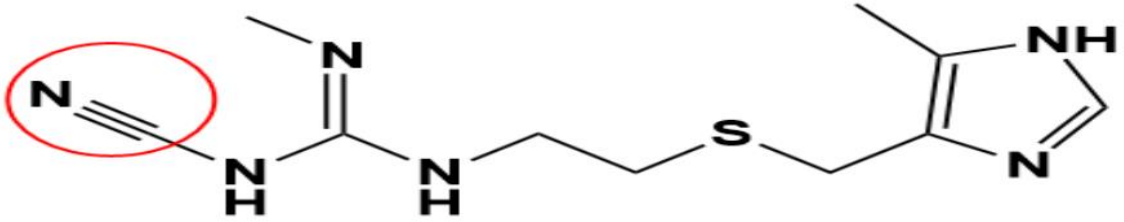




1.Carvone (Spearmint oil) 2.Aspirin (o-Acetoxybenzoic acid)



3.Acetazolamide (Diamox)



4. Cimetidine (Tagamet)

General pathway of drug metabolism:

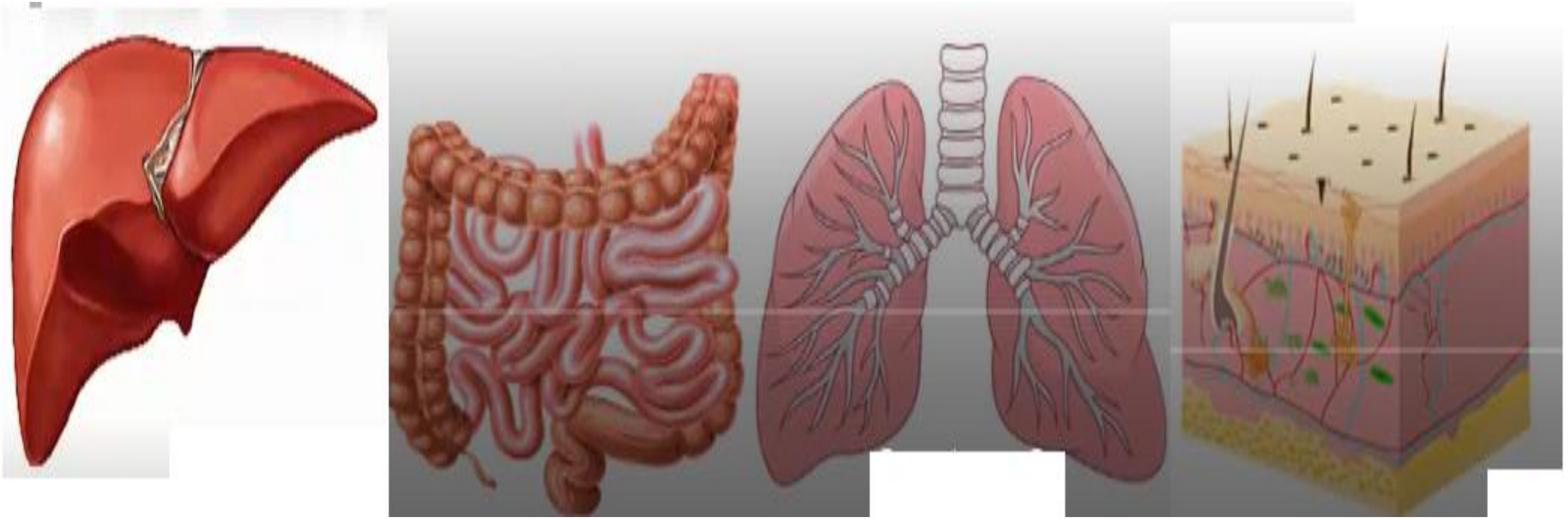
Sites of biotransformation

Rate of cytochrome P450 mono-oxygenase in oxidative biotransformation

Oxidative reactions

Metabolism: (Define)

1. Is all the chemical reactions that occurs in the body cells Which managed the biotransformation of the drugs in the body.
2. The main site of drug metabolism is the liver, but it may also occurs in intestines, lungs and skin.



Drug Metabolism (notes)

1.All substances in the circulatory system, including drugs, metabolites, and nutrients, will pass through the **liver**.

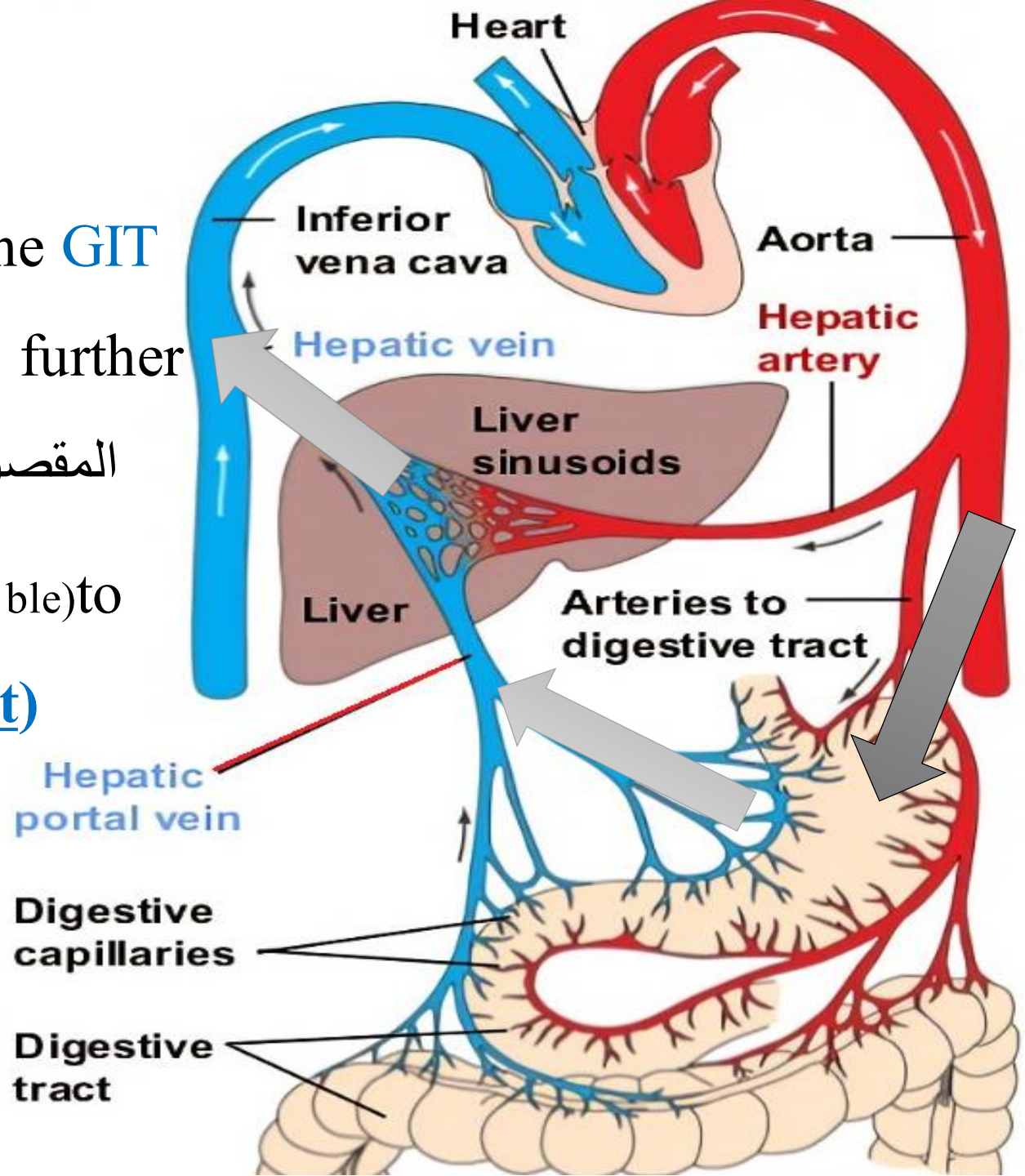
2.Most molecules absorbed from the GIT via the **portal** vein الوريد البوابي الكبدي are initially transported to the liver.

1st pass effect

3.A significant proportion of a drug will partition or be transported into the hepatocyte, where it may be metabolized by hepatic enzymes to inactive chemicals during the initial trip through the liver, by what is known as the 1st pass effect.

Orally administered drugs that are absorbed into the bloodstream through the GIT must pass through the **liver** before being further distributed into body compartments.المقصورات

Therefore, they are susceptible (sa. Sep. te. ble)to hepatic metabolism (**the first-pass effect**) before reaching the systemic circulation.



General Pathways of Drug Metabolism:

The metabolism of drugs and other xenobiotics often involves biotransformations of molecules to less lipophilic, more water-soluble, and more quickly eliminated products.

This typically occurs in two phases:

1.Phase I drug metabolism:

Polar groups are added or exposed (e.g. hydroxylation)

Phase I, or functionalization reactions, include :

Oxidative, **R**eductive, and **H**ydrolytic biotransformations

2.Phase II drug metabolism:

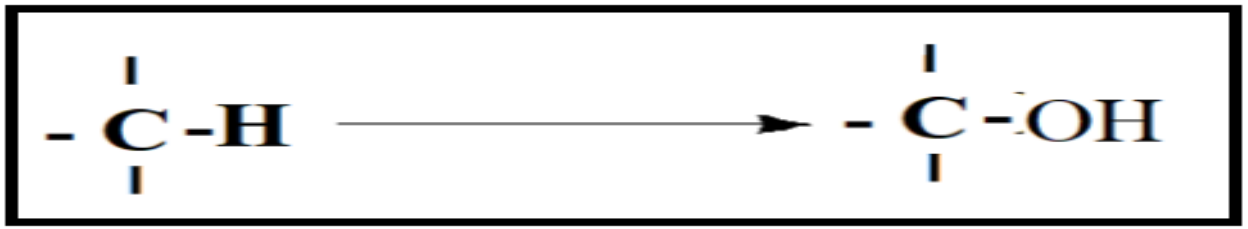
Conjugation of molecules to polar ionic groups (e.g. glucuronidation)

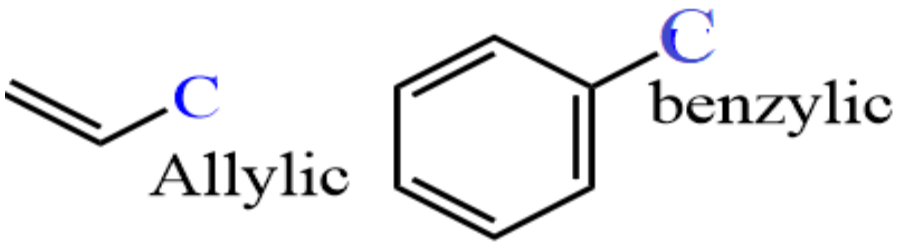
The purpose of Phase I reactions is :(what is the purposes?)

To introduce a functional polar group(s) (e.g., OH, COOH, NH_2, SH) into the xenobiotic molecule to produce a more water-soluble compound.

Introducing a functional polar group(s) can be achieved by two ways:

1. Direct introduction of the functional group (aromatic and aliphatic hydroxylation), by carbon hydroxylation* of aliphatic, allylic(**slide 12**), benzylic





Aliphatic

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* **Introduction a hydroxyl group (−OH) into an organic compound**

2. By modifying the existing functionalities by:(Enumerate the chemical reactions that involved in modifying the existing functionalities)

i. Oxidation of alcohols to acids **(slide 12)**

ii.Oxidative dealkylation (N-, O-, and S-dealkylation) to give NH_2, OH, and SH groups.

اكسدة مع سحب مجموعة مثيل من الاوكسجين او النتروجين او الكبريت

ii. Reduction of ketones and aldehydes to alcohols.

iii. Reduction of azo (R-N=N-) and nitro compounds (RNO_2) to give NH_2 moieties.

iv. Hydrolysis of ester and amides to yield COOH, NH_2, and OH groups

Although phase I reactions may not produce sufficiently hydrophilic or inactive metabolites, they generally tend to provide a functional group or "handle" on the molecule that can undergo subsequent Phase II reactions.

على الرغم من ان تفاعلات الطور الأول قد لا تنتج نواتج أيضية محبة للماء او فعالة كافية ولكنها غالبا ما تميل للتزويد بمجموعه وظيفية او لحمل مجموعه على الجزيئة ومساعدتها لتسلك الطور الثاني

The purpose of phase II reactions:(what is the purposes?)

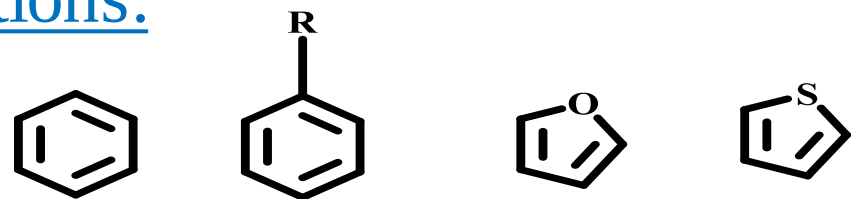
Is to attach small, polar and ionizable endogenous compounds such as glucuronic acid, sulfate and glycine (or other amino acids) to the functional handles of phase I metabolites or parent compounds that already have suitable existing functional groups to form water-soluble conjugated metabolites, which are readily excreted in the urine

General summary الملخص العامof Phase I Metabolic Pathways:

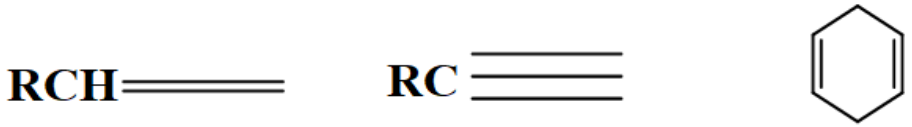
Three reactions:

1st. Oxidative reactions:

1.Oxidation of aromatic moieties:

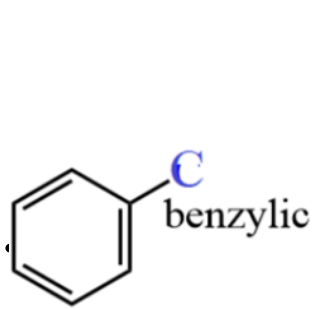


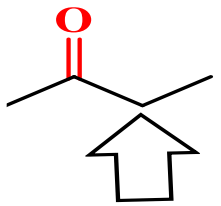
2.Oxidatiion of Olefins*:



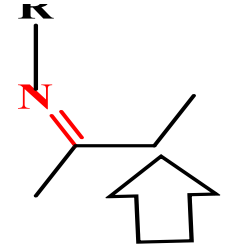
3.Oxidation at benzylic , allylic carbon atoms

and carbon atoms alpha to carbonyl and imins



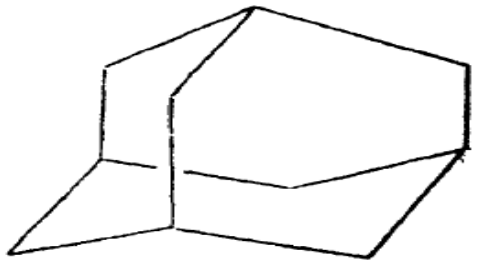


Alpha to carbonyl



Alpha to imine

4.Oxidation at aliphatic and alicyclic carbon atoms (alicyclic = **ali**phatic + **cyclic**).e.g Adamantane



Adamantane

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* Olefins (Oleum = oil)

5.Oxidation involving carbon-heteroatom systems: of three types:

i. Carbon-nitrogen systems (aliphatic and aromatic amines), includes :

N-Dealkylation-Oxidation deamination- N-Oxide formation and N-Hydroxylation.

ii. Carbon-oxygen systems : (O-Dealkylation)

iii. Carbon-sulfur systems : (S-Dealkylation) and (Desulfuration).

6.Oxidation of alcohols and aldehydes RHCO to RCOOH **(slide 12)**

7.Other miscellaneous oxidative reactions.متنوعه

2nd. Reductive reactions: of three types

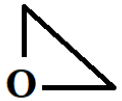
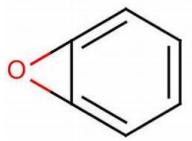
i. Reduction of aldehyde and ketones (-C=O to –CHOH)

ii. Reduction of nitro and azo compounds **(-C-NO_2 to –CNH_2)(RN=NR^1 to RNH_2 and R^1NH_2)**

iii. Miscellaneous reductive reactions

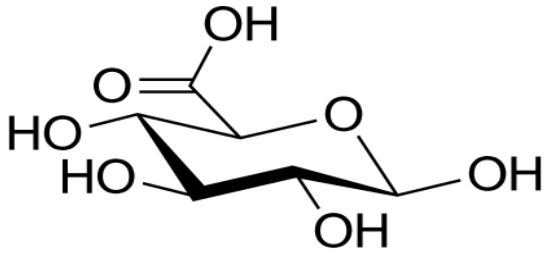
3rd. Hydrolysis reactions : of two types

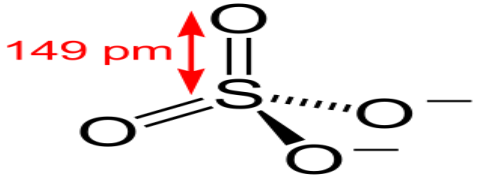
i. Hydrolysis of esters and amide.

ii. Hydrolysis of epoxides  and arene oxides  by epoxide hydrase

General summary of Phase II Metabolic Pathways (Conjugation reactions)

تفاعلات الاقتران

i.Glucuronic acid conjugation 

ii. Sulfate conjugation 

iii. Conjugation with glycine, glutamine and other amino acids

iv. Glutathione or mercapturic acid conjugation

v. Acetylation and vi. Methylation

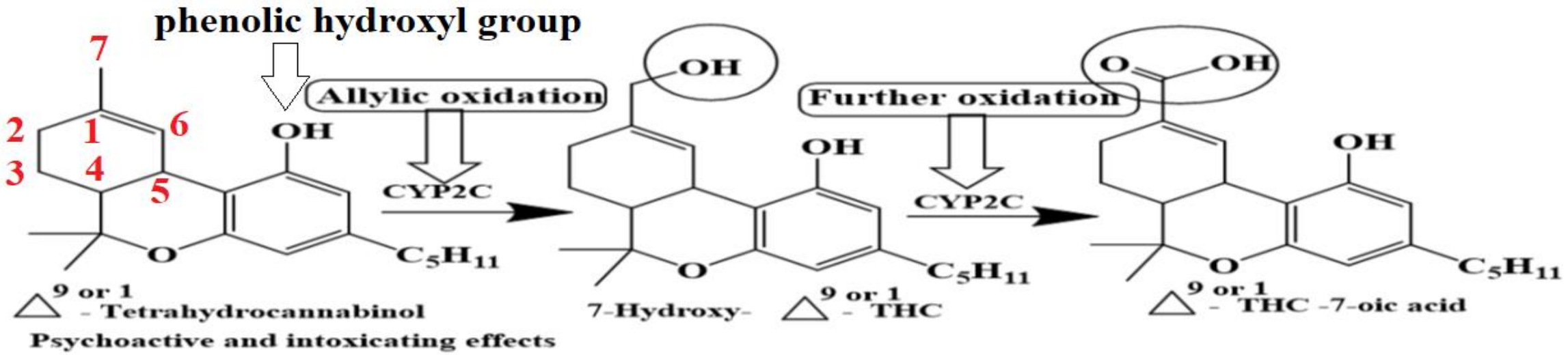
These two pathways, methylation and acetylation, terminate or attenuate biological activity انهاء او تخفيف من الفعالية البايلوجية

Whereas glutathione (GSH) conjugation protects the body against chemically reactive compounds or metabolites. Thus, phase I and phase II reactions complement one another in detoxifying, and facilitating the elimination of, drugs and xenobiotics. Example

Marijuana

The psychoactive constituent of marijuana, $\Delta^{9 \text{ or } 1}$-tetrahydrocannabinol ($\Delta^{9 \text{ or } 1}$-THC). This lipophilic molecule undergoes :

