Medicinal Chemistry

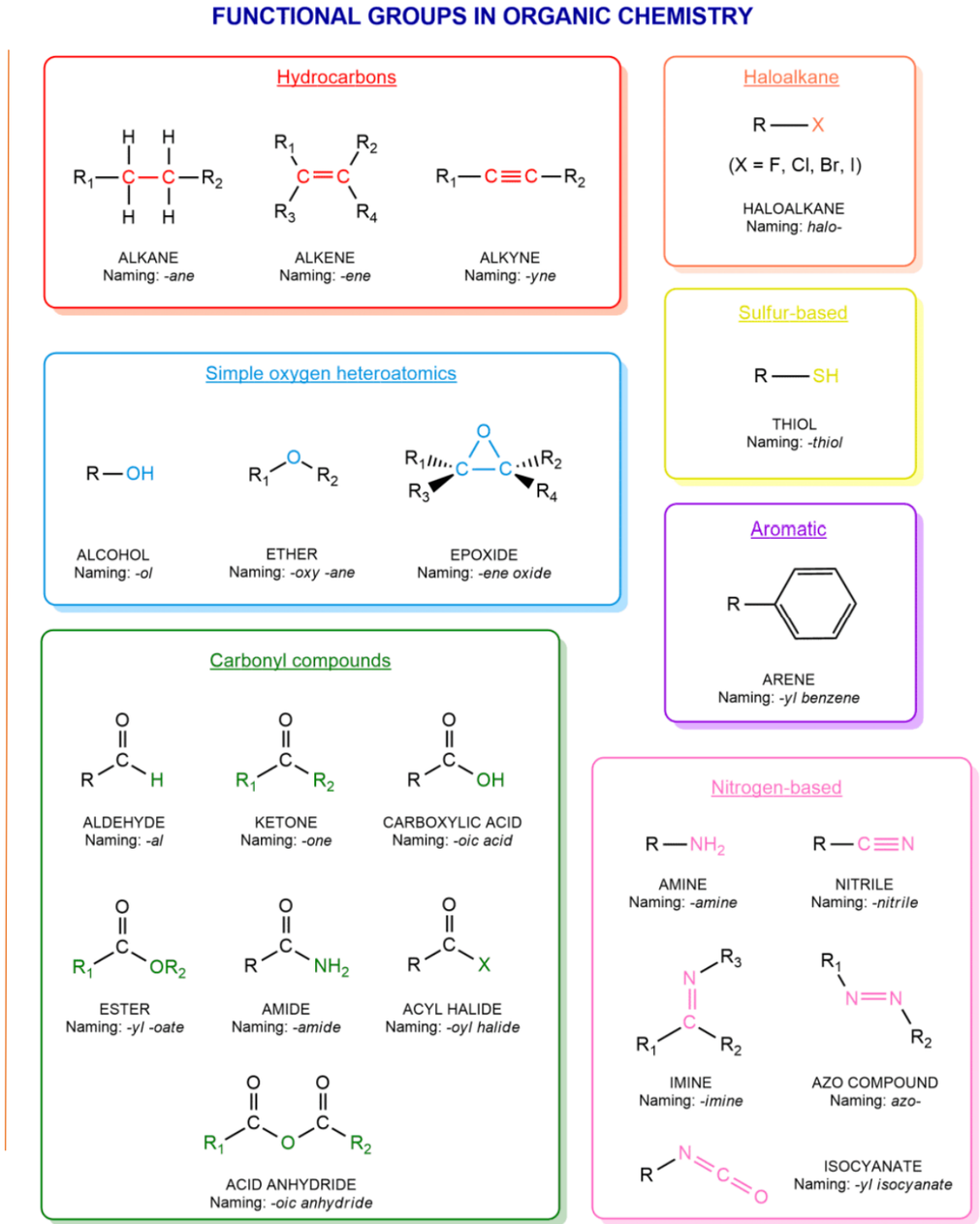
Chapter 2

DRUG DESIGN AND RELATIONSHIP OF FUNCTIONAL GROUPS TO PHARMACOLOGIC ACTIVITY

Contents

RELATIONSHIP BETWEEN MOLECULAR STRUCTURE AND BIOLOGIC ACTIVITY

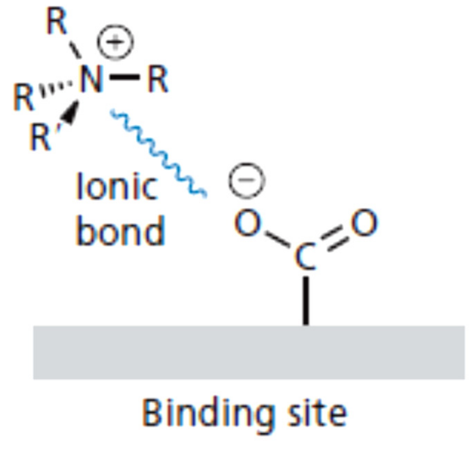
- Molecular structure influences the biological activity of chemical entities and that alterations in structure produce changes in biological action.
- The structure of a molecule, its composition and arrangement of functional groups, determines the type of pharmacologic effect that it possesses as SAR, which is the underlying principle of medicinal chemistry.
- In the quest for better medicinal agents (drugs), it must be determined which functional groups within a specific structure are important for its pharmacologic activity and how these groups can be modified to produce more potent, more selective, and safer compounds.

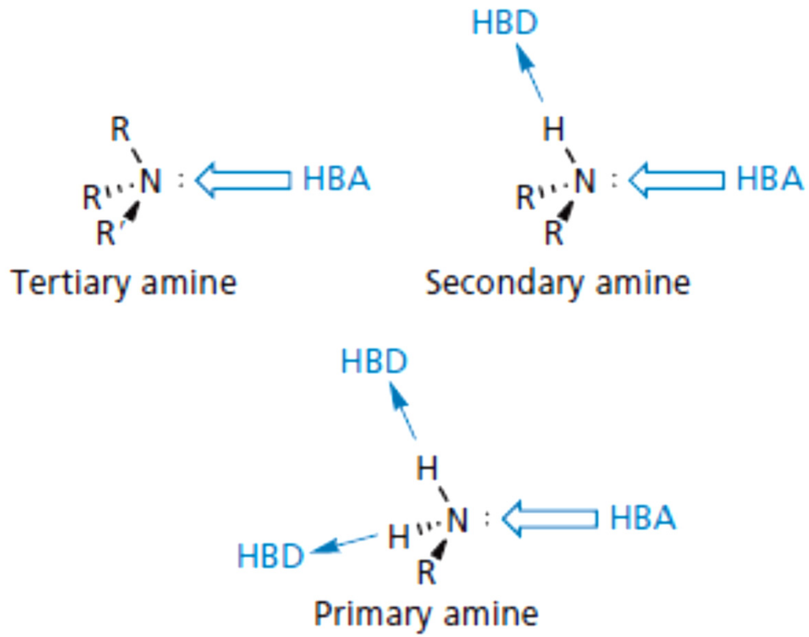


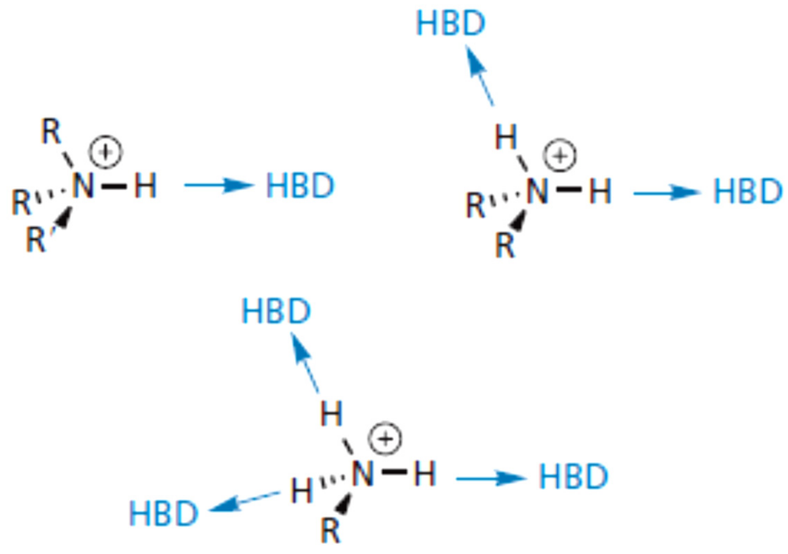
Drug functional groups

Binding role of amines, amides, and quaternary ammonium salts

- The amine group is one of the most important groups responsible for pharmacological activity.
- N's involved in hydrogen bonding, either as a hydrogen bond acceptor or a hydrogen bond donor
- Primary and secondary amines can act as hydrogen bond donors. WHY
- Ionized N cannot act as a hydrogen bond acceptor, but it can still act as a hydrogen bond donor.
- A strong ionic interaction may take place with a carboxylate ion in the binding site

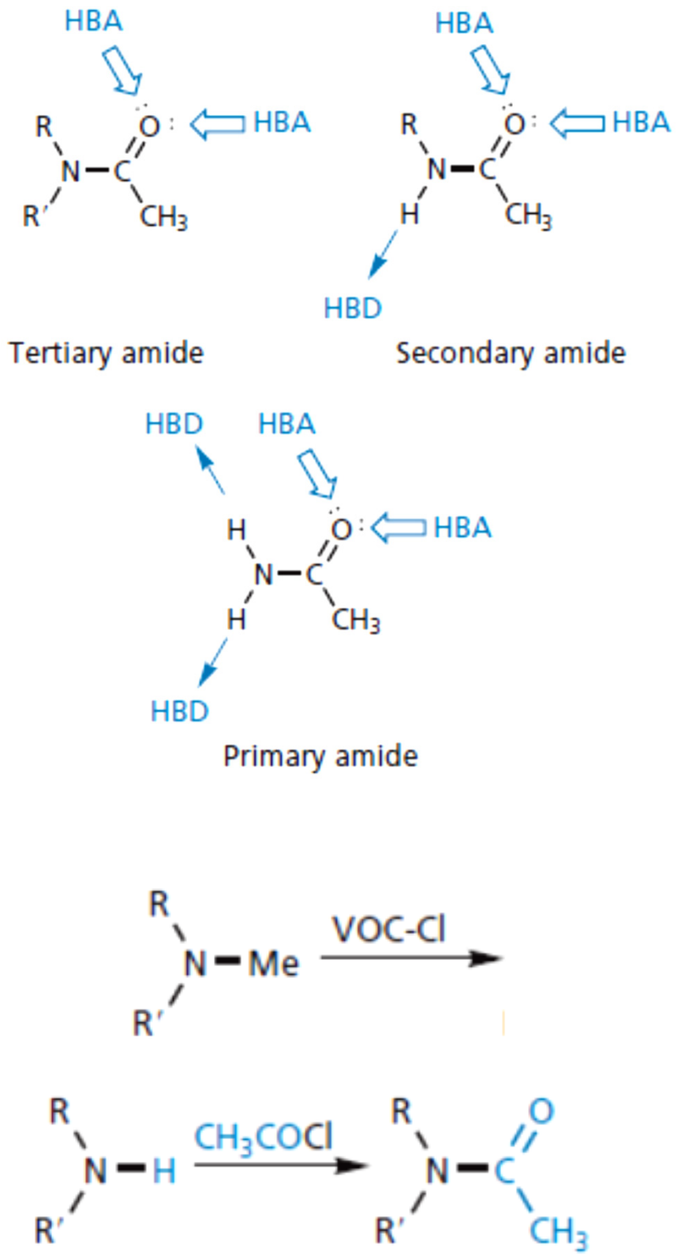






Amide

- Amides are likely to interact with binding sites through hydrogen bonding
- The nitrogen cannot act as a hydrogen bond acceptor because the lone pair interacts with the neighbouring carbonyl group
- Primary and secondary amides have a N–H group, which allows the possibility of this group acting as a hydrogen bond donor.
- The most common type of amide in peptide compounds is the secondary amide.
- It is relatively easy to form secondary and tertiary amides from primary and secondary amines, respectively, tertiary amines cannot be converted directly to amides, but if one of the alkyl groups is a methyl group, it is often possible to remove it with vinyloxycarbonyl chloride (VOC-Cl) to form a secondary amine, which could then be converted to the amide

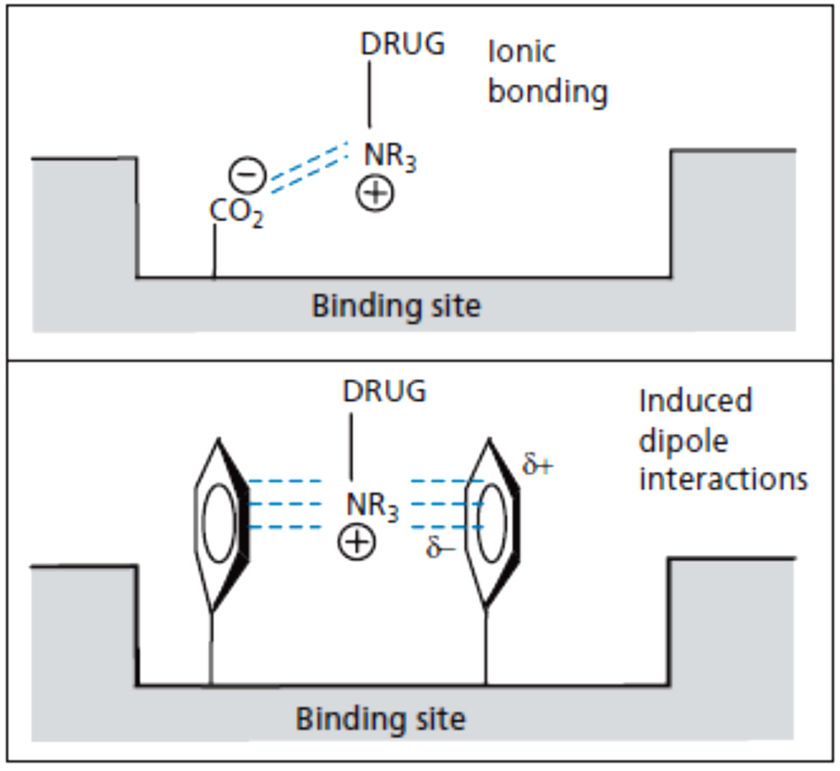


Quaternary ammonium salts

- Quaternary ammonium salts are ionized and can interact with carboxylate groups by ionic interactions

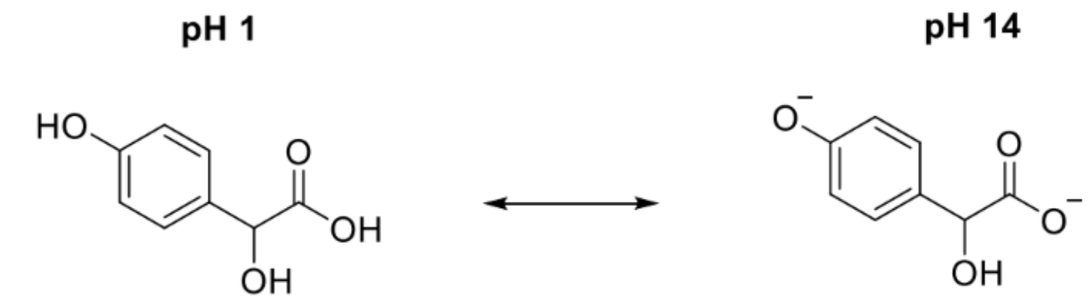
- Another possibility is an induced dipole interaction between the quaternary ammonium ion and any aromatic rings in the binding site.

- The positively charged nitrogen can distort the π electrons of the aromatic ring such that a dipole is induced, whereby the face of the ring is slightly negative and the edges are slightly positive. This allows an interaction between the slightly negative faces of the aromatic rings and the positive charge of the quaternary ammonium ion. This is also known as a π–cation interaction .

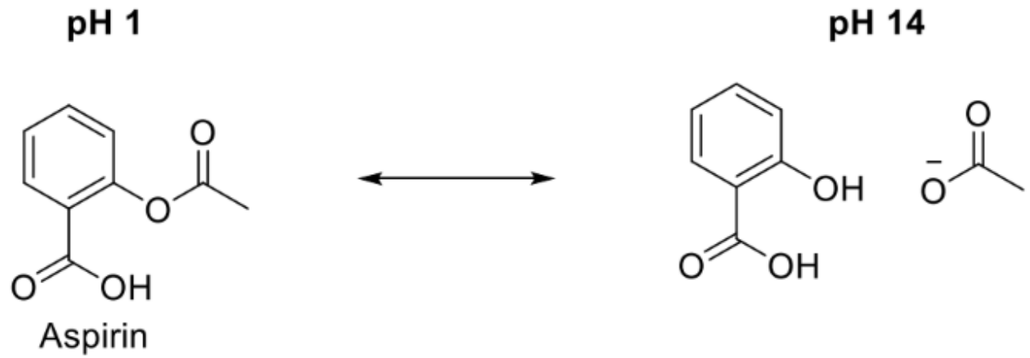


Binding role of alcohols, phenols and esters

- The behavior of oxygen is more straightforward than nitrogen
- Oxygen containing compounds can be neutral or acidic but not basic.
- For example carboxylic acids are acidic, phenols are weakly acidic and alcohols are neutral.
- Oxygen containing groups have another two groups which are neutral:
  - An ether which is neutral and stable to high pH
  - An ester which is neutral but unstable to high pH.

