# Lecture 1
# Introduction to pharmaceutical chemistry

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## Chemistry and pharmacology

- **Chemistry is the defining science of pharmacy.**
- **To understand anything about a drug, we need to know:**
- **The synthesis of the drug.**
- **The determination of its purity.**
- **The formulation into a medicine.**
- **The dose given, the absorption and distribution around the body.**
- **The molecular interaction of drug with its receptor.**
- **The metabolism of the drug.**
- **The elimination of drug from the body.**
- **Understanding of the chemical structure of the drug and how this chemical structure influences the properties and behavior of the drug in the body.**

References used in this course are mainly:

1. **Essentials of Pharmaceutical Chemistry by Donald Cairns, UK.**
2. Fundamentals of Medicinal Chemistry by Gareth Thomas, UK.
3. Youtubes and other online lectures.

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## Drugs behave in solution as either weak acids or weak bases.

- **Most of the drugs used in medicine are small organic molecules that behave in solution as either weak acids or weak bases.**
- **To understand and appreciate these compounds a study must be made of simple acid–base theory.**
- **in 1887, the Swedish chemist Svante August Arrhenius suggested that solutions that conduct electricity (so-called electrolytes) do so….. because they dissociate into charged species called ions.**

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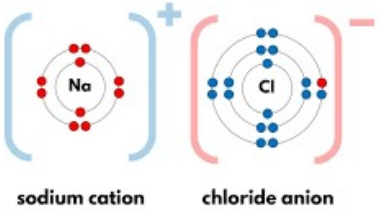
## Cations and anions

- **Positively charged ions (or cations) migrate towards the negative terminal, or cathode.**
- **While negatively charged ions (or anions) migrate towards the positive terminal, or anode.**
- **It is this movement of ions that allows the passage of electric current through the solution.**

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# Electrolytes and mass of action

- **Compounds may be classified as strong electrolytes, which dissociate almost completely into ions in solution, or as weak electrolytes, which only dissociate to a small extent in solution.**
- **Since strong electrolytes are almost completely dissociated in solution, measurement of the equilibrium constant for their dissociation is very difficult.**
- **For weak electrolytes, however, the dissociation can be expressed by the law of mass action in terms of the equilibrium constant.**
- **Considering the reaction: A+B→C+D:**
- **The equilibrium constant (K) for the reaction is given by the product of the concentrations of the reaction products divided by the product of the concentrations of the reactants, or**

$$K = \frac{[C] \times [D]}{[A] \times [B]}$$

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# Equilibrium

- **If the equilibrium lies to the right-hand (or products) side, the numerator in the above expression will be greater than the denominator, and K will be greater than 1.**
- **Conversely, if the reaction does not proceed very far and the equilibrium lies closer to the left hand side, [A] × [B] will be larger than [C] × [D] and K will be less than 1.**
- **The law of mass action can be applied to the dissociation of water, a weak electrolyte widely used as a solvent in biological and pharmaceutical systems: Kw = [H+] × [OH−]**
- **Kw is called the ionic product or autoproteolysis constant of water**

$$H_2O \rightleftharpoons H^+ + OH^-$$

The equilibrium constant for this reaction is given by

$$K = \frac{[H^+] \times [OH^-]}{[H_2O]} \qquad \mathbf{pH} = -\log[H^+] = \log\frac{1}{[H^+]}$$

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# Dissociation of weak acids and bases

- **Acids are compounds that ionise to release hydrogen ions, or protons, to their surroundings. Bases are compounds that can accept hydrogen ions. This is called the Brønsted–Lowry definition of acids and bases**
- **The dissociation of a weak acid is usually represented as follows: HA = H+ + A− .**
- **Since the most common solvent in pharmaceutical and biological systems is water, the ionization of a weak acid is better represented as:**

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

where $H_3O^+$ is a *hydroxonium* ion, and the ionisation of a base can be represented as

$$B + H_2O \rightleftharpoons BH^+ + OH^-$$

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

Consider any weak acid HA, which dissociates as shown below:

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

The equilibrium constant for this reaction is given, as before, by

$$K = \frac{[H^+] \times [A^-]}{[HA]}$$

$$K_b = \frac{[BH^+] \times [OH^-]}{[B]}$$

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# pH and pOH

- **The following equilibrium is extremely useful because they allow the pH of solutions of weak acids and bases to be calculated if the concentrations and dissociation constant are known.**

For weak electrolytes, $\alpha$ is very small and may be neglected so $(1 - \alpha)$ is approximately equal to 1. The simplified expression may now be written as

$$K_a = \alpha^2 c$$

where $c$ is the concentration, in moles per litre, and $\alpha$ is the degree of ionisation of the acid. Then

$$\alpha = \sqrt{\left(\frac{K_a}{c}\right)}$$

The pH of the solution can now be determined:

$$[H^+] = \alpha c$$

Therefore,

$$[H^+] = c\sqrt{\left(\frac{K_a}{c}\right)} = \sqrt{(K_a c)}$$

Taking logarithms,

$$\log[H^+] = \tfrac{1}{2}\log K_a + \tfrac{1}{2}\log c$$

Multiplying throughout by $-1$ gives

$$-\log[H^+] = -\tfrac{1}{2}\log K_a - \tfrac{1}{2}\log c$$

Therefore,

$$\mathbf{pH} = \tfrac{1}{2}\,\mathbf{p}K_a - \tfrac{1}{2}\,\mathbf{log}\,c \qquad (1.2)$$

As before $\alpha$ is very small and can be neglected, so $(1 - \alpha)$ is approximately equal to 1.

$$\alpha^2 = K_b/c$$
$$\alpha = \sqrt{(K_b/c)}$$

From above,

$$[OH^-] = c\alpha$$

Therefore,

$$[OH^-] = c\sqrt{(K_b/c)} = \sqrt{(K_b\, c)}$$

$$\mathbf{pH} = \mathbf{p}K_w - \tfrac{1}{2}\,\mathbf{p}K_b + \tfrac{1}{2}\,\mathbf{log}\,c$$

However,

$$[OH^-] = \frac{K_w}{[H^+]}$$

Therefore,

$$\frac{K_w}{[H^+]} = \sqrt{(K_b c)}$$

$$\mathbf{pH} = \tfrac{1}{2}\,\mathbf{p}K_a - \tfrac{1}{2}\,\mathbf{log}\,c$$

and

$$[H^+] = \frac{K_w}{\sqrt{(K_b c)}}$$

Taking logarithms,

$$\log[H^+] = \log K_w - \tfrac{1}{2}\log K_b - \tfrac{1}{2}\log c$$

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# pKa and pKb

- **It is often useful and convenient to express the strengths of acids and bases using the same term, p*K*a, and this can be done by considering the equilibria that exist between an acid and its conjugate base.**
- **A weak acid (HA) and its conjugate base (A– ) are related as follows:**
- **pKa = – log Ka**

Consider the two carboxylic acids below:

Acetic acid, $CH_3COOH$, $pK_a = 4.7$

Chloroacetic acid, $ClCH_2COOH$, $pK_a = 2.7$

$$HA \rightleftharpoons H^+ + A^-$$
$$A^- + H_2O \rightleftharpoons HA + OH^-$$

From the equations above,

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

and

$$K_b = \frac{[HA] \times [OH^-]}{[A^-]}$$

Then

$$K_a \times K_b = \frac{[H^+] \times [A^-]}{[HA]} \times \frac{[HA] \times [OH^-]}{[A^-]}$$

Cancelling similar terms gives

$$K_a \times K_b = [H^+] \times [OH^-]$$

which can be rewritten as

$$\boldsymbol{K_a \times K_b = K_w = 1 \times 10^{-14}}$$

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# Hydolysis of salts

- **When a salt is dissolved in water, the compound dissociates completely to give solvated anions and cations. This breaking of bonds by the action of water is called hydrolysis and the salt is said to be hydrolyzed.**
- **The pH of the resulting solution depends on whether the salt was formed from reaction of strong or weak acids and bases and there are four possible combinations.**

These relationships can be summarised as follows:

*Strong acid + Strong base → Neutral salt*
*Strong acid + Weak base → Acidic salt*
*Weak acid + Strong base → Basic salt*
*Weak acid + Weak base → Neutral salt*

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# Amphiprotic salts

- **The reactions of salts in water become more complicated if the salt in question is *amphiprotic*; that is, it can function both as an acid and a base.**
- **Examples of amphiprotic anions are bicarbonate (sometimes called hydrogencarbonate), HCO3–, and bisulfite (or hydrogensulfite), HSO3–. These species can donate or accept hydrogen ions in solution.**

The pH of a solution of an amphiprotic salt (e.g. sodium bicarbonate, $Na^+HCO_3^-$) is given by the equation

$$pH = \tfrac{1}{2}(pK_{a1} + pK_{a2}) \qquad (1.6)$$

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# Buffer solutions

- **A buffer solution is a solution that resists changes in pH.**
- **If acid is added then, within reason, the pH does not fall; if base is added, the pH does not rise.**
- **Buffers are usually composed of a mixture of weak acids or weak bases and their salts and function best at a pH equal to the p*K*a of the acid or base involved in the buffer.**
- **The equation that predicts the behaviour of buffers is known as the Henderson–Hasselbalch equation.**
- **It is derived as follows, by considering a weak acid that ionises in solution:**

$$\mathbf{pH = pK_a + \log\frac{[SALT]}{[ACID]}}$$

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# Buffer capacity

- **Buffer solutions work best at controlling pH at pH values roughly equal to the p*K*a of the component acid or base: that is, when the [SALT] is equal to the [ACID].**
- **This can be shown by calculating the ability of the buffer to resist changes in pH, which is the buffer capacity.**
- ***The buffer capacity* is defined as the number of moles per litre of strong monobasic acid or base required to produce an increase or decrease of one pH unit in the solution.**
- **When the concentrations of salt and acid are equal, the log term in the Henderson–Hasselbalch equation becomes the logarithm of 1, which equals 0.**

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# Adjust the pH of a buffer

- **To move the pH of the buffer solution by one unit of pH will require the Henderson–Hasselbalch equation to become:**

$$\mathrm{pH} = \mathrm{p}K_\mathrm{a} + \log \frac{10}{1}$$

- **It will require addition of more acid or base to move the pH by one unit from the point where pH = pKa than at any other given value of the ratio. This can be neatly illustrated by the following example.**

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# An example of a buffer

Suppose 1 litre of buffer consists of 0.1 M $CH_3COOH$ and 0.1 M $CH_3COO^-Na^+$: the pH of this buffer solution will be 4.7 (since the log term in the Henderson–Hasselbalch equation cancels). Now, if 10 mL of 1 M NaOH is added to this buffer, what will be the new pH?

Clearly, the 10 mL of NaOH will ionise completely (strong alkali) and some of the 0.1 M acetic acid will have to convert to acetate anion to compensate. The new pH will be

$$\mathrm{pH} = \mathrm{p}K_a + \log \frac{[\mathrm{SALT}]}{[\mathrm{ACID}]}$$

$$\mathrm{pH} = 4.7 + \log \frac{(0.1 + 0.01)}{(0.1 - 0.01)}$$

$$\mathrm{pH} = 4.7 + \log \frac{0.11}{0.09}$$

$$\mathrm{pH} = 4.79$$

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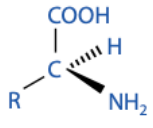
# Biological buffers

- **The human body contains many buffer systems, which control the pH of body compartments and fluids very effectively.**
- **Blood plasma is maintained at a pH of 7.4 by the action of three main buffer systems:**

1. **dissolved carbon dioxide, which gives carbonic acid (H2CO3) in solution, and its sodium salt (usually sodium bicarbonate, NaHCO3), which is responsible for most of the buffering capacity.**
2. **The other two buffers are dihydrogen phosphate (H2PO4– ), also with its sodium salt.**
3. **The protein macromolecules "Proteins are polymers composed of repeating units called amino acids" which containing NH2 and COOH groups:**

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## Proteins capable of acting as both acids and bases

- **Proteins are composed of about 20 different amino acid residues, which are connected to each other by peptide bonds formed between one amino acid and its neighbor.**
- **The side-chain of the amino acid may be acidic (as in the case of glutamic and aspartic acids), basic (as in the case of arginine and lysine) or neutral (as in alanine).**
- **A protein, which may be composed of hundreds of amino acid residues, is, therefore, a polyelectrolyte whose properties depend on the balance of acidic and basic groups on the side-chains.**

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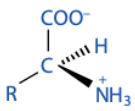
## Proteins capable of acting as both acids and bases

- **Generally, most proteins act as weak acids and form buffers with their sodium salts.**
- **free amino acids usually do not exist in the molecular form, but instead both the amino and carboxyl groups ionise to form an internal salt.**
- **These internal salts are known by the German word zwitterion ('dipolar ion'), and formation of the zwitterion makes the amino acid very polar and, therefore, very soluble in v**

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# Ionisation of drugs

- **When a weakly acidic or basic drug is administered to the body, the drug will ionise to a greater or lesser extent depending on its p*K*a and the pH of the body fluid in which it is dissolved.**
- **The pH of the body varies widely, but the most important biological solution is the blood, which, as stated above, normally has a pH of 7.4.**
- **An equation can be derived that will predict the extent to which the drug ionises, and, as is often the case, the starting point for the derivation is the Henderson–Hasselbalch equation (Eq. (1.7)).**

$$\mathrm{pH} = \mathrm{p}K_\mathrm{a} + \log \frac{[\mathrm{SALT}]}{[\mathrm{ACID}]}$$

$$\mathrm{pH} = \mathrm{p}K_\mathrm{a} + \log \frac{[\mathrm{A}^-]}{[\mathrm{HA}]}$$

Rearranging,

$$\mathrm{p}K_\mathrm{a} - \mathrm{pH} = \log \frac{[\mathrm{HA}]}{[\mathrm{A}^-]}$$

and, therefore,

$$[\mathrm{HA}] = [\mathrm{A}^-] \times \mathrm{antilog}(\mathrm{p}K_\mathrm{a} - \mathrm{pH})$$

The fraction of the total drug that is ionised is given by

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

so that the fraction ionised is

$$\frac{[\mathrm{A}^-]}{[\mathrm{A}^-] \times \mathrm{antilog}(\mathrm{p}K_\mathrm{a} - \mathrm{pH}) + [\mathrm{A}^-]}$$

which simplifies to

$$\textbf{Fraction ionised} = \frac{1}{1 + \mathbf{antilog}(\mathbf{p}K_\mathbf{a} - \mathbf{pH})}$$

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# p*K*a of the drug

- **Equation (1.8) applies to drugs that are weak acids and allows the fraction of the total dose that is ionised to be calculated for any pH if the p*K*a of the drug is known.**
- **The equation is sometimes written as the percentage ionised, which is simply given by**

$$\textbf{Fraction ionised} = \frac{1}{1 + \mathbf{antilog}(\mathbf{p}K_\mathbf{a} - \mathbf{pH})} \qquad (1.8)$$

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# pKa values of drug molecules

- **Most compounds used in medicine are either weak acids or weak bases. This means that the range of possible p*K*a values encountered in drug molecules is huge.**
- **It is important to remember that the value of the p*K*a for a drug tells you absolutely nothing about whether the compound is an acid or base.**
- **Many weak bases have p*K*a values of 2 to 4. Similarly, while a basic drug like cocaine has a p*K*a of 9.5, this does not mean that all compounds with a p*K*a greater than 7 are bases.**
- ***Only a thorough understanding of chemical structure and a knowledge of the functional groups that confer acidity or basicity on a molecule will allow the correct prediction of the acidic or basic nature of a molecule*.**

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# pKa of some common drugs

**Table 1.1 $pK_a$ values of some common drugs**

| Drug | $pK_a$ value |
|---|---|
| *Acidic drugs* | |
| Aspirin | 3.5 |
| Paracetamol | 9.5 |
| Phenobarbital | 7.4 (first ionisation) |
| *Basic drugs* | |
| Cocaine | 8.6 |
| Diazepam | 3.3 |
| Diphenhydramine | 9.0 |
| *Amphoteric drugs* | |
| Morphine | 8.0 (amine), 9.9 (phenol) |
| Adrenaline (epinephrine) | 8.7 (amine), 10.2, 12.0 (phenols) |

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# Lecture 2
# Partition coefficient *P* and Biopharmacy

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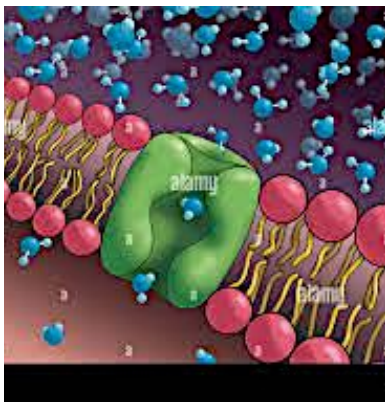
# Partition coefficient and biopharmacy

- **A drug has to pass through a number of biological membranes in order to reach its site of action.**
- **Consequently, organic medium/aqueous system partition coefficients were the clear parameters to use as a measure of the ease of movement of the drug through these membranes.**
- **The accuracy of the correlation of drug activity with partition coefficients will depend on the solvent system used as a model for the membrane.**
- **What is partition coefficients ?**



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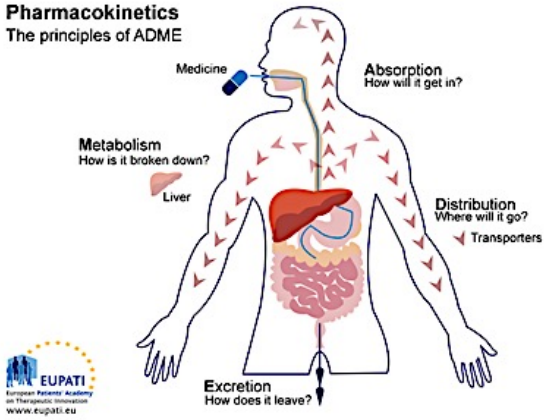
# What is partition coefficients ?

- **The partition coefficient P** is a measure used in chemistry and pharmacology to describe the distribution of a solute (usually a chemical compound) between two immiscible phases, typically a polar and a non-polar solvent.
- It quantifies how a solute distributes or partitions itself between these two phases when they are in contact.

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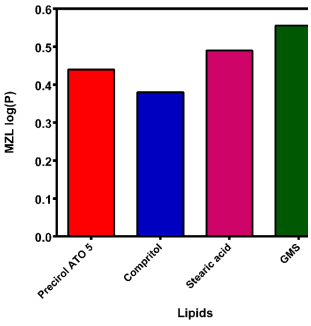
# Partition coefficient and biopharmacy

- **When a substance (or *solute*) is added to a pair of immiscible solvents, it distributes itself between the two solvents according to its affinity for each phase.**
- **A polar compound (e.g. a sugar, amino acid or ionized drug) will tend to favour the aqueous or polar phase.**
- **whereas a non-polar compound (e.g. an unionized drug) will favour the non-aqueous or organic phase.**
- **The added substance distributes itself between the two immiscible solvents according to the partition law, which will '' divide" itself between two immiscible solvents in a constant ratio of concentrations.**

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## Partition coefficient and biopharmacy

$$P = \frac{[\text{organic}]}{[\text{aqueous}]}$$

- **This constant ratio is called the ''*partition coefficient*'' of the substance, and may be expressed mathematically as below:**
- **Where *P* is the partition coefficient of the substance; [organic] is the concentration of substance in the organic, or oil phase; and [aqueous] is the concentration of substance in the water phase.**

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## An example of partition coefficient

where $P$ is the partition coefficient of the substance; [organic] is the concentration of substance in the organic, or oil phase; and [aqueous] is the concentration of substance in the water phase.

As an example, consider the distribution of 100 mg of a drug between 50 mL of an organic solvent (e.g. ether, chloroform or octanol) and 50 mL of water. The drug is added to the two immiscible solvents in a separating funnel and allowed to equilibrate. When the organic layer is analysed, it is found to contain 66.7 mg of compound. From these data the partition coefficient and the percentage of the drug extracted into the organic layer can be calculated (see Fig. 2.1).

The mass of drug in the water phase = 100 − 66.7 mg = 33.3 mg; the concentration of drug in the organic phase = 66.7/50 = 1.33 mg $mL^{-1}$, and the concentration of drug in the water phase = 33.3/50 = 0.67 mg $mL^{-1}$. Therefore, the partition coefficient is given by

$$\frac{[\text{organic}]}{[\text{aqueous}]} = \frac{1.33 \text{ mg mL}^{-1}}{0.67 \text{ mg mL}^{-1}} = 2$$

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Here, we can see explanation

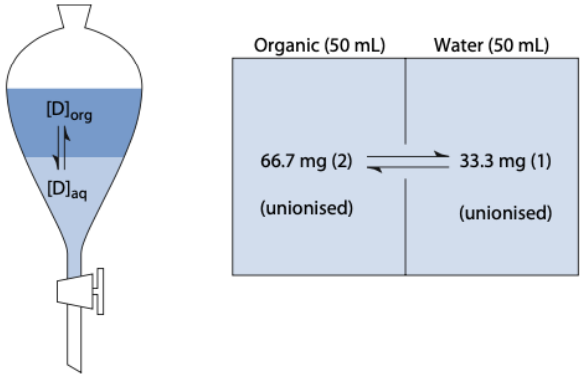


**Figure 2.1.** Simple partition law.

The partition coefficient is a ratio of concentrations, so the units cancel and *P* has no units.

The percentage of drug extracted in the above example is simply given by the mass of drug in the organic phase divided by the total mass of drug, i.e. 66.7/100 = 66.7%.