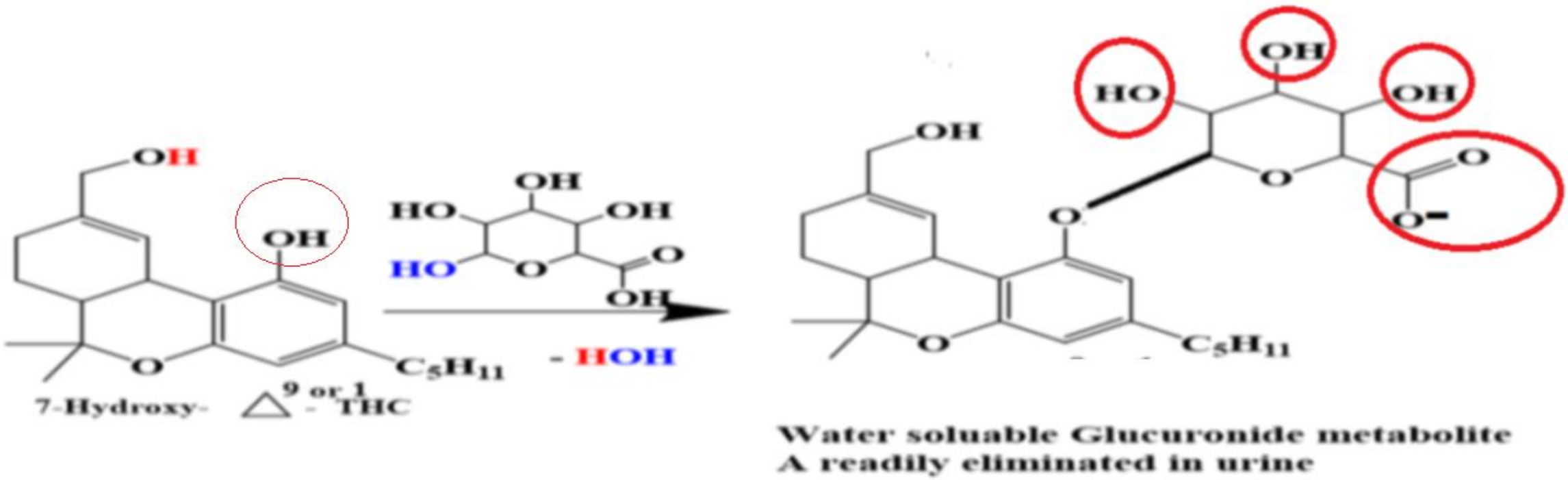
1. **Phase I (functionalization)** allylic hydroxylation to give **7-Hydroxy $\Delta^{9 \text{ or } 1}$-THC** in humans which is **more** polar than its parent, then further oxidation gives **$\Delta^{9 \text{ or } 1}$-THC-7-oic acid.**



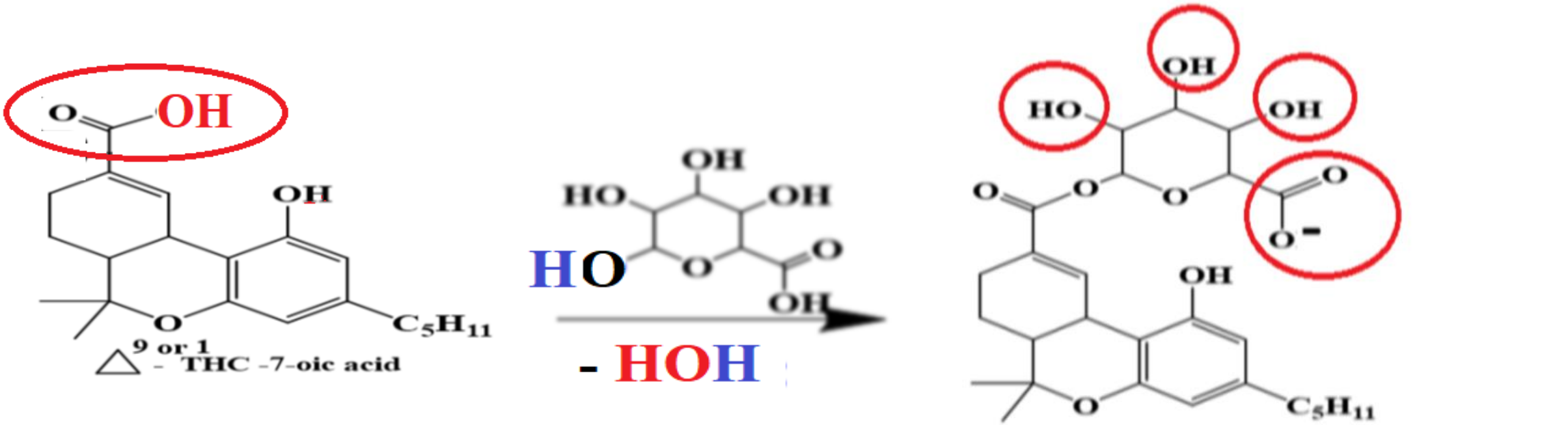
The overall allylic hydroxylation then the further oxidation reaction equations of phase 1 metabolism (functionalization)

2. Phase II(conjugation) reaction of this metabolite

a. Either at the phenolic OH of 7-hydroxy $\Delta^{9 \text{ or } 1}$ with glucuronic acid leads to water soluble Glucuronide conjugate and produce metabolite that is readily eliminated in the urine.



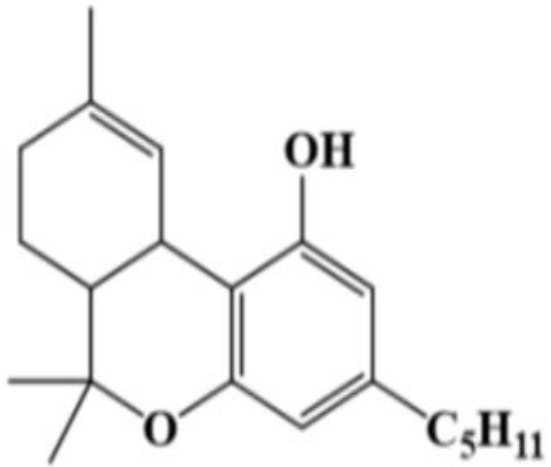
b.Or At allylic carboxylic OH also with glucuronic acid leads to water soluble Glucuronide conjugate and produce metabolite that is readily eliminated in the urine.



Water soluable Glucuronide metabolite
A readily eliminated in urine

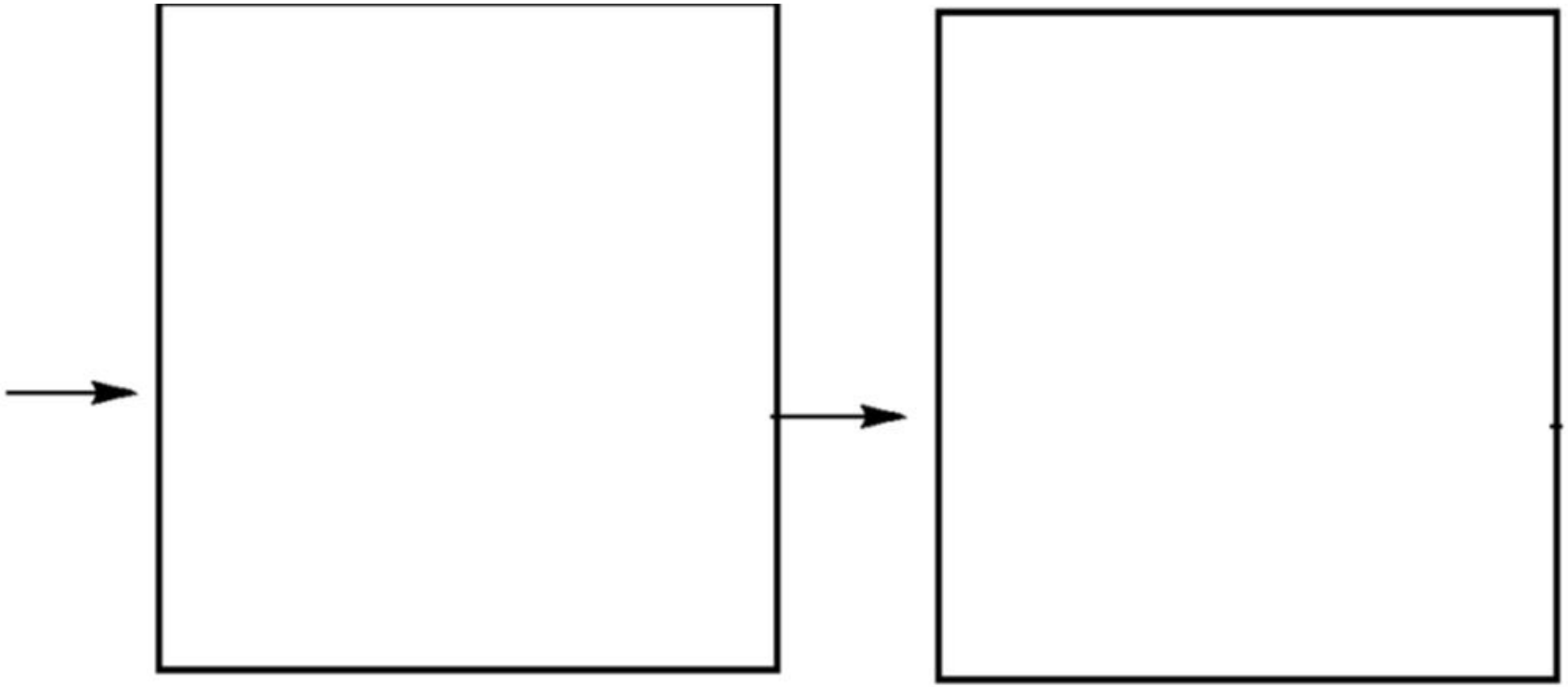
Q1. Phase I and phase II reactions metabolism are complement one another in detoxifying, and facilitating the elimination of, drugs and xenobiotics. An example is The psychoactive constituent of marijuana, $\Delta^{9 \text{ or } 1}$-tetrahydrocannabinol ($\Delta^{9 \text{ or } 1}$-THC).

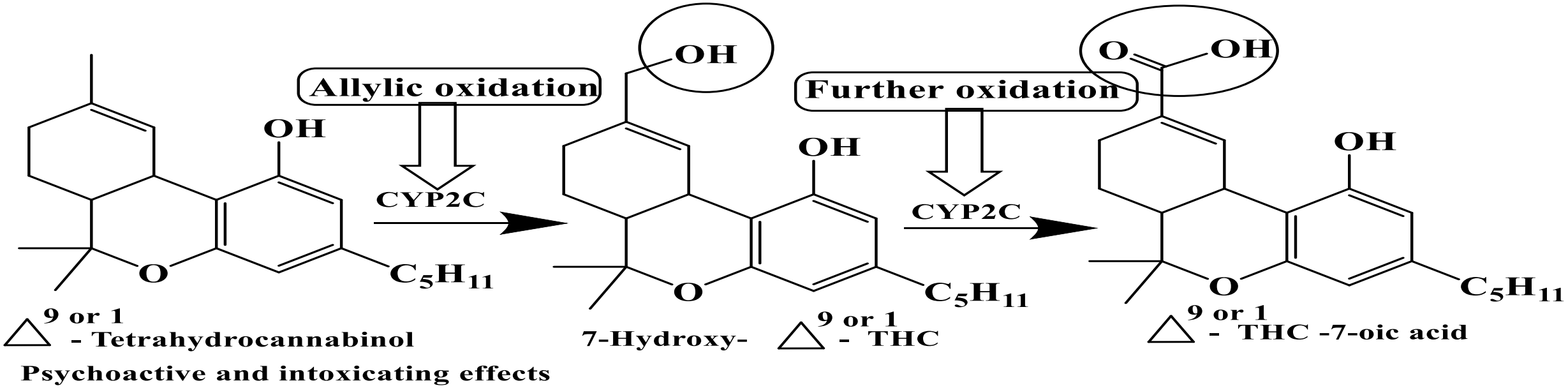
a. Complete by drawing the chemical structures of the overall allylic hydroxylation then the further oxidation reaction equation of phase 1 metabolism (functionalization)



$\Delta^{9 \text{ or } 1}$ - Tetrahydrocannabinol

Psychoactive and intoxicating effects





The overall allylic hydroxylation then the further oxidation reaction equations of phase 1 metabolism (functionalization)

b. Complete by drawing the chemical structure of the phase II(conjugation) reaction metabolism (Glucuronidation) at the phenolic OH of 7-hydroxyΔ^{9or1} – THC with glucuronic acid to produce the water soluble Glucuronide conjugate metabolite which readily eliminated in the urine.

c. Complete by drawing the chemical structure of the phase II(conjugation) reaction metabolism (Glucuronidation) at the allylic carboxylic COOH of Δ^{9or1} – THC – oic acid with glucuronic acid to produce the water soluble Glucuronide conjugate metabolite which readily eliminated in the urine.

In the series of biotransformation's, the parent THC molecule is made increasingly polar, ionizable, and hydrophilic. The attachment of the glucuronyl moiety (with its ionized carboxylate group and three polar hydroxyl groups to the THC metabolites notably favors partitioning of the conjugated metabolites into an aqueous medium. This is an important point in using urinalysis to identify illegal drugs.

Drug metabolism involves:

1.The central role of the cytochrome P450 (CYP) monooxygenase system in oxidative drug biotransformation will be elaborated. تفصل

2.Discussion of other enzyme systems involved in phase I and phase II reactions is presented in their respective sections.

3.In addition to stereochemical factors that may affect drug metabolism, Five biological factors such as:

Age, sex, heredity, disease state حالة المرض, and species variation اختلاف أنواع التأييضare considered.

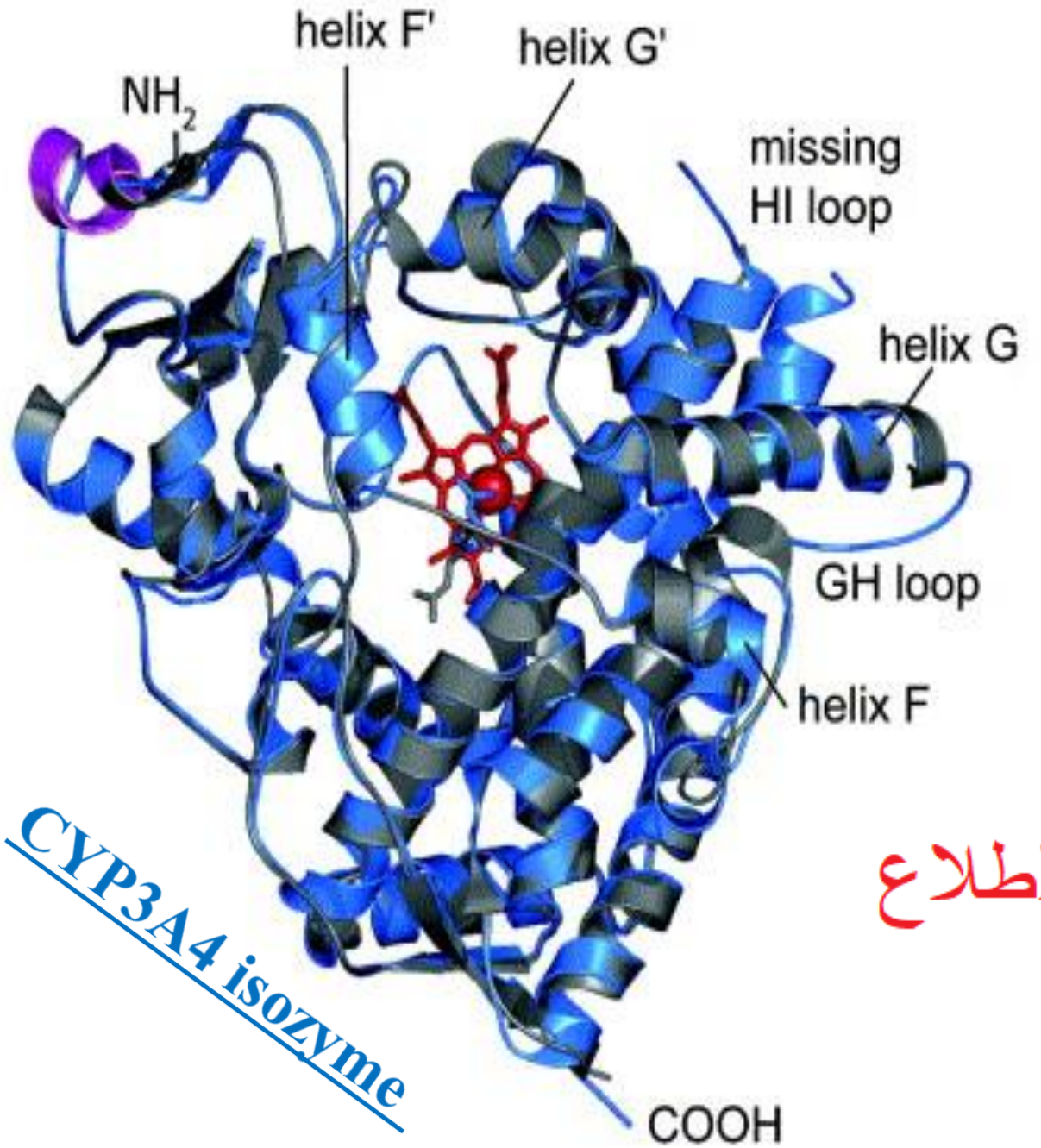
4.The effects of enzyme induction and inhibition on drug metabolism

1.Although biotransformation reactions may occur in many tissues, the **liver** is, by far, the most important organ in drug metabolism and detoxification of endogenous and exogenous compounds.

2.Another important site, especially for orally administered drugs, is the **intestinal mucosa**, which contains the **CYP3A4 isozyme** and **P-glycoprotein*** that can capture the drug and secrete it back into the intestinal tract.

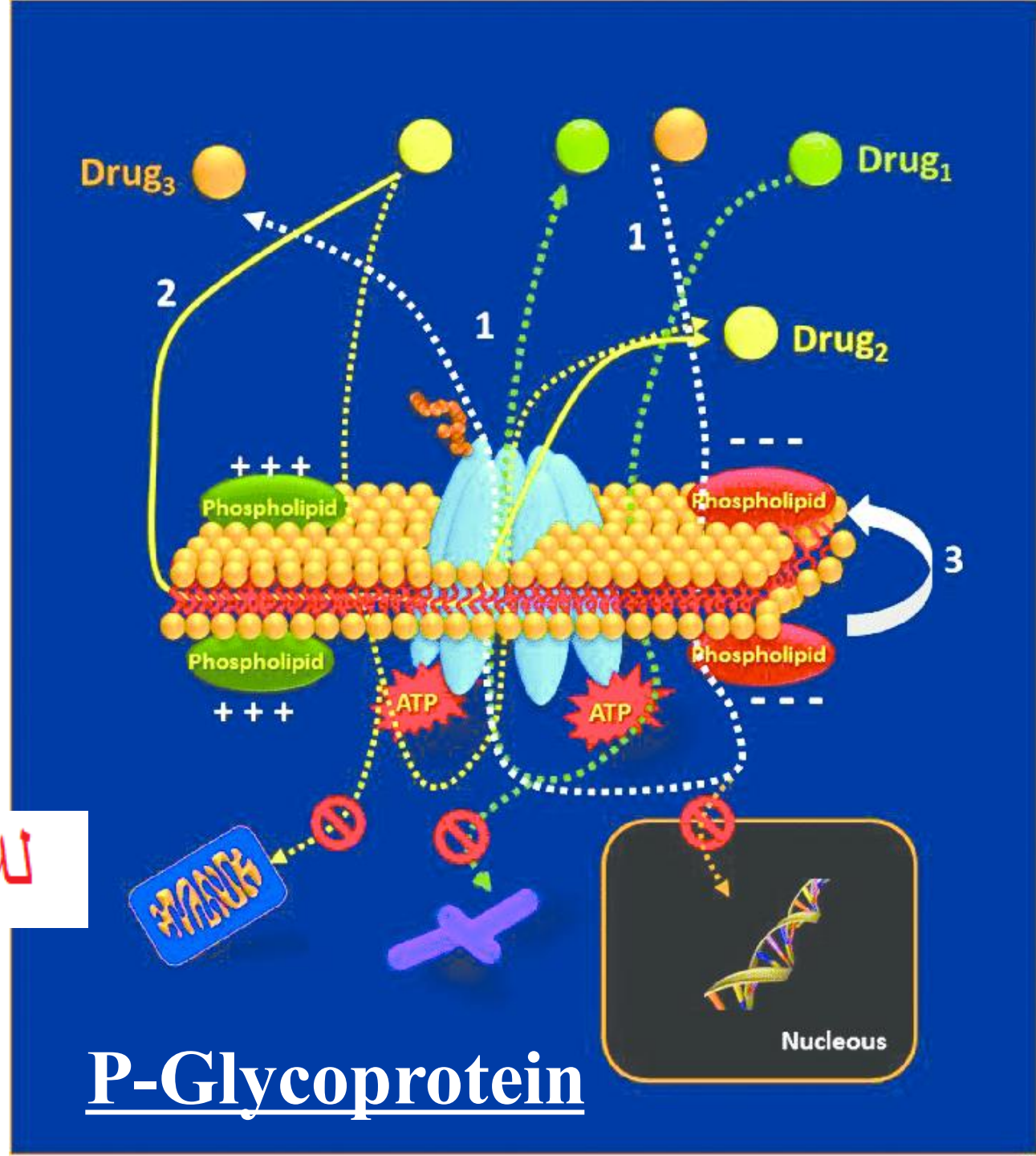
3.In contrast, the liver, a well-perfused organ, is particularly rich in almost all of the drug-metabolizing enzymes.