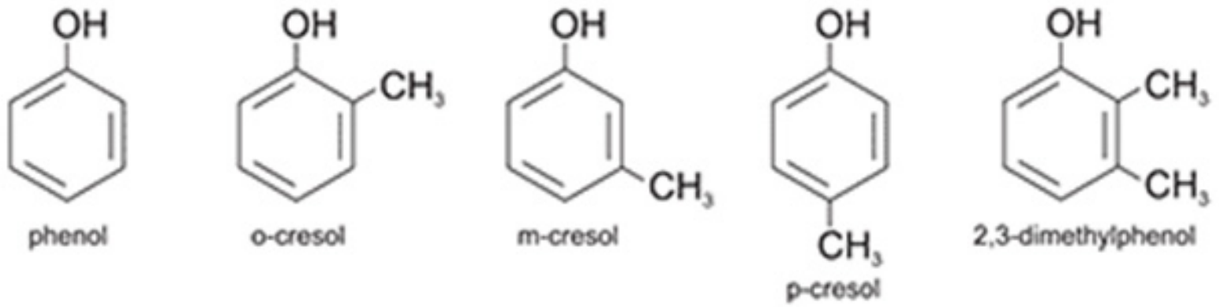


p-hydroxymandelic acid

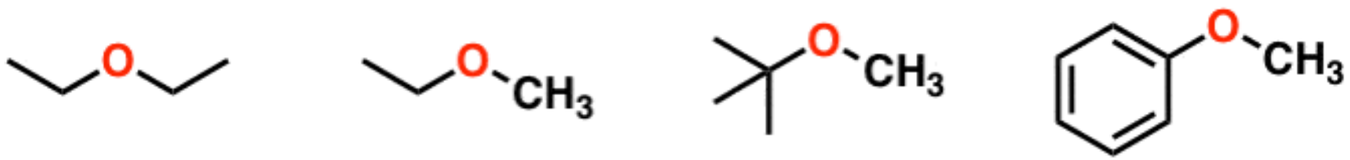


Aspirin

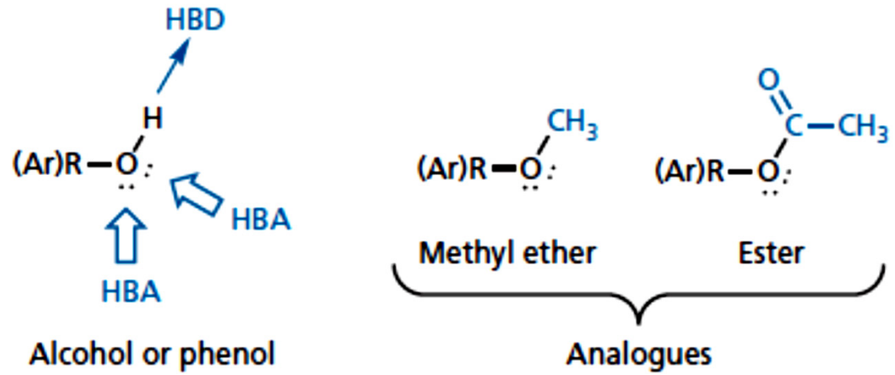
Phenols

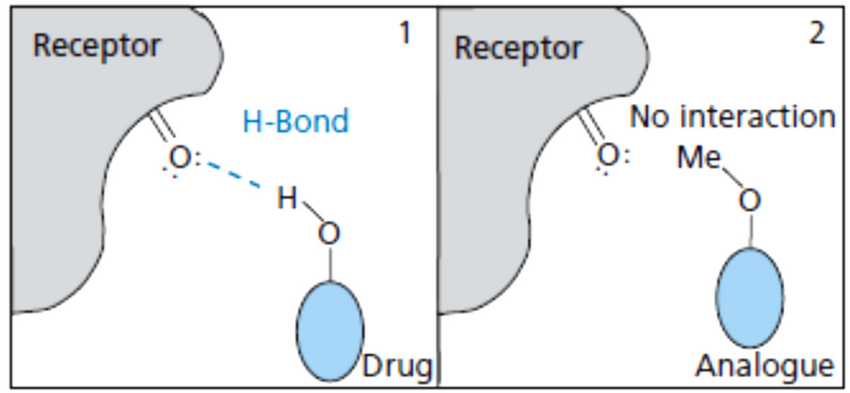


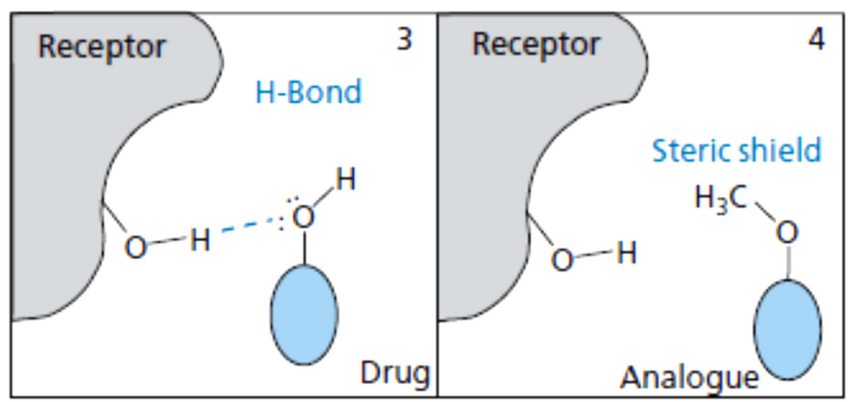
Ether



An ether group (R'OR) might act as a hydrogen bond acceptor through the oxygen atom. This could be tested by increasing the size of the neighbouring alkyl group to see whether it diminishes the ability of the group to take part in hydrogen bonding.

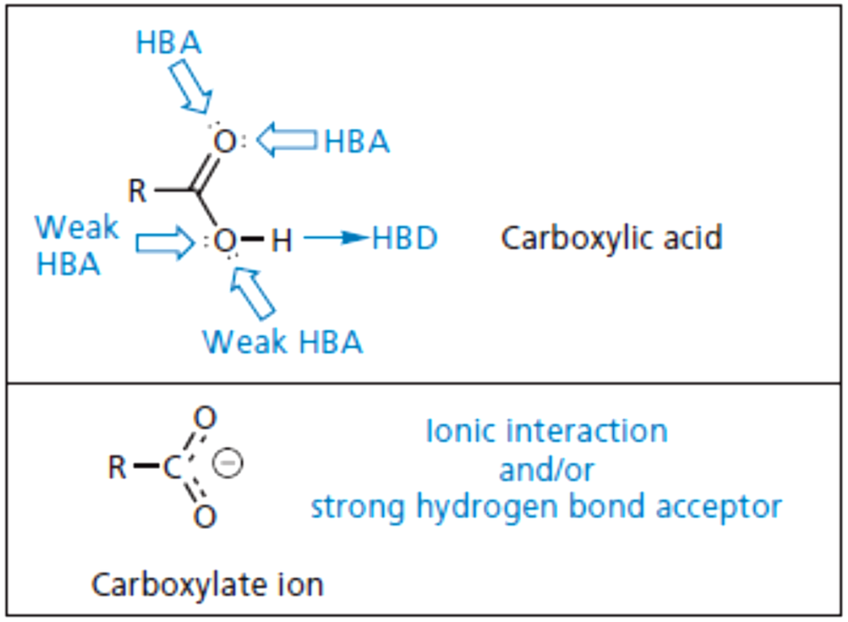


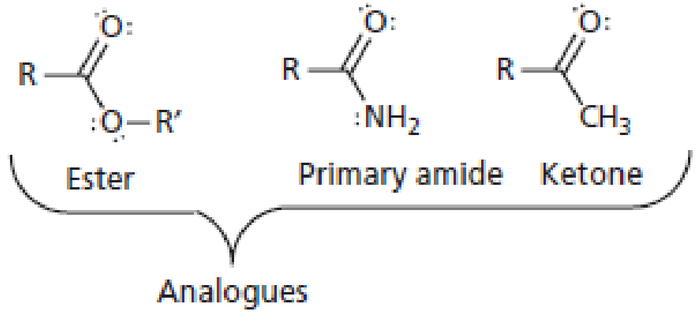




Binding role of carboxylic acids

- It can act as a hydrogen bond acceptor or as a hydrogen bond donor
- It may exist as the carboxylate ion. This allows the possibility of an ionic interaction and/or a strong hydrogen bond where the carboxylate ion acts as the hydrogen bond acceptor.
- Analogues such as esters, primary amides, aldehydes, and ketones

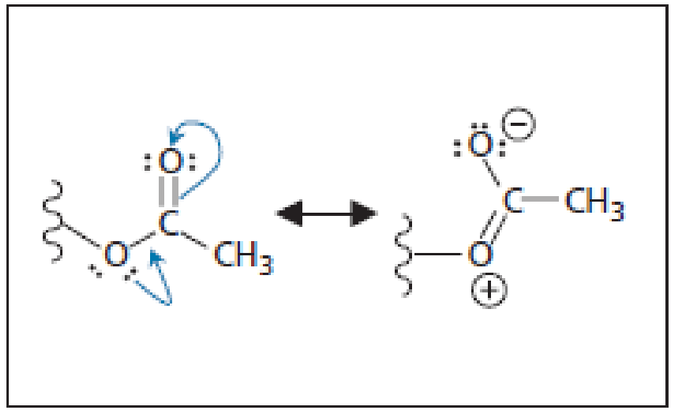


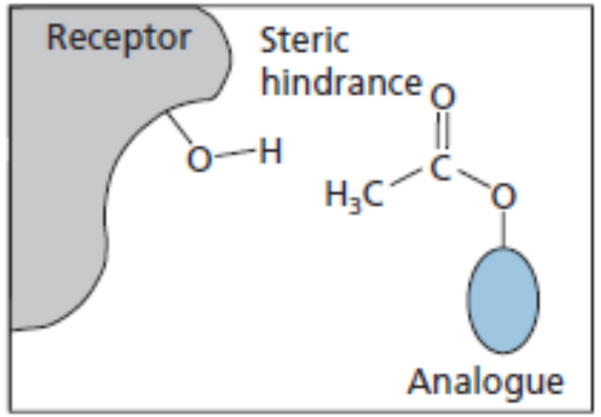


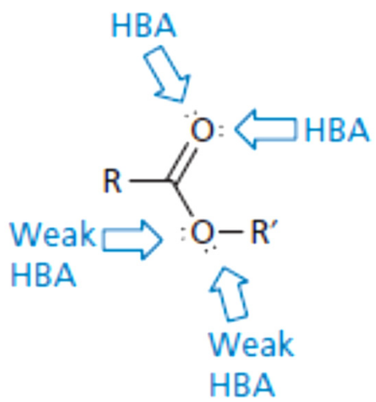
- Ester

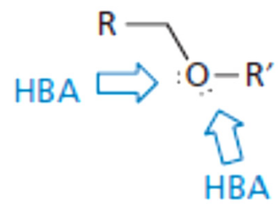
- An ester analogue cannot act as a hydrogen bond donor. It is still the possibility of it acting as a hydrogen bond acceptor, The carbonyl oxygen is more likely to act as the hydrogen bond acceptor than the alkoxy oxygen

- Difference between the electronic properties of an ester and an alcohol. The carboxyl group has a weak pull on the electrons from the neighbouring oxygen, giving the resonance structure





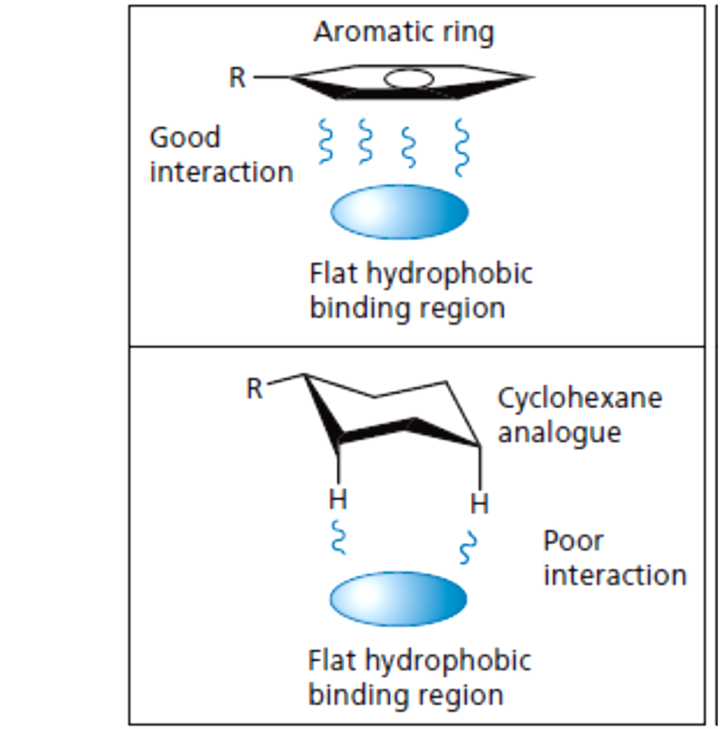


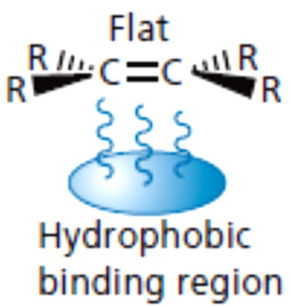


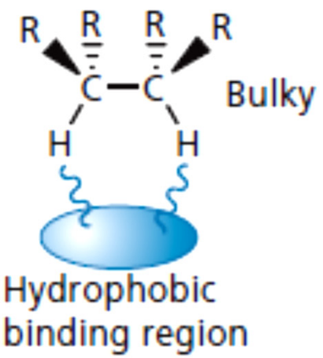
Binding role of aromatic rings and alkenes

- Aromatic rings are planar, hydrophobic structures, commonly involved in van der Waals interactions with flat hydrophobic regions of the binding site.

- Like aromatic rings, alkenes are planar and hydrophobic so they too can interact with hydrophobic regions of the binding site through van der Waals interactions.





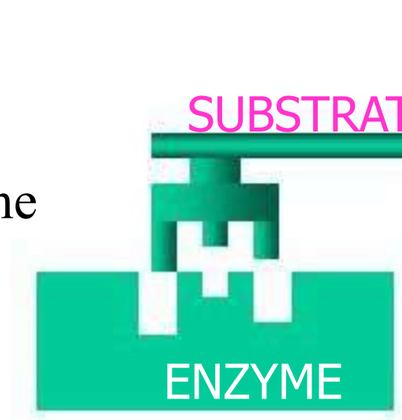


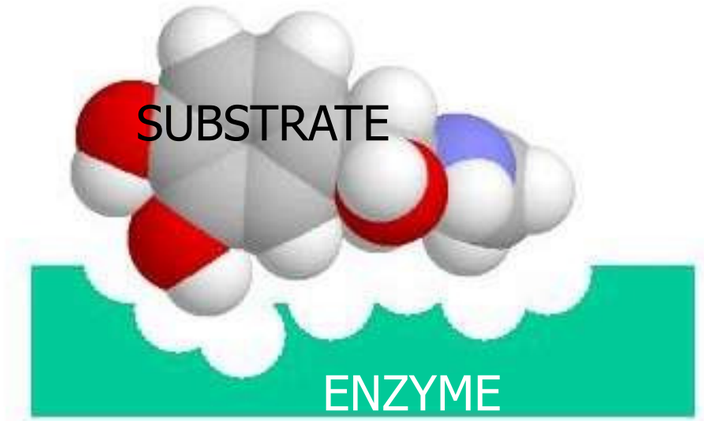
SELECTIVITY OF DRUG ACTION AND DRUG RECEPTORS

Sites of Drug Action

1. Enzyme inhibition

- Enzyme inhibition may be reversible or non-reversible; competitive or non-competitive





2. Drug-Receptor interaction

- A receptor is the specific chemical constituents of the cell with which a drug interacts to produce its pharmacological effects
- This is usually through specific drug receptor sites known to be located on the membrane

3. Non-specific interactions

- Drugs act exclusively by physical means outside of cells
- These sites include external surfaces of skin and gastrointestinal tract.
- Drugs also act outside of cell membranes by chemical interactions
- Neutralization of stomach acid by antacids is a good example

➢ It is important to distinguish between actions of drugs and their effects.

➢ Actions of drugs are the biochemicals, physiological mechanisms by which the chemical produces a response in living organisms.

➢ The effect is the observable consequence of a drug action. For example, the action of penicillin is to interfere with cell wall synthesis in bacteria and the effect is the death of bacteria

WHO IS THE FIRST?

➢ One major problem of pharmacology is that no drug produces a single effect.

✓The primary effect is the desired therapeutic effect.

❖Secondary effects are all other effects beside the desired effect which may be either beneficial (good) or harmful (side effects, bad!!).