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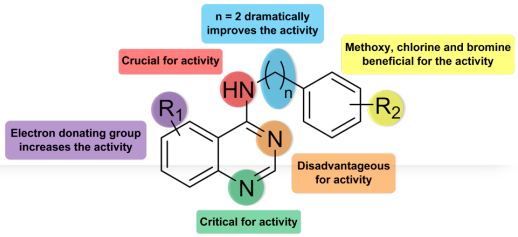
# What is a partition coefficient and QSAR




- **The <u>partition coefficient</u> is an important piece of information as it can be used to predict the absorption, distribution and elimination of drugs within the body.**
- **Knowledge of the value of *P* can be used to predict the onset of action of drugs or the duration of action of drugs, or to tell whether a drug will be active at all.**
- **Part of medicinal chemistry, the science of rational drug design, *involves structure–activity relationships,* where the partition coefficient is used in mathematical equations that try to relate the biological activity of a drug to its physical and chemical characteristics.**

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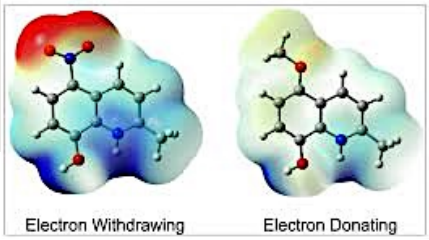
# QSAR and physicochemical properties of Drugs




- **QSAR stands for Quantitative Structure-Activity Relationship.**
- **It is a computational modeling technique used in chemistry and pharmacology to predict the biological activity, potency, or other properties of chemical compounds based on their structural characteristics.**
- **QSAR models relate the chemical structure of a molecule to its biological or physicochemical properties through mathematical equations.**

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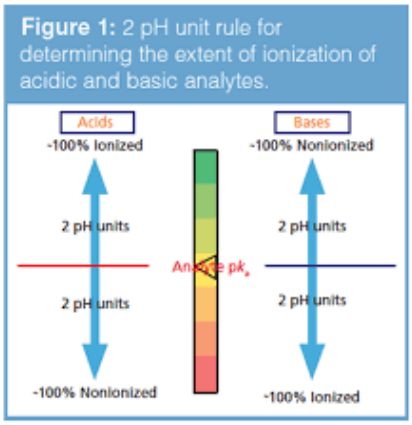
# Ionization and pH

- **This relationship above only applies if the solute in question does not ionize at the pH of measurement.**
- **If the solute is a weak acid or weak base (and a huge number of drugs are), then ionization to form an anion or a cation will considerably alter the solubility profile of the drug.**
- **A fully ionized species will be much more soluble in water than the unionized acid or base, and so the above ratio will vary depending on the pH at which the measurement was carried out.**

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# P value and ionazation

- **There are two ways round this problem: the experimental conditions are adjusted to ensure that the measured *P* is the partition coefficient of the unionized molecule (this means that the *P* value for acids is measured at low pH when the acid is unionized.**
- **OR better, the ratio above is redefined as the *apparent partition coefficient* .**
- ***It depends upon the pH of the solution.***

$$P_{app} = P \times f_{unionised}$$

where $f_{unionised}$ equals the fraction of the total amount of drug union that pH. It follows that if $f_{unionised} = 1$ then $P_{app} = P_{true}$ and the com is unionised.

To illustrate the effect of ionisation, consider again the drug example above. If the pH of the aqueous phase is adjusted so that th becomes 66.7% ionised, only 40 mg of the drug partitions into the o phase (since the ionised drug will be less soluble in the organic solven the partition coefficient can be recalculated (see Fig. 2.2).

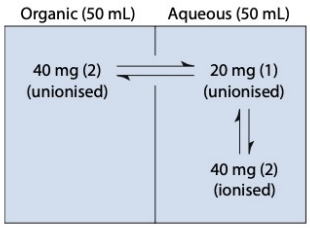


**Figure 2.2.** The partition of ionised drug.

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# *P* value and *quantitative structure–activity relation- ships* (QSAR)

- **The range of possible values of *P* found in drug molecules is huge, from small fractions through to values of several thousand.**
- **For this reason, it is common to quote the logarithm (to the base 10) of the partition coefficient, or log *P*.**
- **This is particularly true in *quantitative structure–activity relation- ships* (QSAR), where the physicochemical properties of a drug (such as hydrophobicity, steric interactions or electronic effects) are quantified and an equation is derived that can be used to predict the biological activity of other, similar drugs.**

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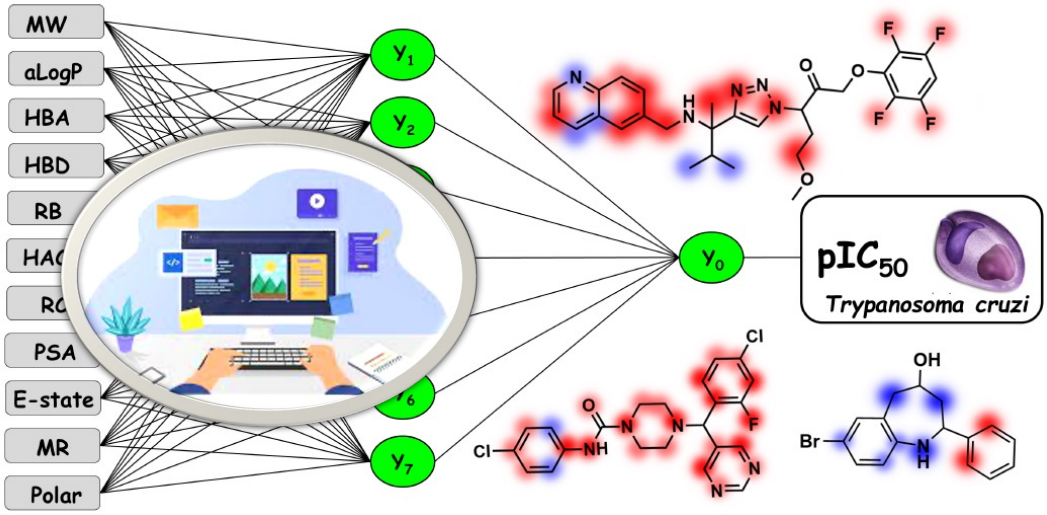
**The technique of QSAR and powerful computers are able to handle the multiple regression analysis**

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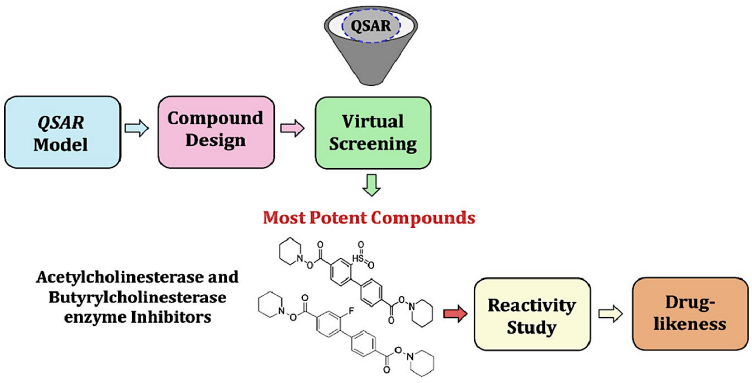
# QSAR and the main properties of a drug




- **QSAR is an attempt to remove the element of luck from drug design by establishing a mathematical relationship in the form of an equation between biological activity and measurable physicochemical parameters.**
- **These parameters are used to represent properties such as lipophilicity, shape and electron distribution, which are believed to have a major influence on the drug's activity.**
- **The main properties of a drug that appear to influence its activity are its, lipophilicity, the electronic effects within the molecule and the size and shape of the molecule (steric effects).**

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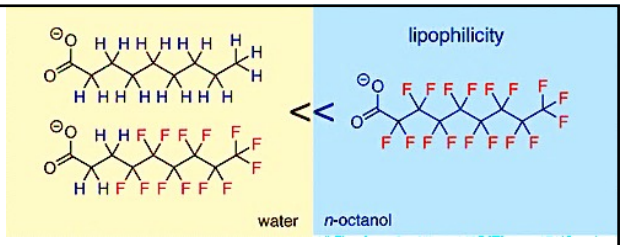
# Lipophilicity




- **Lipophilicity is a measure of a drug's solubility in lipid membranes.**
- **This is usually an important factor in determining how easily a drug passes through lipid membranes**
- **The electronic effects of the groups within the molecule will affect its electron distribution, which in turn has a direct bearing on how easily and permanently the molecule binds to its target molecule.**
- **Drug size and shape will determine whether the drug molecule is able to get close enough to its target site in order to bind to that site.**
- **Two parameters are commonly used to represent lipophilicity, namely the partition coefficient (P) and the lipophilicity substituent constant (p). The former parameter refers to the whole molecule whilst the latter is related to substituent groups.**

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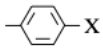
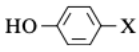
# Lipophilic substituent constants (p or π )

- **Lipophilic substituent constants are also known as hydrophobic substituent constants. They represent the contribution that a group makes to the partition coefficient**
- **The value of p for a specific substituent will vary with the structural environ- ment of the substituent**

**Table 4.4** Examples of the variations of π values with chemical structure

| Substituent X | Aliphatic systems R–X |  |  |  |
|---|---|---|---|---|
| –H | 0.00 | 0.00 | 0.00 | 0.00 |
| $–CH_3$ | 0.50 | 0.56 | 0.52 | 0.49 |
| –F | −0.17 | 0.14 | | 0.31 |
| –Cl | 0.39 | 0.71 | 0.54 | 0.93 |
| –OH | −1.16 | −0.67 | 0.11 | −0.87 |
| $–NH_2$ | | −1.23 | −0.46 | −1.63 |
| $–NO_2$ | | −0.28 | −0.39 | 0.50 |
| $–OCH_3$ | 0.47 | −0.02 | 0.18 | −0.12 |

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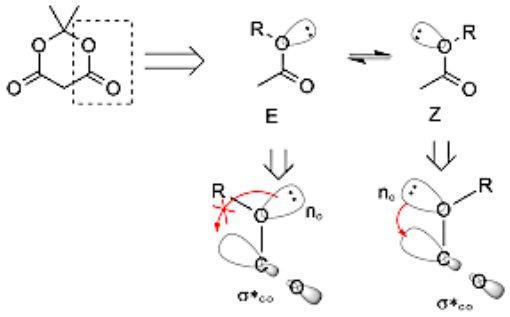
# Electronic effects

- **The distribution of the electrons in a drug molecule has a considerable influence on the distribution and activity of a drug.**
- **In general, nonpolar and polar drugs in their unionized form are more readily transported through membranes than polar drugs and drugs in their ionized forms.**
- **Furthermore, once the drug reaches its target site the distribution of electrons in its structure will control the type of bond it forms with that target, which in turn affects its biological activity**

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# Steric effects

- **The first parameter used to show the relationship between the shape and size (bulk) of a drug, the dimensions of its target site and the drug's activity was the Taft steric parameter (Es).**
- **It was followed by Charton's steric parameter (n), Verloop's steric parameters and the molar refractivity (MR) amongst others.**
- **The most used of these additional parameters is probably the molar refractivity.**

$$E_s = \log \frac{k_{(XCH_2COOCH_3)}}{k_{(CH_3COOCH_3)}} = \log k_{(XCH_2COOCH_3)} - \log k_{(CH_3COOCH_3)}$$

**Table 4.6** Examples of the Taft steric parameter $E_s$

| Group | $E_s$ | Group | $E_s$ | Group | $E_s$ |
|---|---|---|---|---|---|
| H– | 1.24 | F– | 0.78 | $CH_3O$– | 0.69 |
| $CH_3$– | 0.00 | Cl– | 0.27 | $CH_3S$– | 0.19 |
| $C_2H_5$– | −0.07 | $F_3C$– | −1.16 | $PhCH_2$– | −0.38 |
| $(CH_3)_2$ CH– | −0.47 | $Cl_3C$– | −2.06 | PhOCH– | −0.33 |

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# Molar refractivity ( MR)

- **The molar refractivity is a measure of both the volume of a compound and how easily it is polarized. It is defined as:**

$$\mathrm{MR} = \frac{(n^2 - 1)M}{(n^2 + 2)\rho}$$

- **where n is the refractive index, M the relative mass and r the density of the compound. The M/r term is a measure of the molar volume whilst the refractive index term is a measure of the polarizability of the compound.**

**Table 4.7** Examples of calculated MR values. Reproduced by permission of John Wiley and Sons Ltd. from Hansch C. and Leo A.J. *Substituents Constants for Correlation Analysis in Chemistry and Biology* (1979)

| Group | MR | Group | MR | Group | MR |
|---|---|---|---|---|---|
| H– | 1.03 | F– | 0.92 | $CH_3O$– | 7.87 |
| $CH_3$– | 5.65 | Cl– | 6.03 | HO– | 2.85 |
| $C_2H_5$– | 10.30 | $F_3C$– | 5.02 | $CH_3CONH$– | 14.93 |
| $(CH_3)_2CH$– | 14.96 | $O_2N$– | 7.63 | $CH_3CO$– | 11.18 |

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# Lecture 3
# Measurement of partition coefficient

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1

## Experimental measurement to determine the partition coefficient: Shake flask method

- **These are the original *shake flask method*, the use of *thin-layer chromatography* or the use of *reversed-phase, high-performance liquid chromatography*.**
- **Shake flask method:**
- **In the shake flask method, the drug whose P is to be determined is traditionally added to a separating funnel containing the two immiscible phases, although it works just as well to use a centrifuge tube (and requires less sample).**
- **The two immiscible phases chosen are usually 1-octanol and pH 7.4 buffer.**
- **Octanol is used in partition coefficient work because the answers obtained from octanol seem to correlate best with biological data obtained in vivo.**

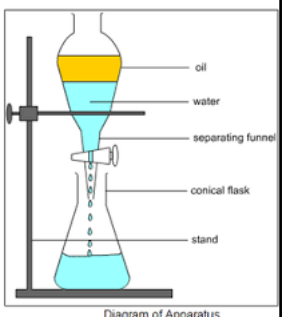
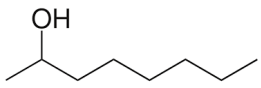


Diagram of Apparatus

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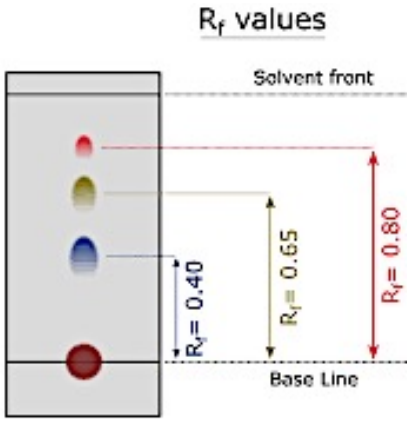
# Continue with…Shake flask method

- This may be because the eight carbon atoms are essentially hydrophobic (or water-hating) and the one hydroxyl group is hydrophilic (water-loving) and together they give the closest balance to that found in human cell membranes.
- The aqueous buffer at pH 7.4 represents aqueous compartments within the body, e.g. blood plasma.
- The two phases are thoroughly mixed to give buffer-saturated octanol in the top phase and octanol-saturated buffer in the bottom. .
- The concentration in the octanol phase is found by subtraction and the value of P is calculated.
- This method works perfectly well if there is sufficient sample and the drug possesses a chromophore to allow spectroscopic assay of the aqueous phase.
- Five extractions of 10 mL organic phase will remove more compound than one extraction of 50 mL, even though the total volume of organic solvent used is the same.

3

# Experimental measurement to determine the partition coefficient: Thin-layer chromatography (TLC)

- In this technique, the *R*f value of the drug is related mathematically to the partition coefficient.
- A thin-layer plate, or a paper sheet, is pre-coated with organic phase (usually paraffin or octanol) and allowed to dry.
- Sample is applied to the origin and the plate is allowed to develop.
- The mobile phase used is either water or a mixture of water and a miscible organic solvent (such as acetone) to improve the solubility of the drug.
- Once the plate has developed, the spots are visualized (using an ultra- violet lamp if the drug possesses a chromophore, or iodine vapor if it does not) and the *R*f for each spot is determined.

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## *Rf* is the distance and *k* is a constant for the given system

$$P = \frac{k}{(1/R_f) - 1}$$

- The *Rf* is the distance moved by the spot divided by the distance moved by the solvent .
- The *Rf* can be related to the partition coefficient by equations of the type
- where *k* is a constant for the given system, which is determined by running a number of standard compounds of known *P* in the system and calculating *k*.
- The TLC method of determining *P* works best for compounds of similar structure and physical properties.
- The advantages of using this technique to determine *P* are that many compounds can be run simultaneously on one plate, and very little sample is required.

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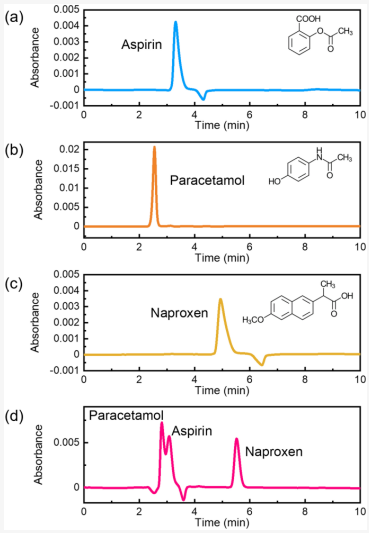
## High-performance liquid chromatography (HPLC)

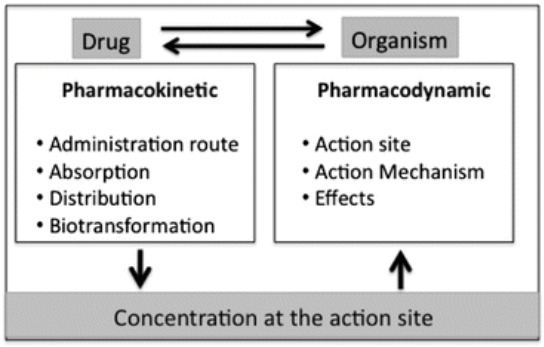
- This method of analysis relies on the same chemical principles as the determination by TLC.
- *The retention time*, as its name suggests, is the time taken for the sample to elute from the HPLC column.
- The major drawback with using this technique to determine *P* is detecting the drug if it does not possess a chromophore, when a UV detector cannot be used.
- There are some advantages to the HPLC method of determining *P*, namely that HPLC does not require much sample and that the sample does not have to be 100% pure.




6

# Drug absorption, distribution and bioavailability

- **The study of the fate of a drug administered to an organism is called *pharmacokinetics*.**
- **This discipline involves measuring or predicting the *absorption, distribution, metabolism and excretion* (usually known by the acronym ADME) of the drug in the body.**
- **Pharmacokinetics is an opposed to *pharmacodynamics*, which is the study of mechanisms of drug action.**

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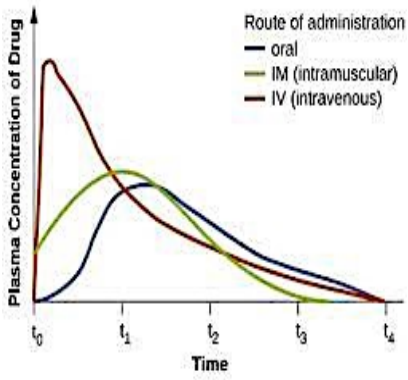
# Bioavailability

- **Bioavailability (symbol *F*) is a measure of the drug extent to reaches the bloodstream and is available at its site of action.**
- **The bioavailability of a drug administered by intra-venous (i.v.) injection is defined as 1 (since the entire dose is available in the systemic circulation).**
- **The most popular method of administering drugs and medicines is the oral route.**
- **By Tablets, capsules or oral liquids are:**
- **swallowed and, once in the stomach, the tablet or capsule disintegrates to release the active drug molecule.**

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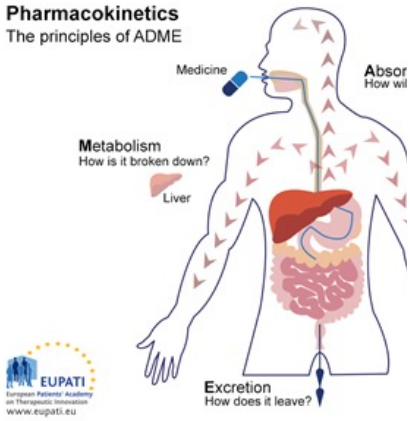
# Drug absorption

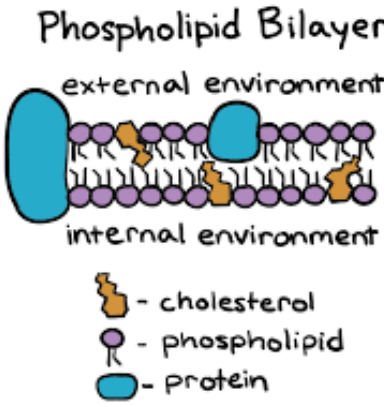
- **The drug is not considered to be *in* the body until it has been absorbed across the gut wall and into the bloodstream by absorption across a biological membrane.**
- **The case of drugs acting on the brain or spinal cord (the central nervous system, or CNS) the drug must partition across the *blood–brain barrier* to gain access to the CNS.**
- **The CNS does require low-molecular-weight molecules to grow and function.**




9

# The cell membrane and absorption

- **A cell membrane is composed of a bilayer of fatty molecules known phospholipids.**
- **These compounds are amphoteric in nature, possessing a non-pol region of hydrocarbon chains that are buried inside the cell membrar and a polar region comprising negatively charged phosphoric acid he groups.**
- **Buried within this lipid bilayer are large globular protein molecul These macromolecules function as ion channels (e.g. the Na+ channel nerve membranes), transmembrane receptors (like the β adrenocepto or transport proteins**

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# Roles of fats in the cell membrane

- In cell membranes, cholesterol increases membrane rigidity and is essential for maintaining the integrity of the membrane — without cholesterol your cells would leak.
- The lipid bilayer of the cell membrane presents a significant barrier to drug transport and for a small drug molecule to travel across membranes, one of two things must happen:
- 1. The drug must cross the membrane by passive diffusion.
- 2. The drug has to be transported across the membrane, against the concentration gradient, a process called active transport.

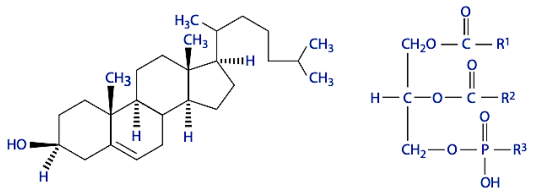


**Figure 2.4.** The structures of cholesterol and phospholipids. $R^1$ and $R^2$ = palmityl, stearyl or oleyl. $R^3$ = ethanolamine, choline, serine, inositol or glycerol.