*** Important protein of the cell membrane that pumps many foreign substances out of cells**



CYP3A4 isozyme

للاطلاع



P-Glycoprotein

الادوية التي تتأيض من خلال العبور الاولي من خلال الكبد
وبذلك يضعف توافرها الحيوي وفعاليتها العلاجية

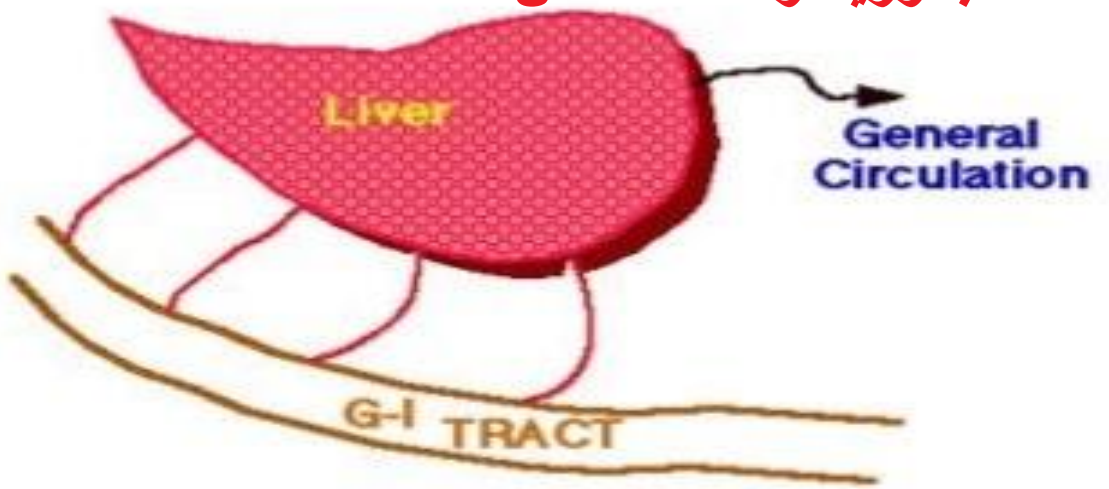
First pass metabolism:

- It means drug metabolism occurring before the drug enters the systemic circulation.
- Results is decreased bioavailability.
- Decreased therapeutic response.

الادوية التي تتجنب التأييض من خلال تجنب
العبور الاولي من خلال الكبد مثل
الادوية المعطاة بالوريد او تحت اللسان

Bypass First pass metabolism:

- IV route
- Sublingual route



4.Orally administered drugs that are absorbed into the bloodstream through the GIT must pass through the **liver** before being further distributed into body compartments.

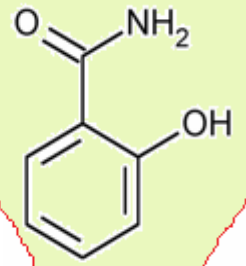
Therefore, they are susceptible to hepatic metabolism (**the first-pass effect)** before reaching the systemic circulation.

5. Depending on the drug, **the first-pass** metabolism can sometimes be quite significant مهمand results in **decreased** oral bioavailability. For example, in humans, several drugs are metabolized extensively by the first-pass effect. **The following list includes some of those drugs:**

حفظ

Isoproterenol	Morphine	Propoxyphene
Lidocaine	Nitroglycerin	Propranolol
Meperidine	Pentazocine	Salicylamide

Salicylamide , Analgesic and antipyretic of medicinal uses are similar to those of aspirin.



A local anesthetic of the amino amide type. It is also used to treat ventricular tachycardia

To treat the symptoms of Adams-Stokes Attacks, Cardiac Arrest, or Heart Block, Shock, and Bronchospasm during Anesthesia

Pethidine, meperidine (Demerol) a synthetic opioid pain medication

Figure (6)

Important Notes:

1.Some drugs (e.g., lidocaine) are removed so effectively by first-pass metabolism that they are ineffective when given orally.

2. Nitroglycerin is administered buccally (via mouth such as Sublingually) to bypass (avoid)the liver.

3.Because most drugs are administered orally, the intestine appears to play an important role in the extrahepatic metabolism of xenobiotics.

For example, in humans, orally administered isoproterenol undergoes considerable sulfate conjugation in the intestinal wall.

الادوية التي تتأيض من خلال العبور الاولي من خلال الكبد
وبذلك يضعف توافرها الحيوي وفعاليتها العلاجية

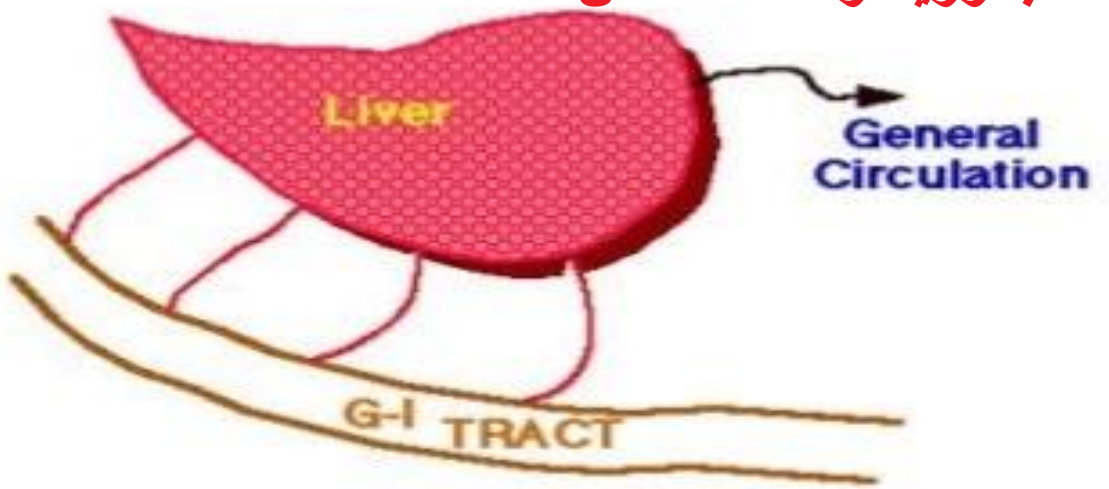
First pass metabolism:

- It means drug metabolism occurring before the drug enters the systemic circulation.
- Results is decreased bioavailability.
- Decreased therapeutic response.

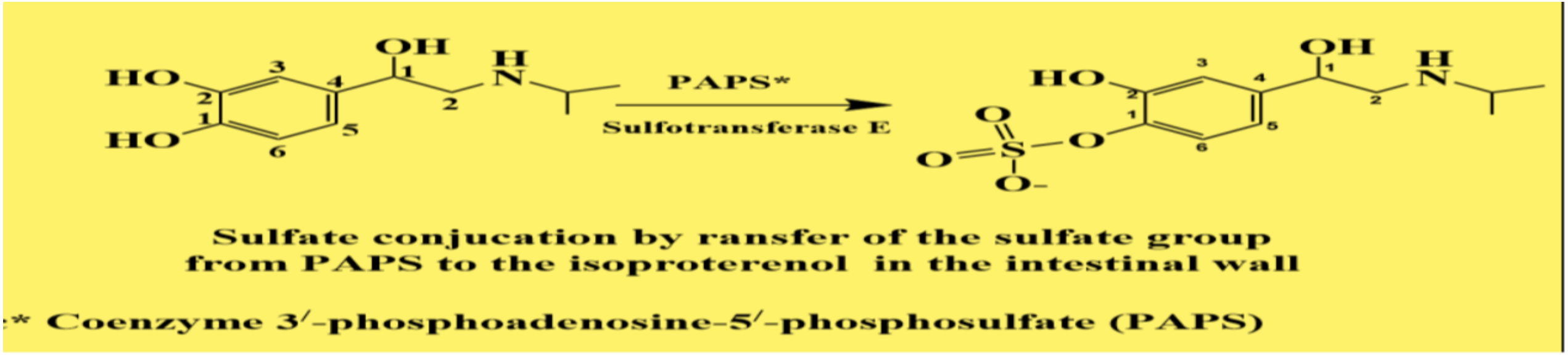
الادوية التي تتجنب التأيض من خلال تجنب
العبور الاولي من خلال الكبد مثل
الادوية المعطاة بالوريد او تحت اللسان

Bypass First pass metabolism:

- IV route
- Sublingual route



Complete the following sulfate conjugation metabolism, give the names of PAPS catalyst and the enzyme



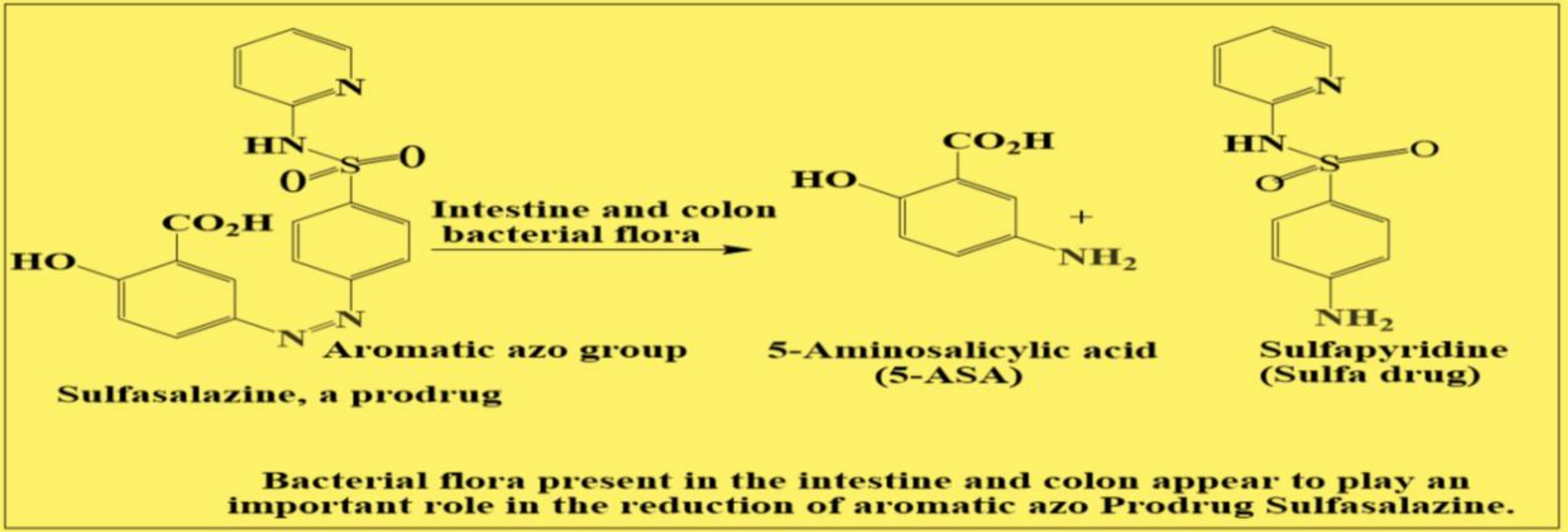
Sulfate conjucation by ransfer of the sulfate group from PAPS to the isoproterenol in the intestinal wall

*** Coenzyme 3′-phosphoadenosine-5′-phosphosulfate (PAPS)**

4.Several drugs (e.g., levodopa, chlorpromazine, and diethylstilbestrol) are also reportedly metabolized in the GIT.

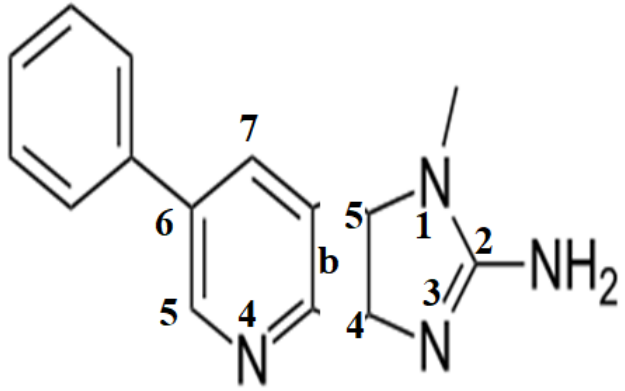
5.Esterases and lipases present in the intestine may be particularly important in carrying out hydrolysis of many ester prodrugs.

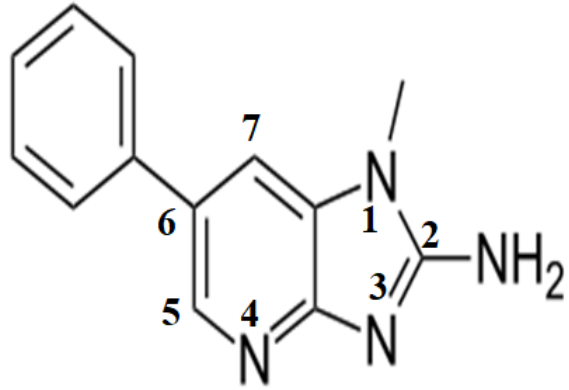
6. Bacterial flora present in the intestine and colon appear to play an important role in the reduction of many aromatic azo and nitro drugs **(e.g., The prodrug Sulfasalazine).**



PhiP (2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine) is one of the most abundant heterocyclic amines in cooked meat reasonably anticipated to be a human carcinogen. It conjugates with glucuronic acid to form glucuronide conjugates excreted

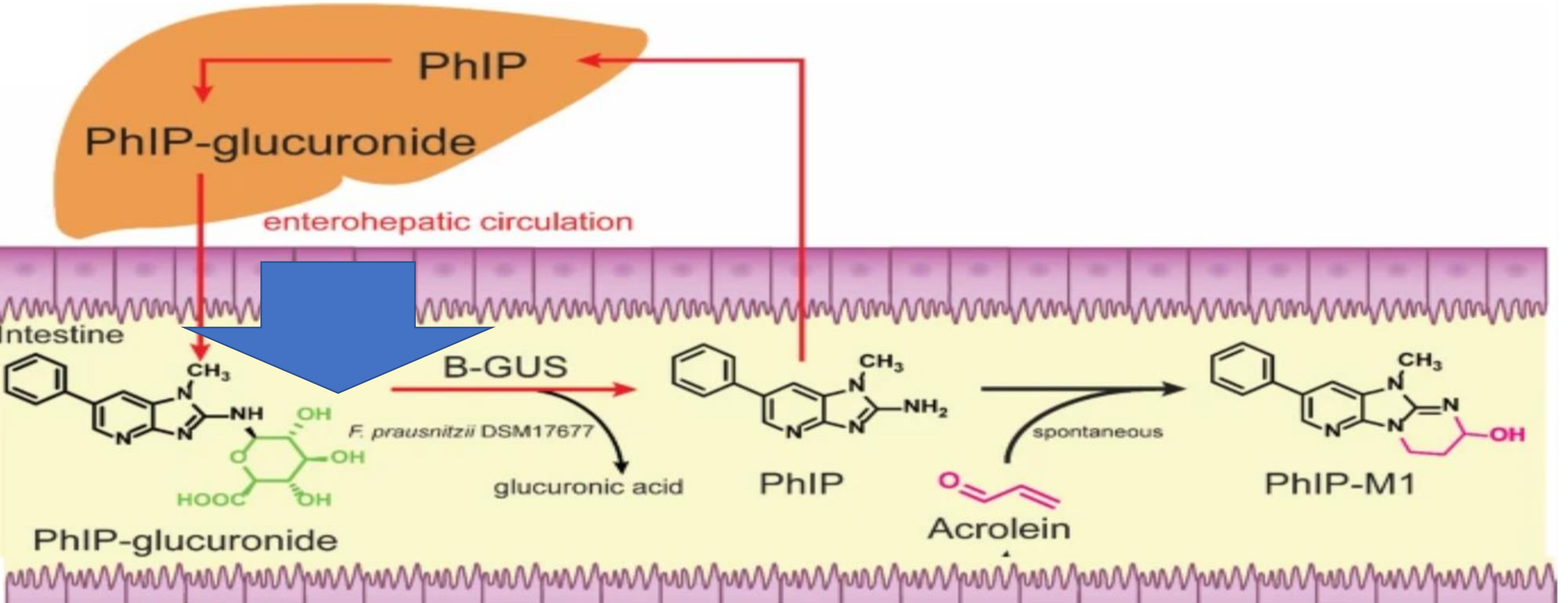
7.Intestinal β-glucuronidase enzymes can hydrolyze glucuronide conjugates excreted in the bile, thereby liberating





the free xenobiotic or its metabolite for possible reabsorption (enterohepatic circulation or recycling).

8.Although other tissues, such as **kidney, lungs, adrenal glands, placenta, brain, and skin**, have some drug metabolizing capability, the biotransformations that they carry out are often more substrate selective and



Role of Cytochrome P450 Monooxygenase in Oxidative Biotransformations

Oxidative biotransformation processes are the most common and important in drug metabolism. The general stoichiometry*that describes the oxidation of many xenobiotics (R-H) to their corresponding oxidized metabolites (R-OH) is given by the following equation:

----------eq.(1)

(NADPH is the reduced form of nicotinamide adenosine dinucleotide phosphate).

The enzyme systems carrying out this biotransformation are referred to as mixed-function oxidases or monooxygenases.