➢The biological effects observed after a drug has been administered are the result of interaction between that chemical and some part of the organism. Mechanisms of drug action

Mechanisms of Actions of Drugs

➢The fundamental mechanisms of drug action can be distinguished into following categories

1. Through Enzymes

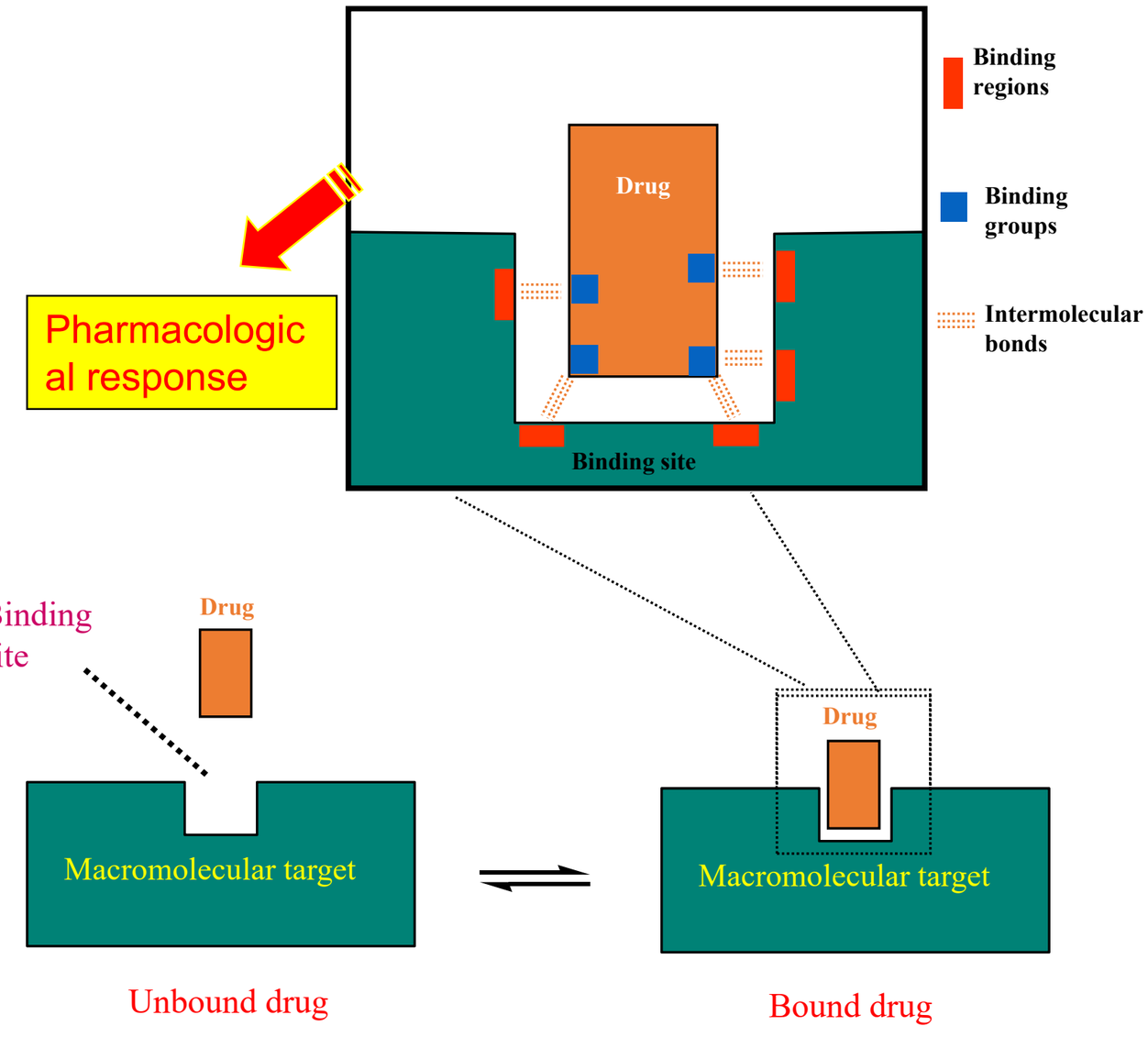
➢ Enzymes are very important targets of drug action because almost all biological reactions are carried out under the influence of enzymes. Drugs may either increase or decrease enzymatic reactions.

❖Ex:

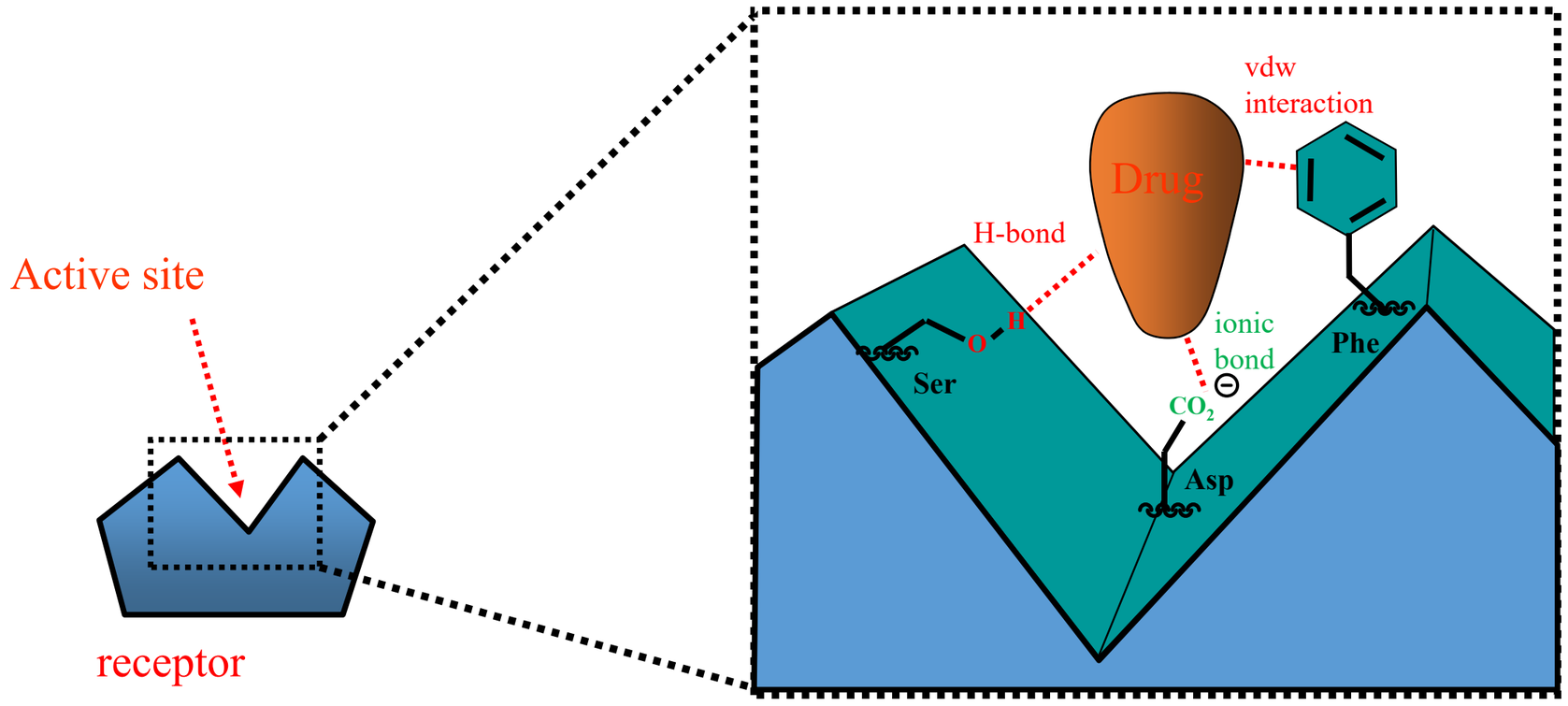
• Physostigmine and neostigmine compete with acetylcholine for cholinesterase

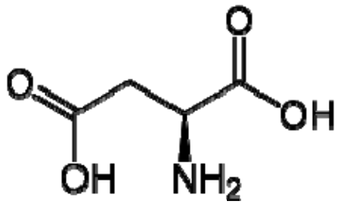
2. Through Receptors

➢ A large number of drugs act through specific macromolecular components of the cell, which regulate critical functions like enzymatic activity, permeability, structural features, template function

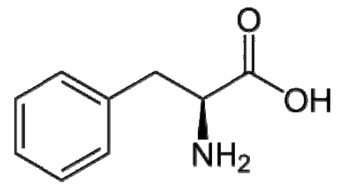


- Receptors/enzymes are proteins, so they are amino acids (Asp, Phe, Ser)
- amino acids contain:
  - ✓ carboxylic acids (ionic interaction)
  - ✓ amines (ionic interaction)
  - ✓ hydroxyl (hydrogen bond)

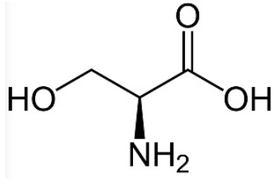




Aspartic acid



Phenylalanine



Serine

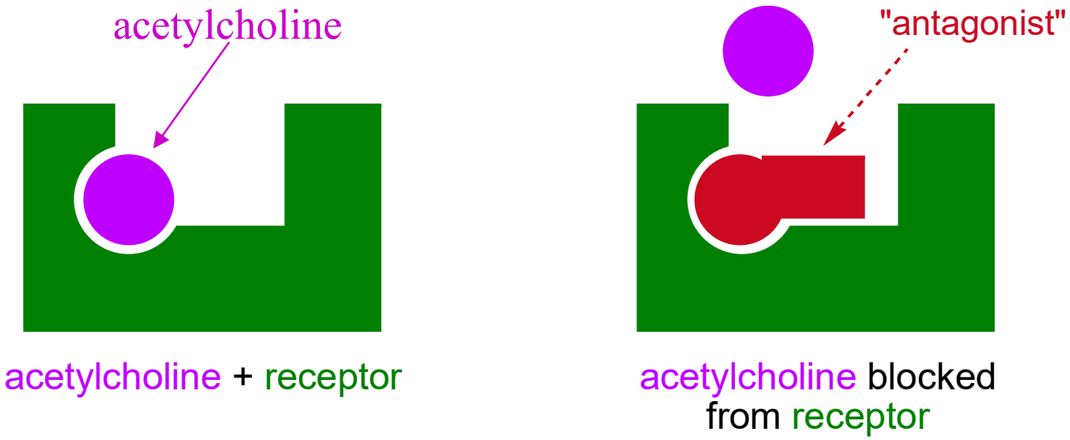
Functional Groups and Pharmacological Activity

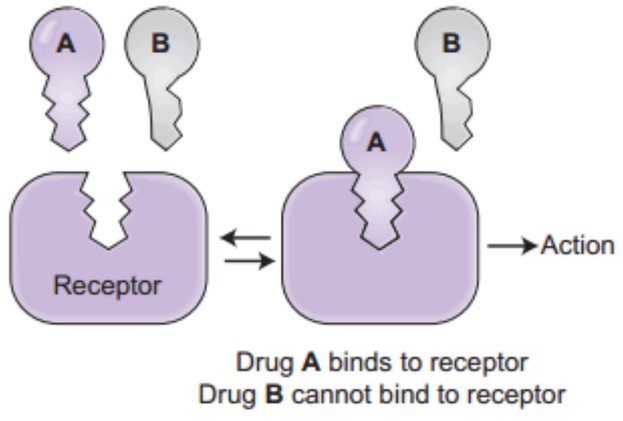
- If acetylcholine interacts with its receptor, then molecules that are structurally similar to acetylcholine would also interact with the receptor

- Antagonists are generally larger in size than the natural substrate

- This is sort of a "lock & key" approach, wherein if you stop acetylcholine from binding to its receptor (by using another molecule that is similar in structure) then you will stop the effect of acetylcholine

  i.e. acetylcholine causes muscles to contract, if you stop it from binding to its receptor, muscles will therefore relax





lock & key

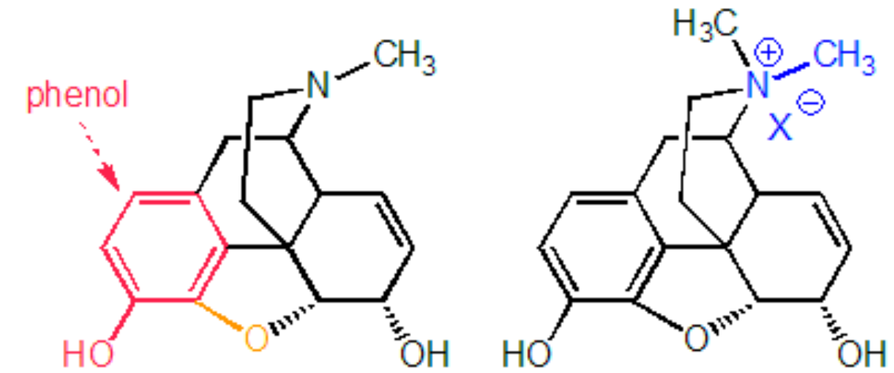
➢ One feature that soon became apparent to the early scientists was that small changes in structure resulted in significant changes in biological activity:

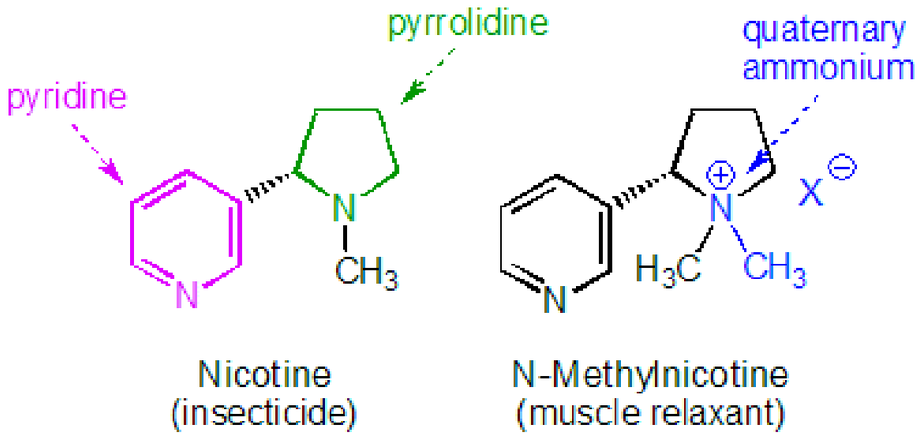
➢ Crum-Brown & Fraser (1869) postulated that "muscle-relaxant activity" was related to quaternary ammonium groups (this was later proved wrong when acetylcholine was discovered)

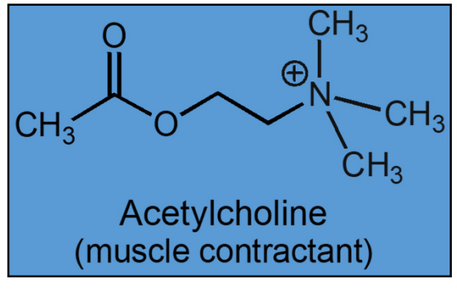
➢ The discovery of acetylcholine (& its activity) prompted questions as to how a given functional group could have two different biological activities

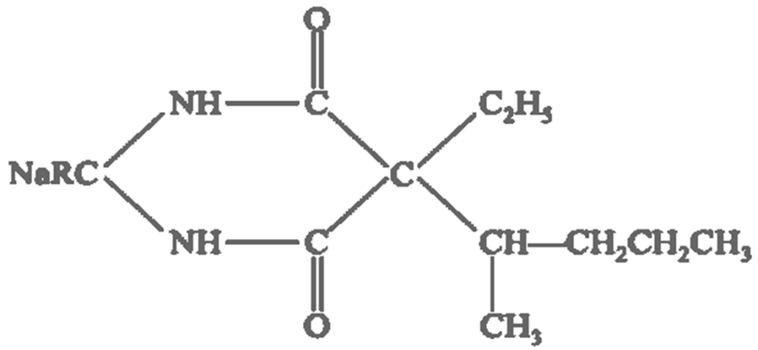
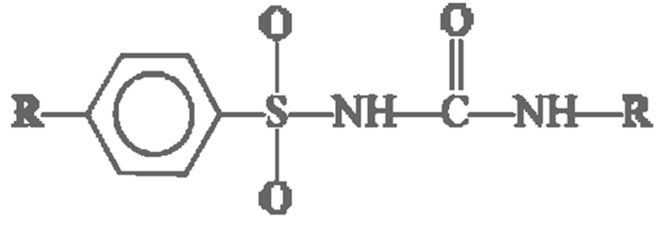
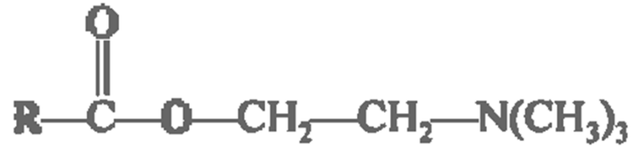
➢ In the early 20th century, scientists speculated that this could be achieved if "drug receptors" were present

If acetylcholine interacts with its receptor, then molecules that are structurally similar to acetylcholine would also interact with the receptor







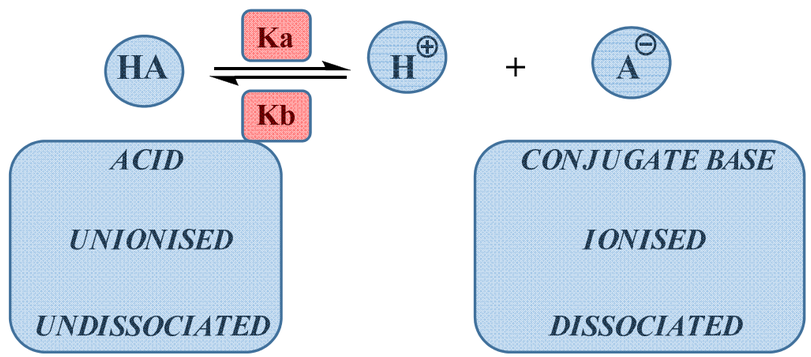
Structure	Biological Activity	Pharmacological Classification
(*a*) 		
R = O, (pentobarbitone sodium)	Short-acting	Hypnotic
R = S, (thiopental sodium)	Ultra-shortacting	
(*b*) 		
$R = CH_3$, $R' = C_4H_9$ (tolbutamide)	Short-acting	Hypoglycemic
R = Cl, $R' = C_3H_7$ (chloropropamide)	Long-acting	
(*c*) 		
$R = CH_3$ (acetylcholine)	Short-acting	Cholinergic
$R = NH_2$ (carbamylcholine)	Long-acting	

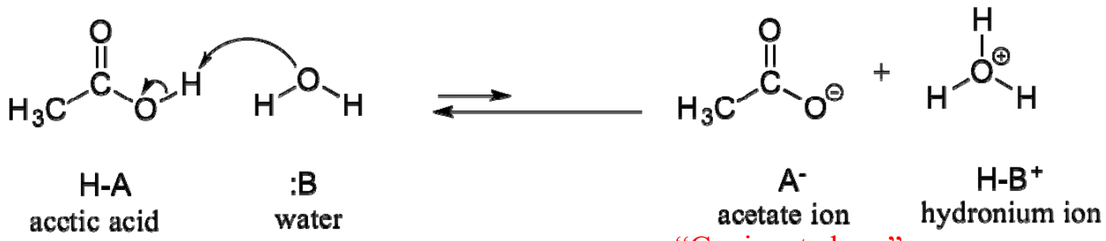
➢ Acid–Base Properties

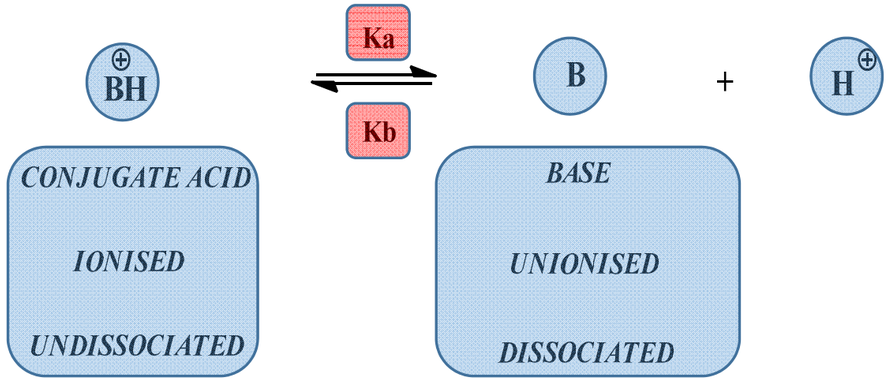
- The human body is 70 to 75% water, which amounts to approximately 51 to 55 L of water for a 160-lb (73-kg) individual.
- When considering the solution behavior of a drug within the body, we are dealing with a dilute solution for which the acid–base theory.
- This is a very important concept in medicinal chemistry, because the acid–base properties of drug molecules have a direct effect on absorption, excretion, and compatibility with other drugs in solution.