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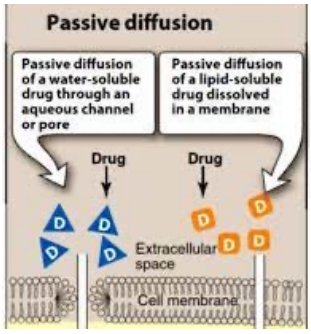
# Passive diffusion of drugs

- Passive diffusion is probably the most important mechanism by which small drug molecules gain access to the body.
- The drug molecule must be in solution, and it partitions into the lipophilic cell membrane, diffuses across the cell and then partitions out of the cell and into the aqueous compartment on the other side.
- Drugs that are very lipid soluble (such as the antifungal agent griseofulvin) are so water insoluble that they partition into the cell membrane.
- However, they stick in the lipid membrane and do not partition out of the membrane and into the aqueous compartments inside the cell.
- Passive diffusion can only occur with small molecules (e.g. drugs with relative molecular masses of approximately 1000 or less). This excludes large macromolecules such as proteins,

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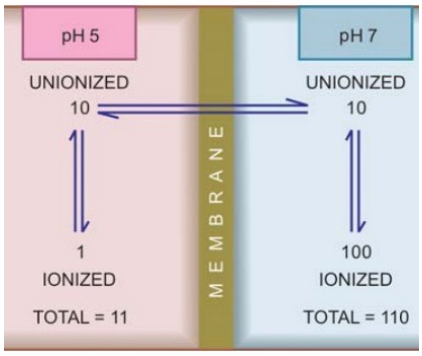
# The pH partition hypothesis

- **Biological membranes are, essentially, non-polar or hydrophobic, due to the long hydrocarbon chains of the phospholipid molecules.**
- **For a drug to cross a membrane of this type, the drug must pass from the aqueous solution of the extracellular fluid, through the lipid membrane to the aqueous solution of the intracellular fluid., i.e. the drug must be sufficiently soluble in both the aqueous and the lipid phases to succeed.**




**2.4:** Influence of pH difference on two sides ogical membrane on the steady-state distribution kly acidic drug with *pKa* = 6

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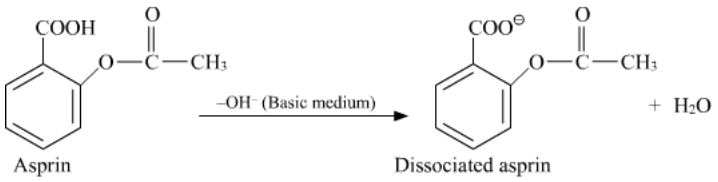
# Ionization and unionization of drug

- **In a region of high pH, the acidic drug will ionise to give A–, which, since it is charged, will not diffuse well through a hydrophobic lipid membrane.**
- **Thus, gastric ulcers are so painful because in the gastric juice of the stomach, due to the high concentration of hydrochloric acid present, is at a pH of 1–2 ).**
- **The hole in the stomach lining allows the acid to burn the underlying muscle layer.**
- **This theory is called the *pH partition hypothesis*, and predicts that weakly acidic drugs such as aspirin, barbiturates, phenytoin, etc.**
- **But, but, in reality, *the vast majority of drugs are absorbed from the small intestine irrespective of their degree of ionization* (Limitations of the pH partition hypothesis).**

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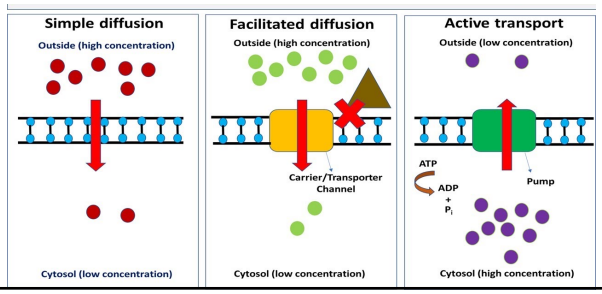
# Active transport mechanisms

- **Glucose and ions such as sodium and chloride must cross membranes efficiently, but they are too polar to diffuse across a phospholipid bilayer passively.**
- **Their transport is 'facilitated' by proteins that span the membrane and allow these chemicals to enter cells.**
- **If the transport occurs down a concentration gradient, the process is described as *facilitated diffusion* and does not usually require expenditure of energy in the form of hydrolysis of ATP (adenosine triphosphate).**
- **The protein complex diffuses across the cell membrane.**

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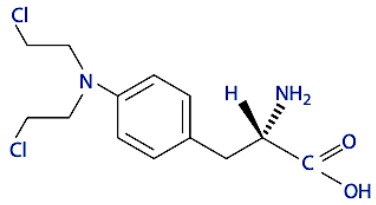
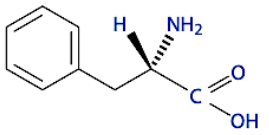
# Anticancer drug




Melphalan




Phenylalanine

The structures of melphalan and phenylalanine.

- **The anticancer drug *melphalan* was synthesised in order to make use of the existing active transport pathway for the amino acid phenylalanine.**
- **The phenylalanine part of the molecule takes no part in the anticancer action;**
- **it is there to improve the molecule's chances of being absorbed across biomembranes.**

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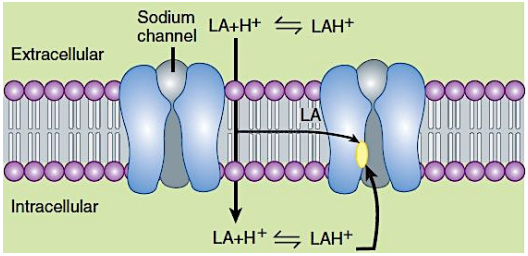
## The action of local anesthetics drugs (LA)




- ***Local anesthetics*** **are basic drugs, all derived originally from cocaine, an alkaloid obtained from the leaves of** ***coca.***
- **Cocaine is a very effective local anesthetic, but due to a profound stimulant action on the CNS it has been replaced in most routine procedures with synthetic, non-addictive, analogues such as lidocaine etc.**
- **These drugs are aliphatic amines, with p*K*a values for their conjugate acids of approximately 8–9.**

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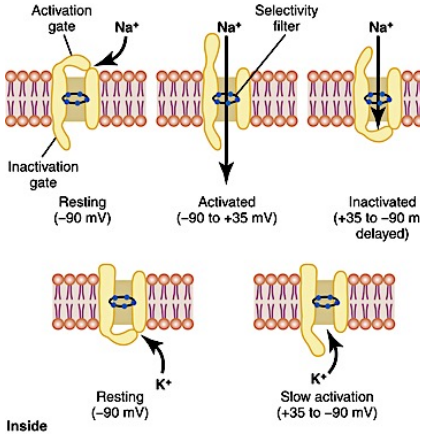
# How does anesthetics work on nerve

- **Applying the 'rule of thumb' shows that local anesthetics will exist approximately 99% ionised at blood pH (7.4).**
- **The site of action of most local anesthetics is a Na+ ion channel found in the cell membrane of nerve cells (or** ***neurons*****).**
- **This sodium channel suggests allows Na+ ions to travel through the cell membrane to depolarise the resting membrane potential and allow the nerve cell to fire.**
- **Local anaesthetics block nerve conduction by attaching to the protein of the sodium channel and disrupting the flow of Na+ ions.**

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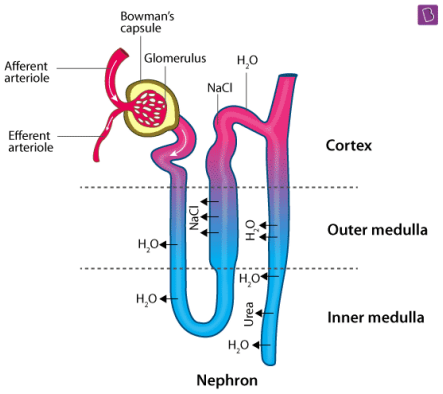
# Excretion and reabsorption of drugs

- **The same types of physicochemical processes occur when drugs are reabsorbed into the bloodstream following excretion by the kidneys.**
- **The two kidneys are situated at the back of the abdomen on either side of the vertebral column.**
- **They carry out many functions in the body, the most important of which is the production of urine and the excretion from the body of low-molecular-weight (relative molecular mass less than 68 000 daltons) water-soluble compounds, including many drugs.**

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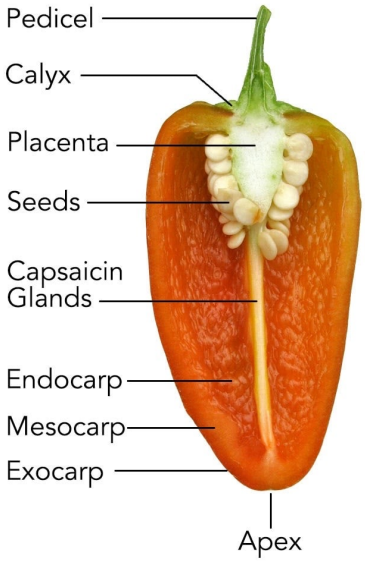
# Food and drink in pharmacological research

- **Spicy foods such as curries and chilies and flavorings such as paprika derive their hot pungent taste from the compound *capsaicin***
- **Capsaicin is found in the fruits of various species of *Capsicum* and is a powerful irritant causing intense pain if administered in a pure form.**
- **Capsaicin is a non-polar compound possessing few polar groups to hydrogen-bond to water.**
- **This means that capsaicin is virtually insoluble in water.**
- **This is important information for people who eat spicy food.**
- **Drinking water with spicy is not useful because capsaicin is not soluble in aqueous solution. (you can eat yogurt with spicy to cool down!).**

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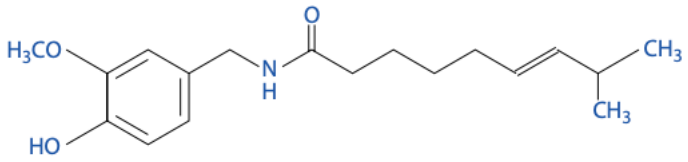
# Capsaicin

- **The irritant properties of capsaicin are employed in pharmacological research, where it is used to stimulate sensory nerves and as an experimental treatment for chronic pain.**
- **Patients suffering intense chronic pain that can no longer be treated by analgesics may gain some relief by the use of capsaicin, which destroys the sensory nerves carrying the painful stimulus.**




**11.** The structure of capsaicin.

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# Lecture 4
# Physicochemical properties of drugs

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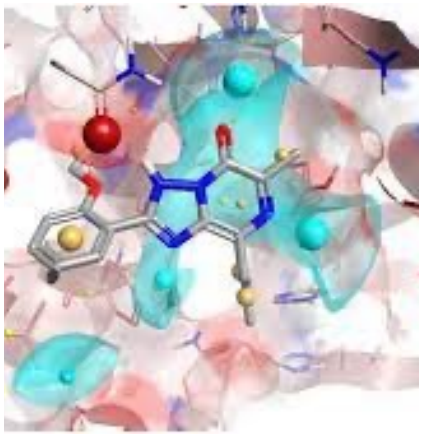
**Department of Applied chemistry**

1

# What do Physical and chemical Properties tells you about drugs?

- **Physical property of drugs is responsible of for its actions.**
- **Chemical property of drugs describe the reaction of drugs extracellularly according to simple reactions like neutralization, chelation oxidation.**



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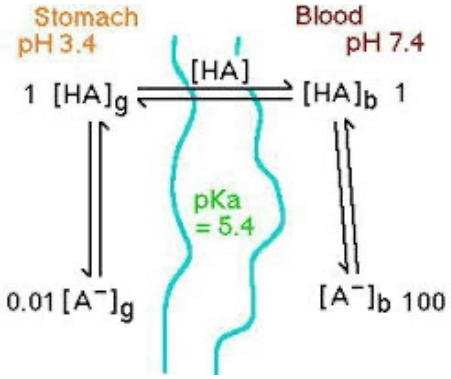
# Physicochemical properties of drugs

- In this lecture we will explore the reasons why drugs behave as acids or bases and what effects ionisation has on the properties of the drug,
- The most important thing to realise about acidic and basic drugs is that values of pKa and pKb.
- It tells you absolutely nothing about whether the drug in question is an acid or a base.
- The pKa and pKb values give information about the strength of acids and bases.

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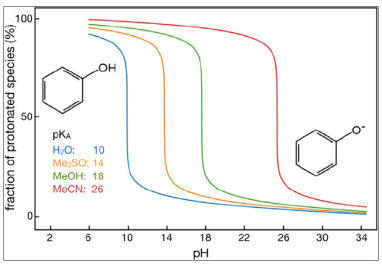
# What do pKa and pKb values tell you?

- The pKa and pKb values tell you the pH at which 50% of the drug is ionised, but *they do not tell you whether a drug behaves as an acid or a base in solution.*
- Amines, for example, are basic and have pKa values of approximately 9, while phenols are acidic and typically have pKa values of around 10.
- The only sure way to know whether a drug is acidic or basic *is to learn the functional groups that confer acidity and basicity on a molecule.*




4

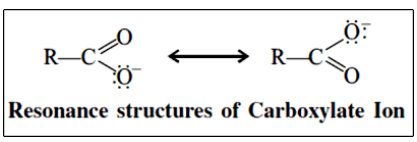
## Carboxylic acids R-COOH

- According to the Brønsted–Lowry definition, an acid is a substance that ionises to donate protons to its surroundings.
- In aqueous solution this is represented as $HA + H_2O \rightleftharpoons H_3O^+ + A^-$
- The most commonly occurring functional group conferring acidity on drug molecules is the carboxyl group, which ionises as shown below:
- A double bond in C=O is much shorter than a C–O single bond (due to sideways repulsion of the electrons in the bond) which are mesured by by X-ray diffraction

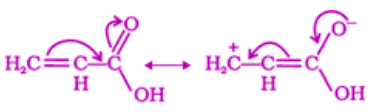
5

## Ionization of Carboxylic acids

- The effect of resonance may be seen when the acidity of a simple carboxylic acid such as acetic acid is compared with the acidity of an alcohol such as ethanol.
- Both compounds can ionise to liberate a proton, but while the anion formed on ionisation of acetic acid is resonance-stabilized.
- The ethoxide anion formed on ionisation of ethanol is not so stabilised and the negative charge resides wholly on the oxygen atom.



Resonance structures of Carboxylate Ion

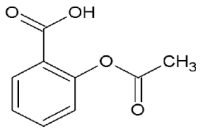




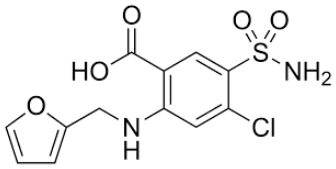
6

## The commonly used drugs are carboxylic acid derivatives

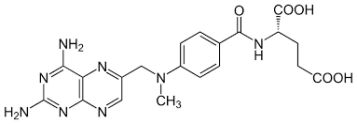
- **A number of commonly used drugs are carboxylic acid derivatives.**
- **These include aspirin (p*K*a 3.5).**
- **The anticancer compound methotrexate (p*K*a 3.8, 4.8 and 5.6)**
- **The the diuretic (previously called frusemide in the UK; p*K*a 3.9).**
- **For aspirin and furosemide acid with p*K*a values of 3.5 and 3.9, the answer is that 99.99% of a given dose of drug will be ionised at the pH of blood or intracellular fluid.**
- **For methotrexate, the answer will be slightly less, but still greater than 99%. This strongly suggests that these drugs are pharmacologically active as the anion, and interact with their individual receptors in the ionic form.**




Aspirin




Furosemide

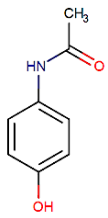


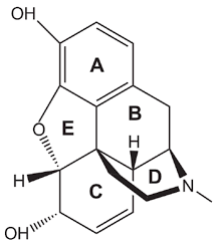

Methotrexate

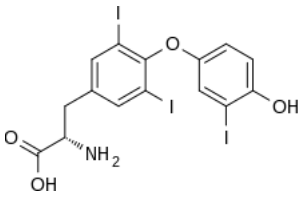
7

## Phenols

- **Another commonly encountered acidic functional group found in drug molecules is phenol, or hydroxybenzene.**
- **Phenols are weak acids that liberate protons to give the phenoxide anion.**
- **This anion is resonance-stabilised and four canonical forms may be drawn.**
- **As with carboxylic acids, the effect of resonance is to distribute the negative charge around the anion.**
- **Phenols are also weaker acids than carbonic acid (H2CO3), which means that they do not react with sodium bicarbonate (cf. carboxylic acids) and may be precipitated from solution of the phenoxide by saturation with carbon dioxide.**
- **Some drugs contain the phenol like paracetamol (p*K*a 9.5), morphine (p*K*a 9.9) and levothyroxine (thy- roxine) (p*K*a 10).**




8

# Warfarin is an anticoagulant

- Warfarin is an anticoagulant that inhibits the clotting action of blood through an action on vitamin K-derived clotting factors.
- Warfarin is used in the UK as the sodium salt, which strongly suggests that the drug is acidic.
- The acidic hydrogen is located between two electron-withdrawing carbonyl groups.
- Upon ionisation, the negative charge can be delocalised onto each of the electronegative oxygen atoms of the dicarbonyl group to yield a resonance-stabilised anion.
- This enhanced stability of the anion allows warfarin to lose a proton and renders the drug acidic with a pKa of 5.0.
- Warfarin exhibits keto–enol tautomerism. This means that warfarin exists in two isomeric forms (tautomers).

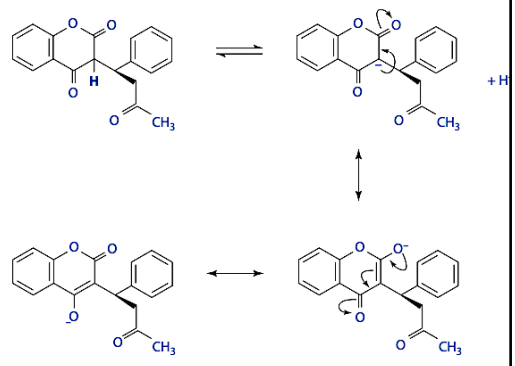


**Figure 3.7.** The ionisation of warfarin.

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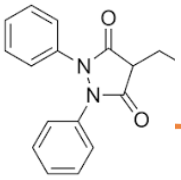
# Phenylbutazone



- Phenylbutazone is a non-steroidal anti-inflammatory drug (NSAID).
- It exerts its anti-inflammatory action through inhibition of the enzyme cyclo-oxygenase COX-1 and COX-2 and inhibition of the production of inflammatory mediators such as prostaglandins.
- Thus, it is a prostaglandin inhibitor with analgesic, anti-inflammatory and antipyretic properties.
- Phenylbutazone, despite containing nitrogen, is a weak acid with a pKa of 4.4.
- The acidic hydrogen is on the 4-position of the pyrazolidinedione ring and upon ionisation the negative charge is delocalised onto the adjacent carbonyl groups in a similar manner to that in warfarin (pKa 5.0).

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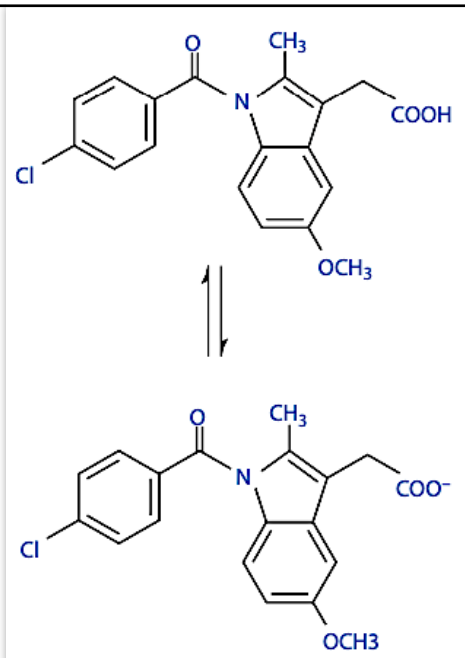
# Indometacin

- **Indometacin is another NSAID with a similar mode of action to that of phenylbutazone.**
- **Indometacin is acidic due to ionisation of the carboxylic acid group and has a p*K*a value of 4.5.**
- **The nitrogen atom in indometacin is present as an amide and is essentially neutral.**




The ionisation of indometacin.

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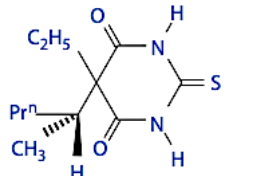
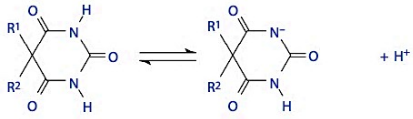
# Barbiturates is an anticonvulsants or antiepileptics

- **Barbiturates are cyclic imides used as hypnotics and (in the case of phenobarbital) as anticonvulsants.**
- **They are all derivatives of barbituric acid (which is not pharmacologically active) and differ only in their substituents on the 5-position of the ring.**
- **Despite Barbiturates contain nitrogen atoms, so barbiturates are not basic.**
- **Instead, they behave as weak acids in solution (diprotic actually, though the second ionisation is very weak).**




The structure of thiopental.

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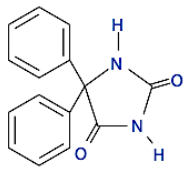
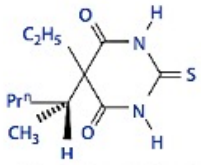
# Phenytoin

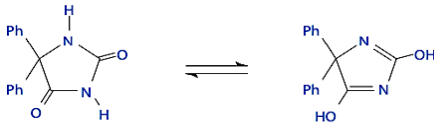
- **Phenytoin is an anticonvulsant widely used in the treatment of epilepsy.**
- **The properties of phenytoin resemble those of barbiturates.**
- **It is a cyclic imide with a p*K*a of 8.3.**
- **The anion is stabilised by resonance of the negative charge onto the oxygens of the carbonyl group and the drug is usually administered as the sodium salt to increase water solubility.**
- **Phenytoin and barbiturates display tautomerism of the imine–imide type.**



The structure of phenytoin.