---

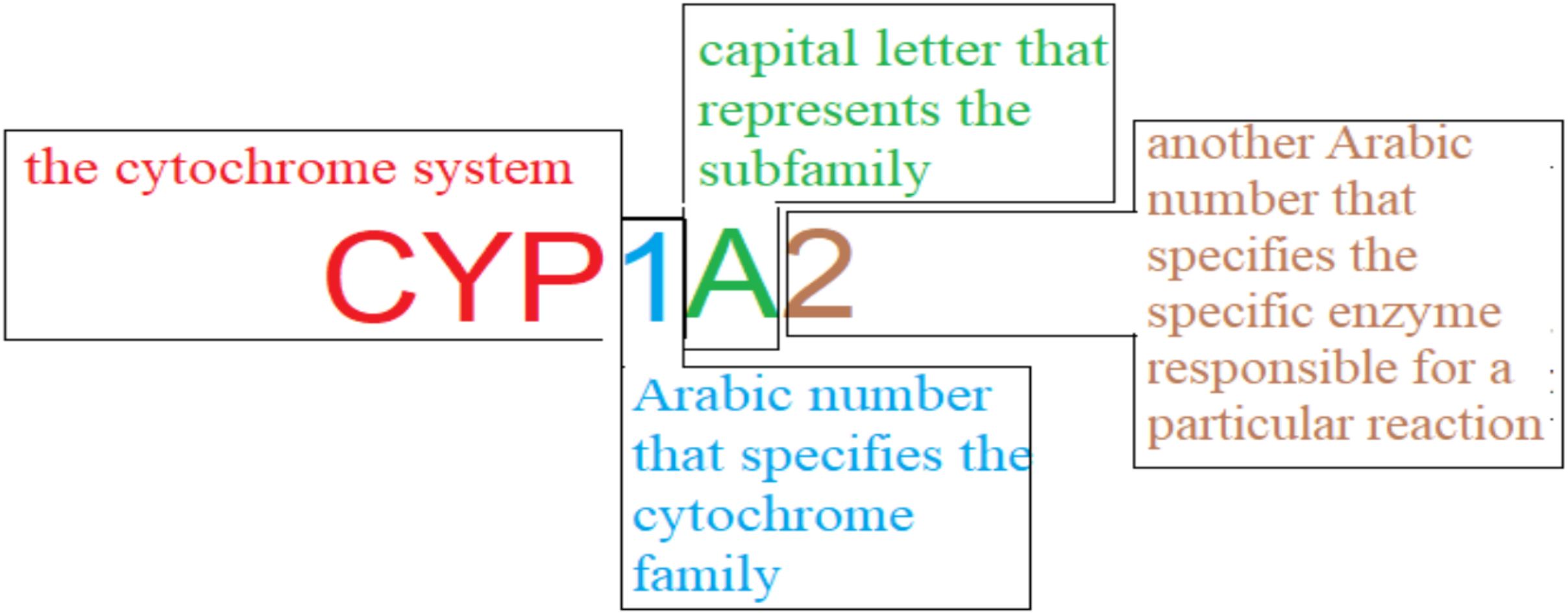
*Is the equation balances moles

Nomenclature of Cytochrome P450 Monooxygenases :

There are four components to the name. CYP refers to the **cy**tochrome system* and P of protein. This is followed by the Arabic number that specifies the cytochrome family (CYP1, CYP2, CYP3, etc.). Next is a capital letter that represents the subfamily (CYP1A, CYP1B, CYP2A, CYP2B, CYP3A, CYP3B, etc.).

Finally, the cytochrome name ends with another Arabic number that specifies the specific enzyme responsible for a particular reaction (CYP1A2, CYP2C9, CYP2C19, CYP3A4, etc.).

*** Cytochromes are redox-active proteins containing a heme, with a central iron (Fe) atom at its core, as a cofactor. They are involved in electron transport chain and redox catalysis.**


the cytochrome system
CYP
1
capital letter that represents the subfamily
A
2
another Arabic number that specifies the specific enzyme responsible for a particular reaction
Arabic number that specifies the cytochrome family

1. The Oxidative biotransformation processes eq. (1) require both:

Molecular oxygen and the reducing agent NADPH (reduced form of nicotinamide adenosine dinucleotide phosphate).

2. During this oxidative process, one atom of molecular oxygen (O_2) is introduced into the substrate R-H to form R-OH and the other oxygen atom is incorporated into water.

3.The mixed-function oxidase system is actually made up of several components, the most important being the superfamily of CYP enzymes (currently at 57 genes , which are responsible for transferring an oxygen atom to the substrate R-H.

4. Other important components of this system include the NADPH-dependent CYP reductase and the NADH-linked cytochrome b5.

These two components, along with the cofactors NADPH and NADH, supply the reducing equivalents (electrons) needed in the overall metabolic oxidation of foreign compounds.

The cofactors NADPH and NADH

NADH dehydrogenase:

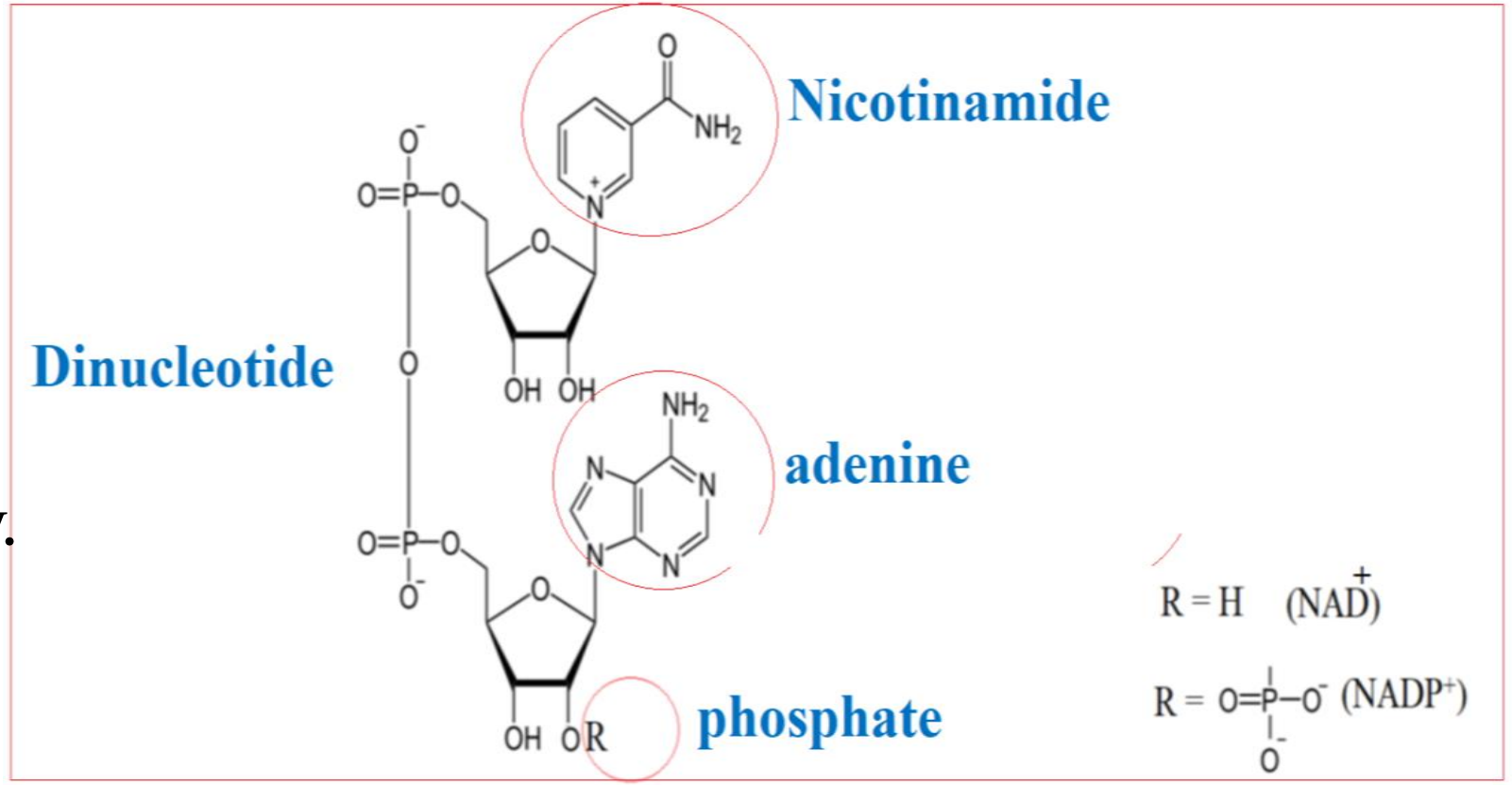
Is an enzyme that converts Nicotinamide Adenine Dinucleotide (NAD) from its reduced form (NADH) to its oxidized form (NAD^+). The chemical reaction these enzymes catalyze are generally represented with the follow equation

$$NADH + H^+ + acceptor \rightleftharpoons NAD^+ + reduced\ acceptor$$

NADH dehydrogenase is a flavoprotein that contains iron-sulfur centers.

Nicotinamide adenine Dinucleotide phosphate, $NADP^+$

The presence of an additional phosphate group on the 2' position of the ribose ring that carries the adenine moiety.



Reduction is the gain of electrons

Oxidation is the loss of electrons

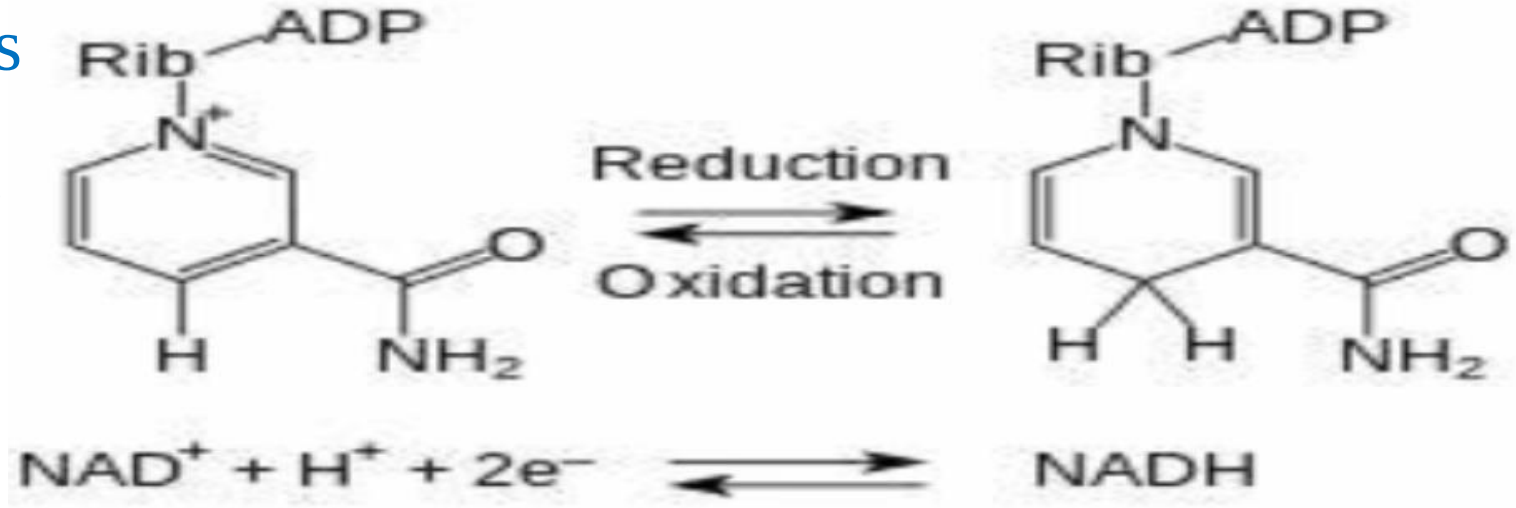
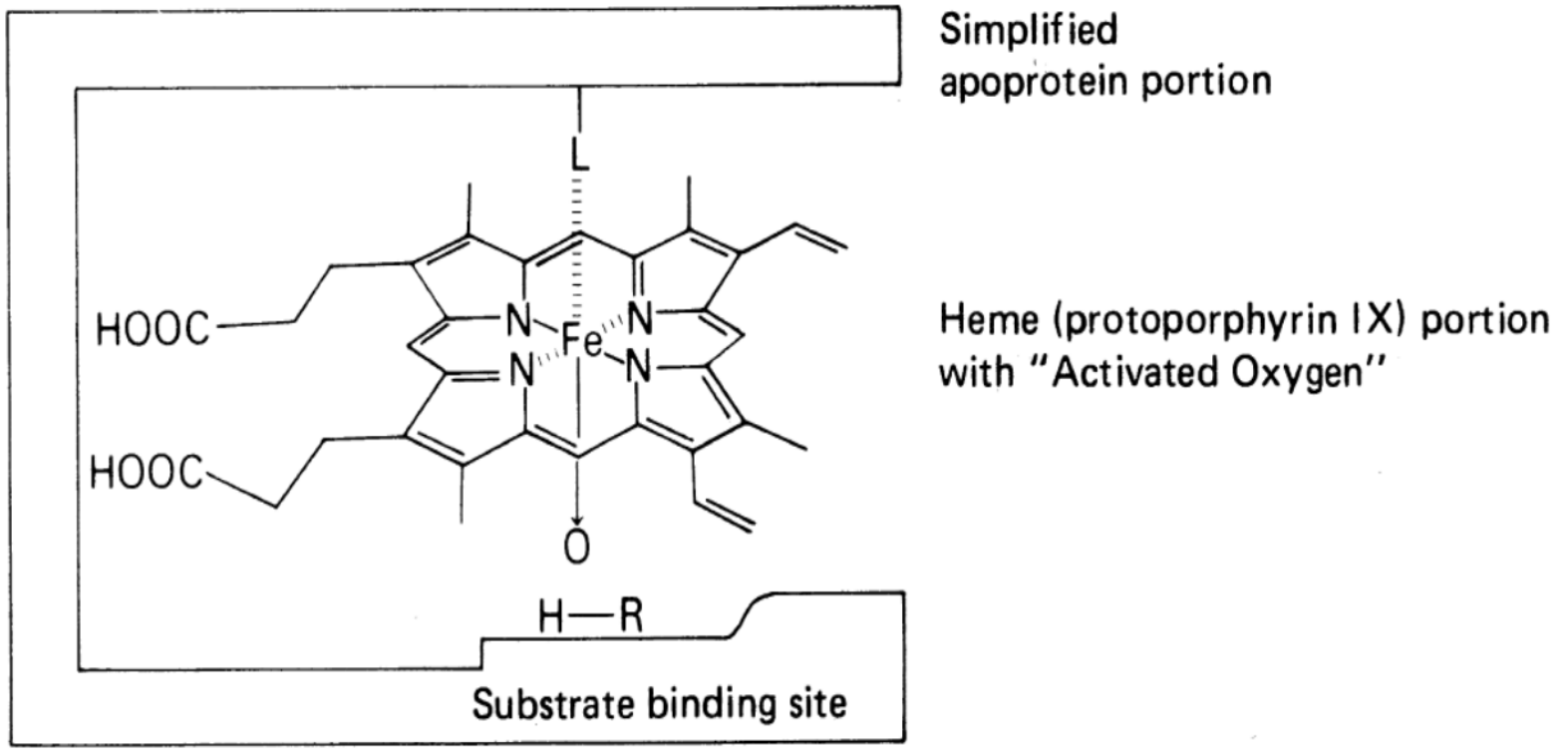


Figure (15)

Reduced form



Simplified depiction of the proposed activated oxygen–cytochrome P450-substrate complex. Note the simplified apoprotein portion and the heme (protoporphyrin IX) portion or cytochrome P450 and the proximity of the substrate R-H undergoing oxidation.

OXIDATIVE REACTIONS (Oxidation of aromatic moieties):

Aromatic hydroxylation refers to the mixed-function oxidation of aromatic compounds (arenes) to their corresponding phenolic metabolites (arenols).

Almost all aromatic hydroxylation reactions are believed to proceed initially through an epoxide intermediate called an "arene oxide," which rearranges rapidly and spontaneously to the arenol product in most instances.

The importance of arene oxides in the formation of arenols and in other metabolic and toxicologic reactions is discussed below. Our attention now focuses on the aromatic hydroxylation of several drugs and xenobiotics.

The many types of oxidative reaction carried out by CYP are summarized schematically in Figure(17).

Fig (17):Schematic summary of cytochrome P450-catalyzed oxidation reactions(Name only ten)

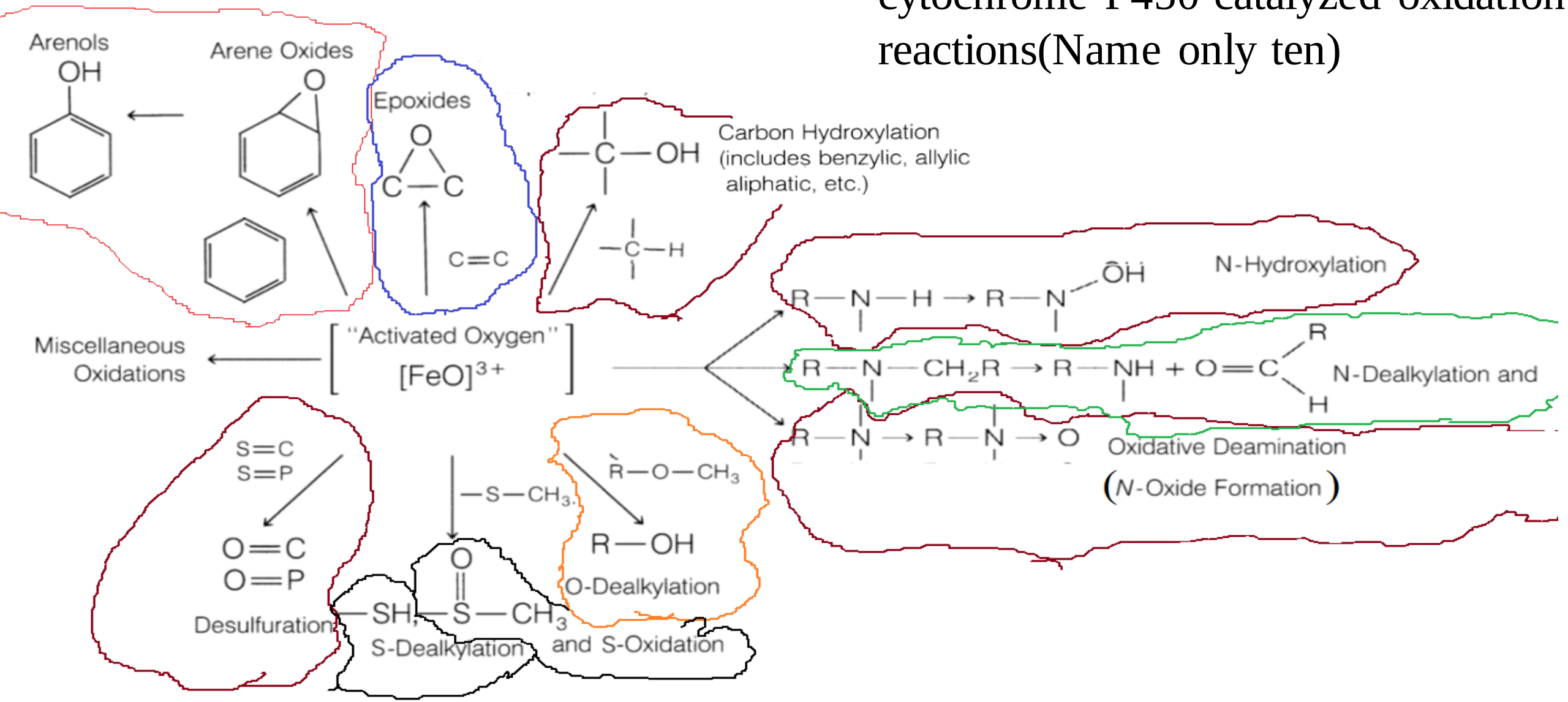
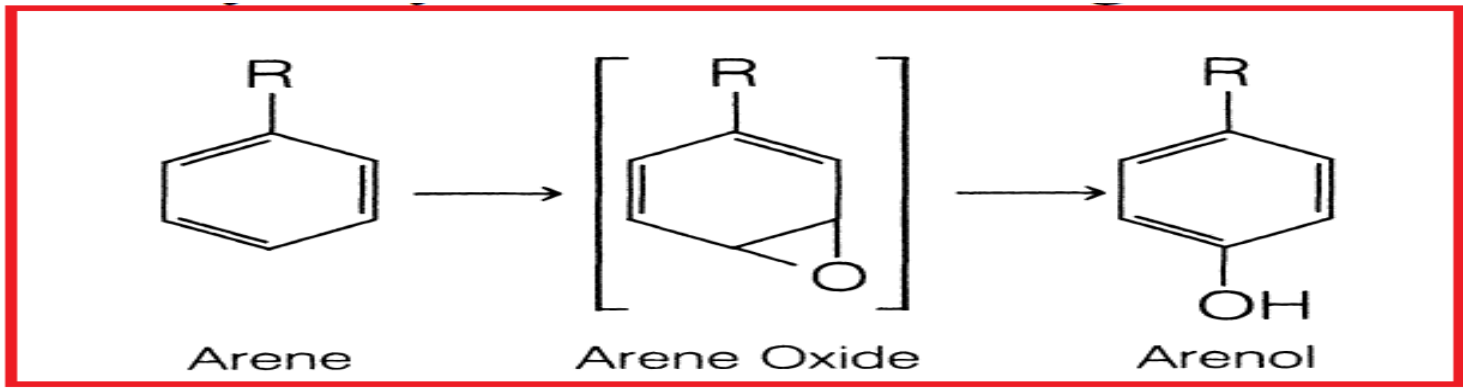


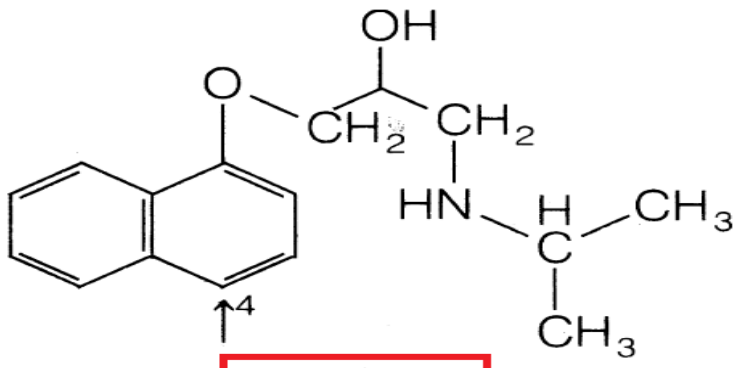
Fig (18)



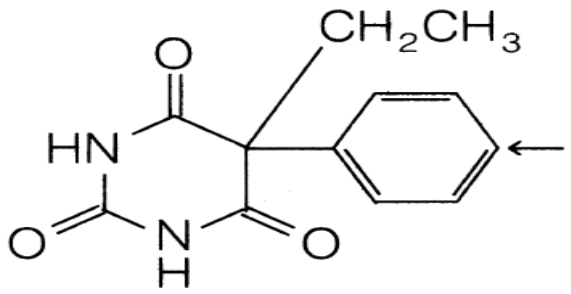
Most foreign compounds containing aromatic moieties are susceptible to aromatic oxidation. In humans, aromatic hydroxylation is a major route of metabolism for many drugs containing phenyl groups.