- Acid is a substance that can dissociate to give H^+ and a negative ion (anion) which is called a conjugate base

- Bases can accept a proton to form the positively charged cation (conjugate acid of the base)



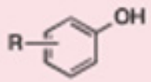
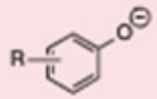
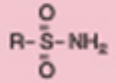
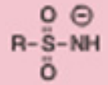
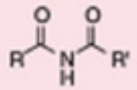
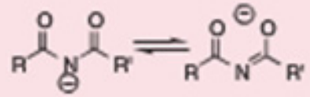
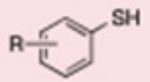
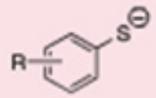
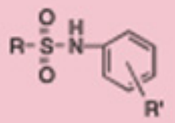
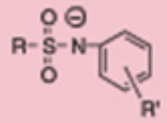
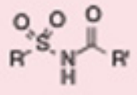
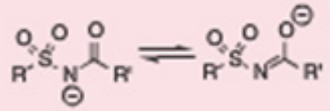
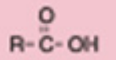
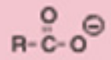
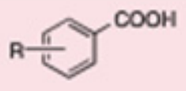
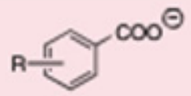
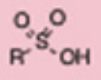
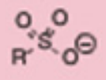




$$CH_3NH_2 + H_2O \rightleftharpoons CH_3NH_3^{\oplus} + {}^{\ominus}OH$$

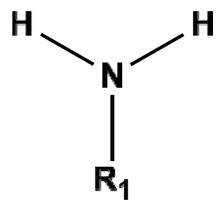
Base (methylamine) | Acid (water) | Conjugate Acid (methylammionium ion) | Conjugate Base (hydroxide ion)

- Ionized form of the acid: when an acidic functional group **loses its proton** (dissociation), it is left with an extra electron and becomes **negatively** charged.
- Ability of the ionized functional group to participate in an ion-dipole interaction with water enhances its water **solubility**.
- Many functional groups behave as acids, were the ability to recognize these functional groups and their relative acid strengths helps to predict absorption, distribution, excretion, and potential incompatibilities between drugs.

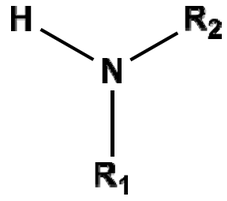
Acids (pKa)			Conjugate Base
Phenol (9-11)			Phenolate
Sulfonamide (9-10)			Sulfonamidate
Imide (9-10)			Imidate
Alkylthiol (10-11)			Thiolate
Thiophenol (9-10)			Thiophenolate
N-Arylsulfonamide (6-7)			N-Arylsulfonamidate
Sulfonimide (5-6)			Sulfonimidate
Alkylcarboxylic acid (5-6)			Alkylcarboxylate
Arylcarboxylic acid (4-5)			Arylcarboxylate
Sulfonic acid (0-1)			Sulfonate

- When a ionized base: the basic functional group is converted to the corresponding conjugate acid.
- The functional group becomes positively charged due to the extra proton.
- Most drugs that contain basic functional groups contain primary, secondary, and tertiary amines or imino amines, such as guanidines and amidines.

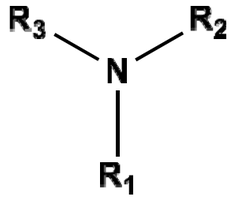
Base		Conjugate Acid (pKa)
Arylamine		Arylammonium (5-6)
Aromatic amine		Aromatic ammonium (4-5)
Imine		Iminium (3-4)
Alkylamines		Alkylammonium (2° 10-11) (1° 9-10)
Amidine		Amidinium (10-11)
Guanidine		Guanidinium (12-13)



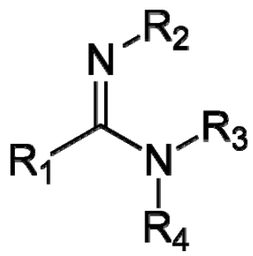
1° amine



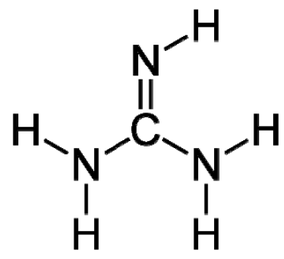
2° amine



3° amine

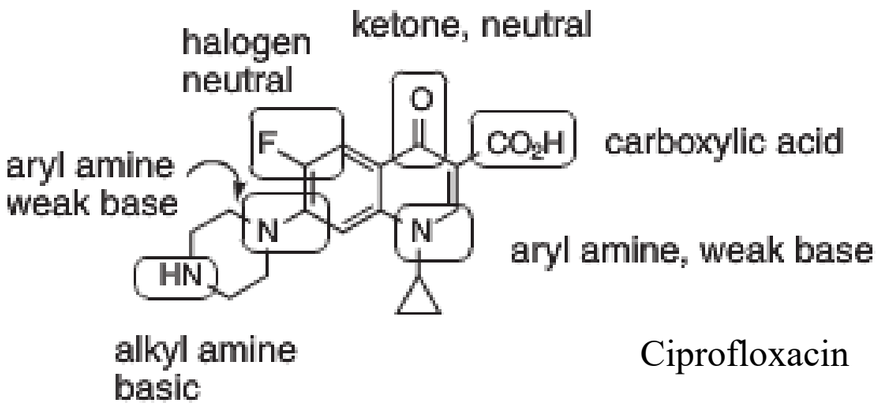


Amidine



Guanidine

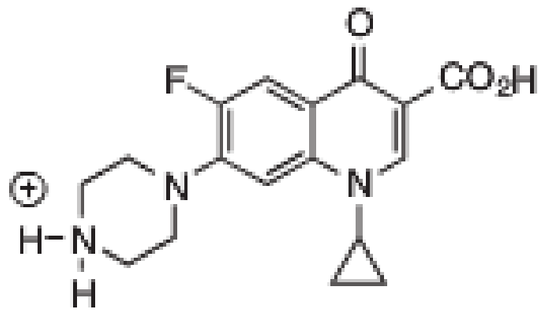
- Some drugs have both acidic and basic functional groups, and therefore can act as a base, an acid, or amphoteric (= both acidic & basic properties)



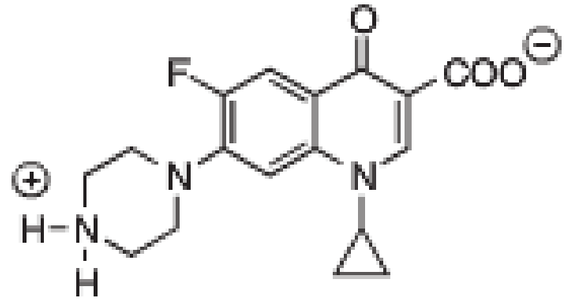
Ciprofloxacin

Contains a secondary alkylamine, two tertiary arylamines (aniline-like amines), and a carboxylic acid. The two arylamines are weakly basic and, therefore, do not contribute significantly to the acid–base properties of ciprofloxacin.

Depending on the pH of the physiologic environment, this molecule will either accept a proton (secondary alkylamine), donate a proton (carboxylic acid), or both. Thus, it is described as amphoteric (both acidic and basic) in nature.



Stomach (pH 1.0–3.5)



Colon (pH 5.6–7)

▪ Relative Acid Strength (pKa)

- Strong acids and bases completely donate (dissociate) or accept a proton in aqueous solution to produce their respective conjugate bases and acids, undergo 100% dissociation in water, with the equilibrium between the ionized and un-ionized forms shifted completely to the right (ionized).

Strong

$$HCl + H_2O \rightarrow H^+ + Cl^- + H_2O$$

$$NaOH + H_2O \rightarrow Na^+ + OH^- + H_2O$$

Weak

Acetic acid — Acetate

$$H_2O() + NH_3(g) \rightleftharpoons NH_4^+(aq) + OH^-(aq)$$

6 Strong Acids		6 Strong Bases	
$HClO_4$	perchloric acid	LiOH	lithium hydroxide
HCl	hydrochloric acid	NaOH	sodium hydroxide
HBr	hydrobromic acid	KOH	potassium hydroxide
HI	hydroiodic acid	$Ca(OH)_2$	calcium hydroxide
HNO_3	nitric acid	$Sr(OH)_2$	strontium hydroxide
H_2SO_4	sulfuric acid	$Ba(OH)_2$	barium hydroxide

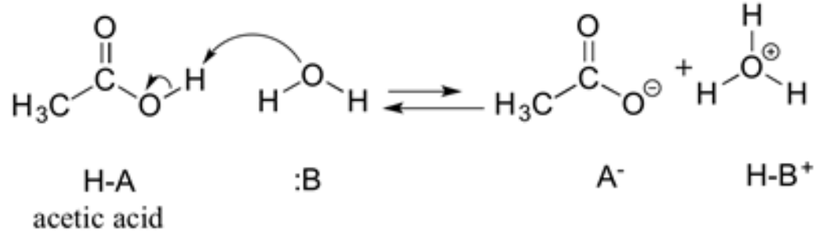
Predicting the Degree of Ionization of a Molecule

- To know if acidic and/or basic functional groups predominantly ionized or un-ionized at a given pH, an equation (Henderson-Hasselbalch) can be used to calculate the percent ionization of a compound at a given pH.

- This equation relates a constant pKa, to the ratio of the acidic form of a functional group to its conjugate base form for acids, and for a base the pKa refers to the conjugate acid or ionized form of the compound.

- For example when acetic acid (pKa 4.76) is in solution at pH 4.76. The Henderson-Hasselbalch equation can be written as follows:

$$pK_a = pH + \log \frac{[\text{acid form}]}{[\text{base form}]}$$



$$pK_a = 4.76 + \log \frac{[CH_3COO^-]}{[CH_3COOH]}$$

When an acid or base is 50% ionised: pH = pKa

•From this relationship for acetic acid it is possible to determine the degree of ionisation of acetic acid at a given pH.

Thus when the pH = 4.76 then:

$$pK_a = 4.76 + \log \frac{[CH_3COO^-]}{[CH_3COOH]}$$

$$4.76 = 4.76 + \log \frac{[CH_3COO^-]}{[CH_3COOH]}$$

$$\log \frac{[CH_3COO^-]}{[CH_3COOH]} = 0 \qquad \text{Then,} \quad \frac{[CH_3COO^-]}{[CH_3COOH]} = 10^0 = 1$$

Acetic acid is 50% ionised at pH 4.76

•When ammonia (pKa 9.25) is in a solution with at pH 9.25. Henderson- Hasselbalch equation can be written as follows:

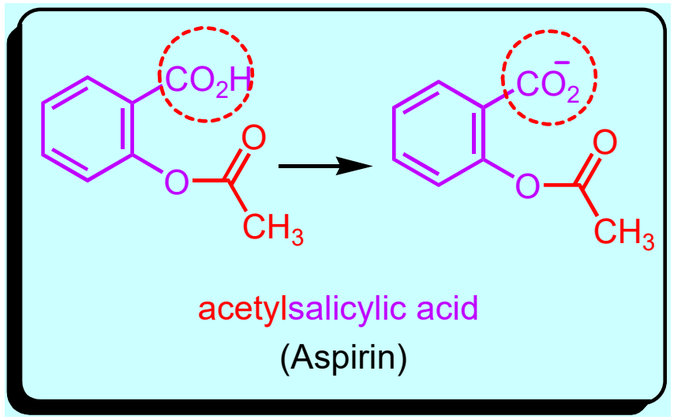
$$9.25 = 9.25 + \log \frac{[NH_3]}{[NH_4^+]}$$

$$\log \frac{[NH_3]}{[NH_4^+]} = 0 \text{ , then} \qquad \frac{[NH_3]}{[NH_4^+]} = 10^0 = 1$$

Ammonia is 50% ionised at pH 9.25.

An alternative way of writing the expression giving the % ionization for an acid or base of a particular pKa value at a particular pH value is:

- pK_a of aspirin (acetylsalicylic acid) is 3.5 and the Physiological pH = 7.4



acetylsalicylic acid
(Aspirin)

$$\% \text{ ionisation} = \frac{100}{1+10^{(3.5-7.4)}} = \frac{100}{1+10^{(-3.9)}}$$
$$= \frac{100}{1+0.000126} = \frac{100}{1.000126}$$
$$= 99.99\%$$

Rule of Thumb (acids)

Weak bases	Weak acids	
$pH = pK_a$	$pH = pK_a$	compound ~ 50% ionised
$pH = pK_a - 1$	$pH = pK_a + 1$	compound ~ 90% ionised
$pH = pK_a - 2$	$pH = pK_a + 2$	compound ~ 99% ionised
$pH = pK_a - 3$	$pH = pK_a + 3$	compound ~ 99.9% ionised
$pH = pK_a - 4$	$pH = pK_a + 4$	compound ~ 99.99% ionised

- pK_a of aspirin is 3.5
- Physiological pH = 7.4

→ • $pH = pK_a + 4$

→ %ionisation= 99.99%

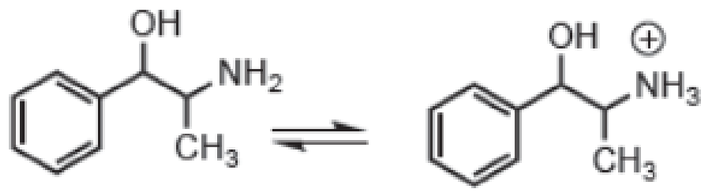
- pK_a of phenylpropanolamine is 9.4
- Physiological pH = 7.4

→ • $pH = pK_a - 2$

→ %ionisation= 99% ionised

For Base:

$$\% \text{ Ionisation} = \frac{10^{pKa - pH}}{1 + 10^{pKa - pH}} \times 100$$



Base form

Conjugate acid form
pK_a 9.4

What is the % ionization of phenylpropanolamine at pH 7.4?

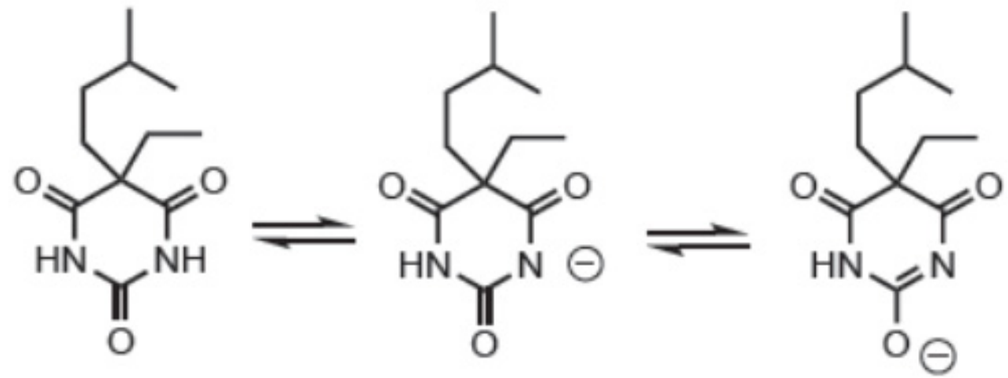
$$9.4 = 7.4 + \log \frac{[acid]}{[base]} \quad , \quad 2.0 = \log \frac{[acid]}{[base]}$$

$$10^2 = \frac{[acid]}{[base]} = \frac{100}{1}$$

$$\% \text{ ionization} = \frac{100 \times 100}{101} = 99\%$$

For Acid:

$$\% \text{ Ionisation} = \frac{10^{pH - pKa}}{1 + 10^{pH - pKa}} \times 100$$



Acid form
pK_a 8.0

Conjugate base

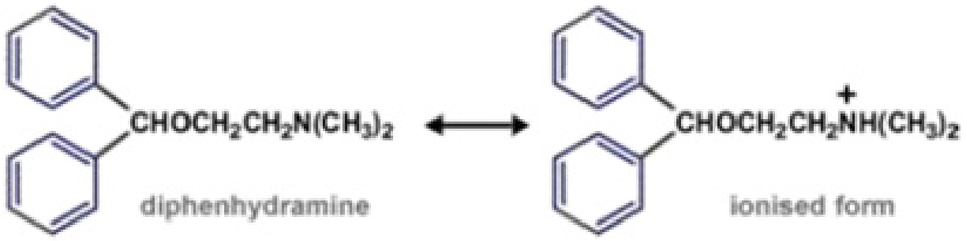
At a pH of 7.4, what is the percent ionization of amobarbital?

$$8.0 = 7.4 + \log \frac{[acid]}{[base]} \quad , \quad 0.6 = \log \frac{[acid]}{[base]}$$

$$10^{0.6} = \frac{[acid]}{[base]} = \frac{3.98}{1}$$

$$\% \text{ acid form} = \frac{3.98 \times 100}{4.98} = 79.9\%$$

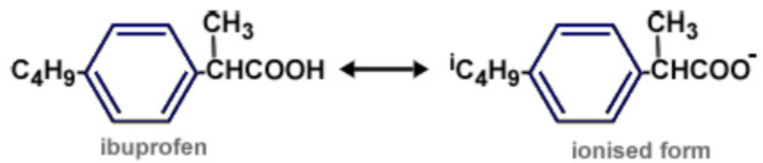
Diphenhydramine This drug contains one basic nitrogen and has a pKa of 9 and at pH 7.0 its % ionisation can be calculated as follows



$$\% \text{ Ionisation diphenhydramine} = \frac{10^{9.0 - 7.0}}{1 + 10^{9.0 - 7.0}} \times 100$$

$$= \frac{10^{2.0}}{1 + 10^{2.0}} \times 100 = \frac{100}{101} \times 100 = 99.0\%$$

Ibuprofen This drug contains one acidic group and has a pKa of 4.4 and pH 7.0 its % ionization can be calculated as follows



$$\% \text{ Ionisation ibuprofen} = \frac{10^{7.0 - 4.4}}{1 + 10^{7.0 - 4.4}} \times 100$$

$$= \frac{10^{2.6}}{1 + 10^{2.6}} \times 100 = \frac{398}{399} \times 100 = 99.8\%$$

➢ Water Solubility of Drugs

❖ Importance of solubility:

1. Formulation of the drug in an appropriate dosage form
2. Affects the routes of administration that are available, as well as its absorption, distribution, and elimination.
3. Bio-disposition: Disposition of OMAs in the living system after administration (absorption, distribution, metabolism, and excretion).
4. Drug must be in solution form to interact with receptors

The solubility expression: in terms of its affinity/philicity or repulsion/phobicity for either an aqueous (hydro) or lipid (lipo) solvent.