The structure of thiopental.




6. The tautomerism of phenytoin.

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# Sulfonamides
# sulfa antibacterial drugs

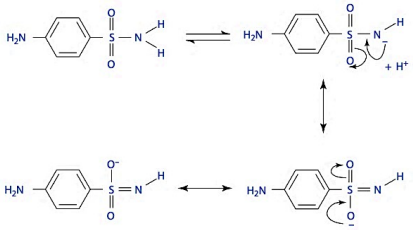

Figure 3.17. The ionisation of a sulfonamide.

- **Sulfonamides are a class of antibacterial compounds, all of which contain the sulfonamido group –SO2NH.**
- **Sulfonamides was used before antibiotics such as penicillin and cephalosporins.**
- **Sulfonamides are all weakly acidic (p*K*a approximately 5–8) due to the powerful electron-withdrawing effect of the –SO2– substituent and stabilisation of the resulting anion by resonance.**
- **Sulfonamides are usually administered in the form of the sodium salt to increase their water solubility.**

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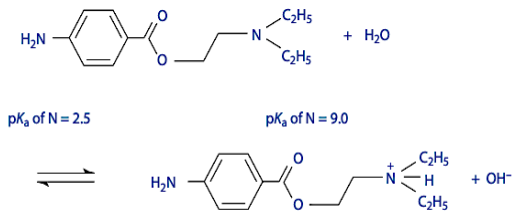
# Basic drugs




**gure 3.18.** The ionisation of procaine.

- **Basic drugs are usually administered as their water-soluble salts (generally the hydrochloride).**
- **An amine in aqueous solution will react with water to release hydroxide ions (OH– ):**

$$R_3N + H_2O \rightleftharpoons R_3NH^+ + OH^-$$

- **The basicity of amines gives the availability of the lone pair of electrons on the nitrogen atom.**
- **If the lone pair is involved in interactions elsewhere in the molecule, then the amine will not be basic.**
- **Conversely, the lone pair of electrons on the amino group attached to the benzene ring is less available for reaction with protons due to delocalisation into the ring.**
- **This delocalisation increases the electron density of the *ortho*- and *para*-carbon atoms and means that the Ar–NH2 group does not ionise at the pH of blood.**

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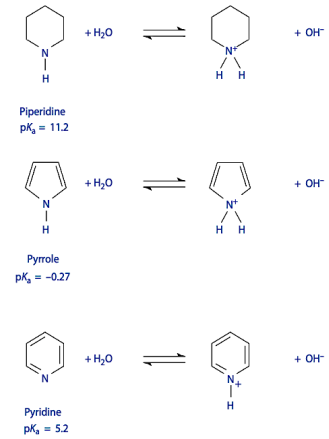
## Basicity of heterocyclic compounds

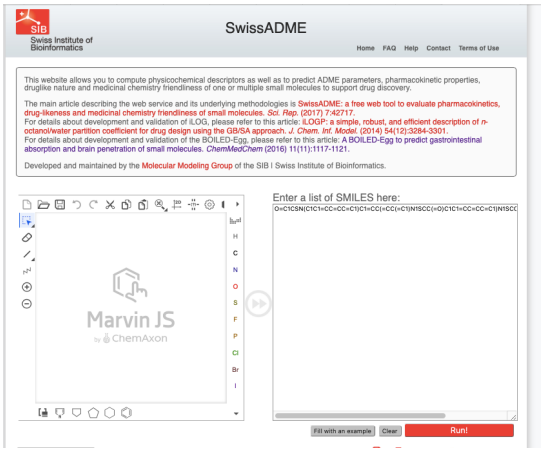
- **Many drugs and biologically active compounds contain nitrogen in a heterocyclic ring.**
- **heterocyclic ring can be aliphatic and aromatic.**
- **In aliphatic heterocyclic compounds, the nitrogen atom is part of a saturated heterocyclic ring and the lone pair of electrons is available for reaction with protons (e.g. piperidine,).**
- **Compounds of this type are similar in base strength to their open-chain aliphatic counterparts, with typical pKa values of 8–9.**
- **In aromatic heterocyclic compounds lone pairs on the nitrogen atoms are involved in interaction with electrons of the aromatic ring.**
- **In pyrrole, the lone pair contributes to the 6-aromatic ring and is not available for reaction with protons.**
- **As a result, pyrrole is a very weak base with a pKa value so low that it is a negative number.**
- **However, pyridine has only one electron from the nitrogen contributes to the 6-aromatic ring. leaves an unshared pair of electrons with a pKa value of 5.2 to be basic.**

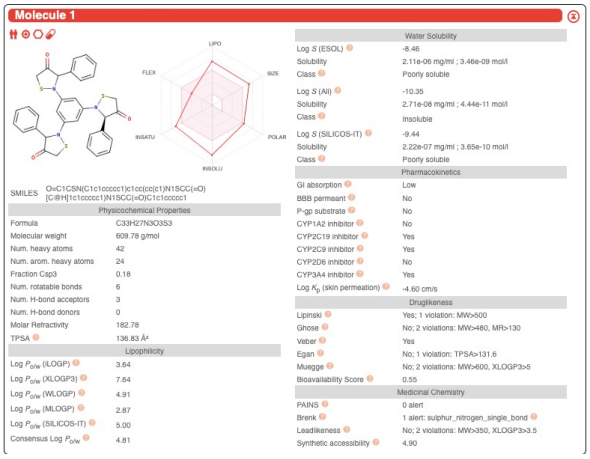



**3.19.** The ionisation of some nitrogen-containing heterocyclics.

16

# Using SwissADME online to do QSAR: here, an example




Visit: http://www.swissadme.ch/index.php

draw your drug using ChemDraw or from Pubchem server https://pubchem.ncbi.nlm.nih.gov

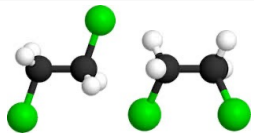
17

# Lecture 5
# Stereochemistry of drugs structure

**Dr Manaf Abdulrahman Guma**
**University Of Anbar- college of Applied sciences-Hit**
**Department of Applied chemistry**

1

## Geometry and isomers of compounds



- **Here, we study the unusual geometry that arises around a carbon atom with four different substituents attached to it — an *asymmetric carbon atom*.**
- **The study of the three-dimensional shape of molecules is important to for drug design.**
- **Chemical compounds that have the same molecular formula, but different structural formulas are said to be isomers of each other.**
- **These structural isomers differ in their bonding sequence, i.e. their atoms are connected to each other in different ways.**
- **Stereoisomers have the same bonding sequence, but they differ in the orientation of their atoms in space.**

2

# Stereoisomerism

- **Stereoisomerism can be further divided into:**
- **optical isomerism (enantiomerism).**
- **geometrical isomerism (cis–trans isomerism).**

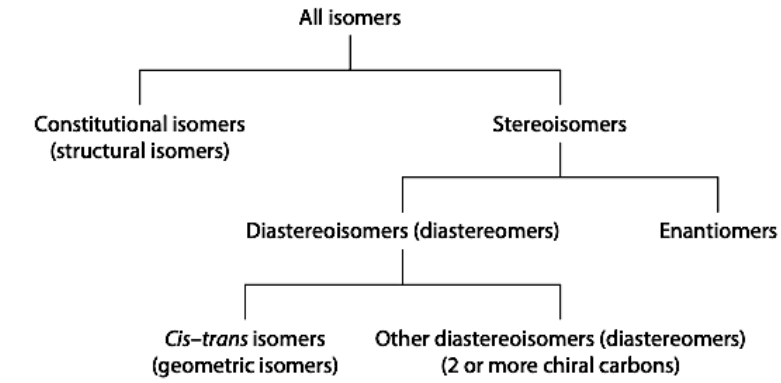
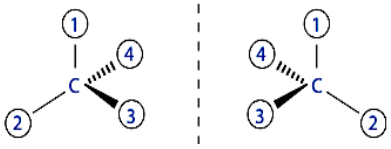



**Figure 4.1.** Different types of isomerism.

3

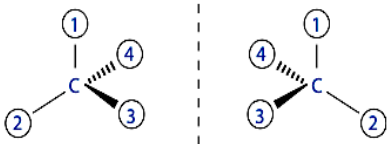
# sp3 hybridization and *chirality*




- **There are a number of atoms that display optical isomerism, including nitrogen and phosphorus.**
- **The most commonly encountered in drugs, is that of an sp3 hybridised carbon atom with four different substituents attached to it.**
- **A carbon like this is said to be chiral and to display the property of chirality.**
- **If the four substituents are different, a pair of non-superimposable mirror image forms can be drawn. These two isomers are called enantiomers.**
- **A chiral compound always has an enantiomer.**
- **whereas an achiral compound has a mirror image that is the same as the original molecule.**

4

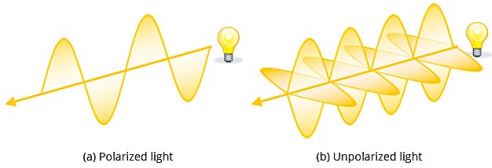
## Enantiomers and the physical properties




- **Enantiomers have identical or nearly identical physical properties unless a reagent or technique is used that is itself chiral.**
- **For example, the two enantiomers have the same boiling point, melting point, refractive index and density since these are bulk effects and cannot discriminate between the two enantiomers.**
- **Differences between enantiomers only become apparent when they interact with chiral reagents such as the active sites of enzymes or the chiral stationary phase of a HPLC column.**

5

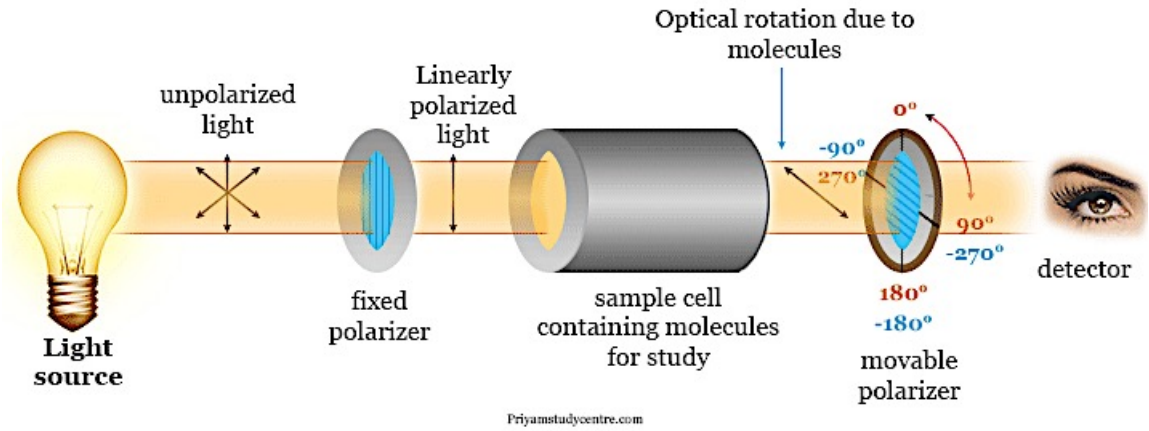
## Polarimetry




- **In the laboratory, the technique of polarimetry is used to distinguish between enantiomers and to measure the extent to which each enantiomer rotates the plane of plane-polarised light.**
- **Most of the light detected by our eyes is not polarized.**
- **It is the light waves vibrate randomly in all directions perpendicular to the direction of propagation of the wave.**
- **If normal light of this type is passed through a material that is itself chiral then the waves of light interact with the chiral material to produce light that is oscillating in only one plane.**
- **This light is called plane-polarised light.**

6

## Instrumentation of polarimetry




7

## The angle of rotation of plane-polarised light.

- **When plane-polarised light is passed through a solution containing an optically active substance.**
- **The chiral compound causes the plane of vibration of the light to rotate (the origin of the expression optical activity).**
- **The number of degrees of rotation can be measured and read off a calibrated scale.**
- **This is a description of an instrument called a polarimeter, which is used to measure the angle of rotation of plane-polarised light.**

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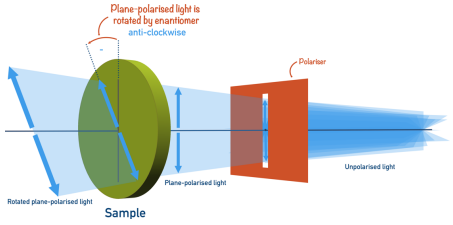
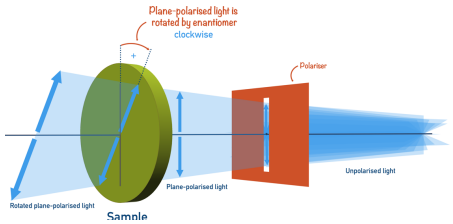
## *Dextrorotatory* & laevorotatory

- Compounds that rotate the plane of polarised light towards the right (clock- wise) are called *dextrorotatory*.
- while compounds that rotate the plane to the left, or anticlockwise, are called *laevorotatory*.
- A *racemic mixture* that is composed of equal amounts of dextrorotatory and levorotatory forms of enantiomers of the same compound and is not optically active.
- Such a mixture is called a *racemic mixture* or a *racemate*.

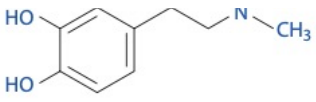



9

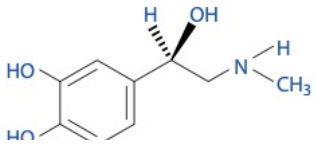
# Enantiomer and biological activity

- The common synthesis of adrenaline (epinephrine hormone), yields a racemic mixture, which has precisely 50% of the biological activity of the natural hormone.
- Once the racemate is resolved into the two pure enantiomers.
- The (*R*)-(−)-adrenaline is found to be identical to the natural hormone produced by the adrenal medulla, while the other enantiomer.
- The (*S*)-(+) isomer, has little or no biological activity.




*R/S* racemic adrenaline

Resolution

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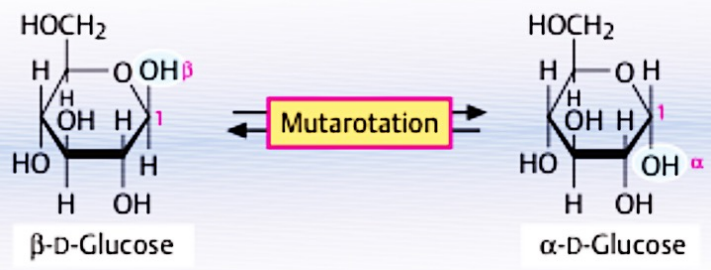
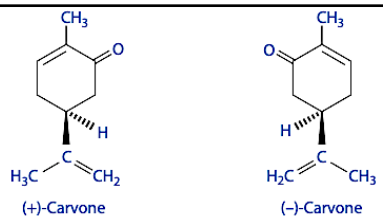
# Mutarotation

- Occasionally, the specific rotation of a compound can change over time.
- This phenomenon called mutarotation and is caused by a change in the molecular structure of the chiral compound.
- A good example of this can be seen with the monosaccharide glucose. α-D-(+)-Glucose has an [α] value of +110◦, while β-D-(+)-glucose has an [α] value of +19.7◦.




11

## Biological systems




- For example, (–)-Carvone is a natural product with the smell of spearmint oil. (+)-Carvone, the enantiomer, has the odour of caraway seeds
- This is an example of a general rule, which is that the body is chiral and body systems can discriminate between enantiomers of chiral drugs.
- when drugs or medicines are administered to the body, there is the opportunity for chiral interactions.
- This is because the human body is composed of enzymes and receptors that are protein in nature.
- These proteins are polymers of 20 or so naturally occurring amino acids. With the exception of glycine, all of these amino acids are chiral and it must be expected that a chiral drug will interact with these chiral receptors differently from its enantiomer.

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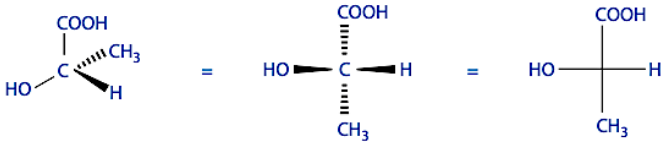
# Fischer projections




(*S*)-Lactic acid

Fischer projection
(*S*)-Lactic acid

- **It is sometimes useful to be able to draw a schematic diagram of the stereochemistry around a chiral carbon, especially when a molecule contains more than one chiral centre.**
- **The German chemist Emil Fischer solved this problem and his method of representing chiral centres is now called a Fischer projection.**
- **A Fischer projection looks like a cross, with the chiral centre at the point where the lines cross.**
- **In this way the tetrahedral arrangement of groups around an sp3 hybridised carbon, for example, may be represented on a page in two dimensions.**
- **An example of a Fischer projection of lactic acid, the acid produced when milk turns sour.**

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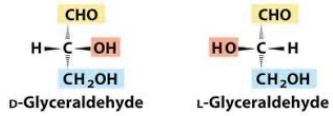
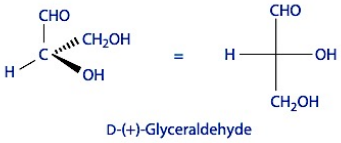
# D and L configurations

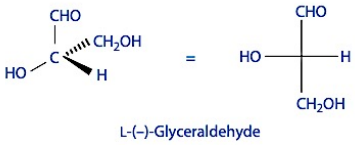
- **The Fischer projection allows the stereochemistry around a chiral centre to be represented in two dimensions.**
- **Using the Fischer projection, a different system of describing the configuration of groups around a chiral centre can now be introduced, the D and L convention.**
- **The dextrorotatory isomer of glyceraldehyde, (+)-glyceraldehyde, was arbitrarily assigned the absolute configuration.**
- **All of the 'natural' amino acids found in human proteins are found to have the NH3+ group on the left-hand side of the Fischer projection and are therefore similar in configuration to L-(−)-glyceraldehyde.**



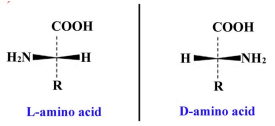

**Perspective formulas**




D-(+)-Glyceraldehyde




L-(−)-Glyceraldehyde

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# The bioactivity of penicillin anti-biotics

- **The mode of action of penicillin anti- biotics depends on the opposite stereochemistry of bacterial amino acids.**
- **In penicillin-sensitive bacteria, the organism synthesizes a cell wall to contain the high osmotic pressure produced inside the bacterial cell.**
- **The bacterial cell wall consists of a polysaccharide (called *peptidoglycan*), which is re-inforced by structural cross-linking of chains of polypeptide.**
- **The final step of the cross-linking is achieved by attaching the terminal amino acid of the cell wall, a glycine, to a D-alanine residue on an adjacent peptide chain.**
- **This cross-linking is catalysed by an enzyme called *transpeptidase* (or transaminase).**
- **Penicillins can inhibit the enzyme transpeptidase and prevent the formation of structural cross-links in the bacterial cell wall.**
- **The cell is weakened, becomes unable to contain the high internal osmotic pressure and bursts.**

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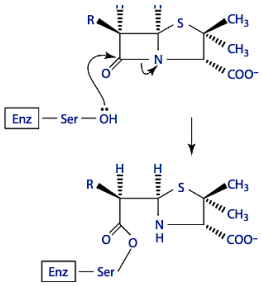
# Mode of action of β-lactam antibiotics

- **The cephalosporins which are antibiotics similar to penicillin, are known collectively as β-lactam antibiotics.**
- **The β-lactam ring is the 4-membered cyclic amide ring common to both classes of antibiotics and fundamental to the molecular mode of action of the drugs.**
- **The β-lactam ring is under immense strain and opens easily if attacked by a nucleophile.**
- **This is because amides contain sp2 hybridised carbon atoms, which normally have a bond angle of 120◦. The bond angle of the amide in a β-lactam ring approaches 90◦.**
- **A serine residue present in the active site of transpeptidase can attack the β-lactam ring, using the lone pair of electrons on the –OH, open the ring and so acylate the active site of the enzyme and prevent cell wall cross-linking.**

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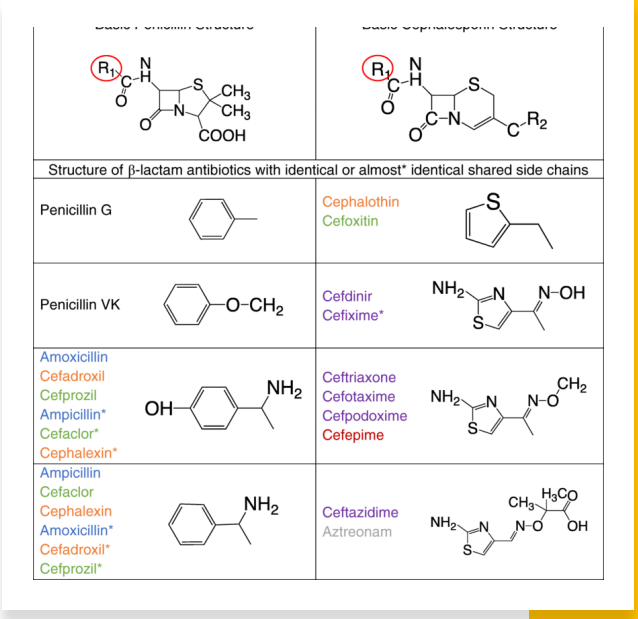
# Penicillin is non-toxic to humans

- **Unfortunately, other nucleophiles can open a β-lactam ring and inactivate penicillin.**
- **Some bacteria have evolved mechanisms to overcome penicillins and are said to be resistant to the drug.**
- **Penicillins are non-toxic to humans because we possess L-alanine, the amino acid with the opposite stereochemistry, in our proteins.**
- **This is an example of an important concept in drug design called *selective toxicity*, which arises when a drug is poisonous to one type of organism or cell (a bacterium in this case) but harmless to another (human cells).**

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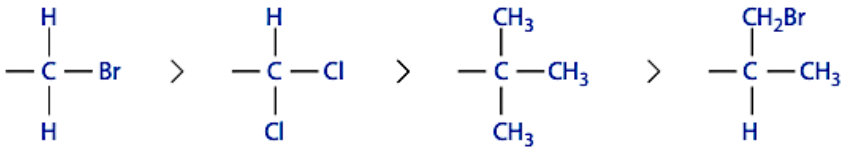
# *R* and *S* configurations

- **The absolute configuration of atoms around a chiral centre may be drawn accurately by use of a Fischer projection and may be described (particularly in biochemistry for chiral carbohydrates and amino acids) by the D/L convention.**
- **This system assigns each chiral centre in a molecule a letter (*R* or *S*) and is the method of choice when assigning the configuration of chiral centres of drug molecules.**
- **for example: If two groups cannot be distinguished on the basis of atomic number, the next atom of the group attached to the chiral centre is considered, and so on until the priorities are clear.**



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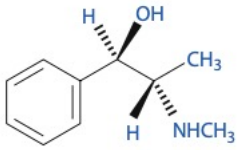
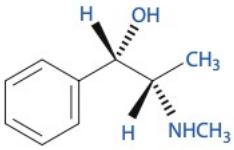
## Molecules with more than one chiral center




Ephedrine




Pseudoephedrine

- Since there are two possible configurations for an asymmetrically substituted carbon atom, a structure containing *n* such centres will, in theory, possess 2*n* stereoisomers.
- The actual number of stereoisomers that exist may be less than this due to steric effects.
- Compounds that have the same stereochemistry at one chiral centre but different stereochemistry at the others are known as *diastereoisomers* (diastereomers).
- A good example is given by the alkaloids ephedrine and pseudoephedrine.
- Ephedrine (the (1*R*,2*S*) diastereoisomer) is a natural product (Chinese medicine) was used in the past century for the treatment of asthma.
- Pseudoephedrine (the (1*S*,2*S*) diastereoisomer) is a decongestant and a constituent of several 'over-the-counter' cold and flu remedies.