Important therapeutic agents such as Propranolol, Phenobarbital, Phenytoin, Phenylbutazone, Atorvastatin, 17-α-Ethinylestradiol and (*S*)(-)-warfarin , among others, undergo extensive aromatic oxidation, Fig(19) shows structure and site of hydroxylation.

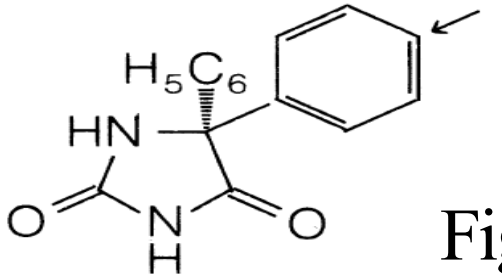
In most of the drugs just mentioned, hydroxylation occurs at the *para* position Fig (19a and b).Most phenolic metabolites formed from aromatic oxidation undergo further conversion to polar and water soluble glucuronide or sulfate conjugates, which are readily excreted in the urine. Fig (20)



Propranolol

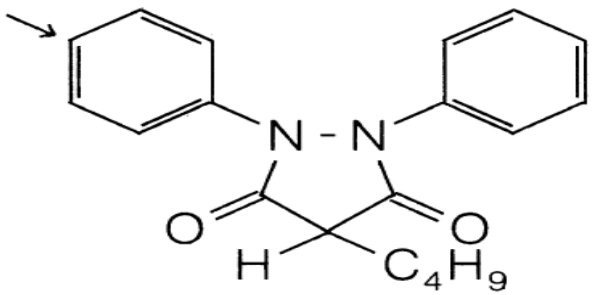


Phenobarbital

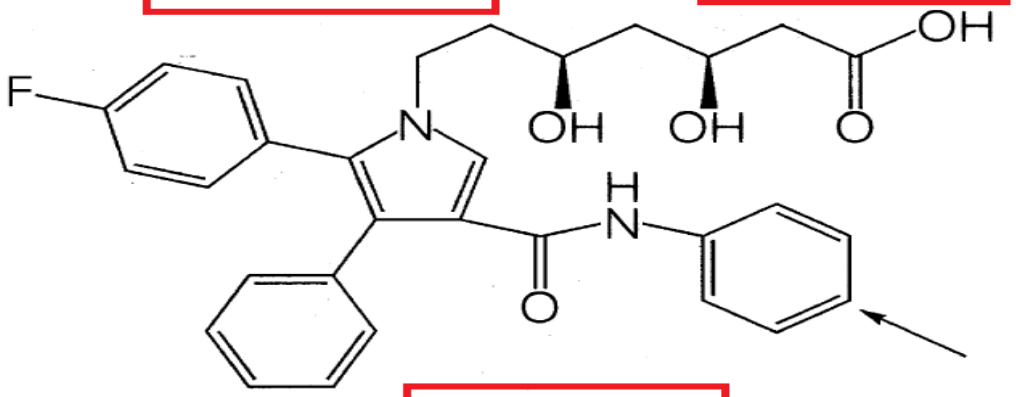


Phenytoin

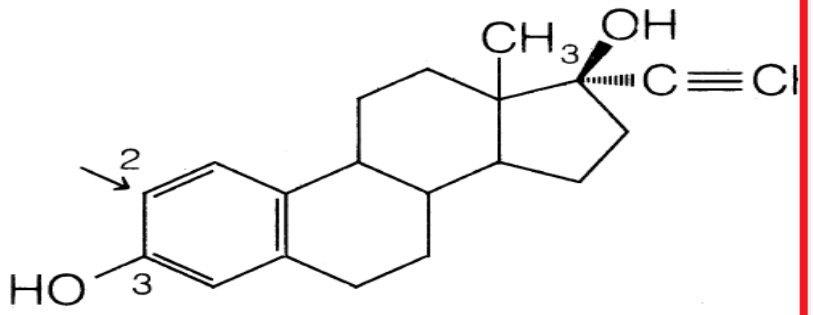
Fig (19a)



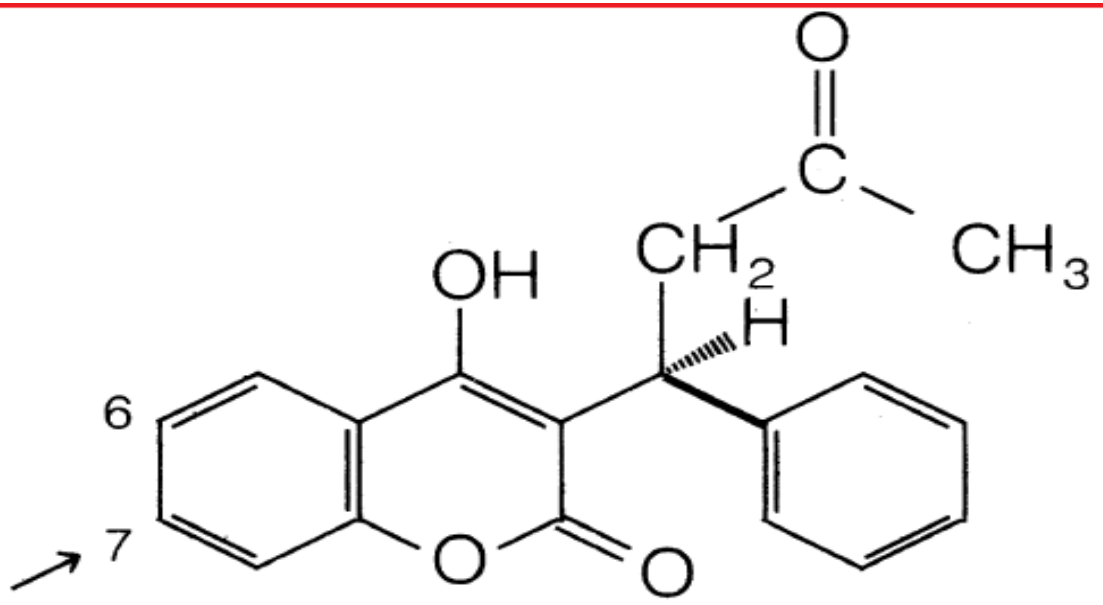
Phenylbutazone



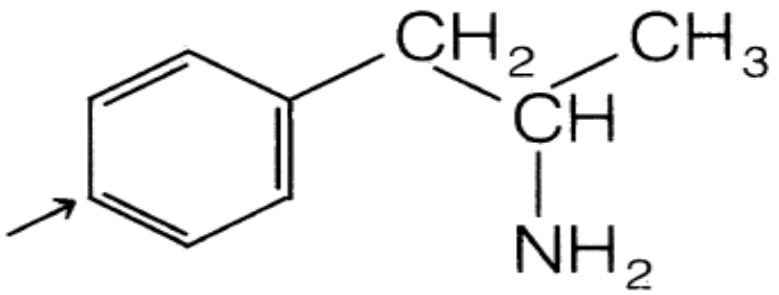
Atorvastatin



17α-Ethinylestradiol



Warfarin
S(−)-Enantiomer
in Humans

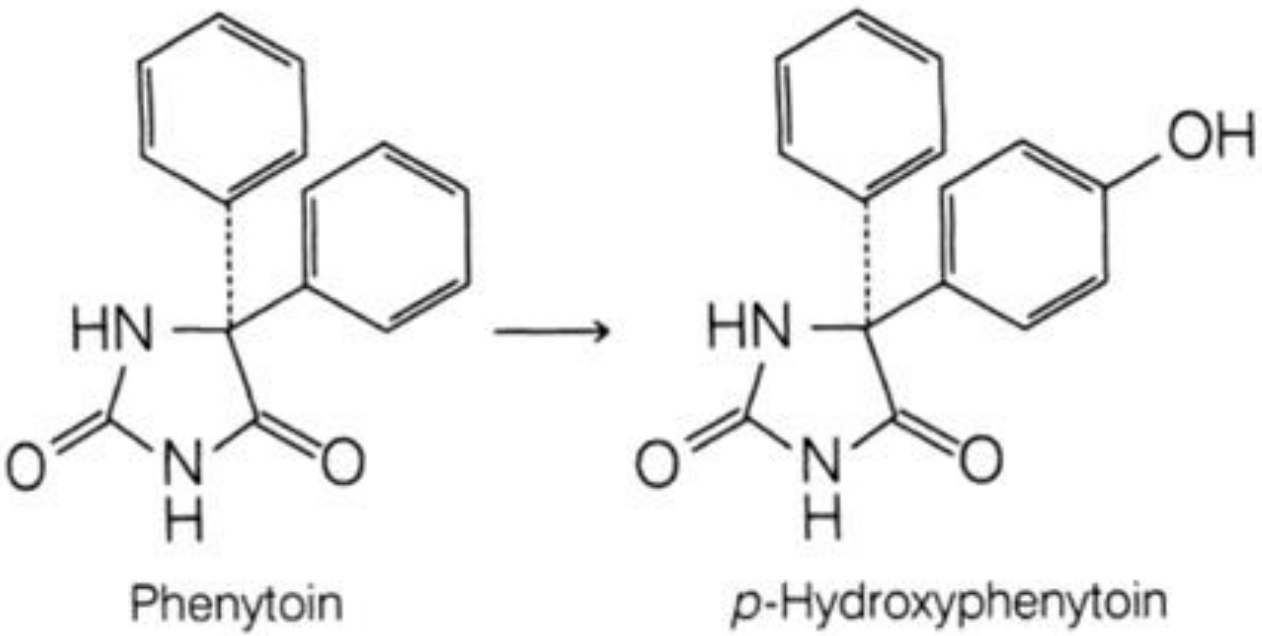


Amphetamine

Examples of drugs and xenobiotics that undergo aromatic hydroxylation in humans. *Arrow* indicates site of aromatic hydroxylation.

Fig (19b)

Q. The major urinary metabolite of phenytoin found in humans is the O-glucuronide conjugate of p-hydroxyphenytoin , Draw this important metabolite



The major urinary metabolite of phenytoin found in humans is the O-glucuronide conjugate of p-hydroxyphenytoin , Fig (20).

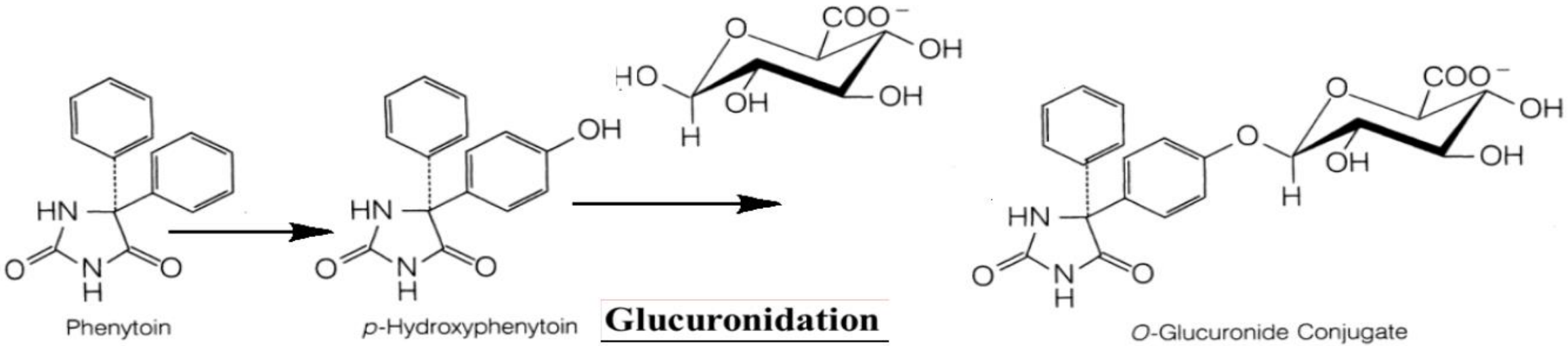


Fig (20).

or

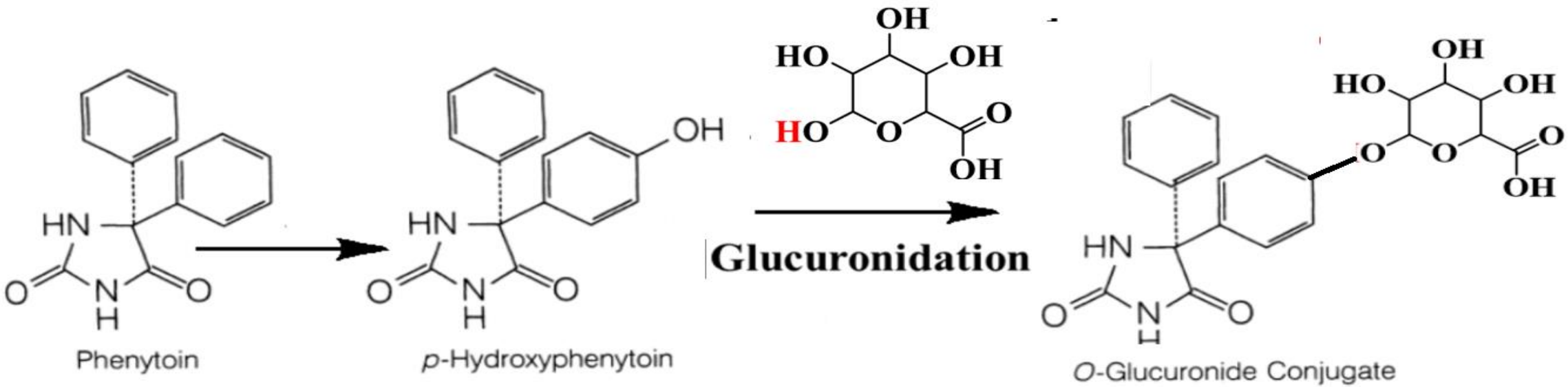

Phenytoin
p-Hydroxyphenytoin
Glucuronidation
O-Glucuronide Conjugate

Fig (20).

Interestingly, the para-hydroxylated metabolite of phenylbutazone, oxyphenbutazone, is pharmacologically active and has been marketed itself as an anti-inflammatory agent (Tandearil, Oxalid).

*Of the two enantiomeric forms of the oral anticoagulant warfarin (Coumadin), only the more active S(-) enantiomer has been shown to undergo substantial aromatic hydroxylation to 7-hydroxywarfarin in humans.

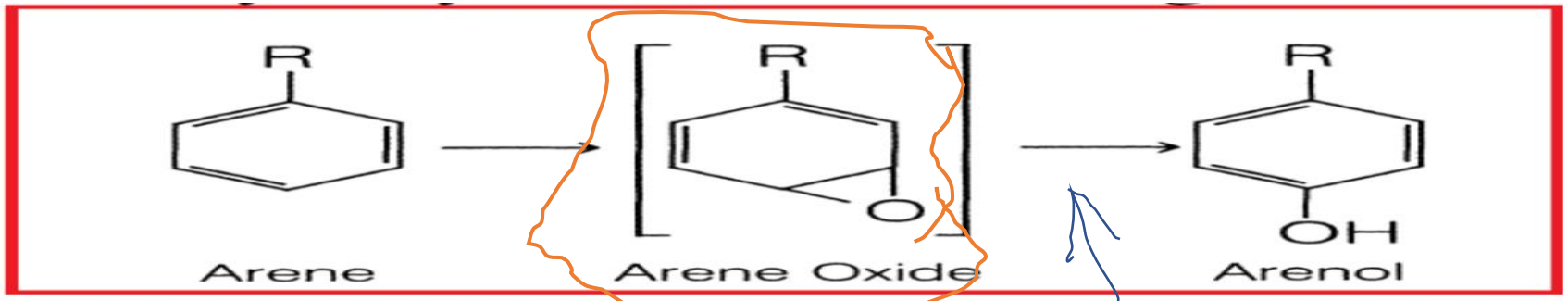
In contrast, the (R)(+) enantiomer is metabolized by keto reduction.

Often, the substituents attached to the aromatic ring may influence the ease of hydroxylation.

As a general rule, microsomal aromatic hydroxylation reactions appear to proceed most readily in activated (electron-rich) rings, whereas deactivated aromatic rings (e.g., those containing electron-withdrawing groups Cl, -NR_3, COOH, SO_2NHR) are generally slow or resistant to hydroxylation.

The deactivating groups (Cl, -NHBC) present in the antihypertensive clonidine (Catapres) may explain why this drug undergoes little aromatic hydroxylation in humans.

The uricosuric agent probenecid (Benemid), with its electron-withdrawing carboxy and sulfamido groups, has not been reported to undergo any aromatic hydroxylation.