♣hydrophilic.....water loving
♣lipophobic.....lipid hating
♣lipophilic.....lipid loving
♣hydrophobic.....water hating

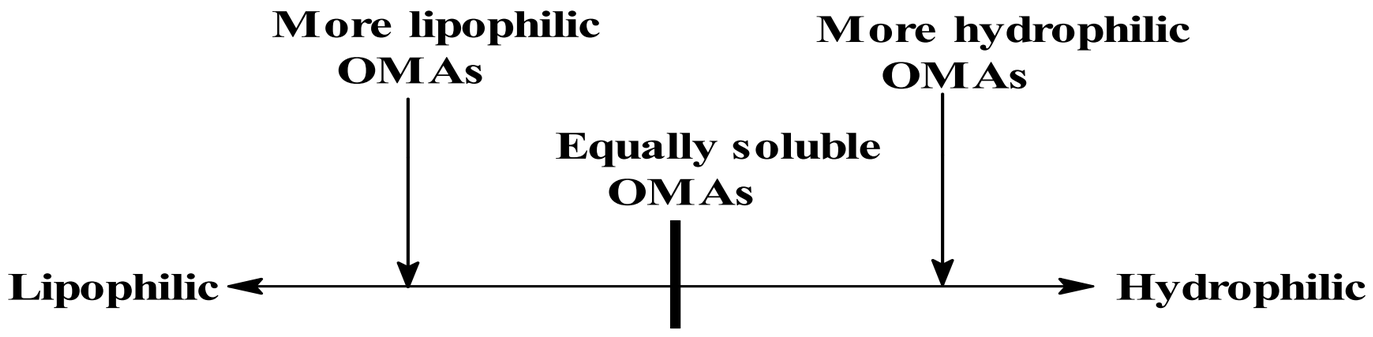
- Majority of OMAs possess balanced solubility (have some degree of solubility in both aqueous and lipid media).

- Because there is a need for OMAs to move through both aqueous (plasma, extracellular fluid, cytoplasm, etc.) and lipid media (biologic membranes) in the biological system.

- In order for a chemical compound to dissolve in a particular solvent/medium the compound must establish attractive forces between itself and molecules of the solvent.

- Solubility of OMAs should be viewed as being on a continuum between high lipophilicity on one end of the spectrum and high hydrophilicity on the other.

- The most important intermolecular attractive forces (bonds) that are involved in the solubilization process are:



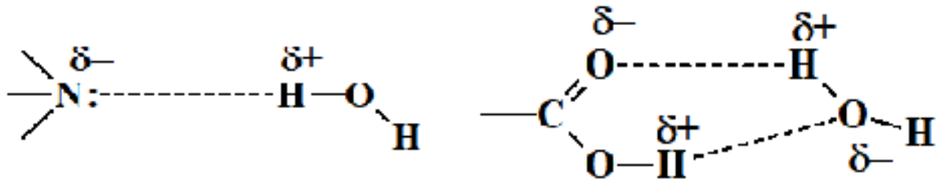
❖ **The most important intermolecular attractive forces (bonds) that are involved in the solubilization process are:**

1. Van der Waals Attraction

- weakest intermolecular force (0.5-1.0 kcal/mole)
- electrostatic
- occurs between nonpolar groups (e.g. hydrocarbons)
- highly distance and temperature dependent

2. Dipole-Dipole Bonding

- stronger (1.0 to 10 kcal/mole)
- occurs electrostatically between electron deficient and electron excessive /rich atoms (dipoles)
- hydrogen bonding is a specific example of this bonding and serves as a prime contributor to hydrophilicity

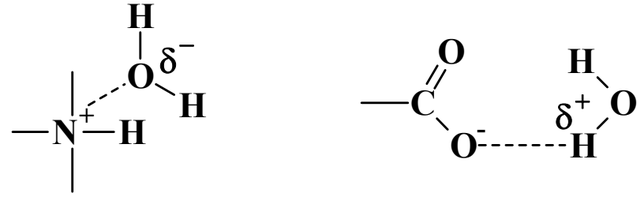


3.Ionic Bonding

- electrostatic attraction between cations and anions
- common in inorganic compounds and salts of organic molecules
- relatively strong (5 kcal/mole)

4.Ion-Dipole Bonding

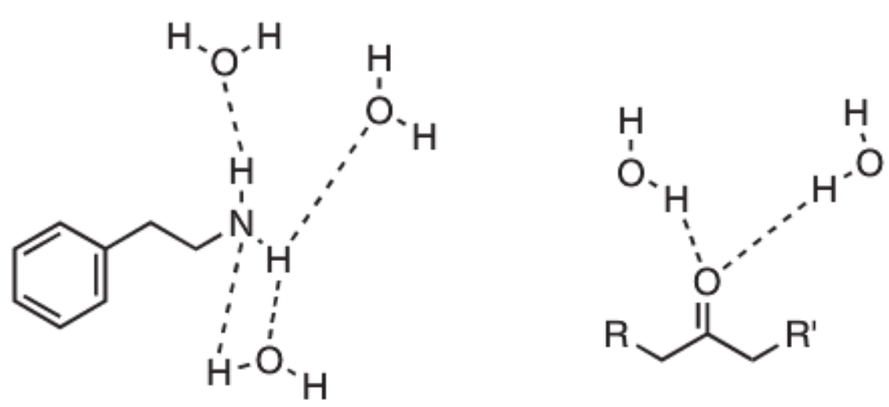
- electrostatic between a cation/anion and a dipole
- relatively strong (1-5 kcal/mole)
- low temperature and distance dependence
- important attraction between OMAs and H_2O



5. Hydrogen Bonds

- Hydrogen bonds are a special case of what are usually referred to as dipole–dipole interactions, one atom has a partial negative charge, and one atom has a partial positive charge. The atom with a partial negative charge has higher electron density than the other atom. When the positive end of the dipole is a hydrogen atom, this interaction is referred to as a "**hydrogen bond" (or H-bond)**.

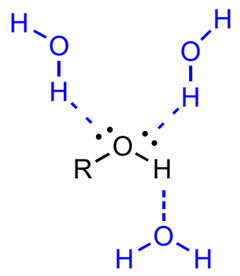
- Each functional group capable of donating or accepting a hydrogen bond contributes to the overall water solubility of the compound and increases the hydrophilic (water-loving) nature of the molecule. Conversely, functional groups that cannot form hydrogen bonds do not enhance hydrophilicity and will contribute to the hydrophobic (water-fearing) nature of the molecule.

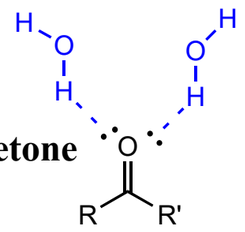


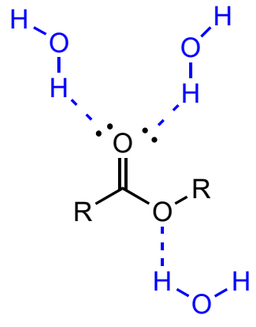
- Hydrogen bonding: more H-bonds => ↑ solubility

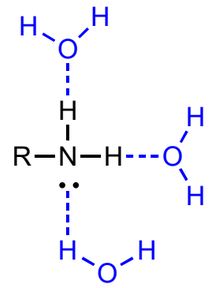
The more H-bonds possible - the more water sol.

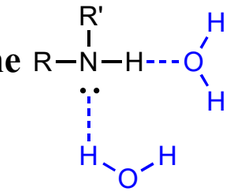
Only oxygen and nitrogen atoms contribute significantly to the dipole, and we will therefore concern ourselves only with the hydrogen-bonding capability (specifically as hydrogen bond donors) of functional groups that contain a bond between oxygen and hydrogen atoms (e.g., alcohols) and functional groups that contain a bond between nitrogen and hydrogen atoms (e.g., primary and secondary amines and amides) (e.g., NH and CONH groups).

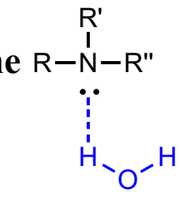
Alchohol  **3 H-Bonds**

Aldehyde / ketone  **2 H-Bonds**

Ester  **3 H-Bonds**

Primary amine  **3 H-Bonds**

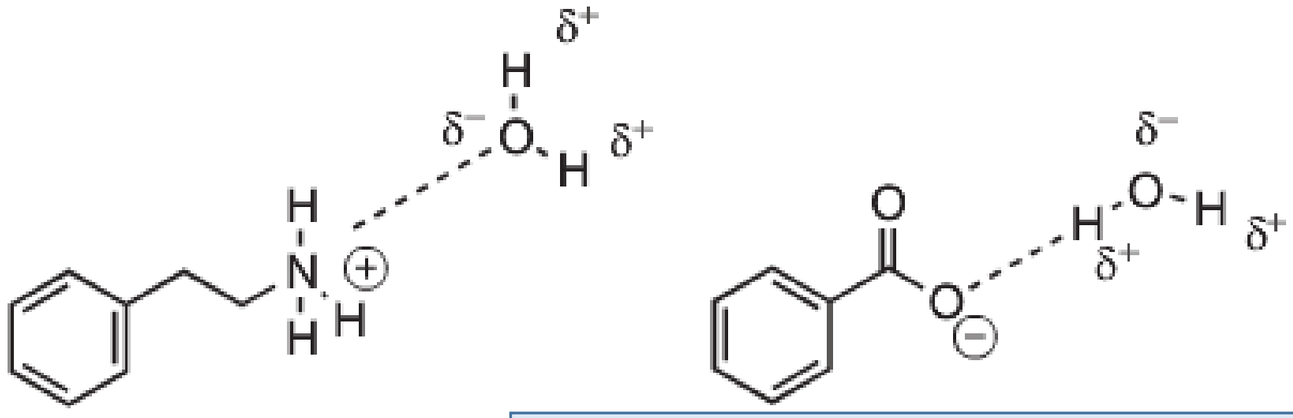
Secondary amine  **2 H-Bonds**

Secondary amine  **1 H-Bonds**

❖ Ionization “ion–dipole interaction”

- Plays an important role in determining water solubility: the ion–dipole interaction, this type of interaction can occur with organic salts.

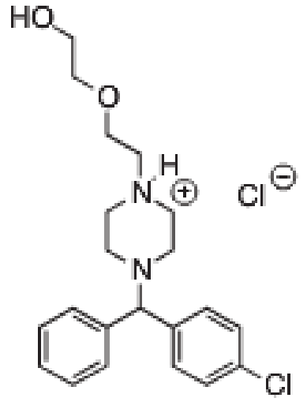
- Occur between either a cation and the partially negatively charged atom found in a permanent dipole (e.g., the oxygen atom in water) or an anion and the partially positively charged atom found in a permanent dipole (e.g., the hydrogen atoms in water)



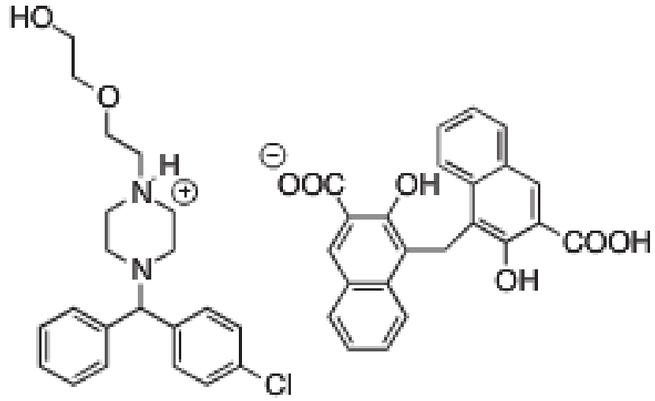
- Ionisation: dissociable ions => ↑ solubility

Drugs and their salt forms

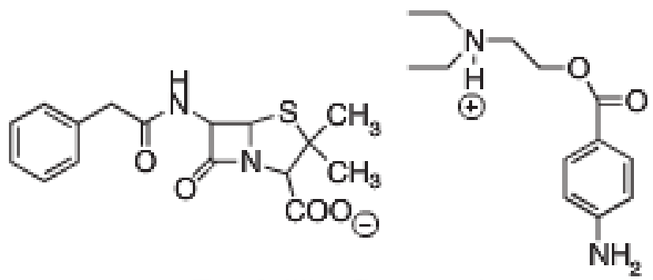
- Organic salts are composed of a drug molecule in its ionized form and an oppositely charged counterion. For example, the salt of a carboxylic acid is composed of the carboxylate anion (ionized form of the functional group) and a positively charged ion (e.g., Na+) and the salt of a secondary amine is composed of the ammonium cation (ionized form of the functional group and a negatively charged ion; e.g., Cl−).
- Not all organic salts are very water soluble. The cation and anion must be able to separate and interact independently with water molecules. Highly dissociable salts are those formed from strong acids with strong bases (NaCl), weak acids with strong bases (e.g., sodium phenobarbital), or strong acids with weak bases (e.g., atropine sulfate).
- In general, low molecular weight salts are water soluble, and high molecular weight salts are water insoluble.



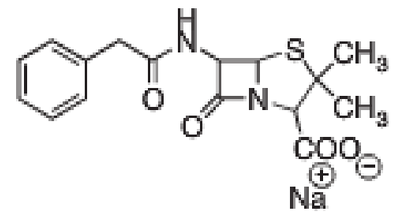
Hydroxyzine hydrochloride
(1g/mL)



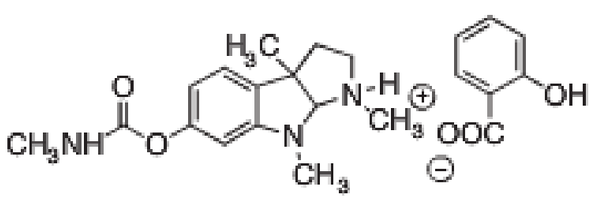
Hydroxyzine pamoate
(1g/1000 mL)



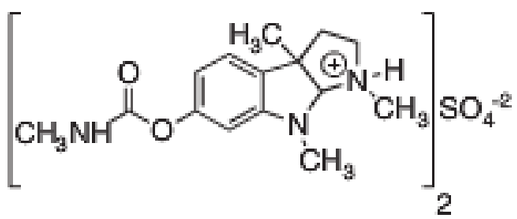
Penicillin G procaine
(1g/250 mL)



Penicillin G sodium
(1g/40 mL)



Physostigmine salicylate
(1g/75 mL)

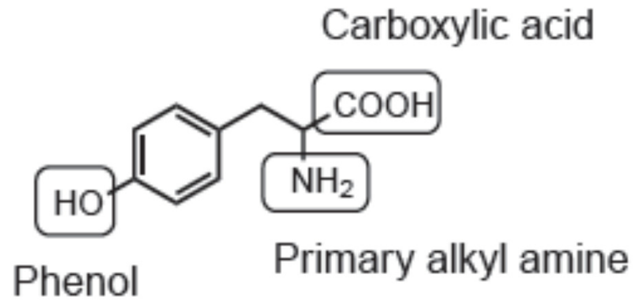


Physostigmine sulfate
(1g/4 mL)

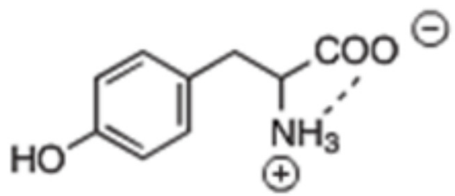
Molecules with ionizable functional groups of opposite charges have the potential to interact with each other rather than with water molecules. When this occurs, these molecules often become water insoluble.

<u>Methods to improve solubility of drugs:</u>

- Structural modification (alter the structure of molecules)
- Use of Cosolvents (Ethanol, sorbitol,PPG,PEG)
- Employing surfactants
- Complexation

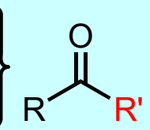
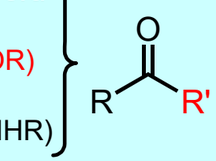


Tyrosine contains three very polar functional groups, alkylamine, carboxylic acid and phenolic hydroxyl group, would expect tyrosine to be very soluble in water, BUT its solubility is only 0.45 g/1,000 mL because the zwitterionic formation of basic alkylamine and carboxylic acid lack of interaction between the ions and the dipoles found in water results in a molecule that is very water insoluble.