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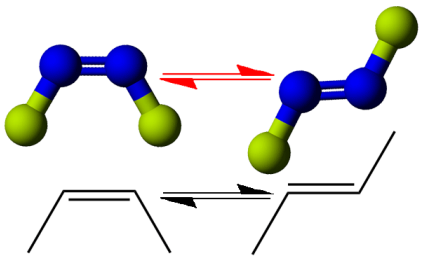
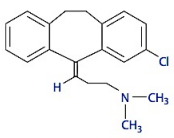
## Geometrical isomerism (cis–trans) isomerism

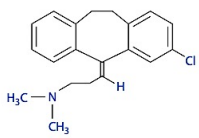
- Compounds that possess a multiple bond do not rotate easily about the bond.
- This gives rise to a type of isomerism called *geometrical* (or *cis–trans*) isomerism.
- If the substituents around the double bond are similar and both are on the same side of the double bond, the term *cis* is used to describe the molecule. If the same groups are on opposite sides of the double bond, the term trans is used to describe the configuration,
- For example, Chlordiazepoxide is used to treat mental depression.



*cis* (*Z*) *trans* (*E*)




Chloroamitriptyline (*Z*) isomer




Chloroamitriptyline (*E*) isomer

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# Lecture 6
# Drug metabolism

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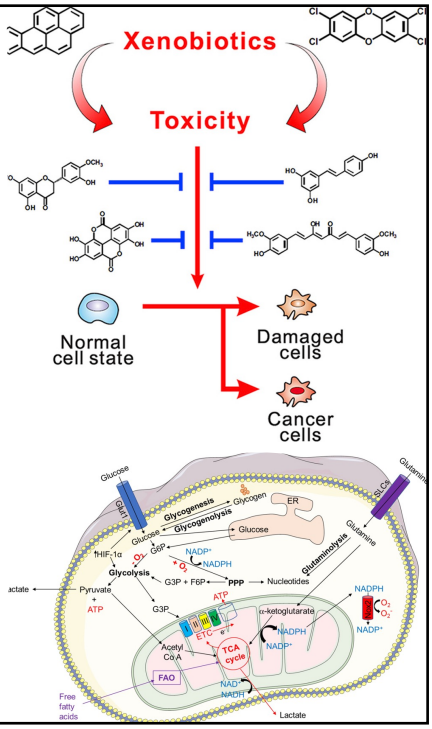
**University Of Anbar- college of Applied sciences-Hit**
**Department of Applied chemistry**

1

# Metabolic pathways

- **Foreign compounds such as drugs taken into the body undergo enzymatic transformations, which usually result in a loss of pharmacological activity. This is known as *detoxification*.**
- **The action of these enzymes may convert an inactive compound (for example, a prodrug) into a pharmacologically active compound.**
- **In this case, the process is described as *bioactivation*.**
- **There are two main types of biotransformation observed in the body, imaginatively called *Phase 1* and *Phase 2* reactions, although many drugs undergo both types of process. (next…)**

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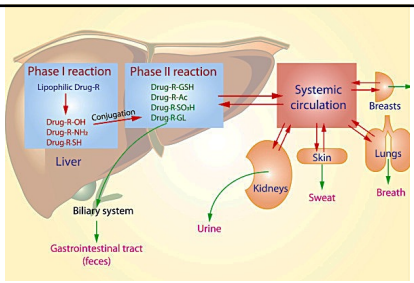
# Biotransformation Phase 1 reactions




- **Definition: modification of the drug molecule via oxidation, reduction, or hydrolysis.**
- **Phase 1 reactions are reactions in which a new functional group is introduced into the molecule, or an existing group is converted into another (usually more water-soluble) derivative.**
- **Microsomal metabolism: Cytochrome P450 isozymes.**
- **Non-microsomal metabolism such as Hydrolysis, Monoamine oxidases and Alcohol metabolism**

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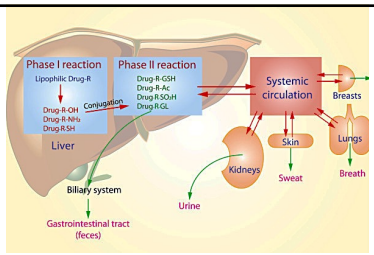
# Biotransformation Phase 2 reactions




- **Definition: Conjugation with endogenous compounds via the activity of transferases.**
- **Phase 2 reactions, or conjugations, are where an existing functional group in the molecule is masked by the addition of a new group.**
- **Types of conjugation: Glucuronidation, Acetylation and Glutathione**

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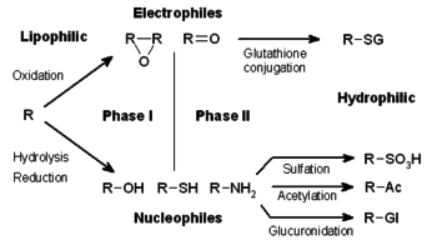
## What happen to the xenobiotics in the body?




- The body's main strategy for dealing with these ''xenobiotics" is to convert the molecule into a more hydrophilic or water-soluble derivative, which can then be excreted via the kidneys in the urine.
- Most small drug molecules are relatively lipophilic and in the body.
- Often these drugs (metabolites) are more hydrophilic than their parent drug.
- Metabolites may possess a different level of activity as the starting compound or none at all..
- In some cases, a parent drug may be inactive but is then converted into the active metabolite in the body.

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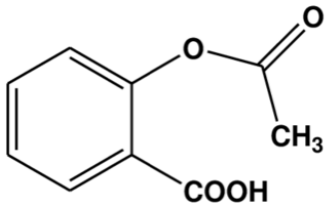
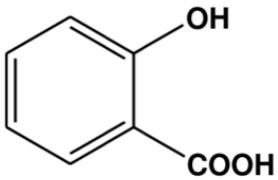



Aspirin (prodrug)




Salicylic acid

## What are *prodrugs?*

- In some cases, a parent drug may be inactive but is then converted into the active metabolite in the body.
- *These drugs are referred to as prodrugs.*
- Prodrugs are pharmacologically inactive derivatives of the active molecule.
- They are designed to break down within the body to release the active drug.
- Examples include anticancer agents such as cyclophosphamide or antibiotics such as pivmecillinam.

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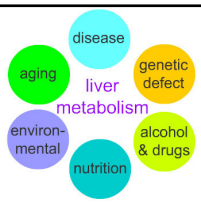
## The chemical reactions are influenced by a number of factors including:




- **The drug metabolism involve simple chemical reactions such as oxidation (the most common), reduction and dealkylation and are influenced by a number of factors including:**

1. ***Genetic factors*: The science of *pharmaco-genomics*.**
2. ***Physiological factors. These include age of the patient, gender, pregnancy and nutritional status*.**
3. ***Pharmacodynamic factors*.**
4. ***Environmental factors*.**

**The most important and most extensively studied drug metabolism system in the body is the superfamily of cytochrome P450 monooxygenases (CYP450).**

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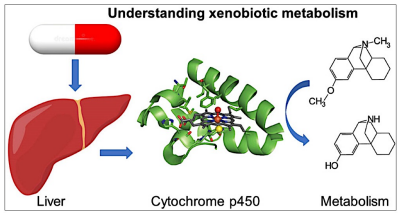
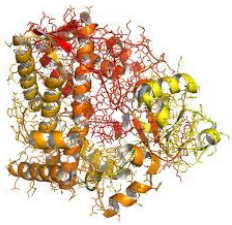
## Cytochromes P450 Microsomal metabolism



- **The cytochrome P450 (CYP) enzymes are membrane-bound hemoproteins that play a pivotal role in the detoxification of xenobiotics, cellular metabolism and homeostasis.**
- **Induction or inhibition of CYP enzymes is a major mechanism that underlies drug-drug interactions.**
- **The most important studied drug metabolism system in the body is the superfamily of cytochrome P450 monooxygenases (CYP450).**
- **Many different forms of these enzymes exist (called isoforms), such as 60 different types of human CYP CYP1A1 CYP1B1, CYP2D.**
- **CYP450 acts as an active electron transport system which is responsible for the oxidative metabolism of a large number of drugs and other xenobiotics such as bile acids, prostaglandins and vitamins.**

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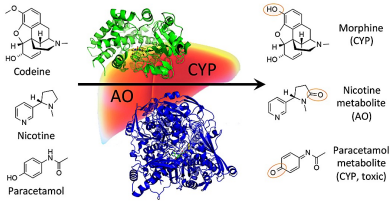
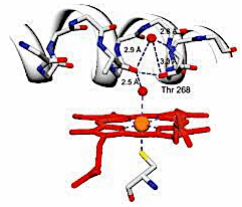
# CYP3A4 substrate and co-enzyme

- **Substrates for CYP3A4 include drugs such as codeine, erythromycin and lidocaine. Other endogenous compounds are substrates such as testosterone and progesterone.**
- **Cytochrome P450s perform all these metabolic transformations due to the presence of an ion of iron Fe at the active site.**
- **Fe can accept or donate electrons to allow oxidation reactions to take place.**
- **The iron in CYP450 is bound within a heme co-factor and can exist in a number of oxidation states, of which Fe2+ (ferrous) and Fe3+ (ferric) are the most important.**
- **The functional group could be affected by CYP450 and therefore change the metabolic pathway which changes on the physicochemical properties of drugs.**




Heme iron centers in cytochrome P450

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# A list of the types of transformation catalysed by CYP450s

Table 5.1 Oxidative biotransformations catalysed by CYP450

| Substrate | Product(s) |
|---|---|
| **1. Side-chain oxidation** | |
| Pentobarbital | |
| Ibuprofen | |
| **2. Aromatic ring oxidation** | |
| Acetanilide | Paracetamol |
| **3. Methyl oxidation** | |
| Tolbutamide | |

Table 5.1 (continued)

| Substrate | Product(s) |
|---|---|
| **10. Sulfoxidation** | |
| Chlorpromazine | Chlorpromazine sulfoxide |

Table 5.1 (continued)

| Substrate | Product(s) |
|---|---|
| **6. *O*-Dealkylation** | |
| Phenacetin | Paracetamol |

| | |
|---|---|
| **8. Deamination** | |
| Amfetamine | + $NH_4^+$ |
| **9. *N*-Oxidation** | |
| Trimethylamine | Trimethylamine oxide |

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## Enzyme induction and inhibition

### Enzyme Inhibitor & Inducer

| Enzyme Inhibitor | Enzyme Inducer |
|---|---|
| Cimetidine | Rifampicin |
| Ketoconazole | Carbamazepine |
| Fluconazole | Phenobarbital |

- **A xenobiotic can lead to an increased rate of metabolism of a wide variety of compounds. This process is known as *enzyme induction* and is dose- dependent.**
- **The CYP450 enzyme system is responsible for a large number of biotransformation, so the possibility of drug interactions is very large.**
- **Environmental chemicals such as polycyclic aromatic hydrocarbons (PAHs) present in cigarette smoke, xanthines and flavones in foods, and other can all change the activity of CYP450 enzymes.**

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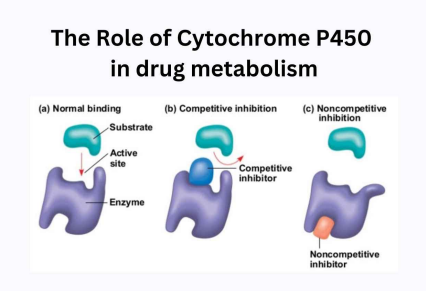
# Type of inhibitions of *CYP450*

- ***Reversible inhibitors*, such as cimetidine, which interact with the complexed iron at the active site of the enzyme to inhibit oxidation of other drugs.**
- ***Metabolite intermediate complexation of CYP450*. Examples of this type of inhibition include alkylamine drugs that undergo oxidation to o-nitrosoalkane derivatives.**
- ***Mechanism-based inactivation of CYP450* (or *suicide inhibition*) occurs when a non-toxic drug is metabolised by CYP450 irreversibly. Examples include the antibiotic chloramphenicol and the anticancer agent cyclophosphamide.**

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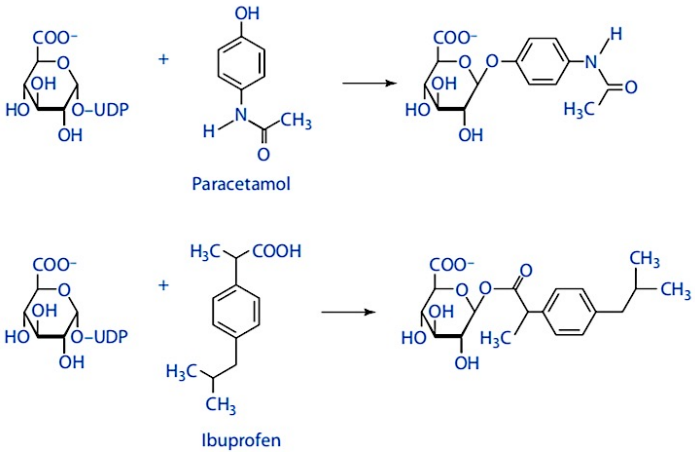
# Drug conjugation reactions (Phase 2)

- **Conjugation reactions are very important in the biotransformation of drugs and foreign chemicals within the body.**
- **The drug conjugate is much less lipophilic and much more water soluble and is excreted easily by the kidneys.**
- **The conjugate is formed between the drug and a hydrophilic compound such as glucuronic acid.**
- **The resulting conjugate (a glucuronide) will usually be much more water soluble than the parent drug.**




**Formation of glucuronides**

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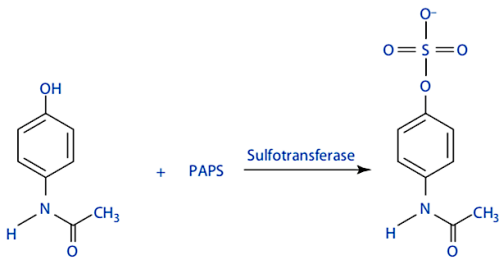
# Sulfate conjugation

- **Drugs and hormones that contain the phenolic functional group are metabolised by conjugation to a sulfate group (a process called sulfation).**
- **Examples of compounds metabolised in this way include the neuro-transmitter noradrenaline (norepinephrine) as well as hormones such as adrenaline (epinephrine), thyroxine and some steroids.**




**Sulfation of paracetamol**

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## Amino acid conjugation

- **Conjugation with amino acids is an important route of Phase 2 metabolism for xenobiotics containing a carboxylic acid functional group. The amino acids involved include glycine, glutamine and taurine (an aminosulfonic acid produced from cysteine).**
- **The major class of drug metabolised by this route is that of the non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and ketoprofen.**

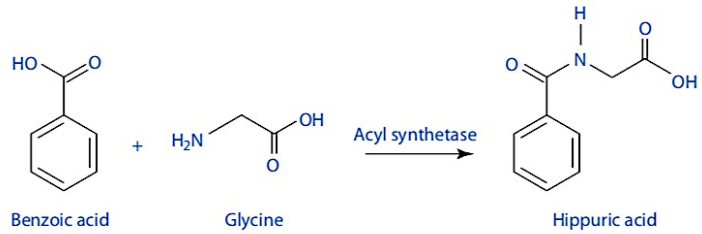


**Figure 5.4.** Glycine conjugation of benzoic acid.

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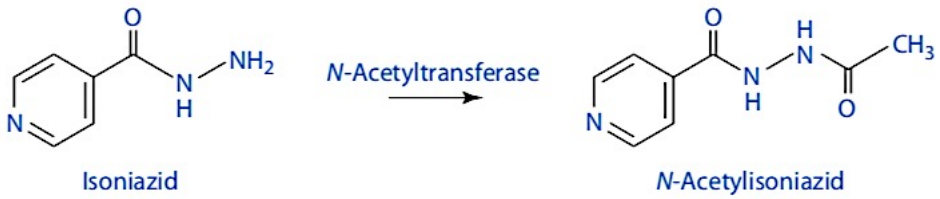
## *N*-acetylation

- **Several other types of conjugation reaction exist in the Phase 2 metabolism of drugs. Compounds possessing an amino group often undergo *N*-acetylation, primarily in the liver although other sites are known.**
- ***N* -Acetylation of an amine is unusual in that the product formed is generally less water soluble than the parent amine, particularly if the solution is slightly acidic.**
- **These two subgroups of the population display differences in the rates of metabolism of a number of drugs, including procainamide, and isoniazid.**




***N*-Acetylation of isoniazid.**

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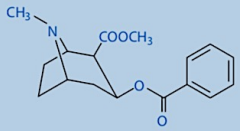
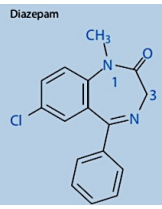
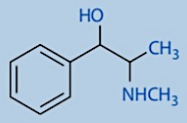
# Metabolic pathways for common drugs

| Drug | Pathway |
|---|---|
| Cocaine  | Hydrolysis of methyl ester<br>Hydrolysis of benzoate ester<br>*N*-dealkylation<br>Both hydrolysis and *N*-dealkylation |
| Diazepam  | *N*-dealkylation at $N^1$<br>Hydroxylation at carbon-3<br>Conjugation of phenolic products with glucuronic acid<br>Both *N*-dealkylation of $N^1$ and hydroxylation at carbon-3 |

| Drug | Pathway |
|---|---|
| Ephedrine  | *N*-dealkylation<br>Oxidative deamination<br>Oxidation of deaminated product to benzoic acid<br>Reduction of deaminated product to 1,2-diol |

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# Lecture 7
# Pharmacodynamic of drugs and medicines

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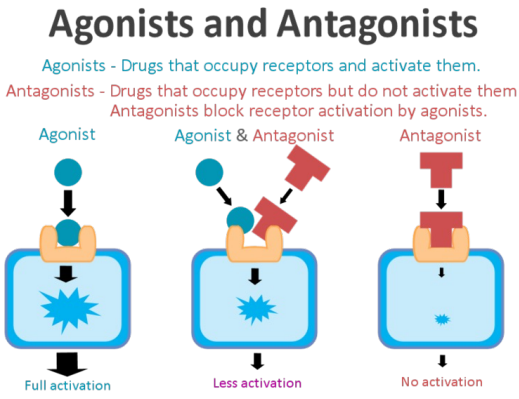
1

# Definitions

- **Pharmacodynamics** relates to drugs binding to receptors and their effects.
- **Agonist**: A drug is called an agonist when binding to the receptor results in a response.
- **Antagonist**: A drug is called an antagonist when binding to the receptor is not associated with a response. The drug has an effect only by preventing an agonist from binding to the receptor.

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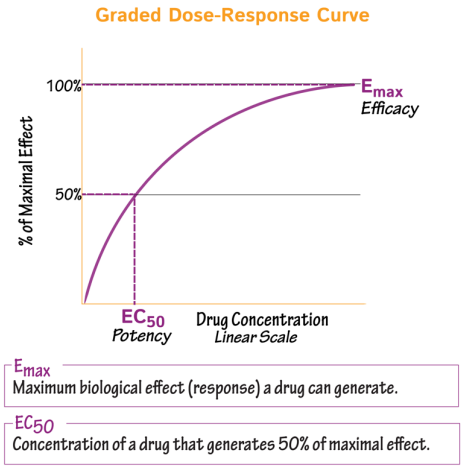
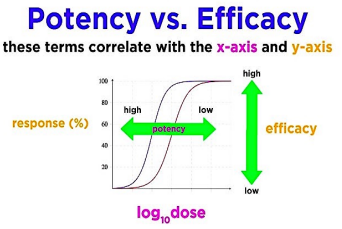
# Affinity



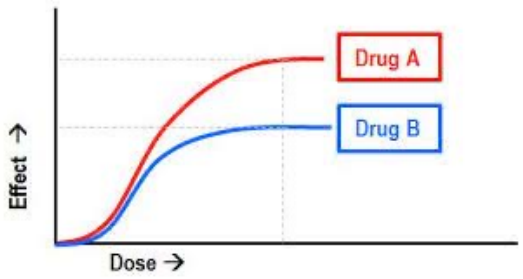

- **Affinity**: ability of drug to bind to receptor, shown by the proximity of the curve to they axis (if the curves are parallel); the nearer they axis, the greater the affinity.
- Also, **Affinity**: how well a drug and a receptor recognize each other.
- Affinity is inversely related to the Kd of the d rug.
- Notice the analogy to the Km value used in enzyme kinetic studies.