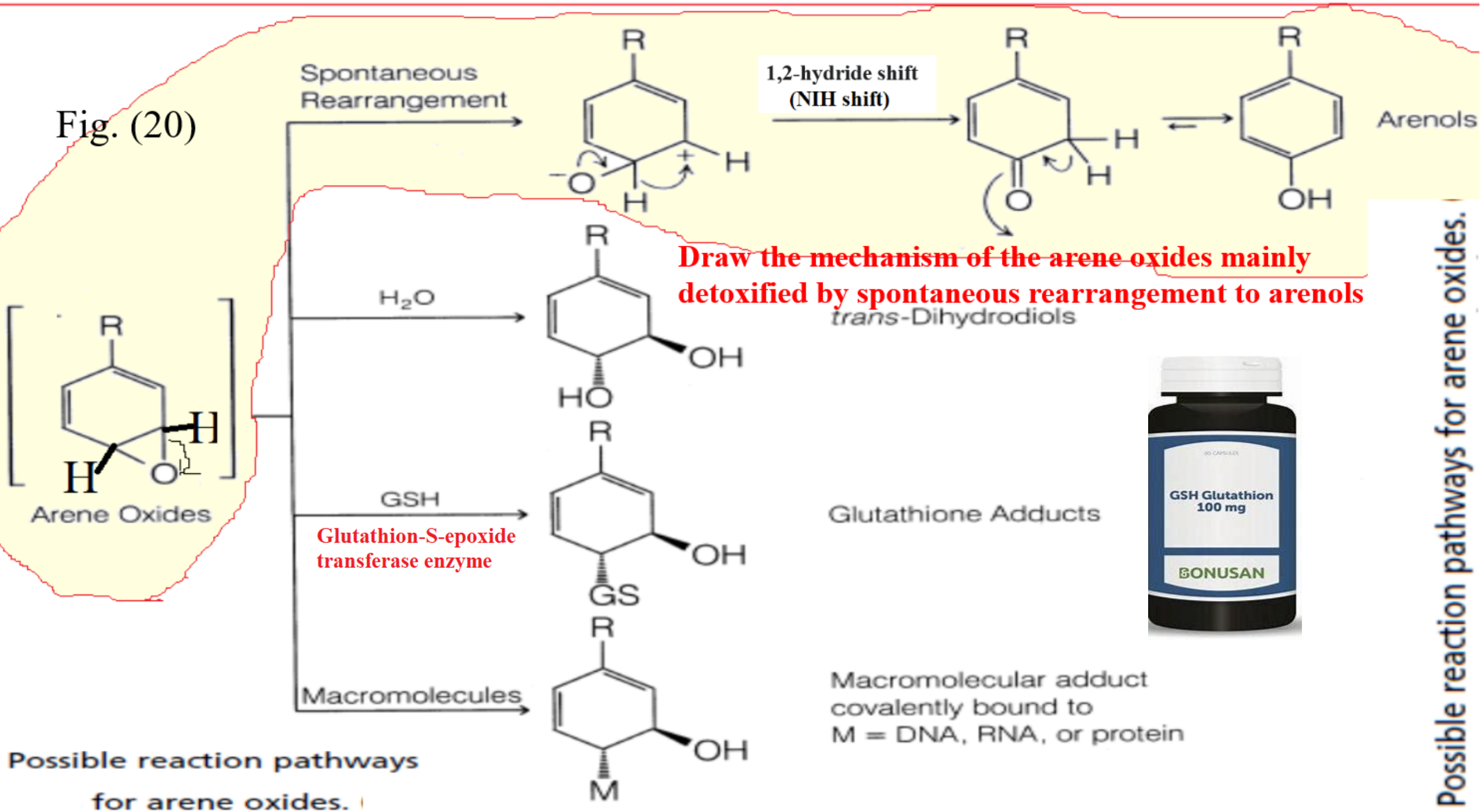
Arene oxide intermediates :

i. Are formed when a double bond in aromatic moieties is epoxidized. Arene oxides are of significant toxicologic concern because these intermediates are electrophilic and chemically reactive (because of the strained three-membered epoxide ring).

ii. Arene oxides are mainly detoxified by spontaneous rearrangement to arenols, but enzymatic hydration to *trans* - dihydrodiols and enzymatic conjugation with GSH also play very important roles (Fig. 21).

iii.If not effectively detoxified by the first three pathways in Figure (210) arene oxides will bind covalently with nucleophilic groups present on proteins, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA), thereby leading to serious cellular damage.

Fig. (20)



Draw the mechanism of the ~~arene oxides~~ mainly detoxified by spontaneous rearrangement to arenols

Possible reaction pathways for arene oxides.

Stereochemistry:

A three dimensional structure of the molecule arrangement in space . It plays a major role in the pharmacological properties because:

1)Any change in stereospecificity of the drug will affect its pharmacological activity.

2)The isomeric pairs have different physical properties (Partion coefficient, PKa.....etc) and thus differ in pharmacological activity:

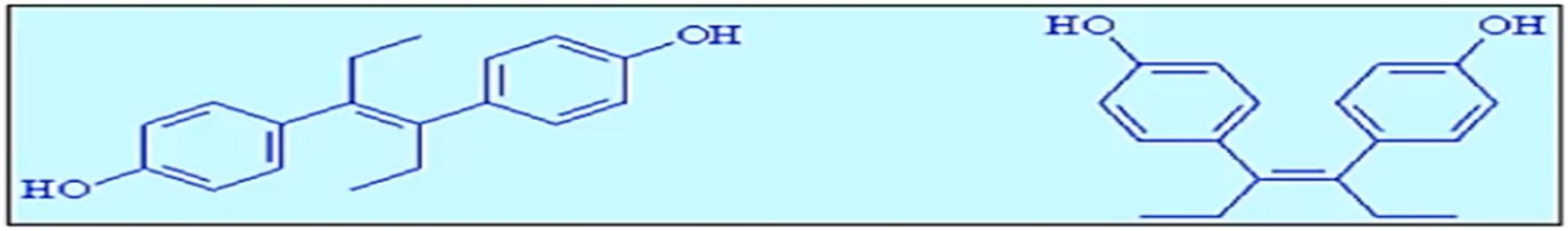
Optical and geometric isomerism

Conformational isomerism

Geometric isomerism (cis-trans isomerisms).

Geometric isomerism is represented by cis/trans isomerism resulting from restricted rotation due to carbon carbon double bond or in rigid ring system.

- For example, diethylstilbestrol exists in two fixed stereoisomeric forms:
  - Trans-diethylstilbestrol is estrogenic, whereas
  - The cis-isomer is only 7% as active.
- In trans-diethylstilbestrol, resonance interactions and minimal steric interference tend to hold the two aromatic rings and connecting ethylene carbon atoms in the same plane.



trans-diethylstilbestrol

cis-diethylstilbestrol

Estrogenic activity

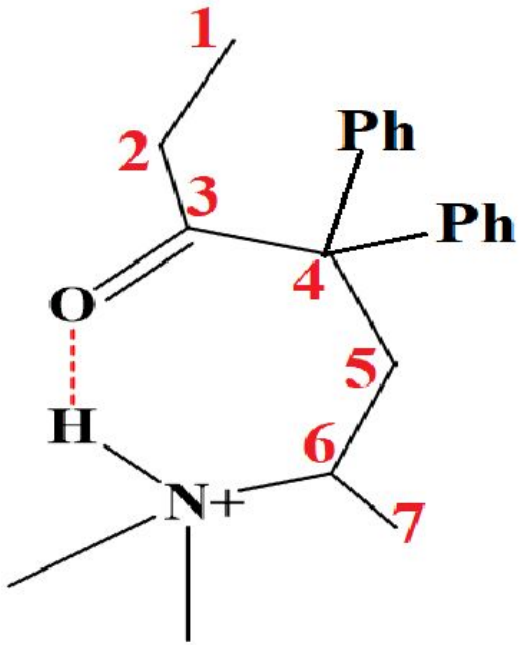
only 7% of trans activity

Methadone, brand name(Dolophine), is a synthetic opioid agonist used for opioid maintenance therapy in opioid dependence and for chronic pain management

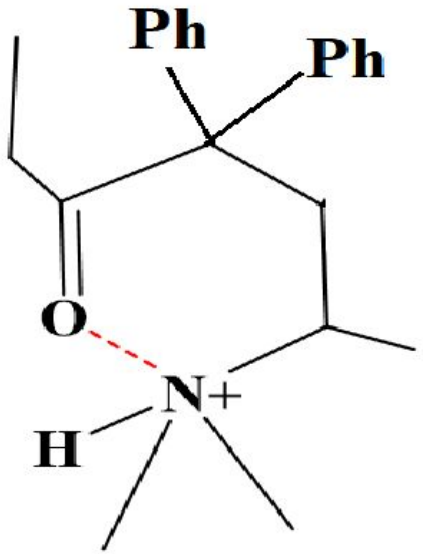
Example of dipole-dipole interactions at same time H-bonding formation which appear to influence structure in solution, it exist partially in a cyclic form in solution due to:

i. Dipolar attractive forces between the basic nitrogen and carbonyl group and

ii. H-Bonding between the hydrogen on the nitrogen and the carbonyl oxygen.



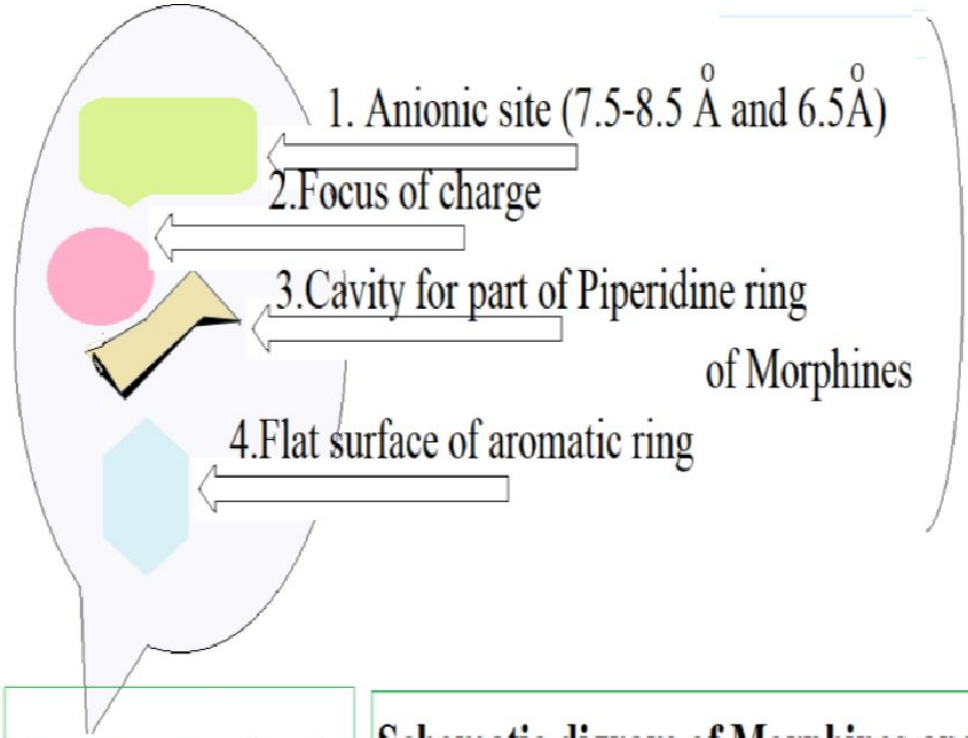
(a)Stabilized by H-bond



(b)Stabilized by dipolar interaction

(RS)-6-(dimethylamino)-4,4-diphenylheptan-3-one
(Methadone)

In either conformation, methadone may resemble conformationally more rigid potent analgesics including morphine, meperidine, and their analog, and it may be this form that interacts with the analgesic receptor. Once the interaction between the drug and its receptor begins, a flexible drug molecule may assume a different conformation than that predicted from solution chemistry.

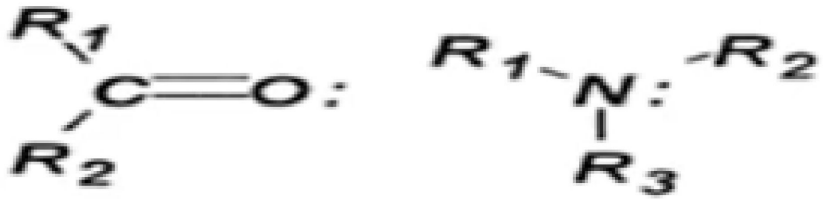


Schematic digram of Morphines analgesic functional groups and specifically oriented four complementry groups on receptors

Hydrogen bond (abbreviated H-bond) is a primarily اساسيةelectrostatic force of attraction between a hydrogen (H) atom which is covalently bound to a more electronegative atom or group, particularly the second-row elements nitrogen (N), oxygen (O), or fluorine (F)—(the hydrogen bond donor (Dn)—and another electronegative atom bearing a lone pair of electrons(the hydrogen bond acceptor (Ac).

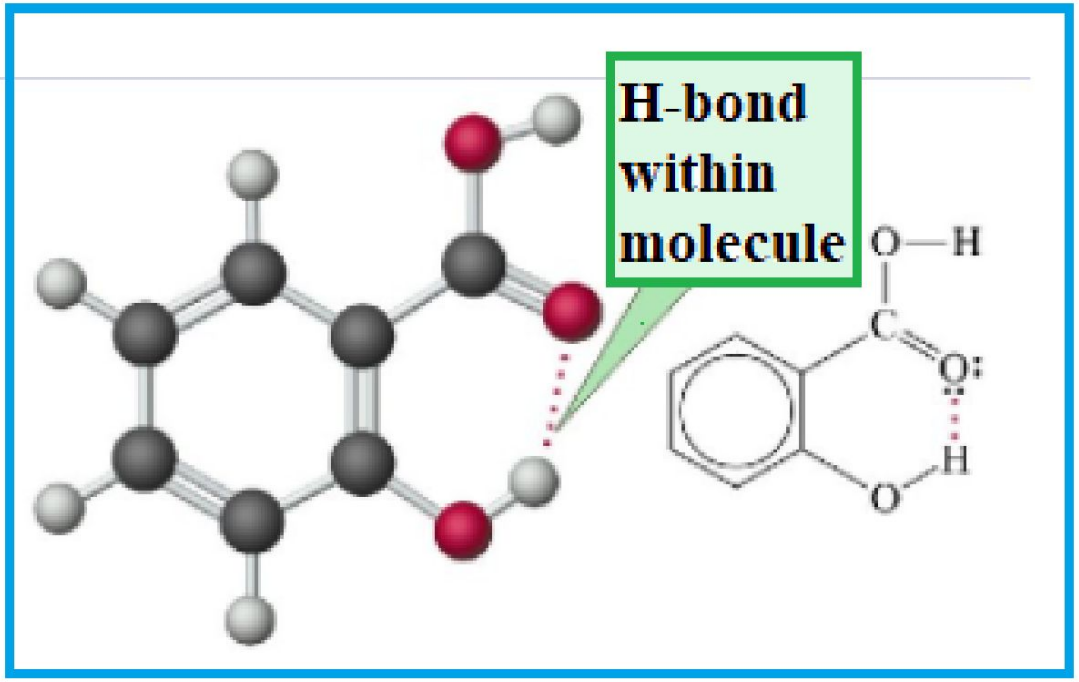
Dn, , e.g. Alcohols & 2°Amines

Ac , e.g. Ketones & 3° Amines

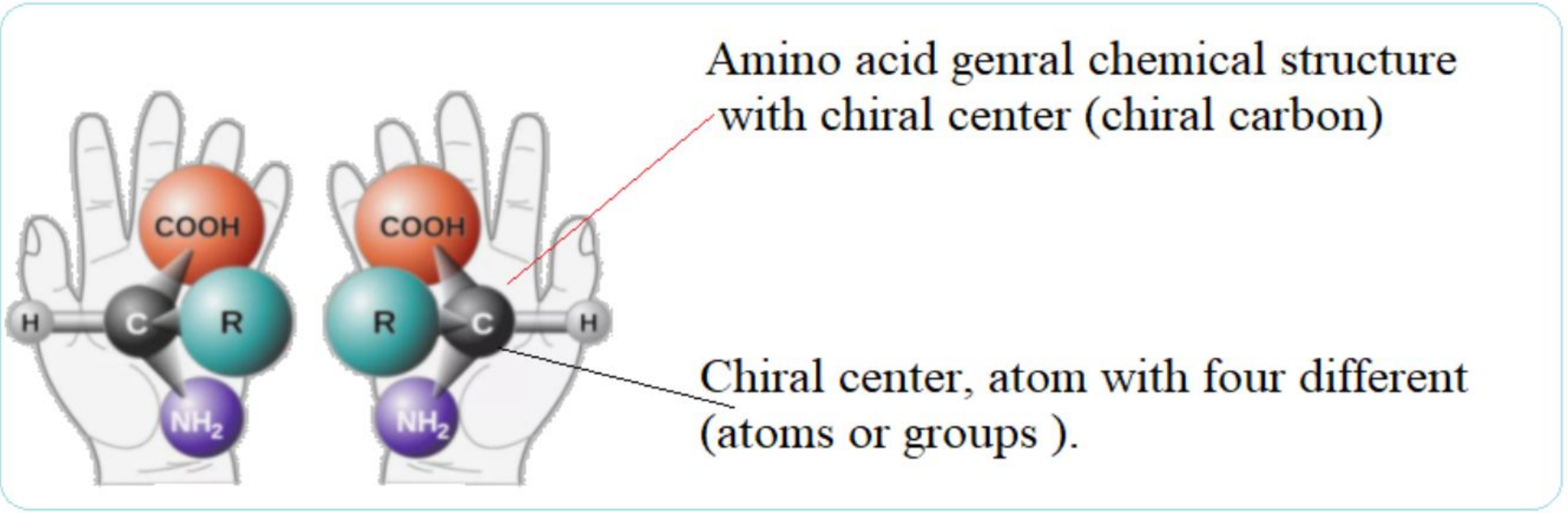


Notes:

Intramolecular H- bond usually formed between Dn hydrogen of hydroxy (O-H) or amino (N-H) groups and Ac oxygen or nitrogen atoms, which add stability to particular conformation of a drug in sol. e.g. Salicylic acid



OPTICAL ISOMERS
&
BIOLOGICAL ACTIVITY OF DRUGS



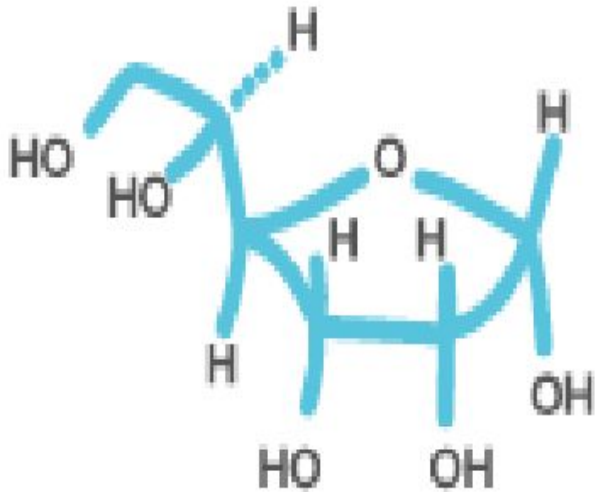
Chiral compounds:

Are stereocenters that hold a set of atoms (ligands) in space such that the structure may not be superimposed on its mirror image . e.g Aminoacids

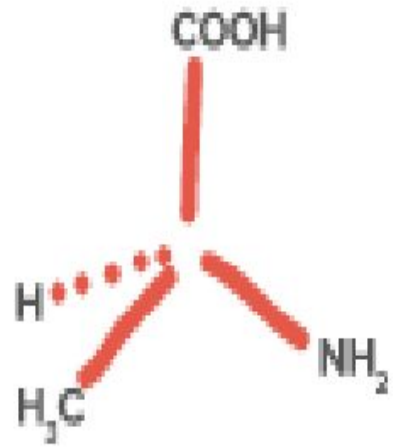
Chiral atom: (in Greek, Kheir means "handed")