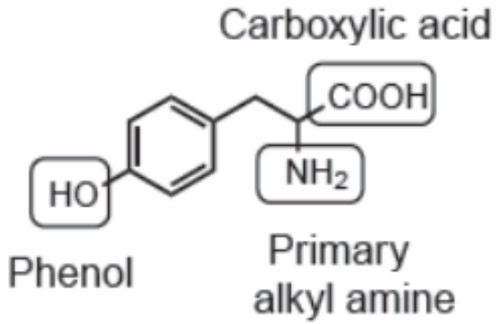


❖ Empirical approach of water solubility

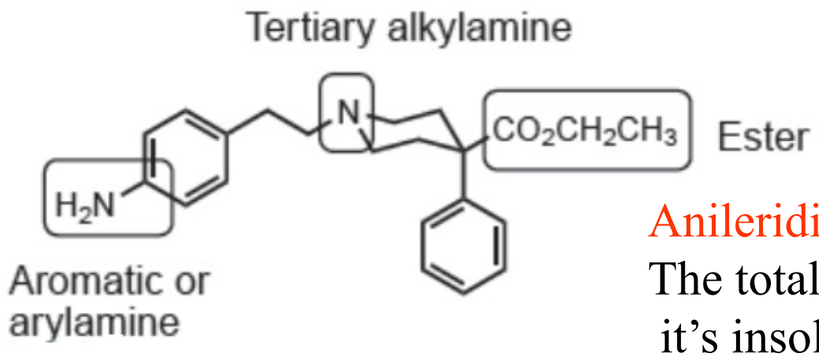
Predicting the water solubility of molecules based on the carbon solubilizing potential of several functional groups. If the solubilizing potential of the functional groups exceeds the total number of carbon atoms present, then the molecule is considered to be water soluble.

Functional Group		Monofunctional molecule	Polyfunctional molecule
alcohol	R—OH	5 to 6 carbons	3 to 4 carbons
phenol	Ar—OH	6 to 7 carbons	3 to 4 carbons
ether	R—O—R	4 to 5 carbons	2 carbons
aldehyde		4 to 5 carbons	2 carbons
ketone		5 to 6 carbons	2 carbons
amine	$R—NH_2$	6 to 7 carbons	3 carbons
carboxylic acid		5 to 6 carbons	3 carbons
ester (R' = OR)		6 carbons	2 to 3 carbons
amide (R' = NHR)		6 carbons	2 carbons

Water-solubilizing potential for several functional groups



Tyrosine: Prediction: 9 – 10 C,
The total carbons is 9, so it's poor Soluble.



Anileridine: Prediction: 9 C,
The total carbons is 22, so it's insoluble.

- However, if we make the hydrochloride salt, then the compound becomes water soluble
  - Lemke estimates that a charge (either anionic or cationic) contributes a "solubilising potential" of between 20 and 30 carbons

❖ Analytical approach of water solubility

- The alternative approach for predicting water solubility utilises the "logP" of molecules. Essentially, logP is a measure of lipophilicity (hydrophobic) properties of a molecule.
- It is determined by measuring the "partition coefficient" between water and octanol for a given molecule (i.e. the solubility of the compound in octanol versus the solubility of the compound in water)
- LogP is calculated by adding the contributions from each functional group in the molecule
- A hydrophobic substituent constant π has been assigned to most organic functional groups, such that LogP = ∑ π (fragments)

$$\log P = \frac{[drug]_{octanol}}{[drug]_{water}}$$

π is the log P of the fragment

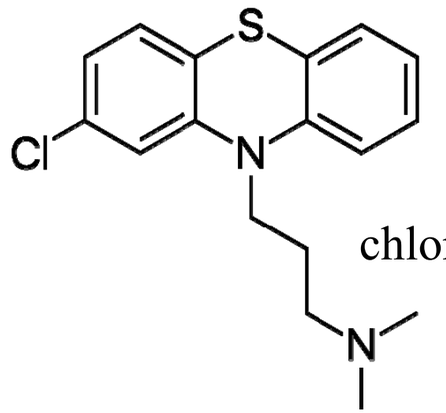
$$\log P_{calc} = \Sigma \pi_{fragments}$$

if calc. logP is > +0.5 then compound is H_2O insoluble

if calc. logP is < +0.5 then compound is H_2O soluble

Fragment	π Value
C (aliphatic)	+0.5
phenyl	+2.0
Br, Cl, F, I	0.60; 0.5; −0.17; 1.00
O_2NO (nitrate)	+0.2
IMHB	+ 0.65
OH	−1.12
O-C-O, O=C-N	-0.7
O, N, ether	-1.0
NO2 (aliphatic)	-0.85
NO2 (aromatic)	-0.28

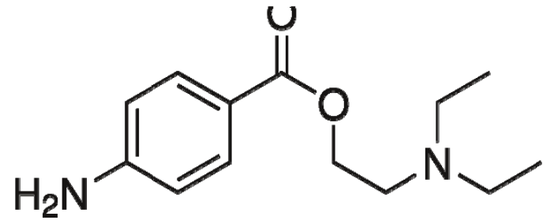
π Values for Organic Fragments



chlorpromazine

5C X +0.5	+2.5
2 Ph X +2	+4.0
Cl	+0.5
2 N X -1	-2.0
S	0.0
	+5.0

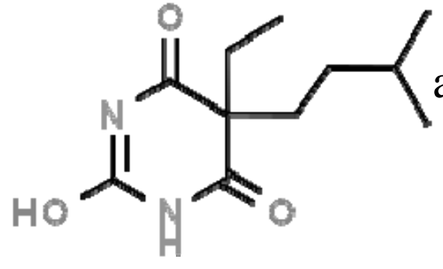
solubility defined as > 0.5



procaine

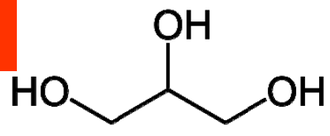
6 C X +0.5	+3.0
phenyl	+2.0
2 N X -1.0	-2.0
O=C-O	-0.7
	+2.3

insoluble



amobarbital

9C X +0.5	+4.5
O X-1	-1.0
2 OCN X -0.7	-1.4
	+2.1



glycerol

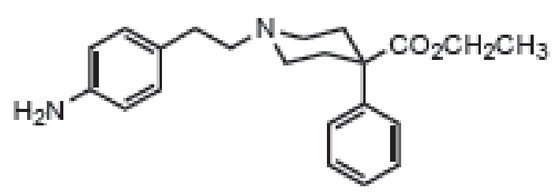
3C X +0.5	+1.5
3 O X -1	-3.0
	-1.5

Miscible

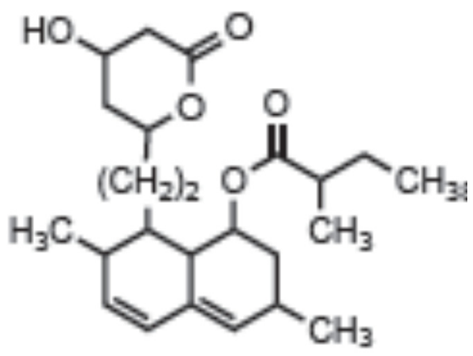
Functional Group	π value (aliphatic)	π value (aromatic)
H		0.00
Alkane	0.50	0.56 (CH_3); 1.02 (CH_2CH_3)
Alkene		0.82
C_6H_5 (phenyl)	2.15	1.96
Br, Cl, F, I	0.60; 0.39; −0.17; 1.00	0.86; 0.71; 0.14; 1.12
NO_2	−0.85	−0.28
NH_2 (primary amine)	−1.19	−1.23
NHR (secondary amine)	−0.67	0.47

Functional Group	π value (aliphatic)	π value (aromatic)
NR_2 (tertiary amine)	−0.30	0.18
-NHC=OR (amide)	−0.97	
SC_6H_5	2.32	
OH	−1.12	−0.67
OCH_3		−0.02
-OC=OR (ester)	−0.27	−0.64
CHO (aldehyde)		−0.65
$C{=}OCH_3$ (ketone)	−0.55	
CO_2H	−0.32	
SO_2NH_2 (sulfonamide)	−1.82	

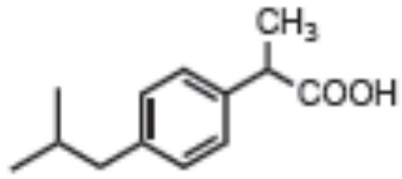
Anileridine



Fragments	π
1 primary alkylamine	-1.23
1 teriary alkylamine	-0.30
9 aliphatic carbons	+4.5
2 phenyl rings	+4.30
1 ester	-0.27
logP	+7.0



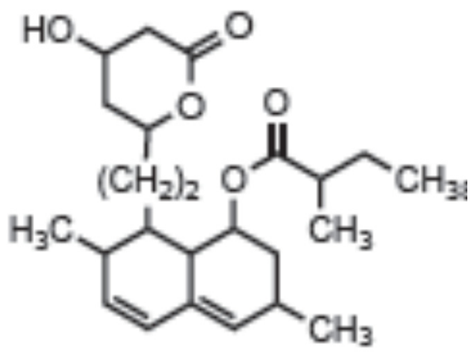
Lovastatin



Ibuprofen

Functional Group	π value (aliphatic)	π value (aromatic)
H		0.00
Alkane	0.50	0.56 (CH_3); 1.02 (CH_2CH_3)
Alkene		0.82
C_6H_5 (phenyl)	2.15	1.96
Br, Cl, F, I	0.60; 0.39; −0.17; 1.00	0.86; 0.71; 0.14; 1.12
NO_2	−0.85	−0.28
NH_2 (primary amine)	−1.19	−1.23
NHR (secondary amine)	−0.67	0.47

Functional Group	π value (aliphatic)	π value (aromatic)
NR_2 (tertiary amine)	−0.30	0.18
-NHC=OR (amide)	−0.97	
SC_6H_5	2.32	
OH	−1.12	−0.67
OCH_3		−0.02
-OC=OR (ester)	−0.27	−0.64
CHO (aldehyde)		−0.65
$C{=}OCH_3$ (ketone)	−0.55	
CO_2H	−0.32	
SO_2NH_2 (sulfonamide)	−1.82	



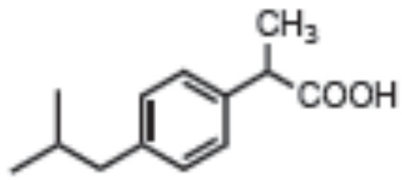
Lovastatin

Fragments	π
22 carbons	+11.0
1 alcohol	-1.12
2 carboxyls	-0.64
logP	+ 9.24

MlogP +4.26; ClogP +4.08

Fragments	π
6 carbons	+3.0
1 phenyl	+2.15
1 carboxyl	-0.32
logP	+4.83

MlogP +3.5; ClogP +3.68

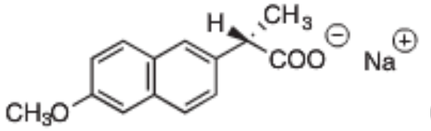


Ibuprofen

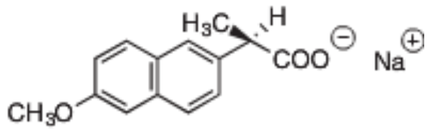
STEREOCHEMISTRY AND DRUG ACTION

- The physicochemical properties of a drug are not only influenced by which functional groups are present, but also by the spatial arrangement (3D) of groups.
- The spatial arrangement of groups is especially important when dealing with biological systems, since receptors are susceptible to the shape of a molecule.
- Stereoisomers contain the same number and kinds of atoms, the same arrangement of bonds, but a different spatial arrangement of atoms.
  - A carbon atom with four different substituents is an asymmetric molecules.
- Stereochemistry is primary:
  - Optical isomerism (Enantiomers, Diastereomers)
  - Geometric isomerism
  - Conformational isomerism

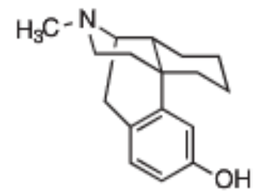
ENANTIOMERS



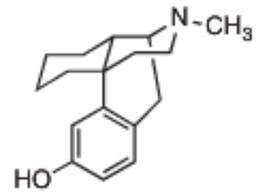
S-(+)-naproxen sodium



R-(-)-naproxen sodium

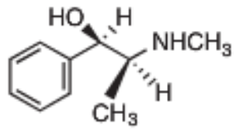


Levorphanol (anagesic)

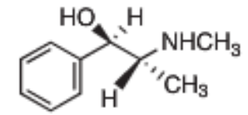


Dextrorphan (antitussive)

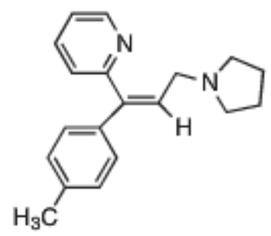
DIASTEREOMERS



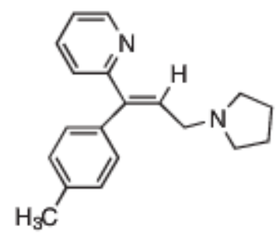
1*R*, 2*S*-(-)-Ephedrine



1*R*, 2*R*-(-)-Pseudoephedrine



Z-triprolidine (inactive)

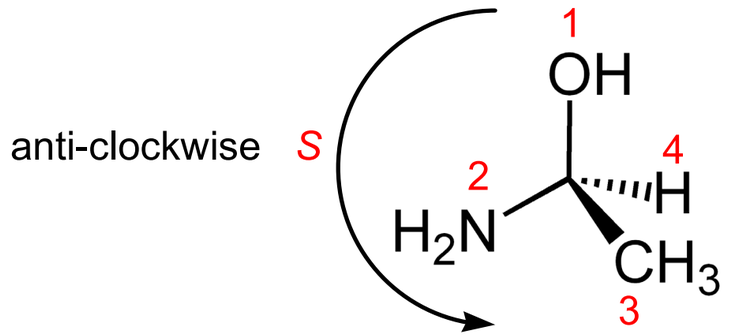


E-triprolidine (active)

❖ Designation of stereoisomerism

➢Cahn, Ingold & Prelog (1956) devised a system of nomenclature for stereoisomer

➢Prioritise atoms around a chiral centre, based upon the atomic weight of the atom



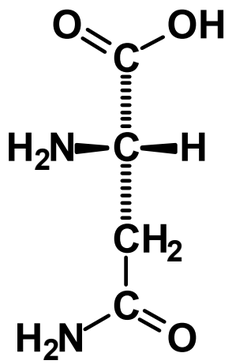
➢Once you have assigned priority from 1 (= highest) to 4 (= lowest), then "look from the chiral centre towards the lowest priority and count from 1 to 3

➔If you count clockwise it is "*R*"

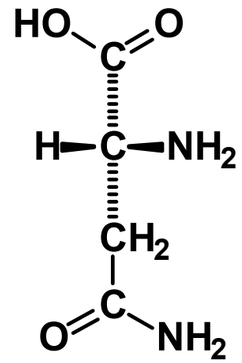
➔If you count anticlockwise it is "*S*"

❖ Optical Isomers & Biological Activity

- Whilst enantiomers have identical physical properties, they can have very different biological properties (e.g. (+)-asparagine is sweet, whilst (–)-aspargine is tasteless). This was one of the earliest observation by in 1886).
- Easson-Stedman hypothesis states that the more potent enantiomer must be involved in a minimum of three interactions with the receptor and that the less potent enantiomer only interacts with two sites

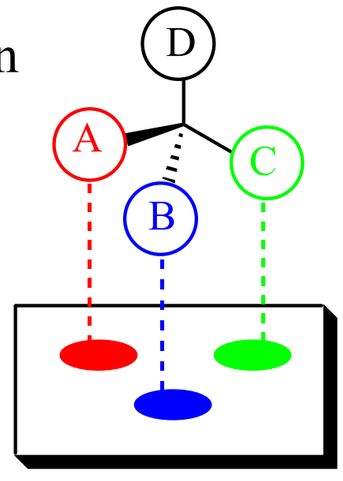


(–)-asparagine
(from asparagus)
bitter taste



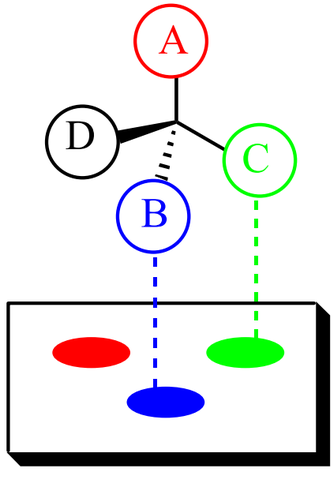
(+)-asparagine
(from vetch)
sweet taste

- reasoned that differences in biologic activity between enantiomers resulted from selective reactivity of one enantiomer with its receptor.
- This difference is due to the asymmetry of receptor – ligand interactions



Drug

Biomolecular target

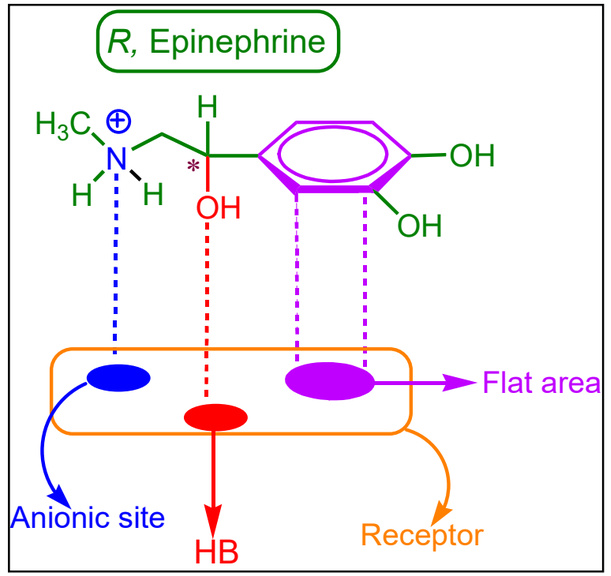


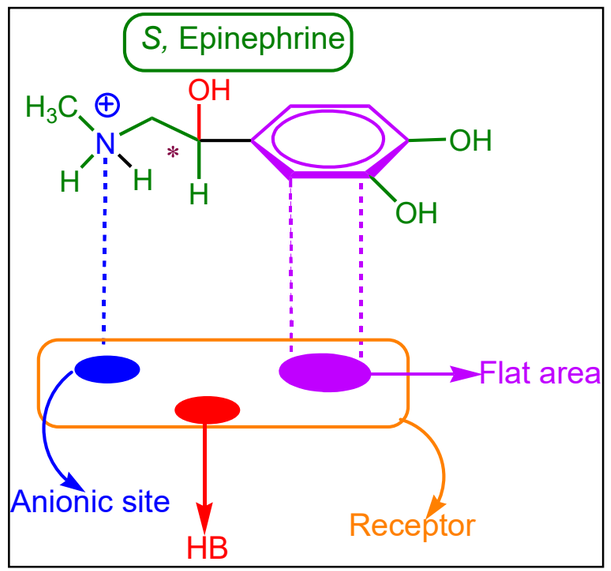
⇓

Desired responce

No desired resonce
Side effects??