3

# Potency



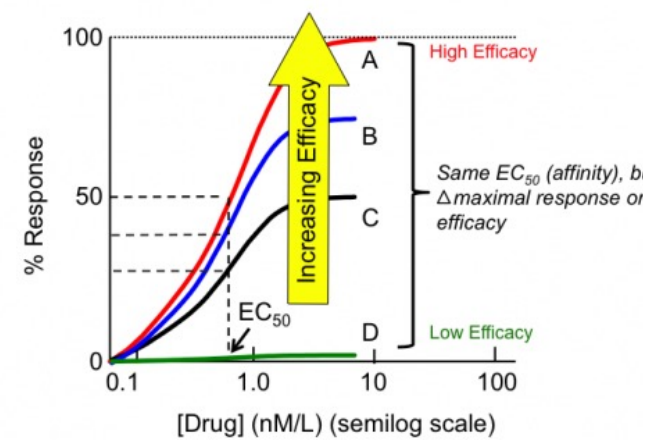

- **Potency**: shows relative doses of two or more agonists to produce the same magnitude of effect, again shown by the proximity of the respective curves to they axis (if the curves do not cross).
- **Potency**: the quantity of drug required to achieve a desired effect.
- In D-R measurements, the chosen effect is usually 50% of the maximal effect, but clinically, any size response can be sought.




4

# Efficacy

- **Efficacy**: a measure of how well a drug produces a response (effective ness), shown by the maximal height reached by the curve.
- **Efficacy**: the maximal effect an agonist can achieve at the highest practical concentration.
- Notice the analogy with the Vmax used in enzyme kinetic studies.

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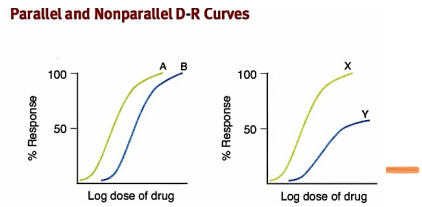
# Graded (Quantitative) Dose-response (D-R) Curves




**Plots of dose (or log dose) versus response for drugs (agonists) that activate receptors can reveal information about affinity, potency, and efficacy of these agonists.**

- **It may be seen from the log dose-response curves in Figure 1-2-1 that:**
- **l. When two drugs interact with the same receptor (same pharmacologic mechanism), the D-R curves will have parallel slopes.**
- **Drugs A and B have the same mechanism; drugs X and Y do not.**
- **2. affinity can be compared only when two drugs bind to the same receptor.**
- **Drug A has a greater affinity than drug B.**
- **3. In terms of potency, drug A has greater potency than drug B, and X is more potent than Y.**
- **4. In terms of efficacy, drugs A and B are equivalent. Drug X has greater efficacy than drug Y.**

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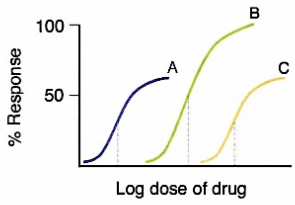
# Full and Partial Agonists

- **Full agonists produce a maximal response-they have maximal efficacy.**
- **Partial agonists are incapable of eliciting a maximal response and are less effective than full agonists.**
- **In Figure 1-2-2, drug B is a full agonist, and drugs A and C are partial.**
- **Drug A is more potent than drug C , and drug B is more potent than drug C.**
- **At low responses, A is more potent than B, but at high responses, the reverse is true.**




2. Efficacy and Potency of Full and Partial Agonists

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## Duality of Partial Agonists

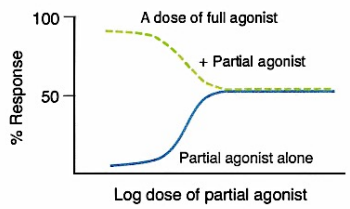


Figure I-2-3. Duality of Partial Agonists

- **In Figure I-2-3, the lower curve represents effects of a partial agonist**
- **when used alone-its ceiling effect = 50% of maximal in this example.**
- **The upper curve shows the effect of increasing doses of the partial ago nist on the maximal response ( 1 00%) achieved in the presence of or by pretreatment with a full agonist.**
- **As the partial agonist displaces the full agonist from the receptor, the response is reduced-the partial agonist is acting as an antagonist.**
- **Bridge to Biochemistry**
- **Parallels between Receptor Antagonists and Enzyme Inhibitors**
- **Competitive antagonists are analogous to competitive inhibitors; they decrease affinity (i Km) but not maximal response (Vmax remains the same).**
- **Noncompetitive antagonists decrease Vmax but do not change the Km.**

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# Toxicity and the Therapeutic Index (TI)

- **Comparisons between ED50 and TD50 values permit evaluation of the relative safety of a drug (the herapeutic index) , as would comparison between ED50 and the lethal median dose (LD50) if the latter is known.**
- **As shown in Figure I-2-5, these D-R curves can also be used to show the relationship between dose and toxic effects of a drug. The median toxic dose of a drug (TD50) is the dose that causes toxicity in 50% of a population.**
- **From the data shown, TI = 10/2 = 5**
- **Such indices are of most value when toxicity represents an extension of the pharmacologic actions of a drug. They do not predict idiosyncratic reactions or drug hypersensitivity.**

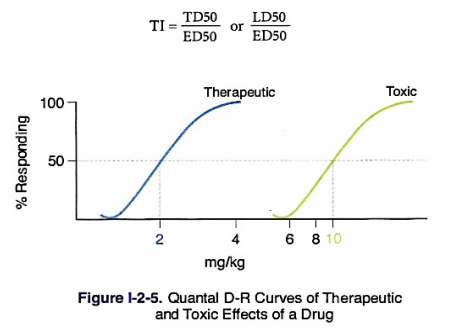


**Figure I-2-5.** Quantal D-R Curves of Therapeutic and Toxic Effects of a Drug

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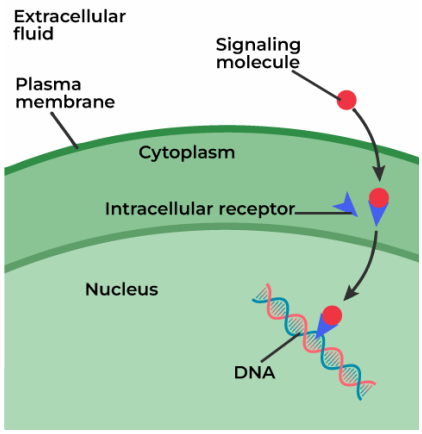
# Signaling Mechanisms: Types Of Drug Responsive Signaling Mechanisms

- **Binding of an agonist drug to its receptor activates an effector or signaling mechanism.**
- **Several different types of drug-responsive signaling mechanisms are known.**

## • 1. Intracellular Receptors

- **These include receptors for steroid, such as binding of hormones or drugs to such receptors releases regulatory proteins.**
- **This interaction leads to changes in gene expression.**
- **For example, drugs interacting with glucocorticoid receptors lead to gene expression of proteins that inhibit the production of inflammatory mediators.**

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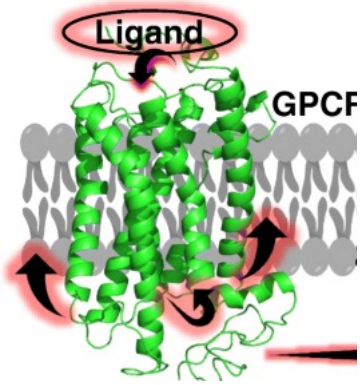
## 2. Membrane Receptors Directly Coupled to Ion Channels

- Many drugs act by mimicking or antagonizing the actions of endogenous ligands that regulate flow of ions through excitable membranes via their activation of receptors.
- These receptors are directly coupled (no second messengers) to ion channels.
- For example, the nicotinic receptor for Acetylcholine protein (in nervous system) is coupled to a Na+/K+ ion channel. The receptor is a target for many drugs, including nicotine, choline esters etc.

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## 3. Receptors Linked Via Coupling Proteins to Intracellular Effectors

- **Many receptor systems are coupled via GTP-binding proteins (G-proteins) to adenylyl cyclase.**
- **Adenylyl cyclase enzyme that converts ATP to cAMP, a second messenger that promotes protein phosphorylation by activating protein kinase A.**
- **Protein kinase A serves to phosphorylate a set of tissue-specific substrate enzymes or transcription factors (CREB), thereby affecting their activity.**

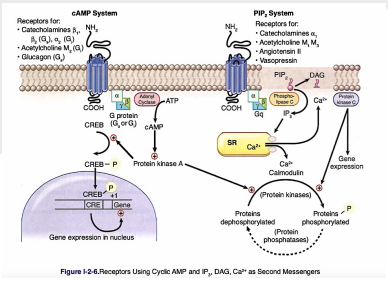
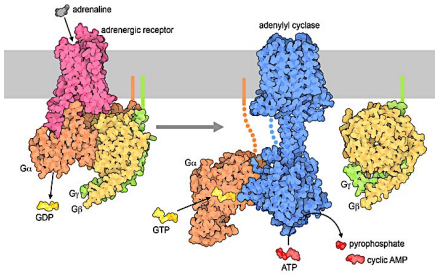



Figure I-2-6.Receptors Using Cyclic AMP and $IP_3$, DAG, $Ca^{2+}$ as Second Messengers




*Signaling with G-proteins. Hormones like adrenaline bind to a GPCR receptor (left), which binds to a heterotrimeric G-protein and releases GDP. Then the G-protein separates into two pieces, and the G-alpha subunit binds to GTP and activates adenylyl cyclase (right).*

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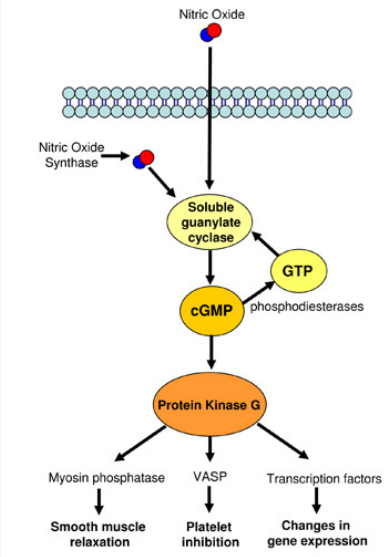
# 4. Cyclic GMP and Nitric Oxide Signaling

- **cGMP is a second messenger in vascular smooth muscle that facilitates dephosphorylation of myosin light chains, preventing their interaction with actin and thus causing vasodilation.**
- **Nitric oxide (NO) is synthesized in endothelial cells and diffuses into smooth muscle.**
- **NO activates guanylyl cyclase, thus increasing cGMP in smooth muscle.**
- **Vasodilators in synthesis of NO by endothelial cells.**

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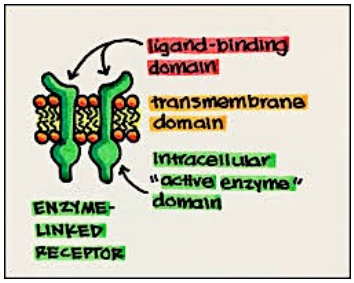
# 5. Receptors That Function as Enzymes or Transporters

1. **Receptors That Function as Enzymes or Transporters**
   - Examples of drug action on transporter systems include the inhibitors of reuptake of several neurotransmitters, including dopamine, GABA, norepinephrine, and serotonin.
2. **Receptors That Function as Transmembrane Enzymes**

- These receptors mediate the first steps in signaling by insulin and growth factors.
- Binding of the ligand causes conformational changes (e.g., dimerization) so that the tyrosine kinase domains become activated, ultimately leading to phosphorylation of tissue-specific substrate proteins.

1. **3. Receptors for Cytokines**
   - These include the receptors for erythropoietin, somatotropin, and interferons.
   - Their receptors are membrane spanning and on activation can activate a distinctive set of cytoplasmic tyrosine kinases Janus kinases [ JAKs ].
   - JAKs phosphorylate signal transducers and activators o f transcription (STAT) molecules.
   - STATs dimerize and then dissociate and modulate gene transcription.

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# The Food and Drug Administration (FDA)

- The FDA regulates both the efficacy and safety of drugs but not of foods, nutritional supplements, and herbal remedies
- Teratogenicity
- The FDA has classified drugs into five categories (A, B, C, D, and X).
- Class A has no risks, and Class X designates absolute contraindication.
- It is based on animal studies and, when available, human studies.
- In Class D, benefits outweigh the risk.


**Table I-2-1.** Drug Development and Testing

| Preclinical | Phase 1 | Phase 2 | Phase 3 | Phase 4 |
|---|---|---|---|---|
| Two different animal species | ~50 healthy volunteers | ~200 patients | ~2,000 patients | Post-marketing surveillance (after FDA approval) |
| Safety and bio-logic activity | Safety and dosage | Evaluate effectiveness | Confirm effectiveness, common side-effects | Common as well as rare side effects |

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# Lecture 8
# Pharmacokinetics of drugs and medicines

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1

## Pharmacokinetic

- **Pharmacokinetic characteristics of drug molecules concern the processes of absorption, distribution, metabolism, and excretion.**
- **The bio disposition of a drug involves its permeation across cellular membrane barriers.**
- **The pharmacokinetic characteristics of a drug are dependent upon the processes of absorption, distribution, metabolism, and excretion.**
- **An important element concerning drug biodistribution is permeation, which is the ability to cross membranes, cellular and otherwise.**

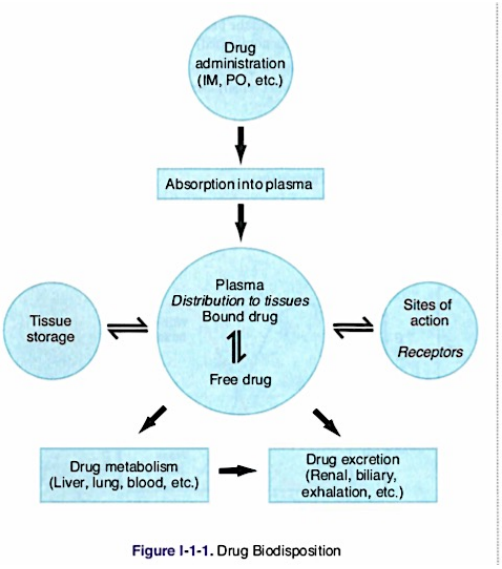


Figure I-1-1. Drug Biodisposition

2

# Permeation

- Drug permeation is dependent on:
- **Solubility**: Ability to diffuse through lipid bilayers (lipid solubility) is important for most drugs; however, water solubility can influence permeation through aqueous phases.
- A drug's ability to permeate is dependent on its solubility, the concentration gradient, and the available surface area, which is influenced by the degree of vascularity.
- **Concentration gradient**: Diffusion down a concentration gradient-only free, unionized drug forms contribute to the concentration gradient.
- **Surface area and vascularity**. Important with regard to absorption of drugs into the systemic circulation. The larger the surface area and the greater the vascularity, the better is the absorption of the drug.
- **Ionization**
- Many drugs are weak acids or weak bases and can exist in either nonionized or ionized forms in an equilibrium, depending on the pH of the environment and the pKa (the pH at which the molecule is 50% ionized and 50% nonionized)
- Only the nonionized (uncharged) form of a drug crosses bio membranes.
- The ionized form is better renally excreted because it is water soluble.

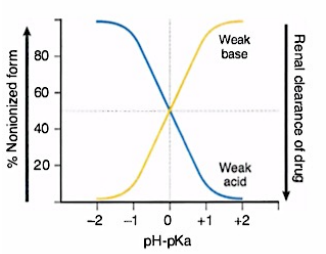



Figure I-1-2. Degree of Ionization and Clearance Versus pH Deviation from pKa

3

## Ionization Increases Renal Clearance of Drugs

- **Only free, unbound drug is filtered.**
- **Both ionized and nonionized forms of a drug are filtered.**
- **Only nonionized forms undergo active secretion and active or passive reabsorption.**
- **Ionized forms of drugs are "trapped" in the filtrate.**
- **Acidification of urine → increases ionization of weak bases → increases**
- **renal elimination.**
- **Alkalinization of urine → increases ionization of weak acids → increases renal elimination.**

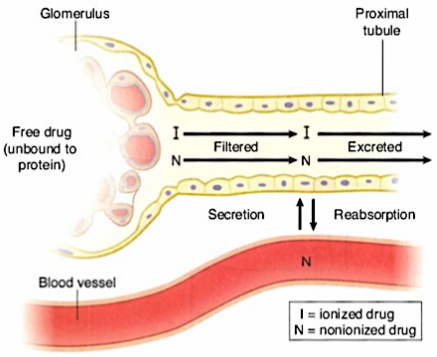
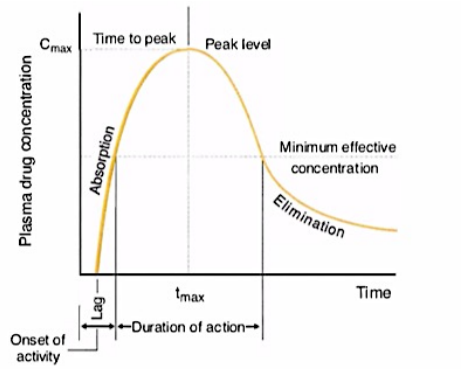



Figure I-1-3. Renal Clearance of Drug

4

# Absorption

- Concerns the processes of entry of a drug into the systemic circulation from the site of its administration.
- The determinants of absorption are those described for drug permeation.
- Intravascular administration (e.g., IV) does not involve absorption, and there is no loss of drug.
- Bioavailability = 100% (discussed in previous lecture)
- With extravascular administration (e.g., per os [PO; oral], intramuscular [IM] , subcutaneous [SC], inhalation), less than 100% of a dose may reach the systemic circulation because of variations in bioavailability.



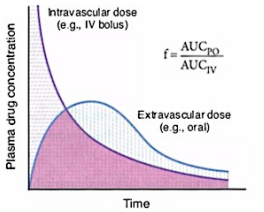

$C_{max}$ = maximal drug level obtained with the dose.
$t_{max}$ = time at which $C_{max}$ occurs.
Lag time = time from administration to appearance in blood.
Onset of activity = time from administration to blood level reaching minimal effective concentration (MEC).
Duration of action = time plasma concentration remains greater than MEC.
Time to peak = time from administration to $C_{max}$.

**Figure I-1-4.** Plot of Plasma Concentration Versus Time

5

# Bioavailability(t)

- Measure of the fraction of a dose that reaches the systemic circulation. By definition, intravascular doses have 100% bioavailability, f = 1.
- First-Pass Effect
- With oral administration, drugs are absorbed into the portal circulation and initially distributed to the liver. For some drugs, their rapid hepatic metabolism de creases bioavailability-the "first-pass" effect.
- Examples:
- Lidocaine (IV vs. PO)
- Nitroglycerin (sublingual) .




**Abbreviations**
AUC: area under the curve
PO: oral
IV: intravenous bolus
$AUC_{IV}$: horizontally striped area
$AUC_{PO}$: vertically striped area

**Figure I-1-5.** Area Under the Curve for an IV Bolus and Extravascular Doses

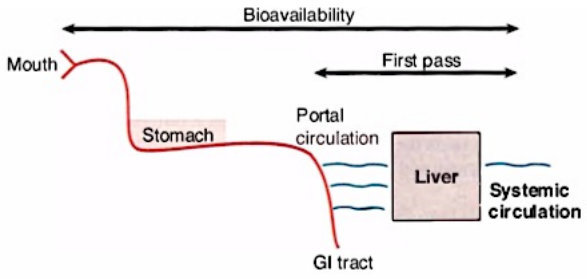



**Figure I-1-6.** Bioavailability and First-Pass Metabolism

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# Distribution

Drug + Protein ⇌ Drug-Protein Complex
(Active, free) (Inactive, bound)

- The processes of distribution of a drug from the systemic circulation to organs and tissue.
- Conditions affecting distribution include:
- Under normal conditions, protein-binding capacity is much larger than is drug concentration. Consequently, the free fraction is generally constant.
- Many drugs bind to plasma proteins, including albumin, with an equilibrium between bound and free molecules (recall that only unbound drugs cross bio membranes).
- Competition between drugs for plasma protein-binding sites may increase the "free fraction;' possibly enhancing the effects of the drug displaced. Example: sulfonamides and bilirubin in a neonate.
- **Special Barriers to Distribution:**
- Placental-most small molecular weight drugs cross the placental barrier, although fetal blood levels are usually lower than maternal. Example: propylthiouracil (PTU) versus methimazole
- Blood-brain-permeable only to lipid-soluble drugs or those of very low molecular weight. Example: levodopa versus dopamine

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# Apparent Volume of Distribution (Vd)

- A kinetic parameter of a drug that correlates dose with plasma level at zero time.

$$V_d = \frac{\text{Dose}}{C^0} \quad \text{where } C^0 = \text{[plasma] at zero time}$$

**Bridge to Physiology**

Approximate $V_d$ Values (weight 70 kg)

- plasma volume (3 L)
- blood volume (5 L)
- extracellular fluid (ECF 12–14 L)
- total body water (TBW 40–42 L)

1. This relationship can be used for calculating Vd by using the dose only if one knows C˚•
2. Vd is low when a high percentage of a drug is bound to plasma proteins.
3. Vd is high when a high percentage of a drug is being sequestered in tis sues. This raises the possibility of displacement by other agents; exam ples: verapamil and quinidine can displace digoxin from tissue-binding sites.
4. Vd is needed to calculate a loading dose in the clinical setting.

8

## Redistribution

- **In addition to crossing the blood-brain barrier (BBB), lipid-soluble drugs redistribute into fat tissues prior to elimination.**
- **In the case of CNS drugs, the duration of action of an initial dose may depend more on the redistribution rate than on the half-life.**
- **With a second dose, the blood/fat ratio is less; therefore, the rate of redistribution is less and the second dose has a longer duration of action.**
- **Biotransformation of drugs (discussed previously).**

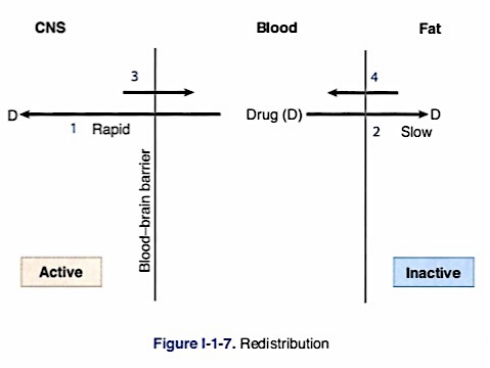
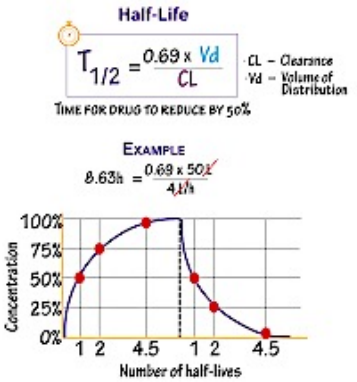



Figure I-1-7. Redistribution

9

## Elimination

- **Concerns the processes involved in the elimination of drugs from the body (and/ or plasma) and their kinetic characteristics.**
- **The major modes of drug elimination are:**
- **Biotransformation to inactive metabolites.**
- **Excretion via the kidney.**
- **Excretion via other modes, including the bile duct, lungs, and sweat.**
- **Definition: Time to eliminate 50% of a given amount (or to decrease plasma level to 50% of a former level) is called the elimination half-life ($t_{1/2}$).**

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# Zero-Order Elimination Rate

- **A constant amount of drug is eliminated per unit time; for example, if 80 mg is administered and 10 mg is eliminated every 4h, the time course of drug elimination is:**

| | 4 h | | 4 h | | 4 h | | 4 h | |
|---|---|---|---|---|---|---|---|---|
| 80 mg | → | 70 mg | → | 60 mg | → | 50 mg | → | 40 mg |

- **Rate of elimination is independent of plasma concentration (or amount in the body).**
- **Drugs with zero-order elimination have no fixed half-life (t112 is a variable).**
- **Drugs with zero-order elimination include ethanol (except low blood levels), phenytoin (high therapeutic doses), and salicylates (toxic doses).**

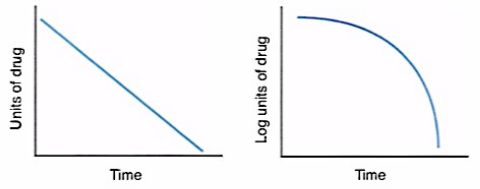


Figure I-1-9a. Plots of Zero-Order Kinetics

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# First-Order Elimination Rate

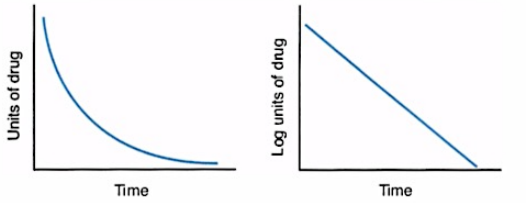
- **A constant fraction of the drug is eliminated per unit time (t1/2 is a constant).**
- **Graphically, first-order elimination follows an exponential decay versus time.**
- **For example, if 80 mg of a drug is administered and its elimination half life = 4h, the time course of its elimination is:**

| | 4 h | | 4 h | | 4 h | | 4 h | |
|---|---|---|---|---|---|---|---|---|
| 80 mg | → | 40 mg | → | 20 mg | → | 10 mg | → | 5 mg |

- **Rate of elimination is directly proportional to plasma level (or the amount present)-the higher the amount, the more rapid the elimination**
- **Most drugs follow first-order elimination rates.**
- **t 1/2 is a constant.**

**Elimination Kinetics**

- Most drugs follow first order—rate falls as plasma level falls.
- Zero order is due to saturation of elimination mechanisms; e.g., drug-metabolizing reactions have reached $V_{max}$.
- Zero order—elimination rate is constant; $t_{1/2}$ is a variable.
- First order—elimination rate is variable; $t_{1/2}$ is a constant.

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# Renal Elimination and Steady State

**Time and Steady State**

50% = 1 × half-life

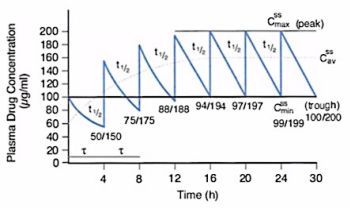
90% = 3.3 × half-life

95% = 4–5 × half-life

"100"% = >7 × half-life

- **Renal Elimination**
- **Rate of elimination= glomerular filtration rate (GFR) +active secretion - reabsorption (active or passive).**
- **Filtration is a non-saturable linear function.**
- **Ionized and nonionized forms of drugs are filtered, but protein-bound drug molecules are not.**
- **• Clearance (Cl):**
  - **Definition: volume of blood cleared of drug per unit of time**
  - **Cl is constant in first-order kinetics**
  - **Cl = GFR when there is no reabsorption or secretion and no plasma protein binding**
  - **Protein-bound drug is not cleared; Cl = free fraction x GFR**

Figure I-1-11 shows plasma levels (solid lines) achieved following the IV bolus administration of 100 units of a drug at intervals equivalent to every **half-life** $t_{1/2}$= **4 h (τ)**. With such intermittent dosing, plasma levels oscillate through peaks and troughs, with averages shown in the diagram by the dashed line.




- **STEADY STATE**
- **• Steady state is reached either when rate in = rate out or when values associated with a dosing interval are the same as those in the succeeding interval.**
- **The time to reach steady state is dependent only on the elimination half-life of a drug and is independent of dose size and frequency of administration, assuming the drug is eliminated by first-order kinetics.**

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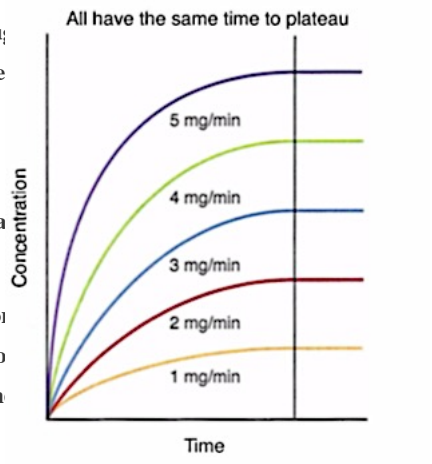
# Rate of Infusion

- **Figure beside shows the increases i n plasma levels o f the same dru infused a t five different rates. Regardless of the rate of infusion, it take the same amount of time to reach steady state.**
- **Rate of infusion ($k_o$) does determine plasma level at steady state.**
- **If the rate of infusion is doubled, then the plasma level of the drug a steady state is doubled.**
- **A similar relationship can exist for other forms of drug administratio (e.g., per oral)-doubling oral doses can double the average plasma levels o a drug. Plot ting dose against plasma concentration yields a straight lin (linear kinetics).**
- **Effect of Loading Dose: It takes 4-5 half-lives to achieve steady state.**




**ure I-1-12.** Effect of Rate of Infusion on Plasma

$$LD = \frac{V_d \times C_p}{f}$$

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# Important Pharmacokinetics Calculations

**Single-Dose Equations**

**(1) Volume of distribution ($V_d$)**

$$V_d = \frac{D}{C^0}$$

**(2) Half-life ($t_{1/2}$)**

$$t_{1/2} = 0.7 \times \frac{V_d}{Cl}$$

**Multiple Doses or Infusion Rate Equations**

**(3) Infusion rate ($k_0$)**

$$k_0 = Cl \times C^{ss}$$

**(4) Loading dose (LD)**

$$LD = \frac{V_d \times C_p}{f}$$

**(5) Maintenance dose (MD)**

$$MD = \frac{Cl \times C^{SS} \times \tau}{f}$$

**Legend**

$C^0$ = conc. at time zero

Cl = clearance

$C_p$ = conc. in plasma

$C^{ss}$ = steady state conc.

D = dose

f = bioavailability

$k_0$ = infusion rate

LD = loading dose

MD = maintenance dose

$\tau$ = dosing interval

$V_d$ = volume of distribution

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# Problems and answers

Example:

What is the estimated IV LD of *Drug A* necessary to achieve a concentration of 10 $^{mg}/_{L}$ in a 55 year old, 60-kg male? The $V_d$ of *Drug A* = 0.5 $^{L}/_{kg}$

$$LD = \frac{C_p \times V_d}{F}$$

$C_p$ = desired plasma concentration

$$LD = \frac{(10\ ^{mg}/_{L})^* [(0.5\ ^{L}/_{kg})\ (60\ kg)]}{F}$$

Problem 5

- For a drug that has an initial plasma concentration of 120 mg/L and a half-life of 3 hours, what would the plasma concentration be 12 hours after the initial concentration?
- A. 15 mg/L
- B. 112.5
- C. 7.5 mg/L
- D. 60

**Pharmacokinetic Problems Solved**

**1) Following the administration of a 250 mg intravenous bolus dose of a drug, the drug-plasma concentration immediately after injection was found to be 17 mcg/mL. Calculate the apparent volume of distribution.**

**Answer:**

Volume of distribution = Dose/$C_0$(conc. at time 0)

= 250/17

= 14.7 L

Note: 1mcg/ml = 1mg/L

**2) A patient received a 300 mg dose of an antibiotic by intravenous bolus injection at 6 A.M. At 10 A.M. the concentration of drug in the body was 2.4 mcg/mL. If the apparent volume of distribution of this drug is known to be 37 L, calculate the amount of drug in the body at 10 A.M.**

**Answer:**

Amount of drug in body = $V_d$ x plasma conc. at that time

= 37 x 2.4

= 88.8 mg

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# Lecture 9
# Pharmacokinetics and drug stability

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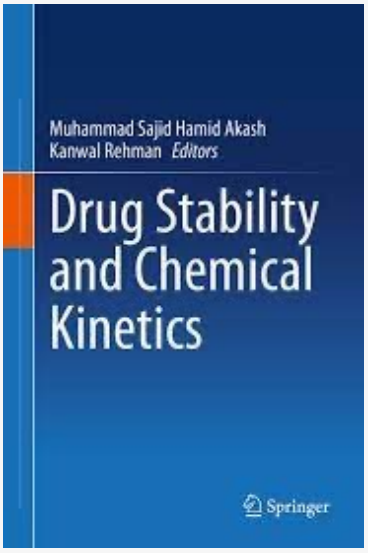
**Department of Applied chemistry**

1

## Kinetics of drug stability

- **The routes of decomposition of drugs, and the steps taken to prevent them, must be considered.**
- **Here, the rates of decomposition will be studied and useful information, such as shelf-life, will be predicted.**
- **Calculations of this type are important as there is little merit in producing the latest wonder drug designed to cure all ills only to watch it fall apart on the dispensary shelf as a result of decomposition.**

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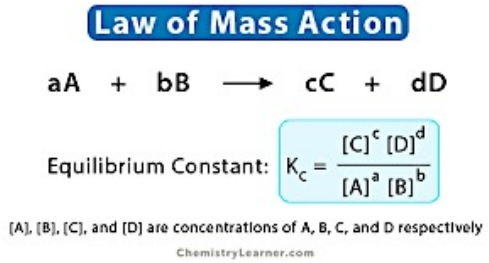
## Rate, order and molecularity




- **Rate, order and molecularity**
- **kinetics is built of the law of mass action.**
- **This states that the rate of a chemical reaction (i.e. the speed of the reaction or, simply, how fast it is) is proportional to the active masses of the reacting substances.**
- **Active mass is a complicated term to measure, but, fortunately, if the solutions in question are dilute, the active mass may be replaced by con- centration, which is much easier to handle.**
- **If the concentration of a solute is greater than about 0.1 mol $L^{-1}$, significant interactions arise between the solute molecules or ions. In cases like this, effective and measured concentrations are not the same and use must be made of activity instead of concentration.**

3

## The rate is proportional to the concentrations

- **The rate of a chemical reaction is, in a dilute solution, proportional to the concentrations of the various reactants each raised to the power of the number of moles of the reactant in the balanced chemical equation.**
- **This sounds too easy, and in fact it is.**
- **In practice, the rate of a chemical reaction depends only on a small number of concentration terms, and the sum of the powers to which these concentrations are raised is termed the *order* of the reaction.**
- **This is because chemical reactions occur in a number of steps, or stages (called a *mechanism*) and the rate of the overall reaction is often governed by the rate of the slowest step (called, not surprisingly, the *rate-determining step*).**
- **Even if every other stage of a chemical reaction occurs instantaneously, the rate of the reaction as a whole cannot exceed that of the slowest stage.**

**Graphical representation of reaction kinetics**

- First-order reaction rate = $k$ [A]
- Rate is directly proportional to the concentration A

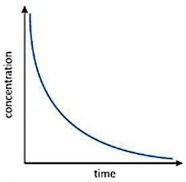



Figure 6.27 Concentration–time graph for a first-order reaction.

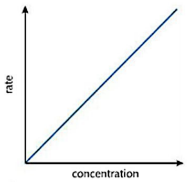



Figure 6.28 Rate–concentration graph for a first-order reaction.

Main Menu

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## If the rate of a chemical reaction depended only on the reactants

For example, if the rate of a chemical reaction depended only on the concentration of compound A, this could be written as

$$\text{Rate} \propto [A]$$

and the reaction would be *first order*, e.g.

$$C_2H_6 \rightleftharpoons C_2H_4 + H_2$$

If the rate of the reaction depended on the concentrations of A and B, or on the concentration of A squared, this could be written as

$$\text{Rate} \propto [A][B] \quad \text{or} \quad \text{Rate} \propto [A]^2$$

and the reaction would be *second order*, e.g.

$$CH_3COOC_2H_5 + NaOH \rightleftharpoons C_2H_5OH + CH_3COONa$$

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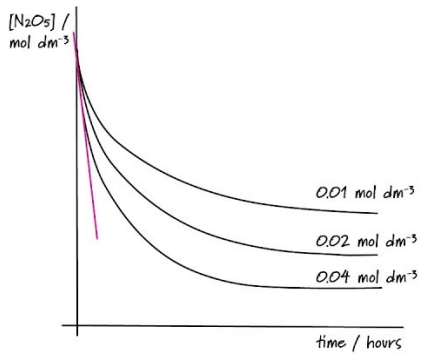
## The order of a reaction is determined *experimentally*

- **To further complicate matters, the order of a chemical reaction cannot be predicted from the chemical equation, even if it has been balanced.**
- **The order of a reaction is determined *experimentally* from accurate measurements of the rate under different conditions.**
- **It is possible for reactions to be third order, zero order (often found in solid-state reactions such as the release of drug from pharmaceutical suspensions) or even of a fractional order.**




6

# *Molecularity*

**Elementary Steps and Their Rate Laws**

| Molecularity | Elementary Step | Rate Law |
|---|---|---|
| *Uni*molecular | A ⟶ products | Rate = $k$[A] |
| *Bi*molecular | A + A ⟶ products | Rate = $k$[A]$^2$ |
| *Bi*molecular | A + B ⟶ products | Rate = $k$[A][B] |
| *Ter*molecular | A + A + A ⟶ products | Rate = $k$[A]$^3$ |
| *Ter*molecular | A + A + B ⟶ products | Rate = $k$[A]$^2$[B] |
| *Ter*molecular | A + B + C ⟶ products | Rate = $k$[A][B][C] |

- **The third term to be considered in this section is *molecularity*.**
- **The molecularity of a reaction is the total number of molecules taking part in the slowest of the elementary reaction steps.**
- **In most chemical reactions, two molecules collide and react; the molecularity is 2 and the reaction is said to be *bimolecular*.**
- **Reactions in which only one molecule is involved (*unimolecular*) are known, but usually occur in the gas phase.**
- **Reactions with a molecularity higher than 2 are very rare, since this would require three or more reactants all encountering each other at the same time.**

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## Rate equations and first-order reactions

- **Differential rate equations like the ones above are not much use to the practising chemist, so it is usual to integrate the rate equation to obtain more useful expressions.**
- **In this reaction, compound A reacts to form products. At the start of the reaction (time 0) the concentration of A is equal to $a$ mol L–1, while the concentration of products will be zero (since the reaction has not started).**
- **At some later time, $t$, the concentration of products has increased to $x$ mol L–1 and as a result the concentration of A has fallen to $(a - x)$ mol L–1. This can be represented mathematically as**
- **The rate constant, $k$, is a very important measure of a reaction rate and has the dimension of time–1 for a first-order process**

At time $= t$,

$$[\mathrm{A}] = (a - x) \quad \text{and} \quad [\text{products}] = x$$

From the law of mass action, the rate of reaction is proportional to [A]. If we rewrite 'rate' as $\mathrm{d}x/\mathrm{d}t$ (i.e. the rate of production of $x$ with respect to $t$), and substituting $(a - x)$ for [A], then

$$\frac{\mathrm{d}x}{\mathrm{d}t} \propto (a - x)$$

and so

$$\frac{\mathrm{d}x}{\mathrm{d}t} = k(a - x)$$

where $k$ is the constant of proportionality. This expression can be integrated to give

$$\int \frac{\mathrm{d}x}{(a - x)} = \int k\mathrm{d}t = k\int \mathrm{d}t$$

$$-\ln(a - x) + c = kt$$

where ln represents the natural (base e) logarithm. To find $c$, recall that at $t = 0$, $x = 0$; therefore,

$$-\ln a + c = 0$$

and so $c = \ln a$ and

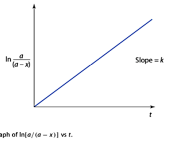
$$-\ln(a - x) + \ln a = kt$$

or

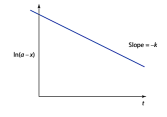
$$\ln\frac{a}{(a - x)} = kt \qquad (10.1)$$

which is equivalent to

$$\ln(a - x) = \ln a - kt \qquad (10.2)$$



Graph of $\ln[a/(a-x)]$ vs $t$.

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# Half-life and Shelf-life

- The half-life is defined as the time taken for the concentration of reactant to fall to half its original value:
- For the first order reactions only is independent of concentration

$$\ln \frac{a}{(a-x)} = kt$$

$$\ln \frac{a}{(a-\frac{1}{2}a)} = kt_{\frac{1}{2}}$$

$$\ln 2 = kt_{\frac{1}{2}}$$

$$t_{\frac{1}{2}} = \frac{0.693}{k}$$

- The shelf-life ($t90$) of a pharmaceutical product is the length of time the product may safely be stored on the dispensary shelf before significant decomposition occurs.
- This is important since, at best, drugs may decompose to inactive products; in the worst case the decomposition may yield toxic compounds.
- The shelf-life is often taken to be the time for decomposition of 10% of the active drug to occur, leaving 90% of the activity.
- A similar expression to Eq. (10.3) can be obtained by substituting ln(100/90) in place of ln 2 to give

$$t_{90} = \frac{0.105}{k}$$

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# Second-order reactions

**2A → products or A + B → products**

$$\frac{dx}{dt} = k(a-x)^2$$

Therefore,

$$\int \frac{dx}{(a-x)^2} = \int k\,dt$$

Hence,

$$\frac{1}{(a-x)} + c = kt$$

At $t = 0$, $x = 0$; therefore $1/a + c = 0$ and $c = -1/a$ to give

$$\frac{1}{(a-x)} - \frac{1}{a} = kt$$

$$\frac{1}{(a-x)} - \frac{1}{a} = kt$$

$$\frac{1}{(a-\frac{1}{2}a)} - \frac{1}{a} = kt_{\frac{1}{2}}$$

$$\frac{1}{\frac{1}{2}a} - \frac{1}{a} = kt_{\frac{1}{2}}$$

$$\frac{1}{a} = kt_{\frac{1}{2}}$$

$$t_{\frac{1}{2}} = \frac{1}{ak}$$

- Equation (10.5) is the equation of a straight line of the type $y - c = mx$; so a plot of $1/(a - x)$ against $t$ yields a straight line of slope $k$, with an intercept on the vertical axis of $1/a$.
- Equation (10.5) is valid for second-order reactions in which the concentrations of the reactants are equal.
- A general second-order equation may also be derived that will apply to reactions of the type A + B → products when [A] does not equal [B],
- The term $k$ is, again, the rate constant for the reaction, but in a second-order process $k$ has dimensions of concentration−1 time−1.
- The relationship between the half-life and the second-order rate constant, $k$, for initial equal concentrations of reactant can be found by substituting $t = t\,1/2$

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# Zero-order reactions

- There are some reactions in which the rate of the reaction is independent of the concentration of the reactants but does depend on some other factor, such as the amount of catalyst present.
- These reactions are termed *zero-order* reactions, and rate equations can be derived as follows:
- In zero-order reactions, the amount of product formed varies with time; consequently, the amount of product formed after 20 minutes will be twice that formed after 10 minutes.
- Reactions that follow zero-order kinetics are quite rare, but they do occur in solid-phase reactions such as release of drug from a pharmaceutical suspension.

$$\frac{dx}{dt} = k[A]^0$$

Therefore,

$$\int dx = \int k\, dt$$

which gives

$$x = kt + c$$

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# Reaction rates and temperature

- For most chemical reactions, an increase in temperature will bring about an associated increase in reaction rate, which can be measured by an increase in $k$, the reaction rate constant.
- if the temperature of a reaction increases by 10 ◦C the reaction rate will approximately double.
- The Swedish chemist Arrhenius first expressed mathematically the relationship between reaction rate and temperature, namely:

$$k = Ae^{-E/RT} \quad \ldots\ldots\ln k = \ln A - E/RT$$

- where $A$ is a constant known as the *frequency factor* and is a measure of the number of collisions taking place between reactants;
- $e^{-E/RT}$ is the small fraction of the total number of collisions that result in a successful reaction;
- $E$ is the activation energy for the reaction (i.e. the energy required to force the reactants to collide with enough energy to form a product);
- $R$ is the universal gas constant($R$ = 8.314 J K−1 mol−1).

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**Tutorial example**

**Q** *1 The reaction between aspirin and gastric acid may be followed by titrating the liberated salicylic and acetic acids with sodium hydroxide. In an experiment using equimolar amounts of reactants, the following data were obtained:*

| *Time (s)* | *0* | *89* | *208* | *375* | *625* | *803* |
|---|---|---|---|---|---|---|
| *[Aspirin] (mol $L^{-1}$)* | *1.6* | *1.4* | *1.2* | *1.0* | *0.8* | *0.7* |

*Determine the order of the reaction and determine the rate constant.*

**A** 1 The order of a chemical reaction cannot be determined by inspection, it must be determined experimentally. In practice, this means measuring the decomposition of the compound under controlled conditions and applying each of the rate equations in turn to see which type of equation fits the data and gives the best straight line. This is what scientists term an empirical method, and what the man in the street calls 'trial and error'!

In the case of the hydrolysis of aspirin, it would be sensible to try the second-order rate equation first (especially since the question stresses that the reactant concentrations are equal). For a second-order process, Eq. (10.5) is valid, i.e.

$$\frac{1}{(a-x)} - \frac{1}{a} = kt$$

where $(a - x)$ is the concentration of each reactant at time $t$, and a plot of $1/(a - x)$ vs $t$ should yield a straight line of slope $k$.

This plot was carried out and a straight line was obtained with a slope of $1.0 \times 10^{-3}$. This proves that the reaction is second order with a rate constant, $k = 1.0 \times 10^{-3}$ (mol $L^{-1})^{-1}$ $s^{-1}$.

# Problems and answers

**Problems**

**Q10.1** Determine the first-order rate constant for the hydrolysis of acetyl-β-methylcholine at 85 °C from the information given below.

| [Drug] (mg $mL^{-1}$) | 9.35 | 7.45 | 4.52 | 3.46 | 1.26 | 0.90 |
|---|---|---|---|---|---|---|
| $t$ (days) | 0.08 | 0.75 | 1.96 | 2.96 | 5.75 | 6.75 |

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# Lecture 10
# Medicinal chemistry: the science of rational drug design

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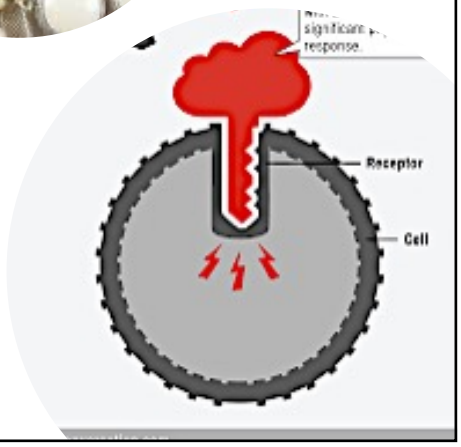
1

## How do drugs work?

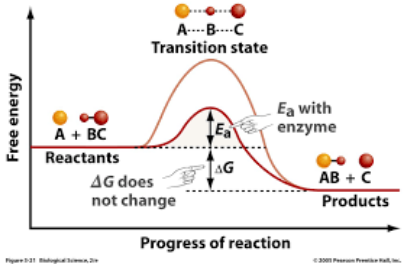
- **Here, we will introduce the subject of *medicinal chemistry*, which may be defined as *the planning and synthesis of new chemical entities for the treatment of disease*.**
- **Medicinal chemistry also includes aspects of molecular pharmacology (i.e. drug action at the molecular level), which, in turn, leads to the holy grail of structure–activity relationships.**
- **It looks at….How do drugs work?, Where do drugs come from?' and 'Why do we need new drugs?'**




2

# How do drugs work?

- Enzyme inhibition
- Enzymes are soluble proteins which function as biological catalysts which increase the rate of chemical reactions without being consumed in the process.
- Most chemical reactions are equilibrium reactions and the presence of the enzyme allows the reaction to reach equilibrium more rapidly than it would in the absence of the enzyme.
- Enzymes do not alter the *position* of the equilibrium, but they do affect the speed with which the reaction reaches equilibrium.
- They do this by forming a high-energy *transition state*, an unstable intermediate formed from the reactants, which decomposes to yield the products of the reaction.




3

## Drugs work as enzymes' inhibitors.

- Drugs work as enzymes' inhibitors.
- they allow the body to undertake complex chemical transformations in cells, in salty water at a temperature of 37 ◦C.
- Enzymes are critical components of all human biochemistry.
- Many drugs achieve their therapeutic action by inhibition of these key catalysts.
- Many of these drugs are commonly prescribed treatments.

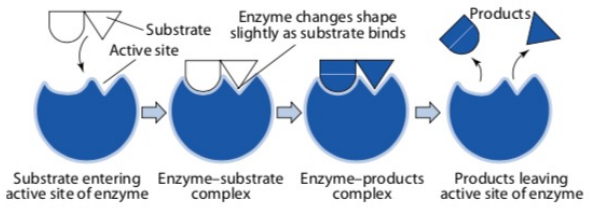


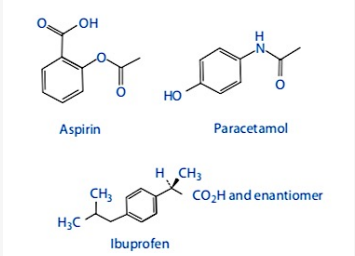

**Figure 12.1.** Enzymes as catalysts.

| Drug | Target enzyme | Field of therapy |
|---|---|---|
| Aspirin | Cyclo-oxygenase | Anti-inflammatory |
| Captopril and enalapril | Angiotensin-converting enzyme (ACE) | Antihypertension |
| Simvastatin | HMG-CoA-reductase | Lowering of cholesterol levels |
| Desipramine | Monoamine oxidase | Antidepressant |
| Clorgiline | Monoamine oxidase-A | Antidepressant |
| Selegiline | Monoamine oxidase-B | Treatment of Parkinson's disease |
| Methotrexate | Dihydrofolate reductase | Anticancer |
| 5-Fluorouracil | Thymidylate synthase | Anticancer |
| Gefitinib and imatinib | Tyrosine kinases | Anticancer |
| Sildenafil (Viagra) | Phosphodiesterase (PDE5) | Treatment of male erectile dysfunction |
| Allopurinol | Xanthine oxidase | Treatment of gout |
| Zidovudine | HIV reverse transcriptase | AIDS therapy |
| Saquinavir | HIV protease | AIDS therapy |
| Aciclovir | Viral DNA polymerase | Treatment of herpes |
| Pencillins and cephalosporins | Bacterial transpeptidase | Antibacterial |
| Clavulanic acid | Bacterial β-lactamases | Antibacterial |
| Sulfonamides | Dihydropteroate synthetase | Antibacterial |
| Fluoroquinolones | Bacterial topoisomerases | Antibacterial |
| Ro41 0960 | Catechol-*O*-methyltransferase | Treatment of Parkinson's disease |
| Omeprazole | $H^+/K^+$ ATPase proton pump | Ulcer therapy |
| Organophosphates | Acetylcholinesterase | Treatment of myasthenia gravis and Alzheimer's disease |
| Acetazolamide | Carbonic anhydrase | Diuretic |
| Zileutin | 5 Lipoxygenase | Anti-asthmatic |

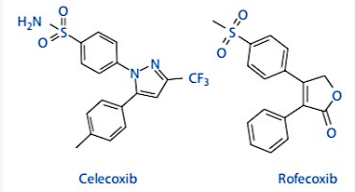
4

# Cyclo- oxygenase forms prostaglandins

- Cyclo- oxygenase, for example, is the enzyme responsible for the formation of inflammatory mediators such as prostaglandins (e.g. prostacyclin) and thromboxane.
- These mediators increase the pain and inflammation associated with minor injury and trauma through vasodilatation, platelet aggregation and release of additional inflammatory mediators.
- Inhibition of the enzyme by drugs such as aspirin, paracetamol or ibuprofen (see Fig) reduce the synthesis of the inflammatory mediators and reduce pain, swelling, inflammation and fever.
- Recent research has shown that there are three isoenzyme variants of cyclo-oxygenase, known as COX-1, COX-2 and COX-3. Established NSAIDs inhibit all variants of the enzyme.




Structures of aspirin, paracetamol and ibuprofen.

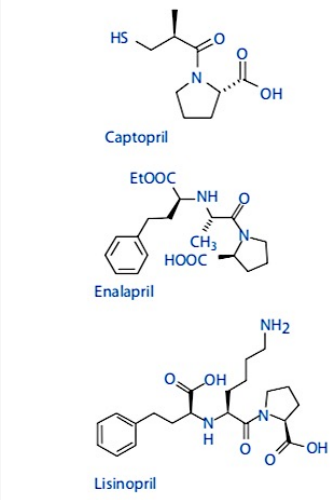



Structures of celecoxib and rofecoxib.

5

# Hypertension inhibitors

- Angiotensin-converting enzyme (ACE) is an enzyme produced in the kidney.
- it catalyses the conversion of a short peptide of 10 amino acid residues (a decapeptide), called angiotensin I, into an octapeptide (eight amino acid residues), called angiotensin II.
- This latter peptide is a very potent vasoconstrictor that rapidly increases blood pressure.
- Inhibition of ACE by drugs lowers blood pressure and is used in the treatment of hypertension and congestive heart failure.
- Commonly prescribed ACE inhibitors include captopril, enalapril and lisinopril.




Structures of captopril, enalapril and lisinopril.

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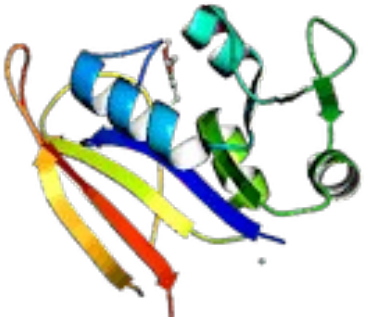
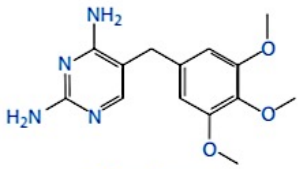
# Trimethoprim inhibits DHFR

- Dihydrofolate reductase (DHFR) is an enzyme that catalyses the reduction of dihydrofolic acid to tetrahydrofolic acid, an essential component for the synthesis of purine bases in DNA and certain amino acids.
- Inhibition of DHFR results in a decrease in DNA synthesis and a slowing down of cell division.
- Drugs such as trimethoprim (an antibacterial) achieve their therapeutic action by inhibition of this enzyme.
- Trimethoprim is more active against bacterial DHFR.






Trimethoprim

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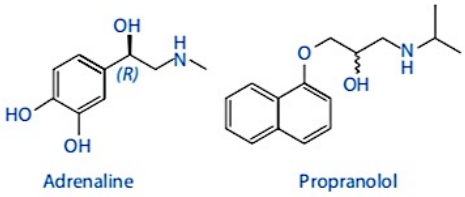
# Receptor activation/blocking




Adrenaline Propranolol

Structures of adrenaline and propranolol.

- Such as adrenaline (epinephrine), acetylcholine or histamine.
- These small molecules act as neurotransmitters or hormones.
- Once released, bind to the receptor, thus activating it and initiating a physiological effect.
- The protein of the receptor is located within the cell membrane (half out and half in).
- This allows messages to be conveyed into the cell without the messenger molecule.

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# The β-adrenoceptor is a G-protein-coupled receptor

- **The β-adrenoceptor is a G-protein-coupled receptor found in the cell membranes of many cells.**
- **Activation of the receptor by adrenaline (epinephrine) results in a response such as an increase in heart rate, an increase in blood pressure etc.**
- **Blockade of the receptor by drugs like propranolol is useful in the treatment of conditions.**
- **The propranolol is the natural agonist of the β-adrenoceptor.**

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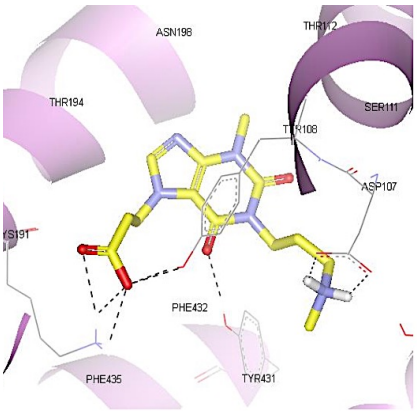
# Anti histamines

- **There are four subtypes of Histamine receptors (H1 to H4) but all are activated by histamine.**
- **It is a small, polar amine released from mast cells in response to tissue injury.**
- **Antihistamines are a class of drug that blocks the action of histamine on its receptor and so reduces its action throughout the body.**
- **Also, the H2 receptor antagonists include the well-known (and well-prescribed) anti-ulcer drugs cimetidine and ranitidine.**




. The docking pose of Model 3 against histamine-H1 rece

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# Where do drugs come from?

- **Has Mother Nature got there before us and done all the hard work herself?**
- **Examples of a few of the important drugs derived from natural sources,**
- **local anaesthetics, e.g. lidocaine, derived from cocaine**
- **narcotic analgesics, e.g. morphine, derived from opium**
- **antimalarials, e.g. chloroquine, derived from *Cinchona* ACE inhibitors, e.g. captopril, derived from snake venom.**
- **antibiotics, e.g. penicillin, derived from microorganisms.**
- **The role of the medicinal chemist is to identify the lead compound and modify it chemically to produce more effective treatments.**

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# Lecture 11
# Protein-Ligand docking

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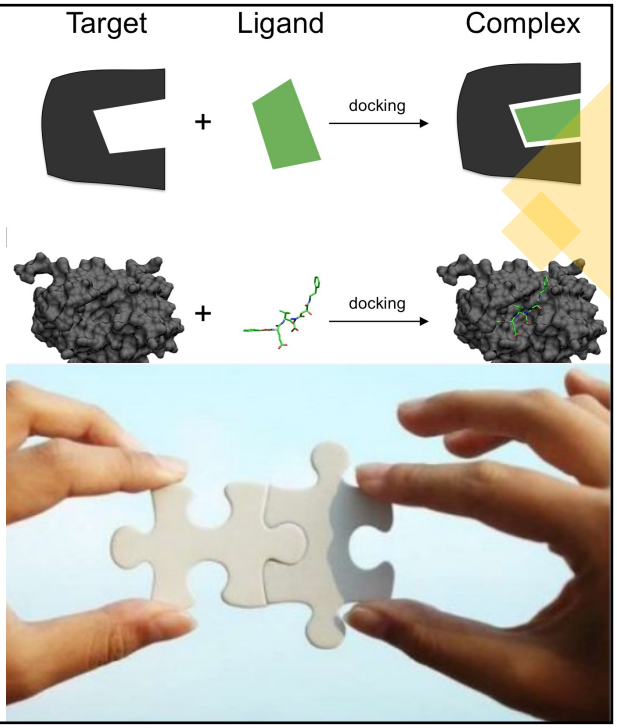
## Basics Of Molecular Docking

- Docking is a structure-based technique which attempts to find the “best” match, between two molecules.
- What Is Molecular Docking?
- In the field of molecular modelling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex.





- **References :**
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- [Jean-Michel_Claverie_Ph._D.,_Cedric_Notredame_Ph.(z-lib.org).pdf
- [Bioinformatics Jonathan M. Keith Volume 1-2 (z-lib.org)-2.pdf
- Google and wiki


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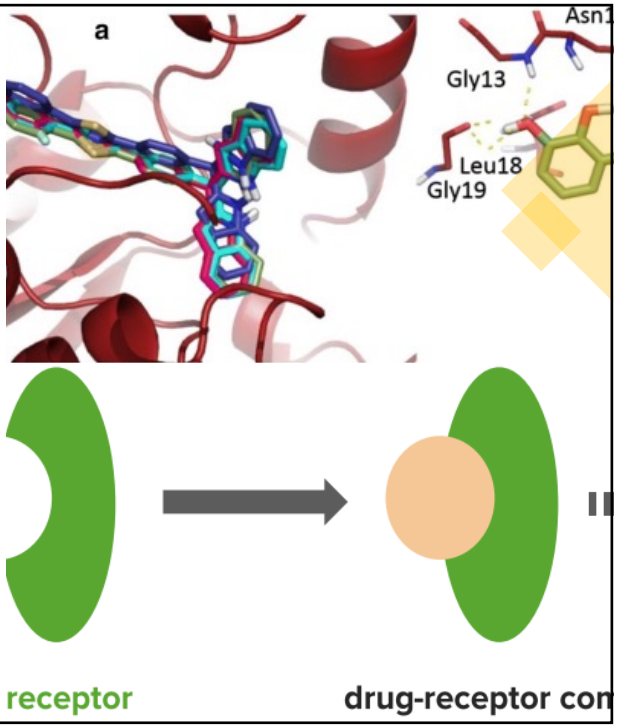
# Ligand-receptor Complex

- Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions.

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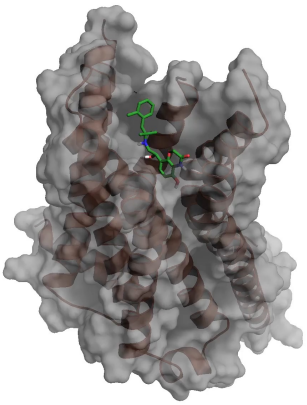

# Introduction to protein-ligand docking

- Protein–ligand docking is a molecular modelling technique.
- The goal of protein–ligand docking is to predict the position and orientation of a ligand (a small molecule, chemical molecule) when it is bound to a protein receptor or enzyme.
- For example ligand: Paracetamol or any.
- Example of enzyme or protein: lipase, globulin etc.

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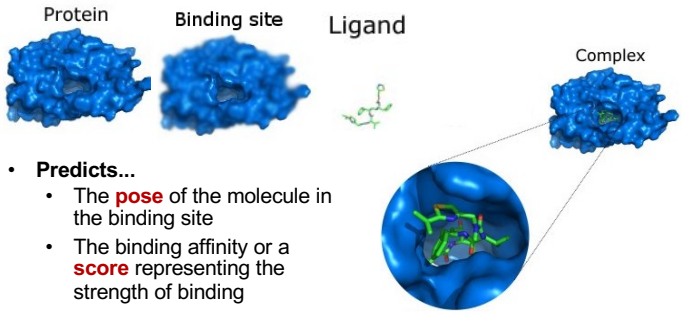
# Protein-ligand docking

- A Structure-Based Drug Design (SBDD) method… "structure" means "using protein structure"
- Computational method that mimics the binding of a ligand to a protein …**Given..**




- **Predicts...**
  - The **pose** of the molecule in the binding site
  - The binding affinity or a **score** representing the strength of binding

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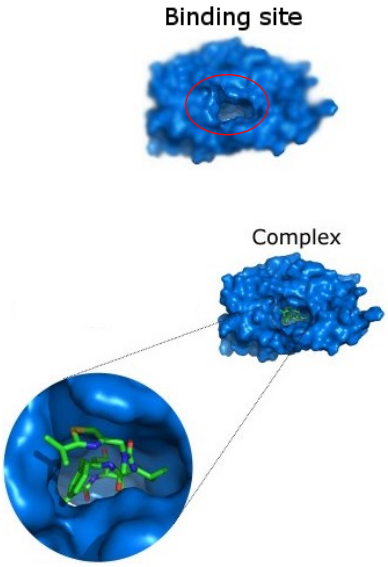
# Pose vs. binding site

- **Binding site** (or "active site")
  - the part of the protein where the ligand binds
  - generally a cavity on the protein surface

  We must have the crystal structure of the protein bound with a known inhibitor.

- **Pose** (or "binding mode")
  - The *geometry* of the ligand in the binding site
  - Geometry = **location, orientation and conformation**
- *Protein-ligand docking is **not** about identifying the binding site*

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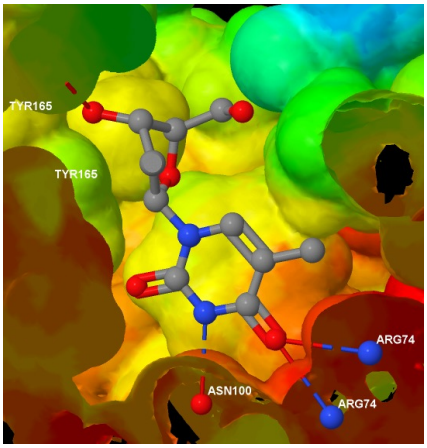
# Uses of docking

- The main uses of protein-ligand docking are for
  - Virtual screening,
  - Pose prediction




- **Pose prediction**
- If we know exactly where and how a known ligand binds...
  - We can see which parts are important for binding
  - We can suggest changes to improve affinity
  - Avoid changes that will 'clash' with the protein

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# $\Delta G_o$ calculation

- **In analogy with any spontaneous process, protein–ligand binding occurs only when the change in Gibbs free energy (ΔG) of the system is negative when the system reaches an equilibrium state at constant pressure and temperature.**
- **The binding free energy can be calculated using the rate constants $k_{on}$ and $k_{off}$ as**
- **$\Delta G = G_{bound} - G_{unbound} = -kT \ln K_{eq} C_0 = -kT \ln C_0 k_{on}/k_{off}$**
- **where $K_{eq}$ is the binding equilibrium constant, $C_0$ is the reference concentration of 1 mol/L, k is Boltzmann's constant and T is the temperature in Kelvin**

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## $\Delta G_o$ calculation reflect the various contributions to binding.

- **The ΔG values on the right of the equation are all constants.**
- **$\Delta G_o$ is a contribution to the binding energy that does not directly depend on any specific interactions with the protein**
- **The hydrogen bonding and ionic terms are both dependent on the geometry of the interaction, with large deviations from ideal geometries (ideal distance R, ideal angle α) being penalized.**
- **The lipophilic term is proportional to the contact surface area (Alipo) between protein and ligand involving non-polar atoms.**
- **The conformational entropy term is the penalty associated with freezing internal rotations of the ligand. It is largely entropic in nature. Here the value is directly proportional to the number of rotatable bonds in the ligand (NROT).**

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## Tutorial A: online ligand protein docking

- Step to find the ligand-protein docking: we can use CB-dock a web server for cavity detection guided protein ligand blind docking.
- You need to choose the pdb structure that aim to target the ligand
- from https://www.rcsb.org
- You need also to find the ligand that aim to target your protein from https://pubchem.ncbi.nlm.nih.gov
- Then you can use the server to dock http://clab.labshare.cn/cb-dock/php/
- Take the complex and upload it to the web https://plip-tool.biotec.tu-dresden.de/plip-web/
- Follow the link below:
- https://www.youtube.com/watch?v=xFVglxbkoSQ&t=42s

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