An atom (usually carbon in sp3 hybridization) attached to four different substituents (atoms or groups of atoms) is called a stereogenic center* or stereocenter, with lack a planer of symmetry and non- superimposable with their mirror images.(putting a star on this carbon C*)

chiral carbon centers

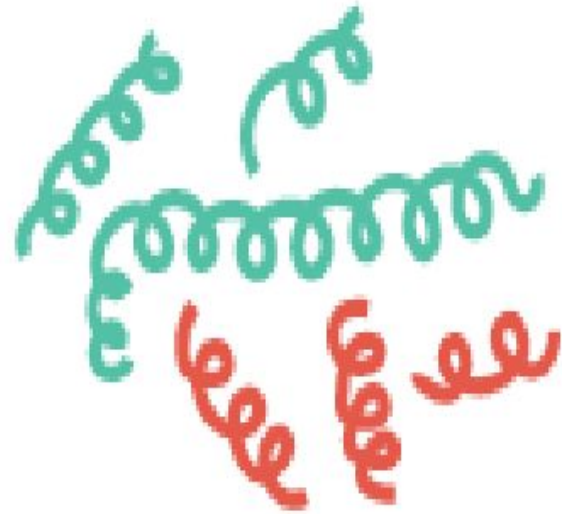


Sugars



Amino Acids

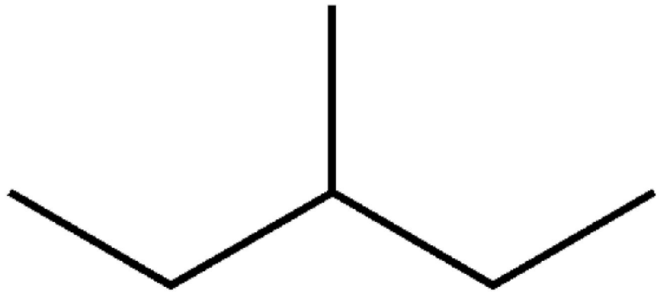
DNA



Enzymes

:ACHIRAL

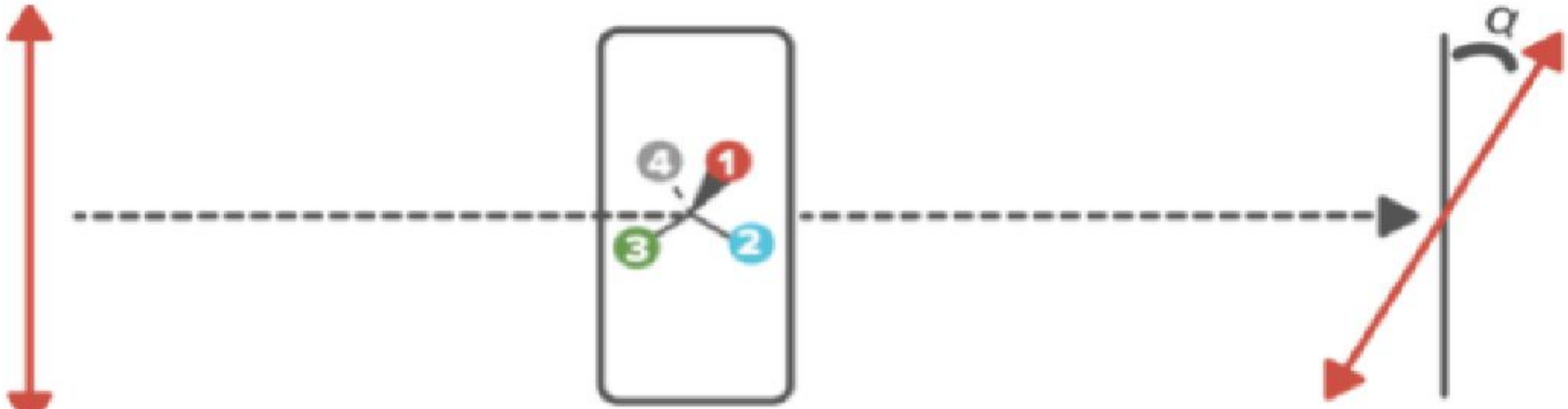
Carbon with sp,sp2 or sp3 or attached to three or less different atoms or groups is considered nonsterogenic center scince it has a plane of symmetry. These compounds are superimposable .with their mirror image are called achiral. 3-methylpentane is an achiral molecule



Achiral. 3-methylpentane

Note that:

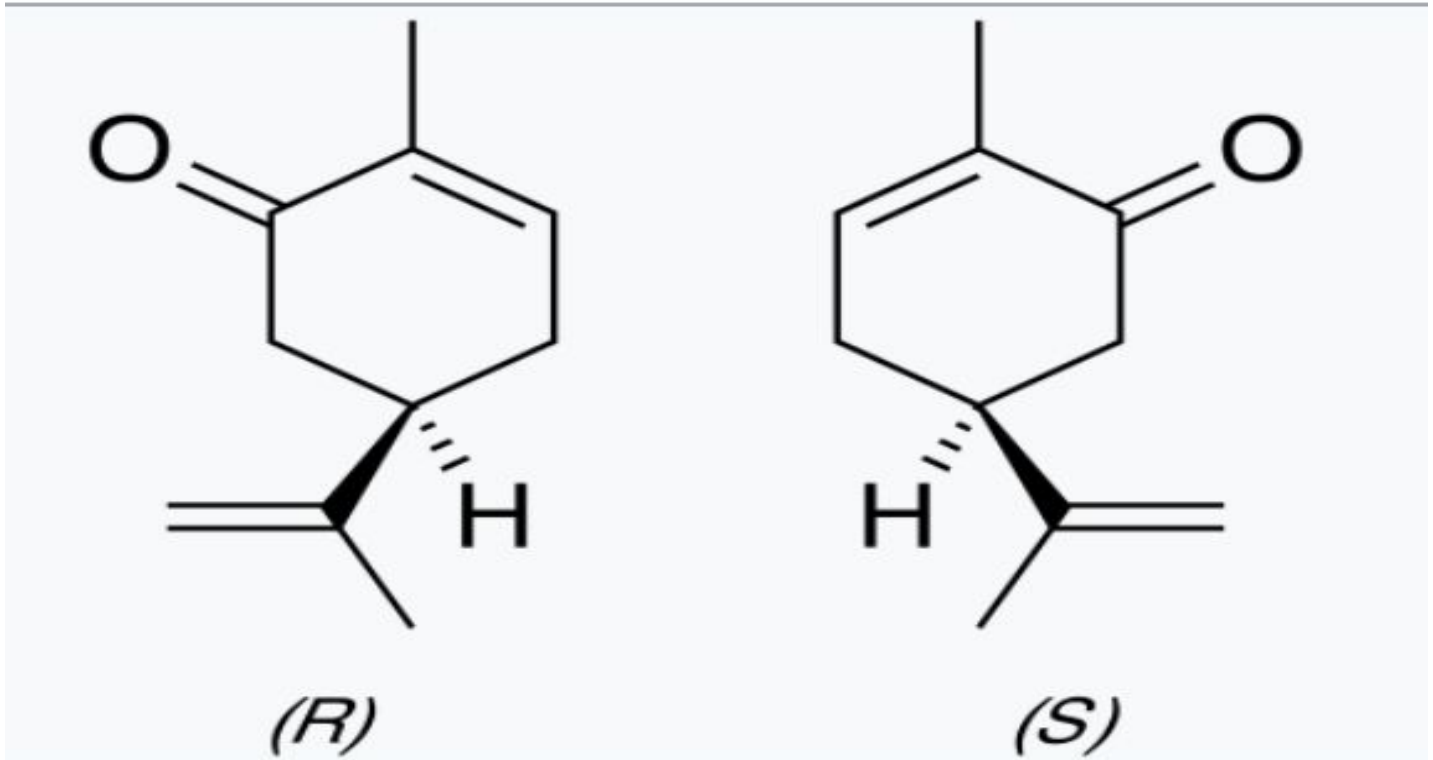
Chiral molecules are optically active, while achiral molecules are not.



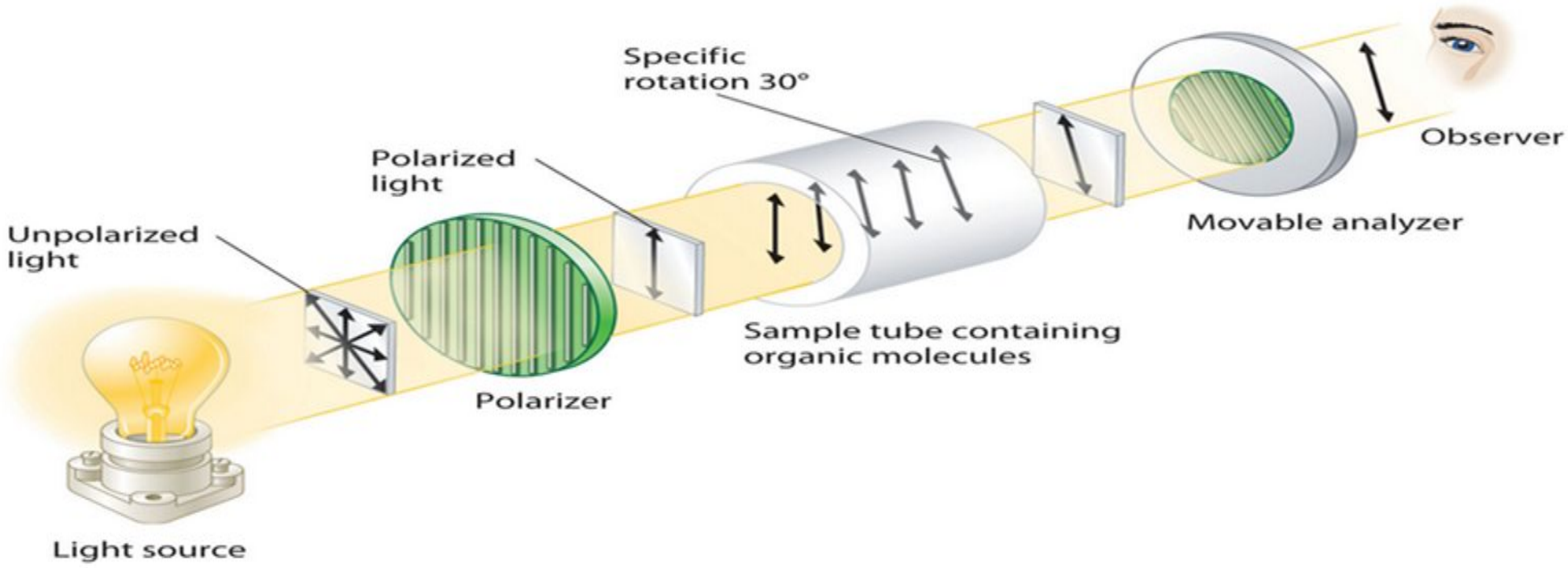
plane-polarized light **chiral sample** **rotated light**

A pair of enantiomers always rotate plane-polarized light to an equal but opposite degree. Example: If a pure sample of (*S*)-carvone rotates plane-polarized light by +10°(clockwise), then a sample of (*R*)-carvone (in the exact same concentration and under the same experimental conditions) will rotate the plane polarized light by (–)10° (counterclockwise).

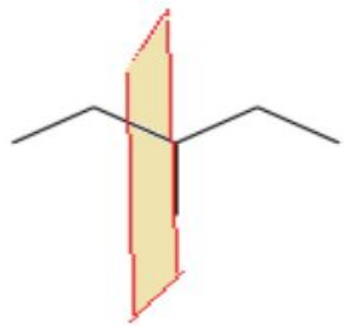
Carvone

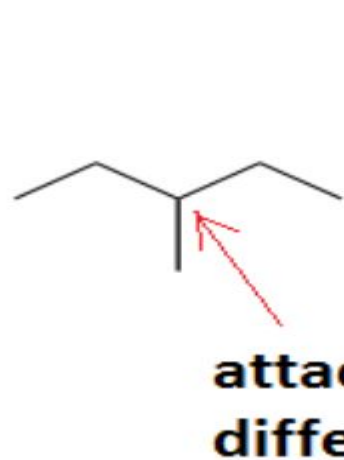


PPL, is the light vibrates in one direction, either (+) (dextrorotary) or (-) (levorotatory).

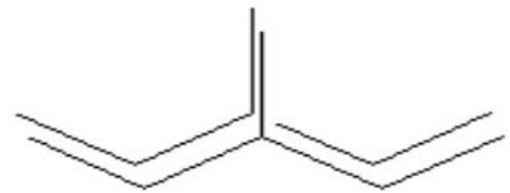


has a plane of symmetry





attached to three or less different groups

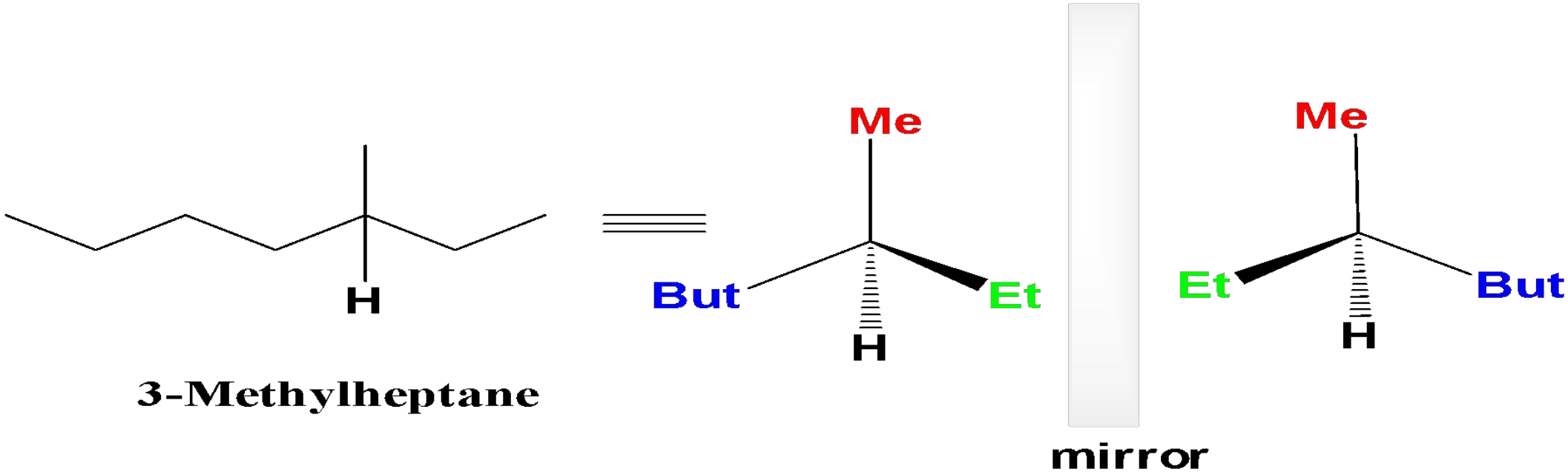


mirror images superimposable

3-Methylpentane

Achiral compound with achiral center

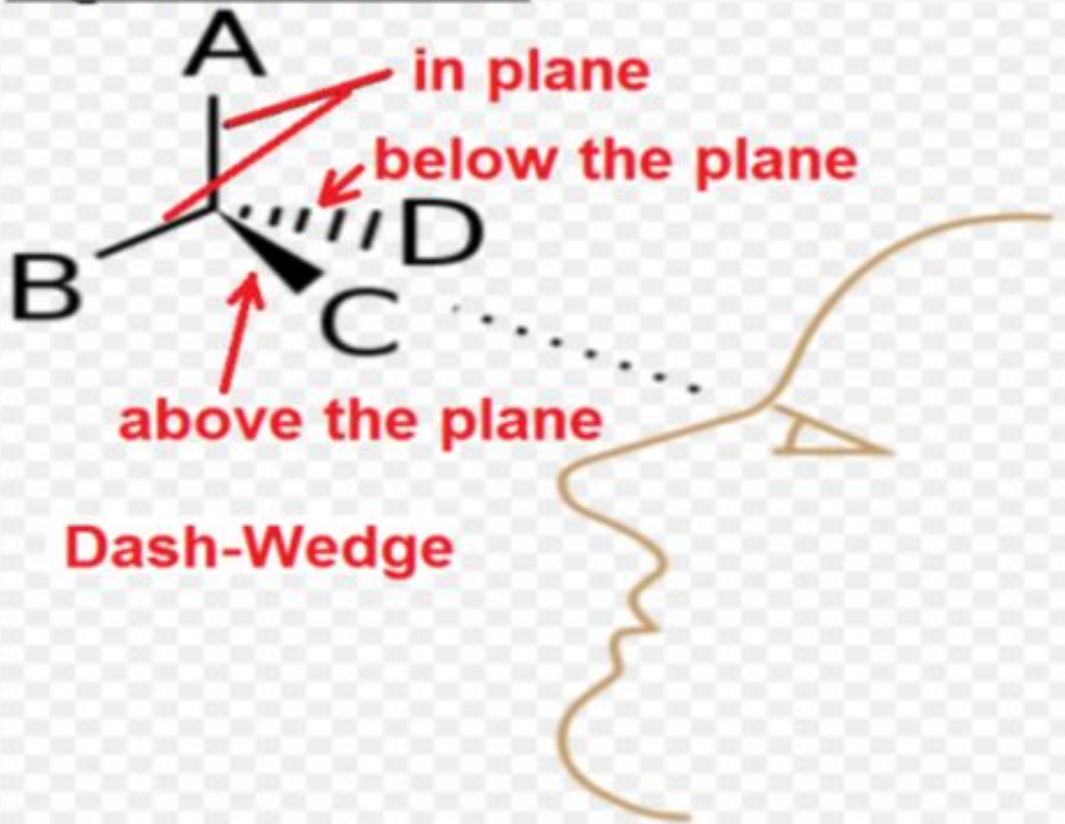
Examples of Chiral centers:



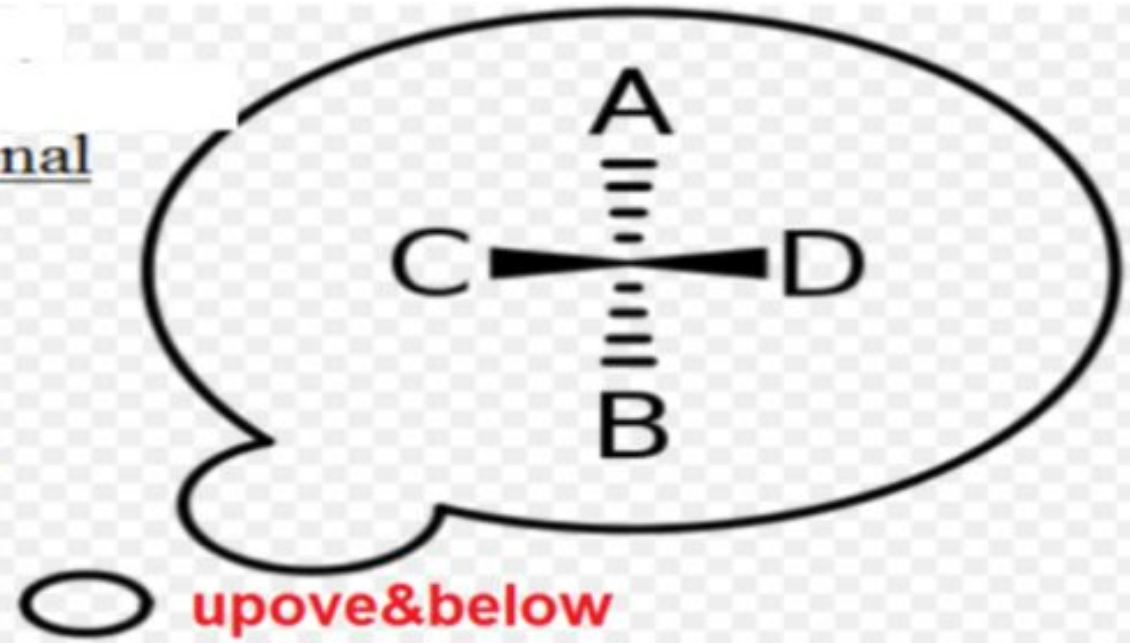
3-Methylheptane

To superimpose the mirror images, bonds must be broken and reformed. These two optical isomers are Enantiomers

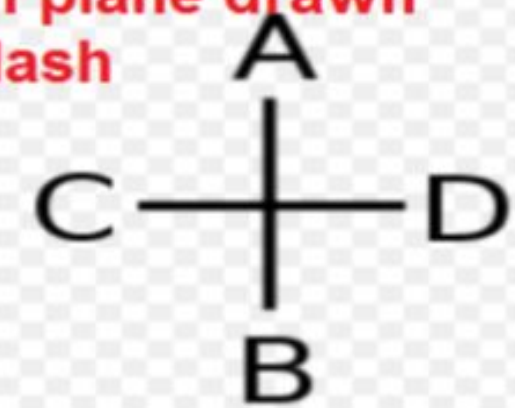
The **Fischer projection**,
, is a two-dimensional representation of a three-dimensional organic molecule