- The Easson-Stedman Hypothesis states that the more potent enantiomer must be involved in a minimum of three intermolecular interactions with the surface of the biologic target and that the less potent enantiomer only interacts with two sites.
- With *R*-(−)-epinephrine, the three points of interaction with the receptor site are the substituted aromatic ring, hydroxyl group, and the protonated secondary ammonium group.
  With *S*-(+)-epinephrine, only two interactions are possible, the protonated secondary ammonium and the substituted aromatic ring. The hydroxyl group is located in the wrong place in space and, therefore, cannot interact properly with the receptor.

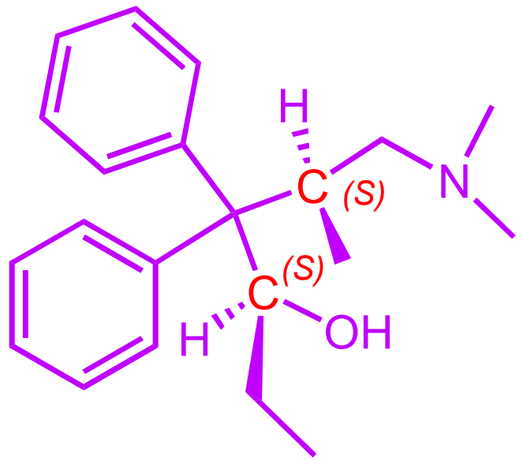


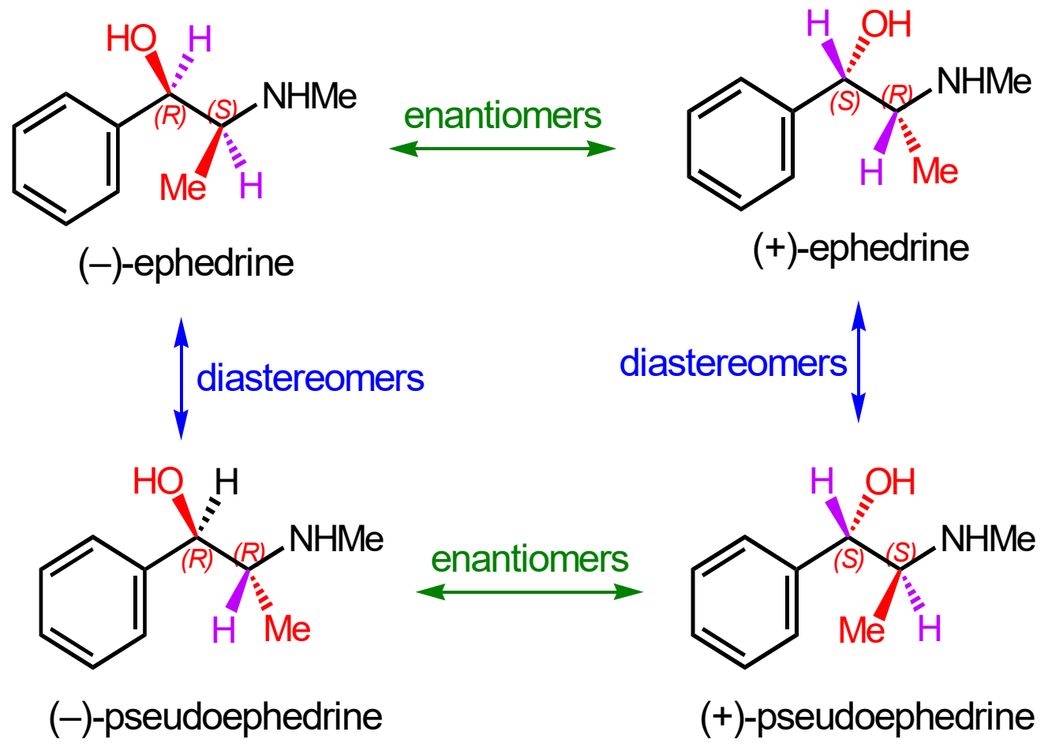


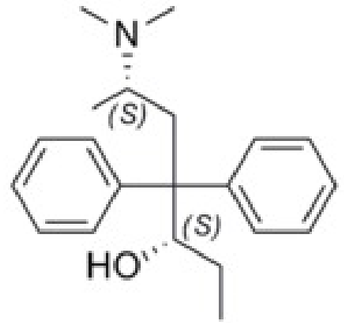
❖ Diastereomers

Diastereoisomers are molecules that are nonsuperimposable, non–mirror images. This type of isomer can result from the presence of more than one chiral center in the molecule, double bonds, or ring systems.

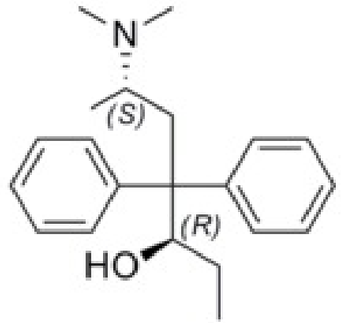
- These compounds have different physical and chemical properties
- These arise from compounds possessing two or more asymmetric centres
- Consider isomethadol
- 2 asymmetric carbons
- 4 isomers (2 pairs of isomerism)
- only the (3*S*,5*S*)-isomer has analgesic activity.



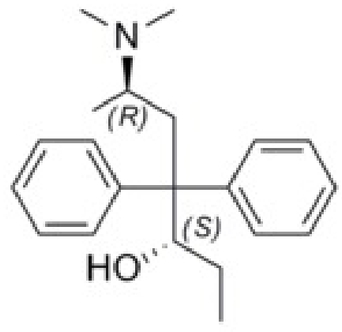




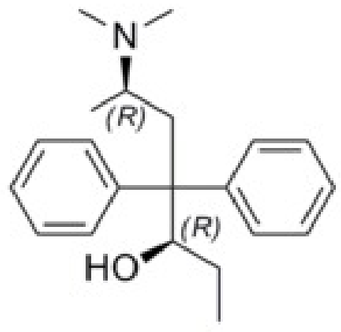
(-)-α-Methadol
CAS: 14019-10-4



(+)-ß-Methadol
CAS: 15529-92-7



(-)-ß-Methadol
CAS: 17199-55-2



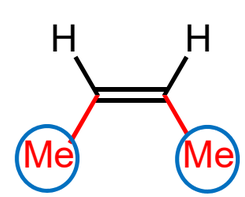
(+)-α-methadol
CAS: 17199-54-1

❖ Geometric isomers

- Restricted bond rotation caused by carbon–carbon double bonds (alkenes or olefins) and similar systems, such as imines (C=N), can produce stereoisomers.

- In this situation, substituents can be oriented on the same side or on opposite sides of the double bond. The alkene 2-butene is a simple example.

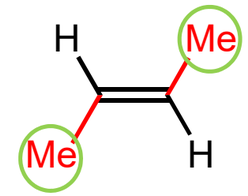
2-butene



cis- or *Z*-isomer

Me's, same sides

Z- comes from German "Zusammen" (= together)



trans- or *E*-isomer

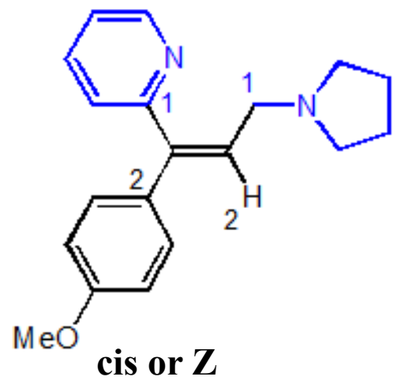
Me's, opposite sides

E- comes from German "Entgegen" (= opposite)

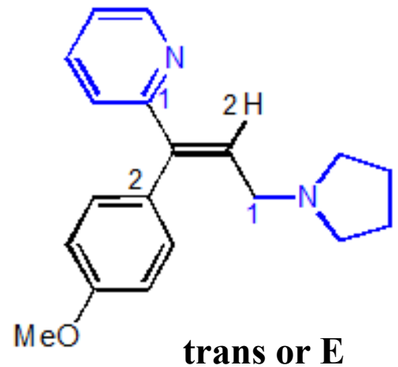
- Blackwood, 1968, assigned a priority of 1 or 2, depending on the atomic number of the atom attached to the double bond. When two substituents of higher priority are on the same side of the double bond, this isomer is given the designation of cis or Z. When the substituents are on opposite sides, the designation is trans or E.

- E-isomer of triprolidine is more active both in vitro and in vivo, indicating that the distance between the pyridine and pyrrolidine rings is critical for binding to the receptor.

Triprolidine



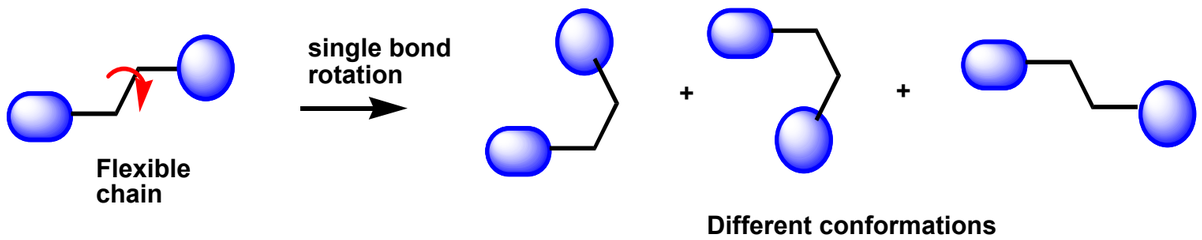
cis or Z
same side

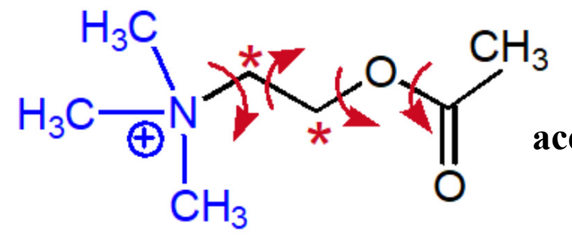


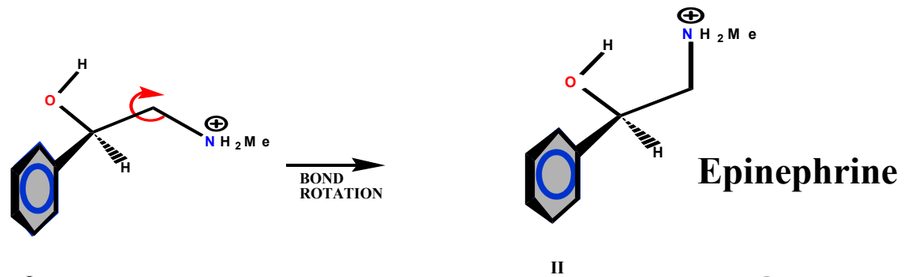
trans or E
opposite sides

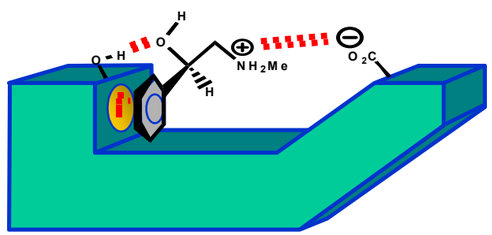
❖ Conformational Isomerism

Takes place via rotation about one or more single bonds. Such bond rotation results in nonidentical spatial arrangement of atoms in a molecule. This type of isomerism does not require much energy because no bonds are broken. In the conversion of one enantiomer into another (or diastereomer) bonds are broken, which requires significantly more energy. The neurotransmitter acetylcholine can be used to demonstrate the concept of conformational isomers.

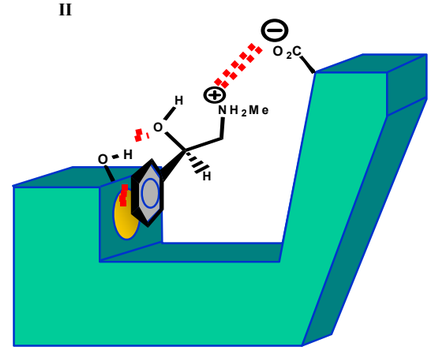








RECEPTOR 1



RECEPTOR 2

DRUG DESIGN:
DISCOVERY AND STRUCTURAL MODIFICATION OF LEAD COMPOUNDS

➢ Process of Drug Discovery

- Drug discovery and development is mainly concerned with enhancing the properties of drugs that are in clinical use and developing novel ways of treating medical conditions.
- Getting a drug into the market generally takes over a decade and involves many individuals with different expertise from a broad range of disciplines.
- In general, medicinal chemists are heavily involved in stages 3 to 6.

The main stages of modern drug discovery

1.identification of new, previously undiscovered, biologically active compounds “hits”
2.Selecting the medical condition to be treated
3.Identification of the drug target
4.Finding suitable bioassays
5.Identification of a **lead compound**(s)
6.Examination of SAR of the lead
7.Drug design and optimisation
8.Manufacturing process design and patent application
9.Clinical Trials
10.Regulatory Approval
11.Release of drug to the market
12.Postmarketing surveillance

❖ Lead Identification

1. Study the molecular mechanisms behind the disease:
   a. Study the cellular and genetic factors involved in the disease
   b. identification of potential targets
2. Study target validation stage by in vitro (isolated cells) and in vivo (animal models) tests

The results of the target validation stage can assist in lead compound identification.

3. The resulting compounds from drug design go through a series of preclinical studies and become clinical candidates if the compounds don't exhibit adverse effects or toxicity during in vitro and in vivo studies.
4. After going through marketing obstacles and clinical trials, compounds that pass are released on the market as new **drug entities**. New drug entities are generally monitored for safety after their release on the market. This is known as post-marketing surveillance or Phase IV clinical trials.

Lead compounds are chemical compounds that show desired biological or pharmacological activity and may initiate the development of a new clinically relevant compound. Lead compounds are typically used as in drug design to give new drug entities. Drug design strategies can be used to improve the compound's pharmacodynamic and pharmacokinetic properties.

❖ **Sources of lead compounds and novel drugs include:**

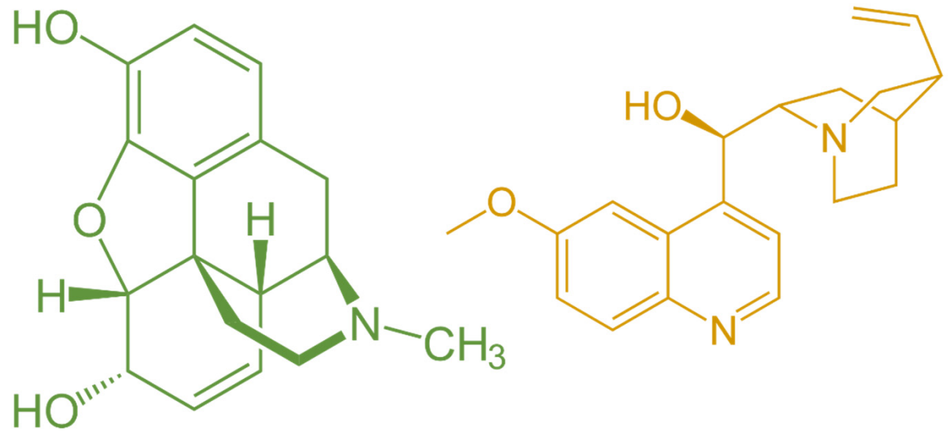
1. Natural Products

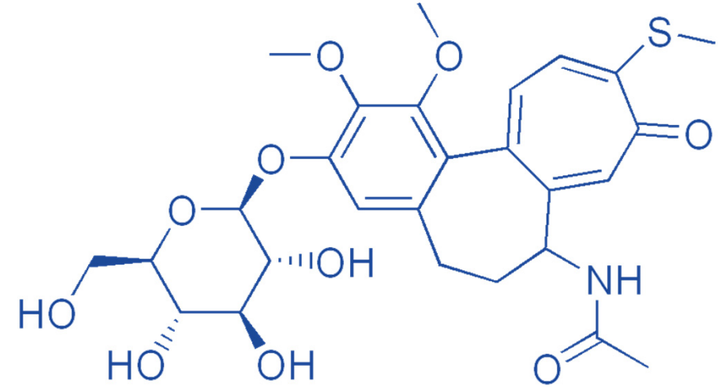
A. Plants

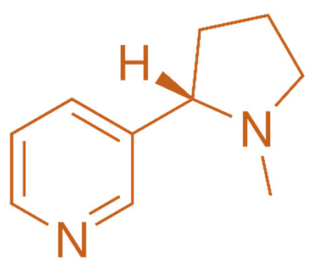
Plants are rich sources of pharmaceuticals molecule as well as lead compounds.

- **Quinine,** an antimalarial drug, is isolated from the bark of the cinchona tree.
- **Morphine** is the most abundant opiate derived from opium which is the dried latex acquired from *Papaver somniferum* (opium poppy)

Thiocolchicosid, berberine, vinblastine, scopolamine, **nicotine**, cocaine, & ephedrine, etc……

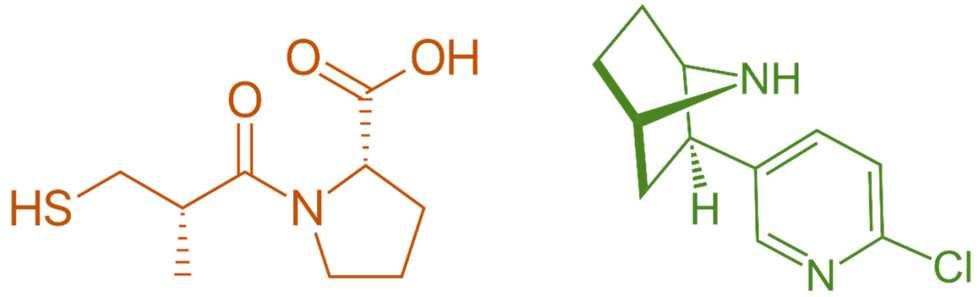






B. Animals

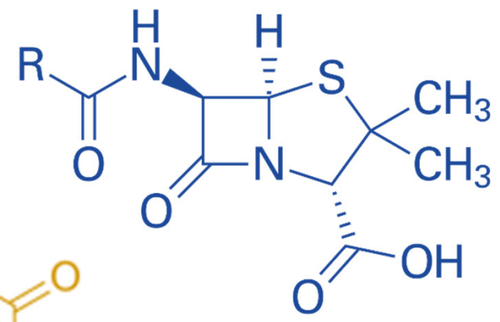
- **Epibatidine** is a potent analgesic isolated from the skin of *epipedobates tricolor* frog.



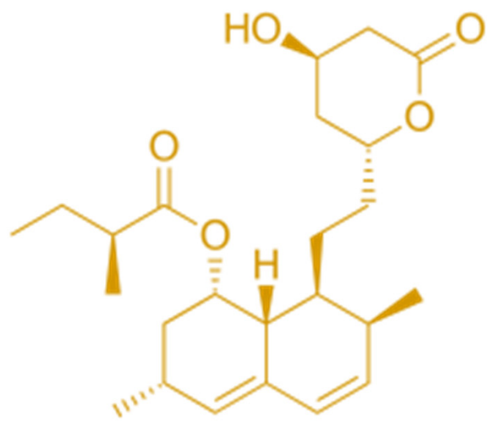
- Teprotide is a nonapeptide isolated from the venom of *bothrops jararaca* (Brazilian pit viper).Its the lead compound of **captopril**.

C. Microorganisms

- **Penicillins** were discovered by serendipity from *penicillium* fungi

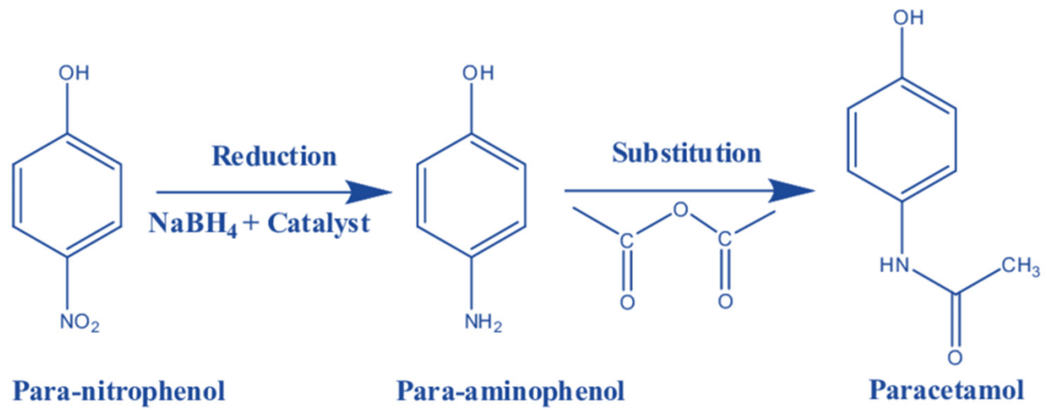


- **lovastatin** was one of the compounds that served as the lead for the development of other statins. Lovastatin is produced by several species of fungi such as the common edible mushroom, *pleurotus ostreatus*

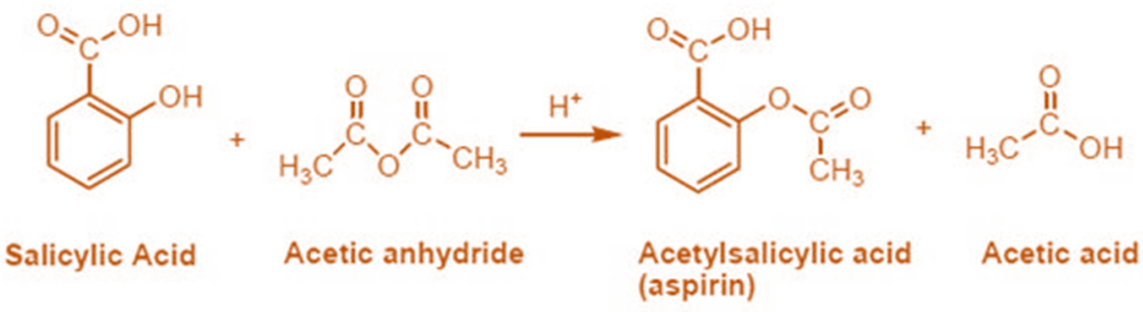


2. Chemical Libraries

A. Synthesis compounds: either pure synthesis or synthesis naturally occurring compounds (e.g. morphine, atropine, steroids and cocaine) to reduce their cost. Or completely synthesized drugs as **paracetamol**, **acetylsalicylic acid**, guaifenesin.



B. Semi-synthesis compounds: Some compounds either can not be purely synthesized or can not be isolated from natural sources in low cost. Therefore, the natural intermediate of such drugs could be used for the synthesis of a desired product (e.g. semi synthetic penicillins).



➢ Natural Product Screening (plant)

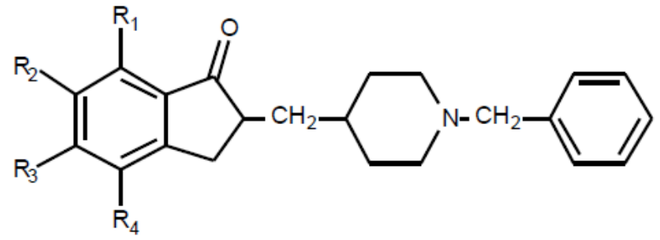
1. Selection of promising plant materials.
2. Proper collection & authentication of selected plants.
3. Drying of plant materials.
4. Grinding of the dried plants.
5. Packing, storage and preservation
6. Extraction of constituents.
7. Methods of separation and purification.
8. Methods of identification of isolated compounds
9. Method of testing for quality
10. Establish safety & Efficacy of drugs

Drug	Action or clinical use	Plant source
Acetyldigoxin	Cardiotonic	*Digitalis lanata* Ehrh.
Adoniside	Cardiotonic	*Adonis vernalis* L.
Aescin	Anti-inflammatory	*Aesculus hippocastanum* L.
Aesculetin	Antidysentery	*Fraxinus rhynchophylla* Hance
Agrimophol	Anthelmintic	*Agrimonia eupatoria* L.
Pseudoephedrine	Sympathomimetic	*Ephedra sinica* Stapf.
Quisqualic acid	Anthelmintic	*Quisqualis indica* L.
Quinine	Antimalaric	*Cinchona ledgeriana*
Rescinnamine	Antihypertensive	*Rauvolfia serpentina*

➢ Drug Discovery from Targeted Dedicated Screening and Rational Drug Design

- Rational drug design is a more focused approach that uses greater knowledge (structural information) about the drug receptor (targets) or one of its natural ligands as a basis to design, identify, or create drug "leads." Testing is usually done with one or two models (e.g., specific receptor systems or enzymes) based on the therapeutic target.
- The drug design component often involves molecular modeling and the use of quantitative structure–activity relationships (QSARs) to better define the physicochemical properties and the pharmacophoric groups that are essential for biologic activity. The development of QSARs relies on the ability to examine multiple relationships between physical properties and biologic activities.
- This approach needs evaluation of the nature of interaction forces between a drug and its biological target, as well as the ability to predict activity in molecules. The methodology is better for the development of a lead compound into a drug candidate than for the discovery of a lead compound.

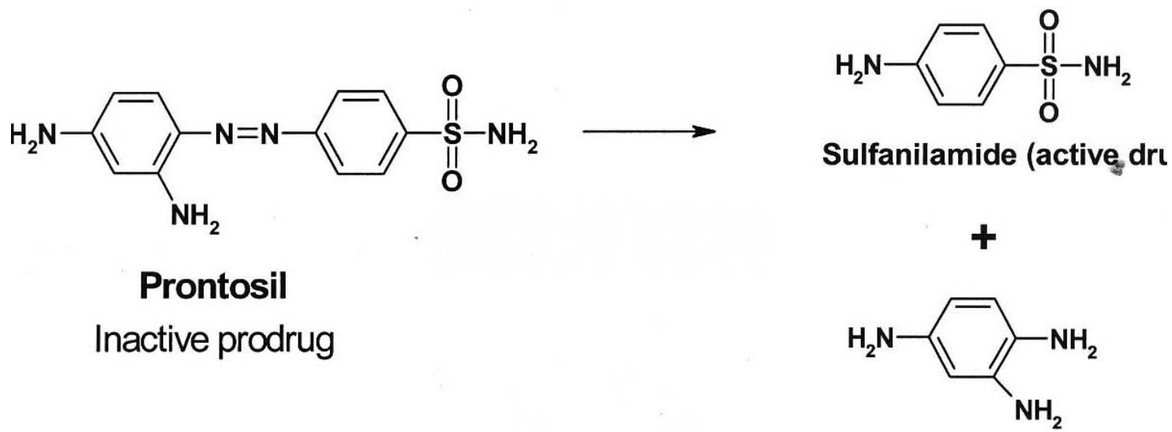
Acetylcholinesterase with Inhibitor E2020



Compound No.	R_1	R_2	R_3	R_4	Inhibition of AChE IC_{50} [nM] [a]
9	H	H	H	H	150
14	H	OMe	H	H	81
15	H	H	OMe	H	6.4
16	H	H	H	OMe	12
E2020	H	OMe	OMe	H	5.7
17	OMe	OMe	H	H	85
18	OMe	H	OMe	H	25
19	OMe	H	H	OMe	36
20	H	H	OMe	OMe	20
21	OMe	OMe	OMe	H	13

➢ Drug Discovery via Drug Metabolism Studies

In most cases, the metabolite is not radically different from the parent molecule and, therefore, would be expected to exhibit similar pharmacologic effects. One advantage of evaluating this type of drug candidate is that a metabolite can possess better pharmacokinetic properties, such as a longer duration of action, better oral absorption, or less toxicity with fewer side effects.

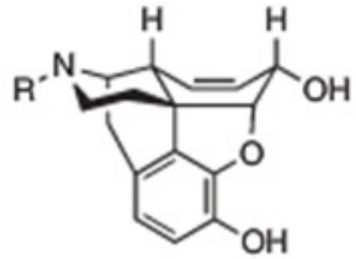


Refinement of the Lead Structure

➢ Determination of the Pharmacophore

- Once a "hit" compound has been discovered for a particular therapeutic use, the next step is to identify the pharmacophoric groups. The pharmacophore of a drug molecule is that portion of the molecule that contains the essential functional group(s) that directly bind with the active site of the biologic target to produce the desired biologic activity. Because drug–target interactions can be very specific (think of a lock [receptor] and key [drug] relationship), the pharmacophore can constitute a small portion of the molecule.

Effect of alkyl chain length on activity of morphine.



R	Pharmacological activity
$-CH_3$	Analgesic (morphine)
$-CH_2CH_3$	Opioid agonist activity decreased
$-CH_2CH_2CH_3$	Opioid antagonist activity increased
$-CH_2CH_2CH_2CH_3$	Inactive as opioid agonist or antagonist
$-CH_2CH_2CH_2CH_2CH_3$	Opioid antagonist activity increased
$-CH_2CH_2CH_2CH_2CH_2CH_3$	
$-CH_2CH_2-C_6H_5$	14X potency of morphine

➢ Functional Group Modification: Bioisosterism

Bioisosterism is the procedure of the synthesis of structural analogues of a *lead compound* by substitution of an atom or a group of atoms in the parent compound for another with similar electronic and steric characteristics. Bioisosetres are functional groups which have similar spatial and electronic character, but they retain the activity of the parent.

Bioisosterism is important in medicinal chemistry because:

1-Maintain similar biological properties.

2-Resolved biological problems effectively (potency, side effects, separate biologic activities and duration of action)

They are classified into two types

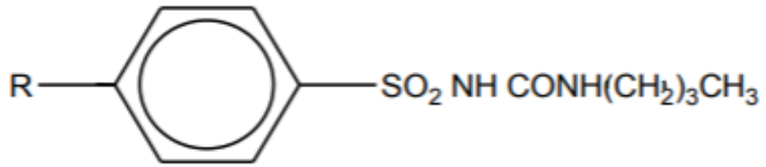
i)Classical biososteres

ii)Non classical bioisosters.

❖ Classical Bioisosteres

They have similarities of shape and electronic configuration of atoms, groups and molecules which they replace.

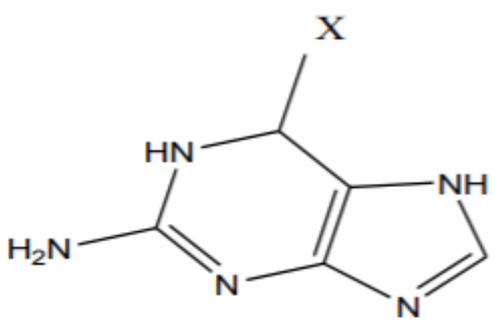
i) Replacement of –NH 2 group by –CH3 group.



Carbutamide R= NH2

Tolbutamide R= CH3

ii)Replacement of –OH & -SH



Guanine= -OH

6-Thioguanine = -SH

The classical bioisosteres may be:

Monovalent bioisosteres

F, H

OH, NH

F, OH, NH or CH_3 for H

SH, OH

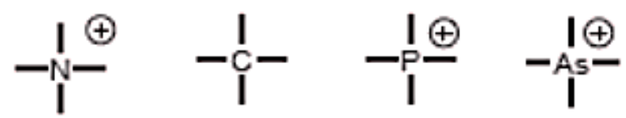
Cl, Br, CF_3

Divalent bioisosteres:

—C=S, —C=O, —C=NH, —C=C—

Trivalent atoms or groups:

Tetrasubstituted atoms:



Ring equivalents:

❖ Non classical Bioisosteres

- Non-classical biosteres are functional groups with dissimilar valence electron configuration.

- Specific characteristics:
  - ✓ Electronic properties
  - ✓ Physicochemical property of molecule
  - ✓ Spatical arrangement
  - ✓ Functional moiety for biological activity

- Example: replacement of m-OH of isoproterenol with a sulfonamide group and similar hydrogen-bonding capacity to a possible drug receptor.

The non classical bioisosteres

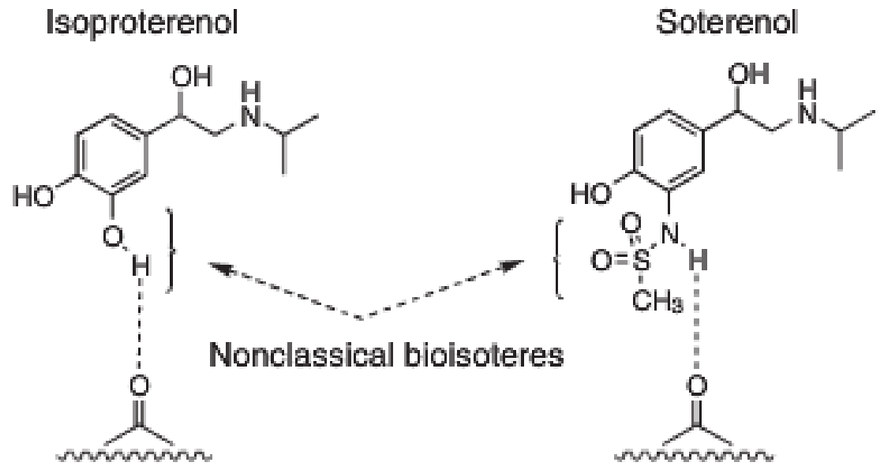
Halogens Cl, F, Br, CN

Ether -S-, -O-

Carbonyl group

Hydroxyl group –OH

$-NHSO_2R$, CH_2OH

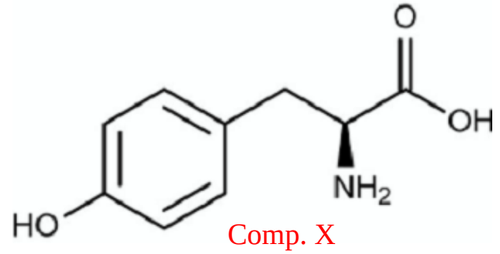


Homework: 2

Why we need to distinguish between the aliphatic and aromatic carbon atoms in the analytical approach of water solubility?

Comp. X insoluble in water even though it contains three highly polar functional groups, Why?? and what is these groups??

Please predict the analytical Water Solubility of paracetamol and atenolol



Comp. X

According to Easson-Stedman theory of "Optical Isomers & Biological Activity", explain the reason of the difference in the biological activity between R-(−)-epinephrine and N-methyldopamine

Please find the material from the link: http://u.pc.cd/eKkotalK