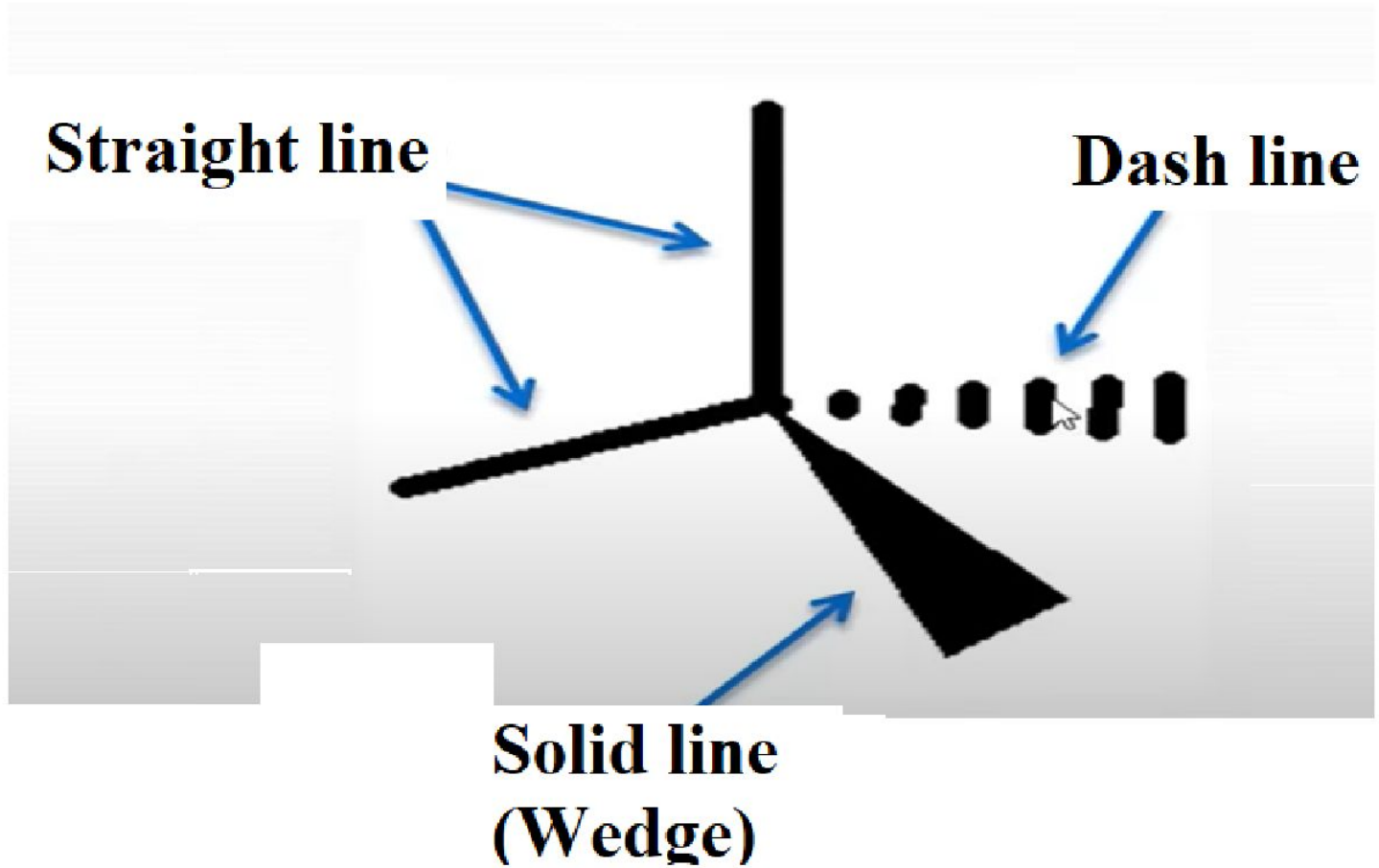


Dash-Wedge



upove&below drawn wedge, in plane drawn dash




Straight line
Dash line
Solid line
(Wedge)

ENANTIOMERS:

الأنداد

Enantio = opposite , mers = parts

The two non superimposable mirror images are known as A PAIR OF ENANTIOMERS: which have the same chemical and physical properties like:

melting point, solubility and reactions except their ability for the rotation of plane polarized light(PPL), they rotate it in the same magnitude but opposite direction. They have optical activity

Enantiomers :

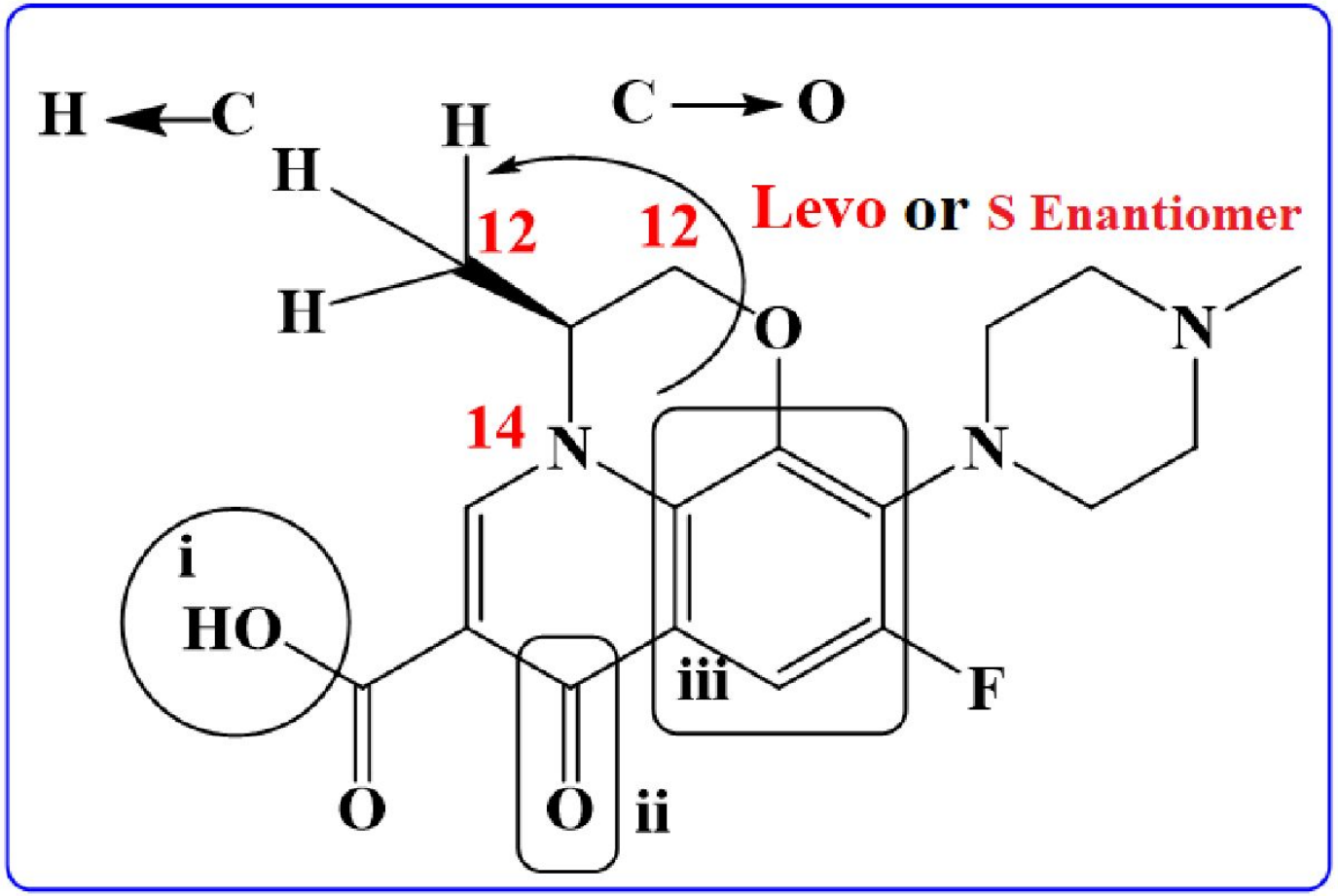
If the plane polarized light is rotated to the right or in a clockwise direction, the stereoisomers are said to be the (+) or the *Dextrorotatory isomer*. On the other hand, if the plane polarized light is rotated to the left or in a counter-clockwise direction, the stereoisomer is called as the (−) or the *Laevorotatory isomer*.

Levofloxacin is the levo isomer of the racemate floxacin, a quinolone antimicrobial agent.

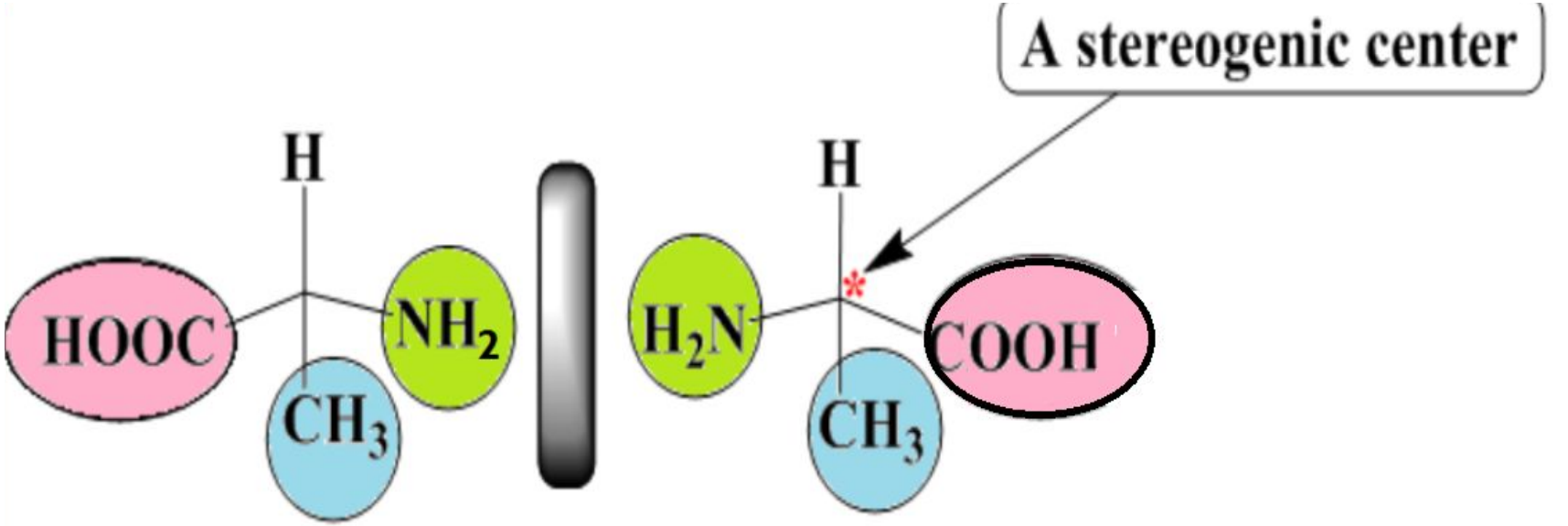
Levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (−)-(*S*)-enantiomer of the racemic ofloxacin.

Distinct functional groups on this molecules include a i. Hhydroxyl group ii. Carbonyl group, and iii. An aromatic ring.

Levofloxacin is the S-enantiomer and it binds more effectively to the DNA gyrase enzyme and topoisomerase IV than its counterpart نظیرہ.



Levofloxacin is the S-enantiomer and it binds more effectively to the DNA gyrase enzyme and topoisomerase IV than its counterpart.



2-Aminopropanoic acid

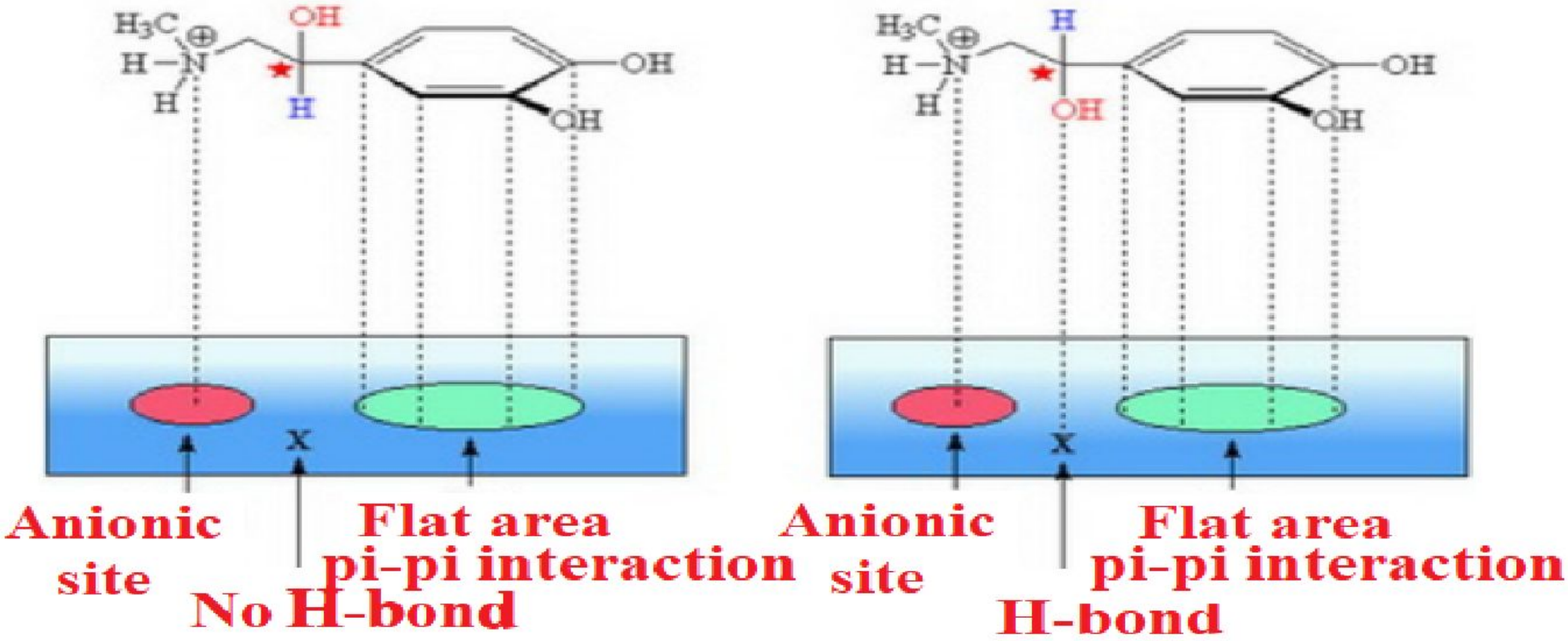
The two Alanine, non superimposable mirror images PAIR OF ENANTIOMERS, have the same chemical and physical properties

(+) & (-) Adrenaline (Epinephrine):

The differences in biological (or drugs pharmacological) activities for enantiomers of (Adrenaline enantiomers for example) are due to that (-) isomer being able to achieve three points of attachments of drug-receptor interactions with less points of attachments of the (+) isomer (two points) with the same receptor , e.g..

The three points of attachments are:

- an anionic site for the quaternary ammonium ion
- a hydrogen-bonding site for the β-hydroxyl group
- a flat site for π-π interaction with the aromatic ring



(+) Epinephrine
less active

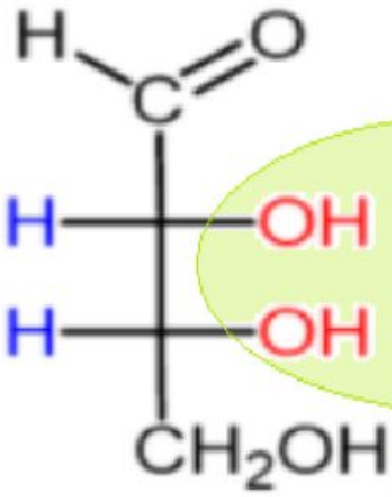
(-) Epinephrine
more active

Diastereomers :

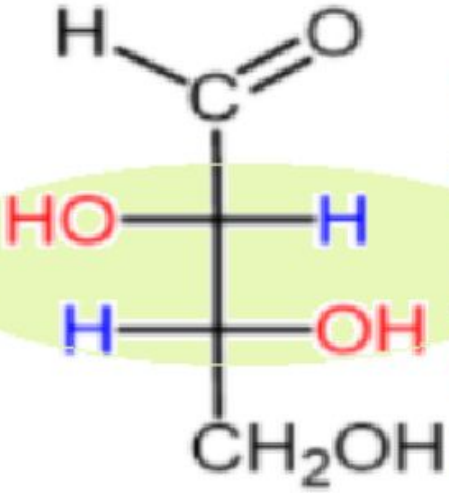
Enantiomers of a compound with more than one stereocenter that are not mirror image and with different physical properties and often different chemical reactivity, like

Erthyro and Threo.

Erythro and threo are common terms in stereochemistry used for naming molecules with two stereogenic centers . The names derive from the saccharides erythrose and threose, so let’s draw their Fischer projection to understand the basis of this notation:



Erthro:
When two like groups lie on the same side of the chiral center



Threo:
When two like groups lie on the different sides of the chiral center

Erythrose

Two H's on the same side

Two OH's on the same side

Threose

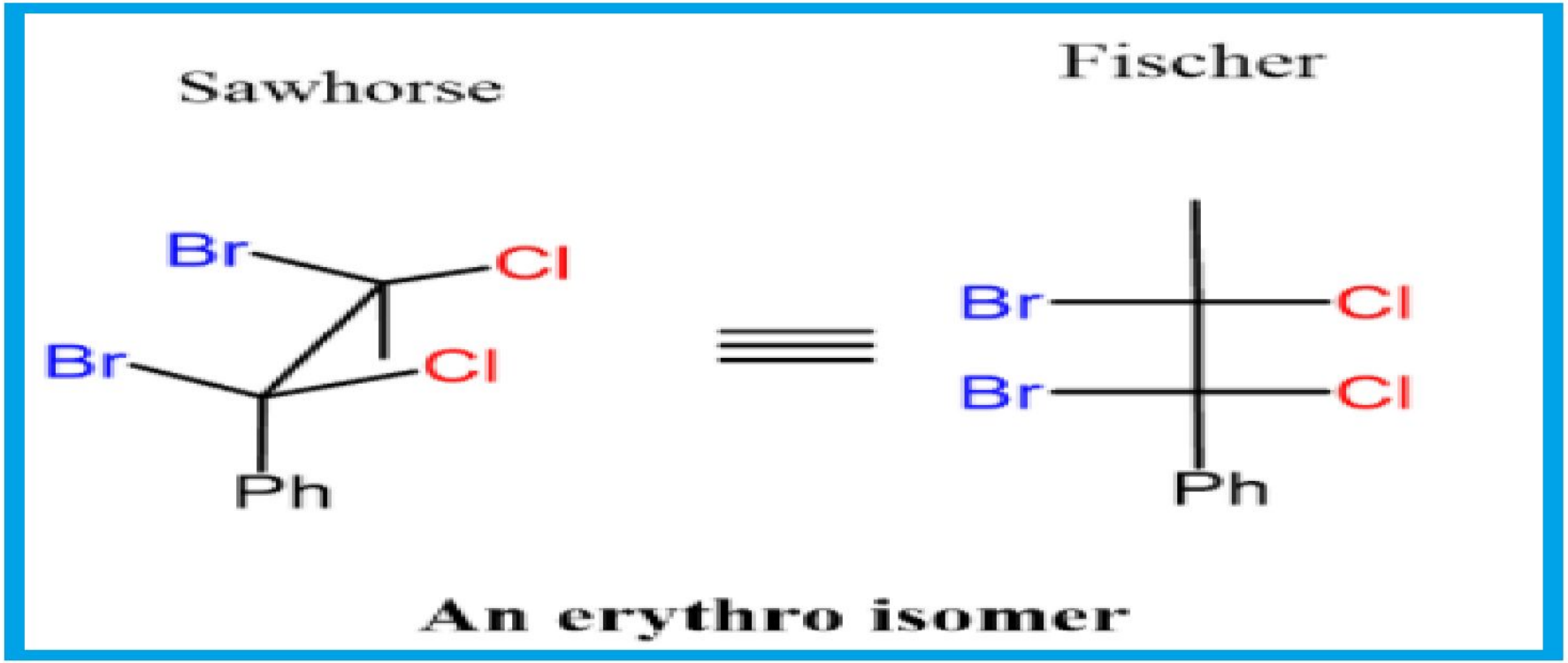
Two H's on opposite sides

Two OH's on opposite sides

not mirror images nor superimposable

Threose and erythrose exist in two enantiomeric forms which are designated as D and L enantiomers.

Erythro or threo configurations can also be evident in sawhorse projections.



Examples of drug as diastereomers is Ephedrine and Pseudoephedrine: