Medicinal Chemistry

Chapter 1

DRUGS & DRUG TARGETS

Contents

What is a drug?

Def 1: Chemical compounds designed and synthesized with therapeutic agents have a desired biological effect on the human body or other living systems.

•Many scientists dislike this word 'DRUG' because society views the term with suspicion.

•Trying to divide drugs into two categories—safe or unsafe, good or bad—is futile and could even be dangerous. **WHY?????**

- Case one: Penicillin, relatively safe drug but not good……
- Case Two: Morphine, excellent analgesic but unsafe…….
- Case Three: Heroin, the best painkillers but causing addiction….

•So all drugs have their good and bad points. Some have more good points than bad and vice versa,

What is a drug?

Def 2: One definition could be to classify drugs as ‘compounds which interact with a biological system to produce a biological response’

There are chemicals that we take every day and which have a biological effect on

- Case Four: caffeine, nicotine in cups of tea, coffee and cigarettes
- Case Five: alcohol, sterilized but it causes addiction and intoxication

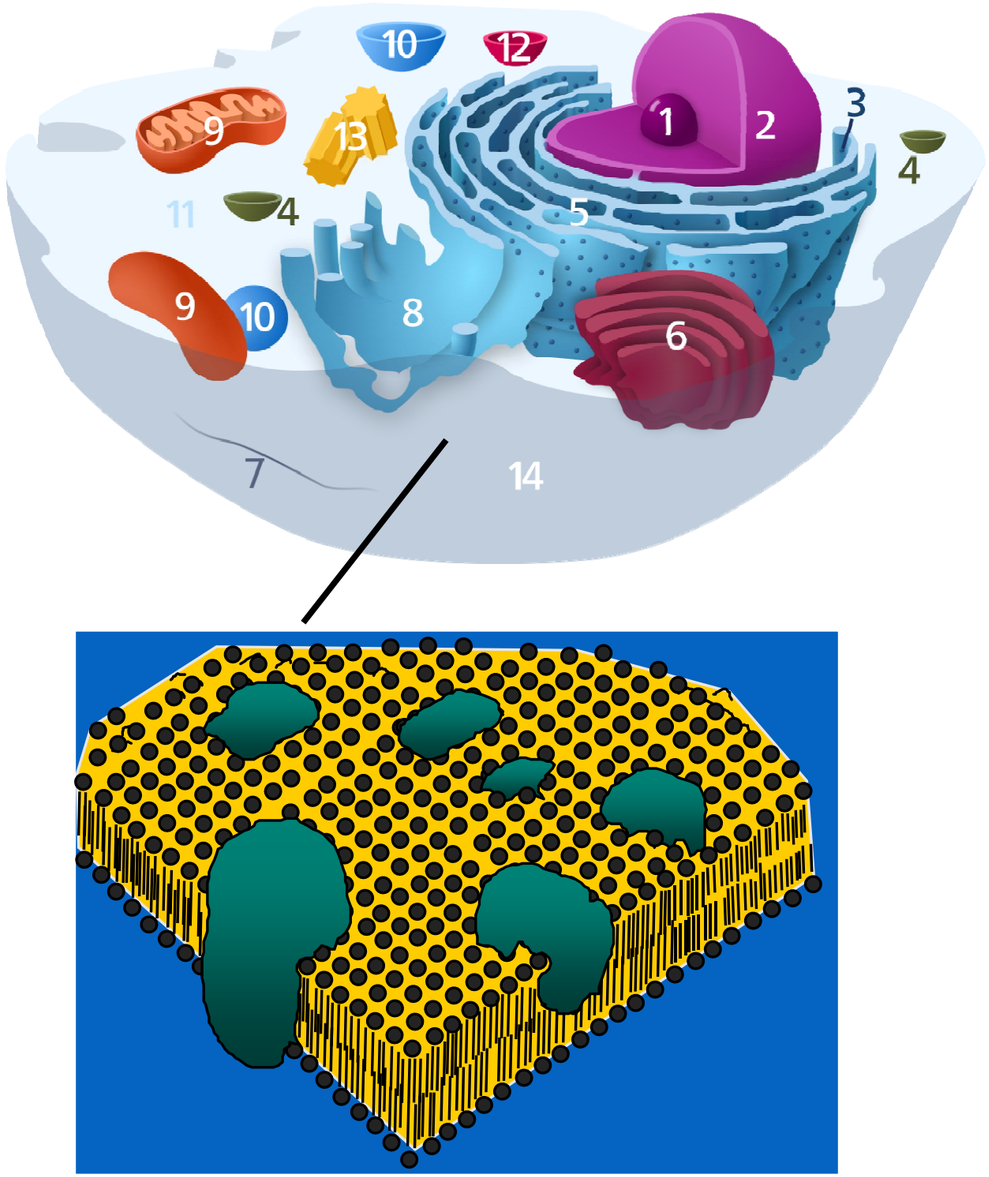
Def 3: One definition of a drug can also be used to include other compounds which may not be obvious as drugs, for example poisons and toxins as

- Case Six: penicillin interacts with bacteria and kills them,
- Case Seven: morphine at high doses, it is a poison which kills by the suppression of breathing

What is a drug?

- Can a poison be a medicine at low doses?
- **Arsenic** is well known as a poison, but arsenic-derived compounds are used as antiprotozoal and anticancer agents.
- **Curare** is a deadly poison which was used by the native people of South America to tip their arrows such that a minor arrow wound would be fatal, are used in surgical operations to relax muscles.

1. Cell Structure



Phospholipid bilayer

1.Nucleolus
2.Nucleus
3.Ribosome (little dots)
4.Vesicle
5.Rough endoplasmic reticulum
6.Golgi apparatus (or "Golgi body")
7.Cytoskeleton
8.Smooth endoplasmic reticulum
9.Mitochondrion
10.Vacuole
11.Cytosol (fluid that contains organelles, comprising the cytoplasm)
12.Lysosome
13.Centrosome
14.Cell membrane

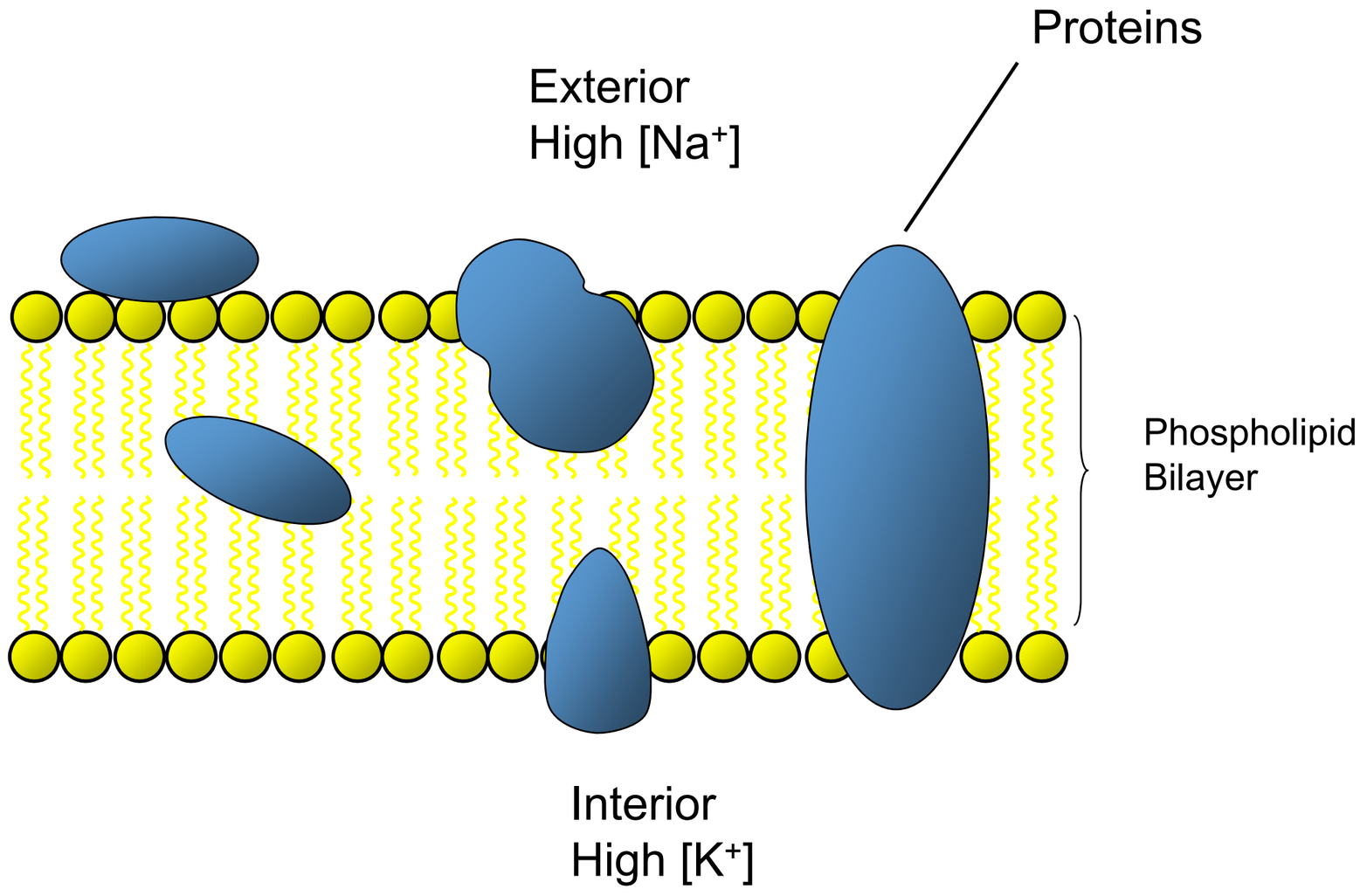
1. Cell Structure

Notes:

- Human, animal and plant cells are eukaryotic cells
- The nucleus contains the genetic blueprint for life (DNA)
- The fluid contents of the cell are known as the cytoplasm
- Structures within the cell are known as organelles
- Mitochondria are the source of energy production
- Ribosomes are the cell's protein 'factories'
- Rough endoplasmic reticulum is the location for protein synthesis

2. Cell Membrane

- In the cell membrane, the two layers of phospholipids are arranged such that the hydrophobic tails point towards each other and form a fatty, hydrophobic center, while the ionic head-groups are placed at the inner and outer surfaces of the cell membrane. This is a stable structure because the ionic,



2. Cell Membrane

Notes:

- The cell membrane is made up of a phospholipid bilayer

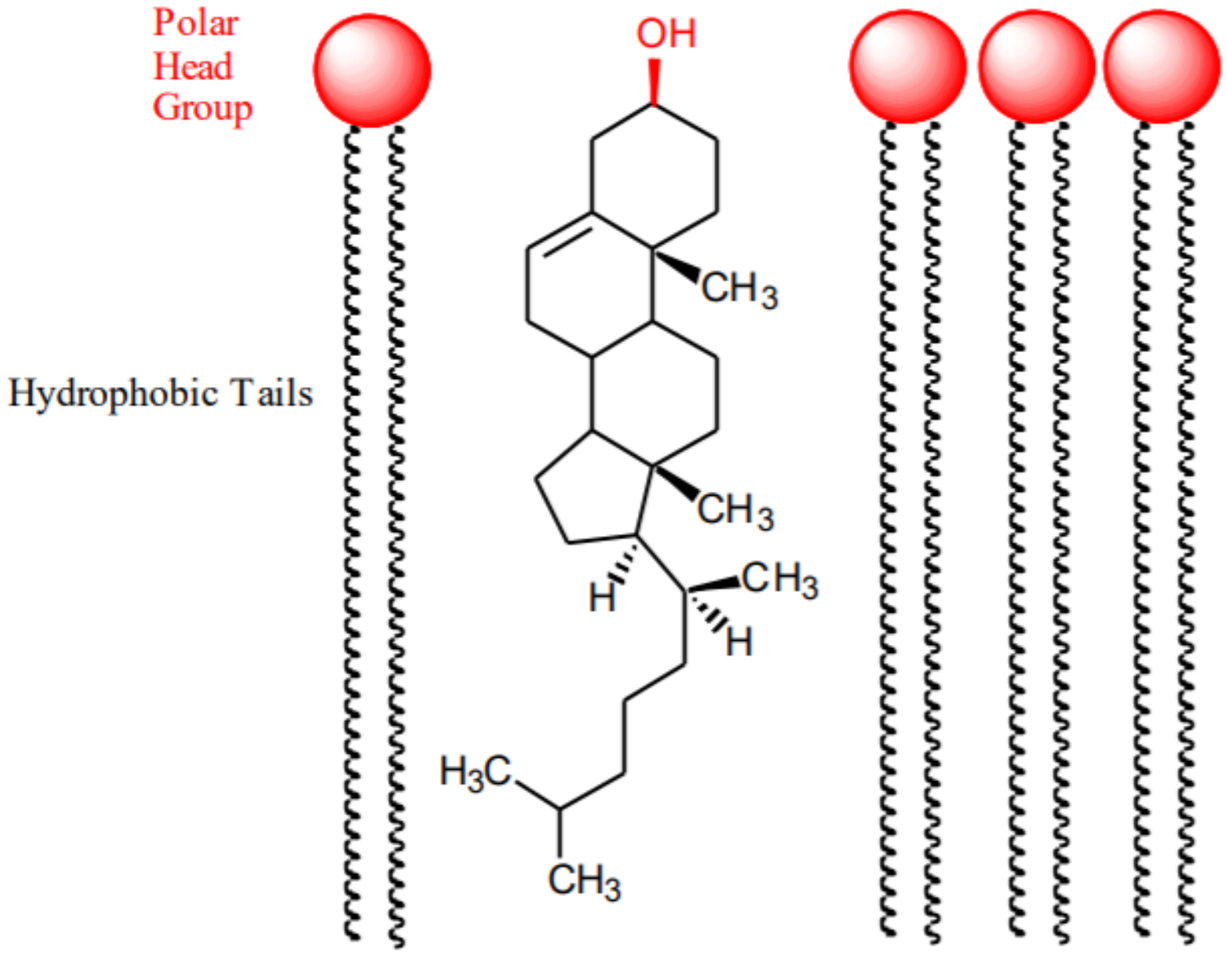
- The hydrophobic tails interact with each other by van der Waals interactions and are hidden from the aqueous media

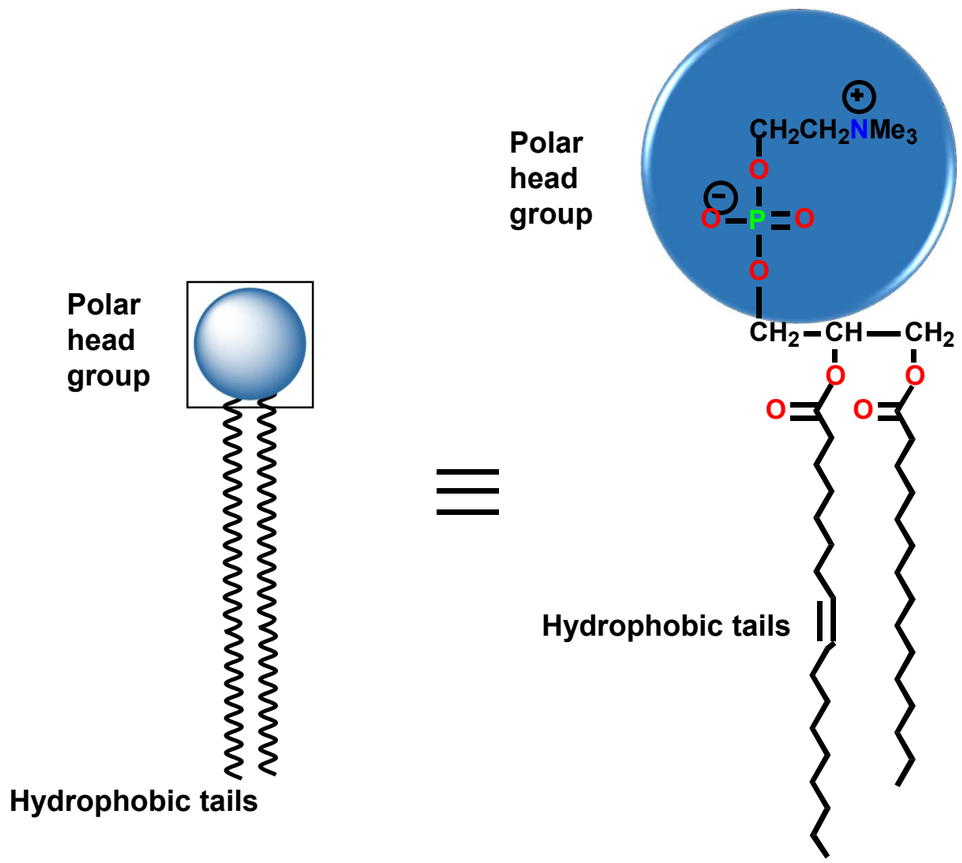
- The polar head groups interact with water at the inner and outer surfaces of the membrane

- The cell membrane provides a hydrophobic barrier around the cell, preventing the passage of water and polar molecules

- Proteins are embedded in the cell membrane (ion channels, receptors, enzymes and transport proteins)

2. Cell Membrane





3. Drug targets

Lipids

Cell membrane lipids

Proteins

Receptors
Enzymes
Transport proteins
Structural proteins (tubulin)

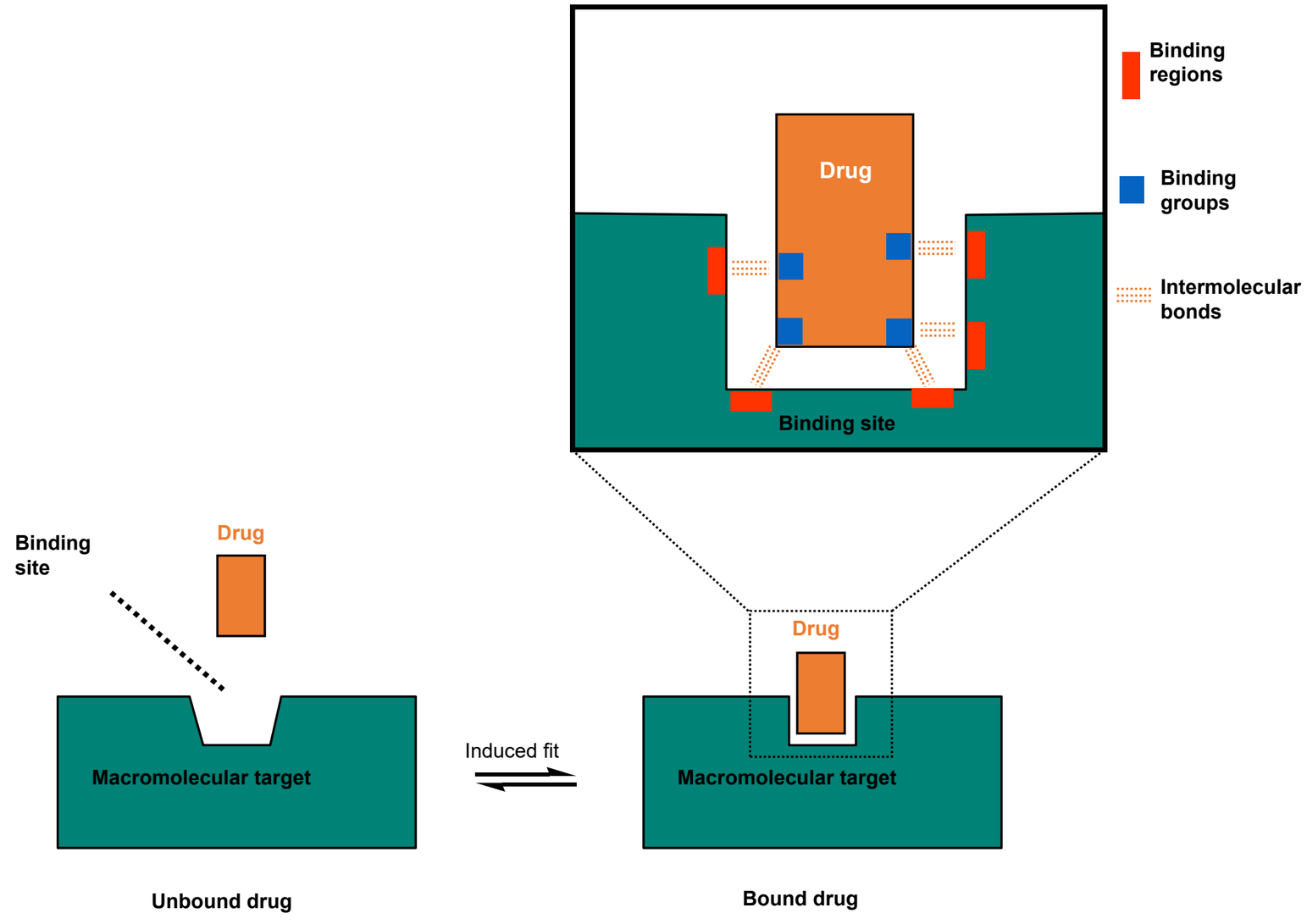
Nucleic acids

DNA
RNA

Carbohydrates

Cell surface carbohydrates
Antigens and recognition molecules

3. Drug targets



3. Drug targets

Notes

- **Drug targets are large molecules - macromolecules**
- **Drugs are generally much smaller than their targets**
- **Drugs interact with their targets by binding to binding sites**
- **Binding sites are typically hydrophobic hollows or clefts on the surface of macromolecules**
- **Binding interactions typically involve intermolecular bonds**
- **Most drugs are in equilibrium between being bound and unbound to their target**
- **Functional groups on the drug are involved in binding interactions and are called binding groups**
- **Specific regions within the binding site that are involved in binding interactions are called binding regions**

3. Drug targets

Notes

- **Binding interactions usually result in an induced fit where the binding site changes shape to accommodate the drug**

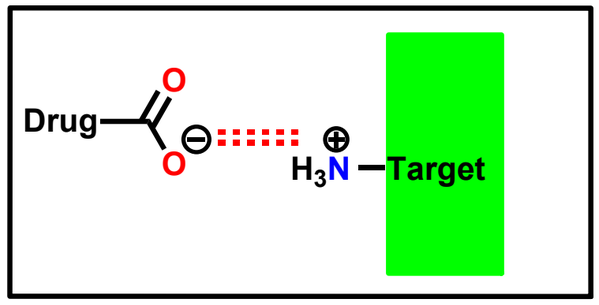
- **The induced fit may also alter the overall shape of the drug target**

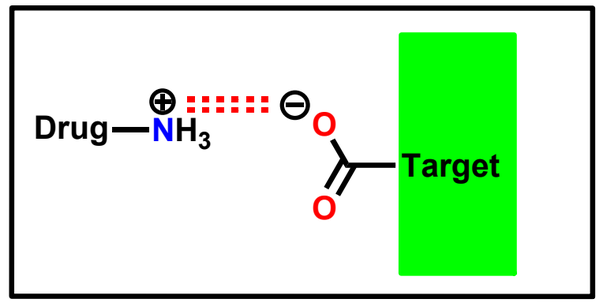
- **Important to the pharmacological effect of the drug**

4. Intermolecular bonding forces

4.1 Electrostatic or ionic bonds

- **Strongest of the intermolecular bonds (20-40 kJ mol^{-1})**
- **Takes place between groups of opposite charge**
- **The strength of the ionic interaction is inversely proportional to the distance between the two charged groups**
- **Stronger interactions occur in hydrophobic environments**
- **The strength of interaction drops-off less rapidly with distance than with other forms of intermolecular interactions**
- **Ionic bonds are the most important initial interactions as a drug enters the binding site**



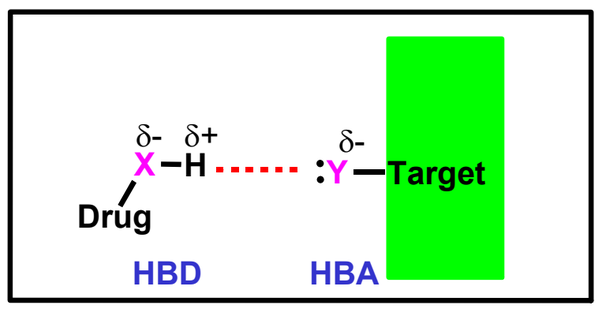


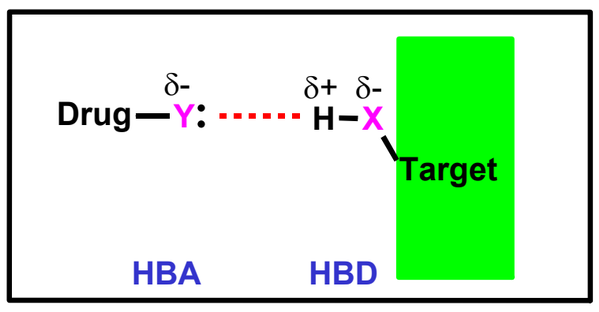
4. Intermolecular bonding forces

4.2 Hydrogen bonds

- **Vary in strength**
- **Weaker than electrostatic interactions, but stronger than van der Waals interactions**
- **A hydrogen bond takes place between an electron-deficient hydrogen and an electron-rich heteroatom (N or O)**
- **The electron-deficient hydrogen is usually attached to a heteroatom (O or N)**
- **The electron-deficient hydrogen is called a hydrogen bond donor (HBD)**
- **The electron-rich heteroatom is called a hydrogen bond acceptor (HBA)**

X, Y = oxygen or nitrogen

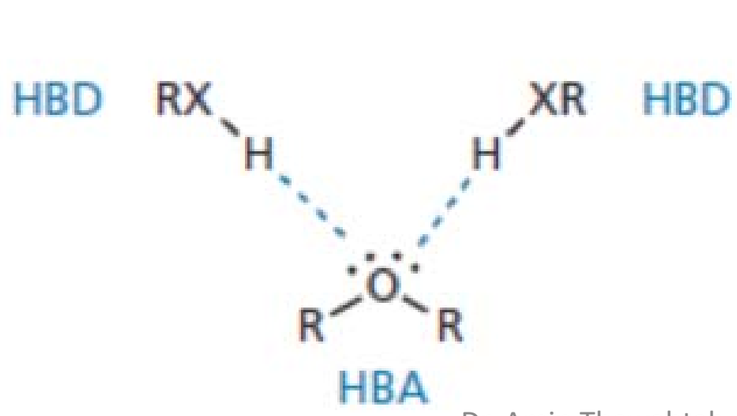


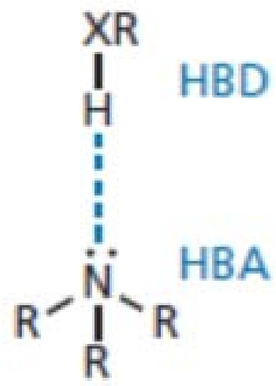


4. Intermolecular bonding forces

4.2 Hydrogen bonds

- **Examples of strong hydrogen bond acceptors**
  - **carboxylate ion, phosphate ion, tertiary amine**
- **Examples of moderate hydrogen bond acceptors**
  - **carboxylic acid, amide oxygen, ketone, ester, ether, alcohol**
- **Examples of poor hydrogen bond acceptors**
  - **sulphur, fluorine, chlorine, aromatic ring, amide nitrogen, aromatic amine**
- **Example of good hydrogen bond donors**
  - **ammonium ions ($\underline{H}NR_3^+$)**

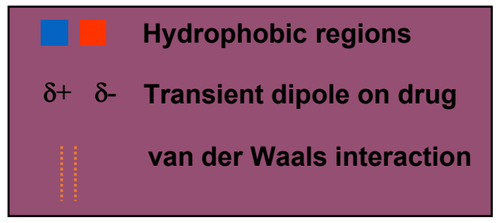


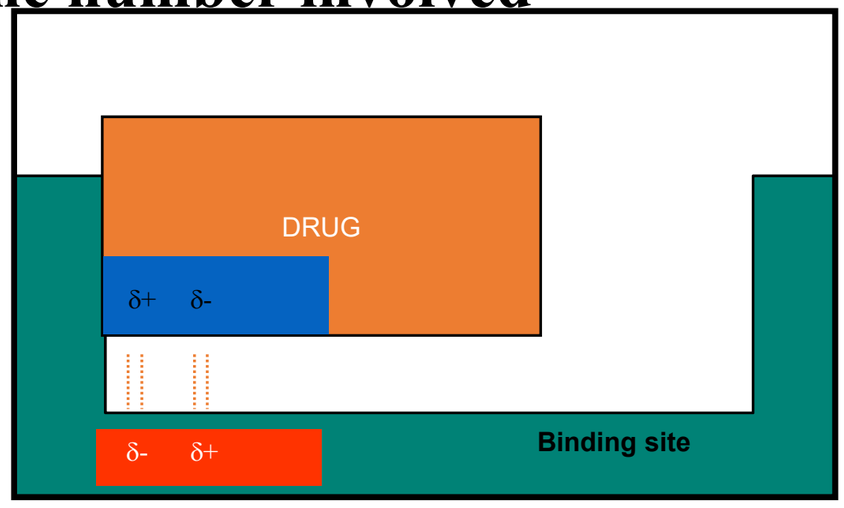


4. Intermolecular bonding forces

4.3 Van der Waals interactions

- **Very weak interactions (2-4 kJ mol^{-1})**
- **Occur between hydrophobic regions of the drug and the target**
- **Transient areas of high and low electron densities cause temporary dipoles**
- **Interactions drop off rapidly with distance**
- **Drug must be close to the binding region for interactions to occur**
- **The overall contribution of van der Waals interactions can be crucial to binding because of the number involved**





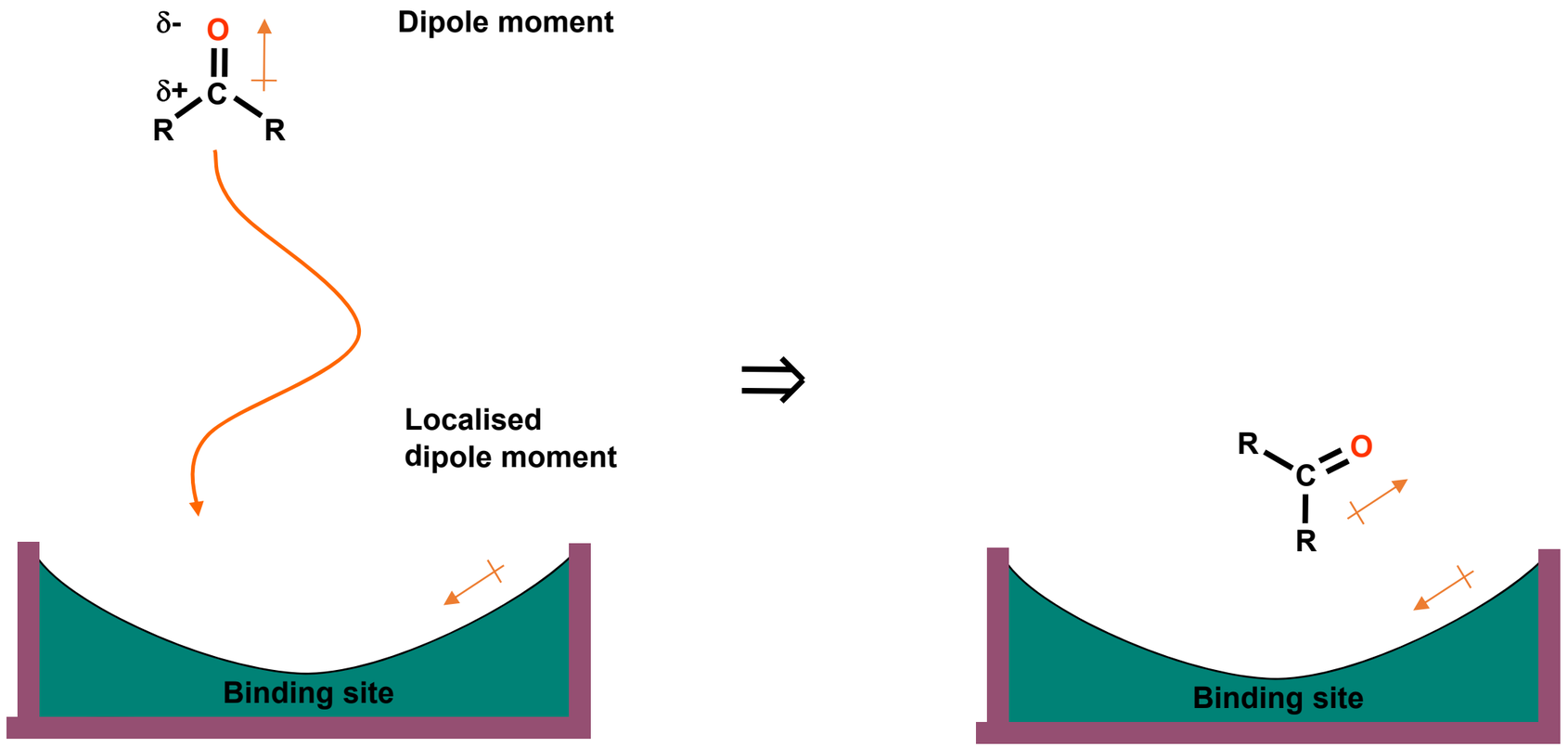
4. Intermolecular bonding forces

4.4 Dipole-dipole interactions

- **Can occur if the drug and the binding site have dipole moments**
- **Dipoles align with each other as the drug enters the binding site**
- **Dipole alignment orientates the molecule in the binding site**
- **Orientation is beneficial if other binding groups are positioned correctly with respect to the corresponding binding regions**
- **Orientation is detrimental if the binding groups are not positioned correctly**
- **The strength of the interaction decreases with distance more quickly than with electrostatic interactions, but less quickly than with van der Waals interactions**

4. Intermolecular bonding forces

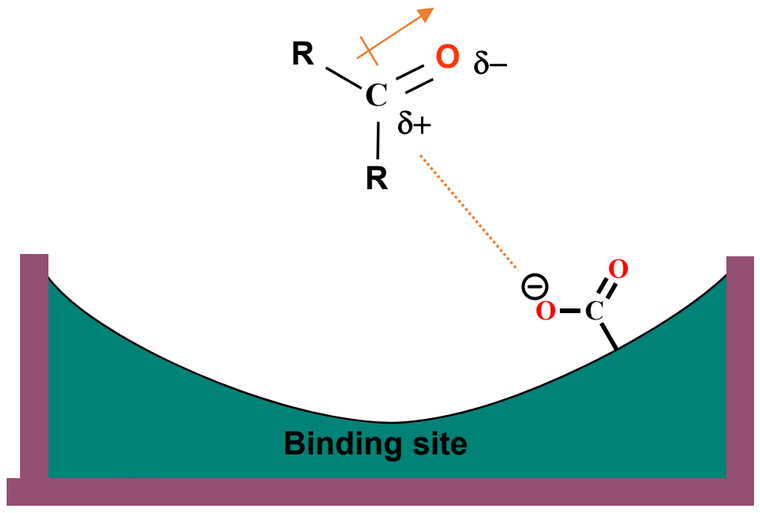
4.4 Dipole-dipole interactions

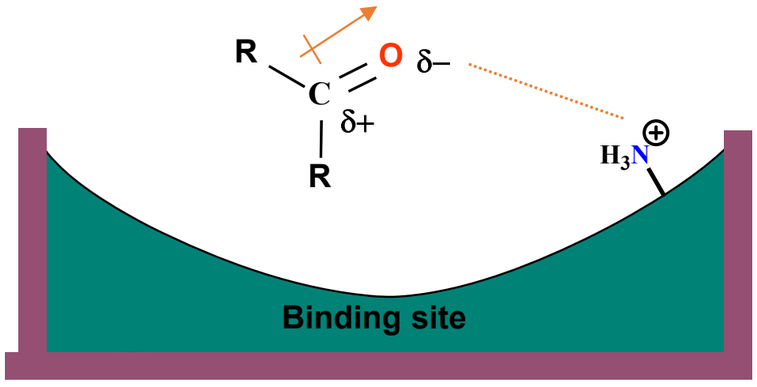


4. Intermolecular bonding forces

4.5 Ion-dipole interactions

- **Occur where the charge on one molecule interacts with the dipole moment of another**
- **Stronger than a dipole-dipole interaction**
- **Strength of interaction falls off less rapidly with distance than for a dipole-dipole interaction**

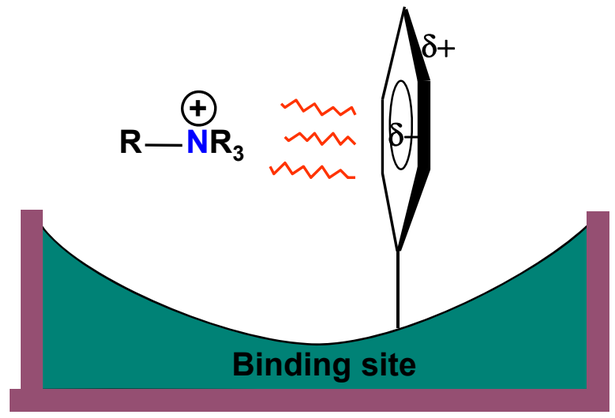




4. Intermolecular bonding forces

4.6 Induced dipole interactions

- **Occur where the charge on one molecule induces a dipole on another**
- **Occur between a quaternary ammonium ion and an aromatic ring**

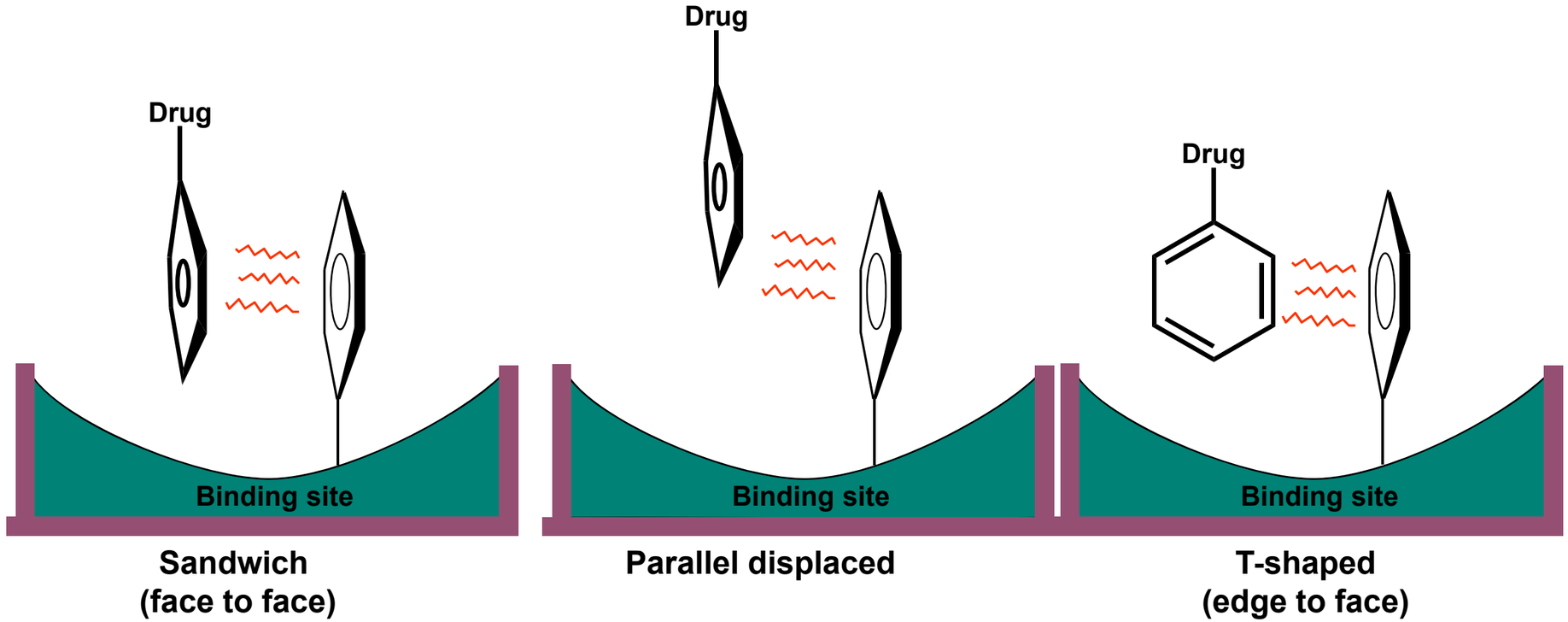


4. Intermolecular bonding forces

4.7 Pi-stacking (π-π stacking)

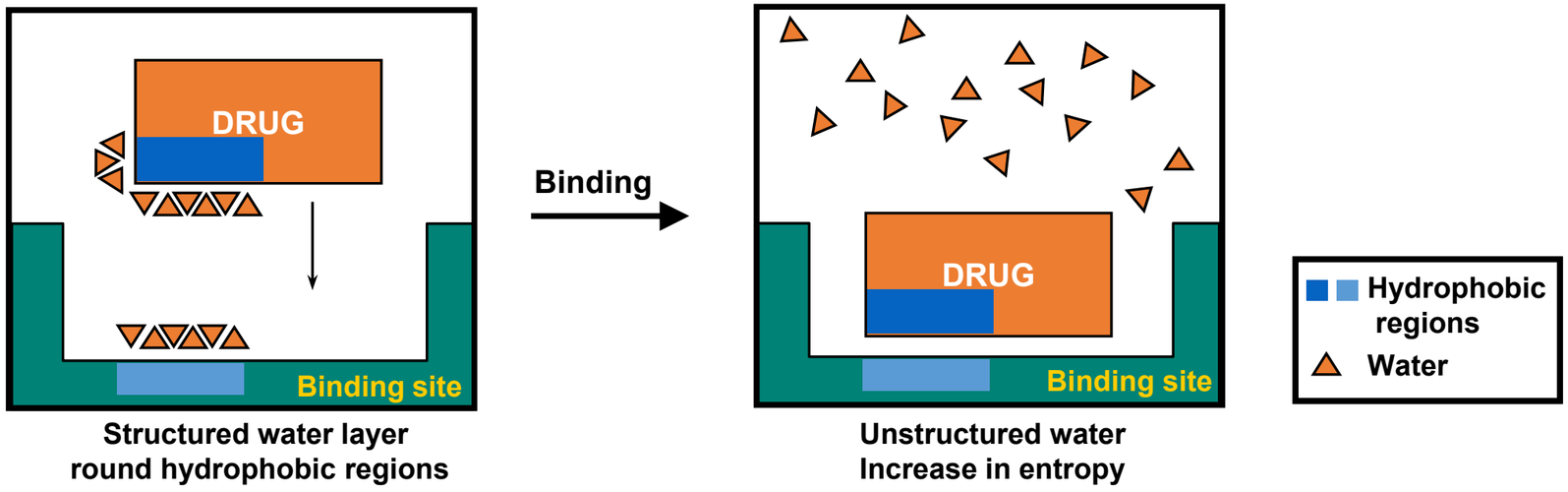
•Interactions involve a balance of quadrupole-quadrupole interactions and London dispersion forces

• Interacting rings may be arranged as sandwich (face to face), T-shaped (edge to face) or parallel displaced



5. Hydrophobic interactions

- Hydrophobic regions of a drug and its target are not solvated
- Water molecules interact with each other and form an ordered layer next to hydrophobic regions - negative entropy
- Interactions between the hydrophobic regions of a drug and its target ‘free up’ the ordered water molecules
- Results in an increase in entropy
- Beneficial to binding energy



Structured water layer round hydrophobic regions

Unstructured water Increase in entropy

❖ Classification of drugs

➢there are four main ways in which drugs might be classified or grouped.

1. **Pharmacological effect**:

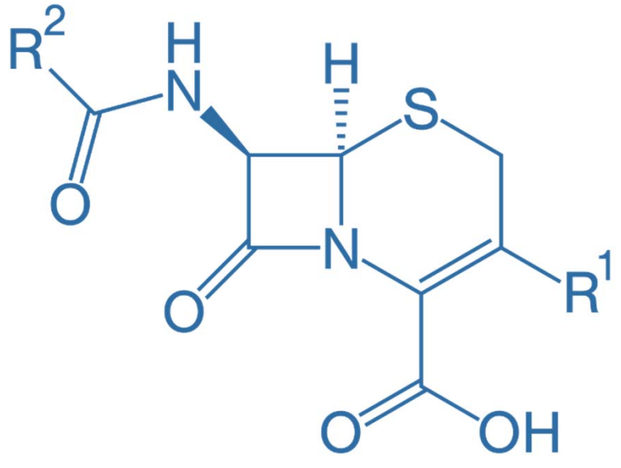
- ➢ Drugs are grouped according to its biological effect e.g. analgesics, antipsychotics, antihypertensives, antiasthmatics, antibiotics, etc.

- ➢ **Advantages**: is to know the full scope of drugs available for a certain disease or ailment.

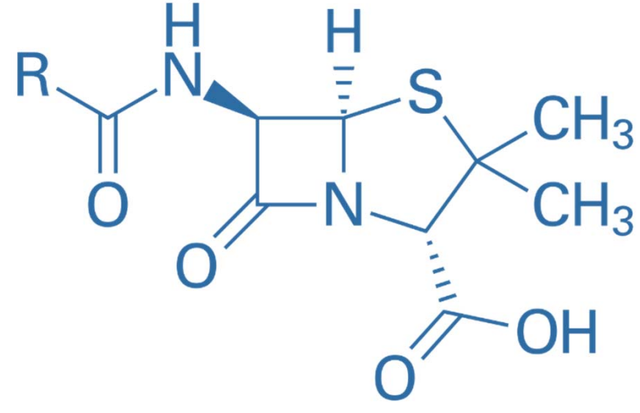
- ➢ **Disadvantages**: This grouping contains a large and extremely varied group of drugs, e.g. it is impossible to compare different pain killers and expect them to look alike or have some common mechanism of action.

2. Chemical structure:

- They have a common skeleton are grouped together, e.g penicillins, barbiturates, opiates, steroids, catecholamines, etc.

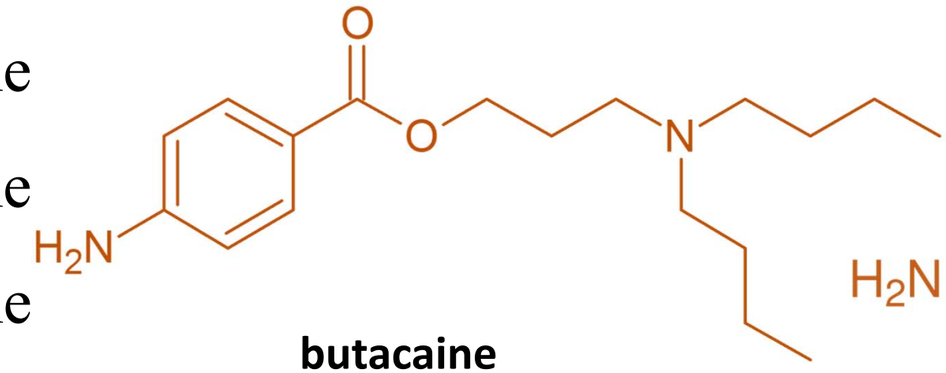


Cephalosporin

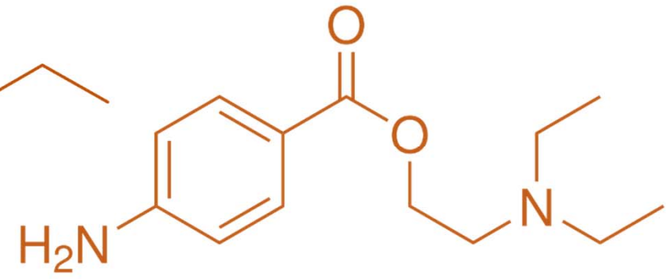


Penicillin

- **Advantages**: In some cases, the mechanism of action and the biological activity is the same for the structures involved (e.g. antibiotic activity for penicillins).

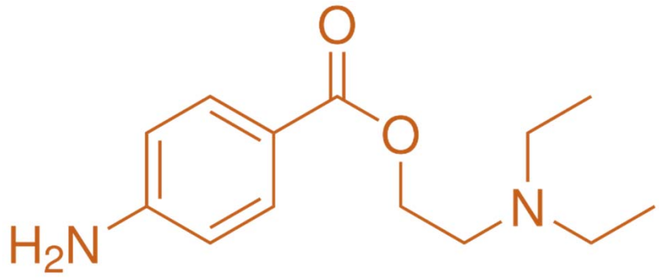


butacaine

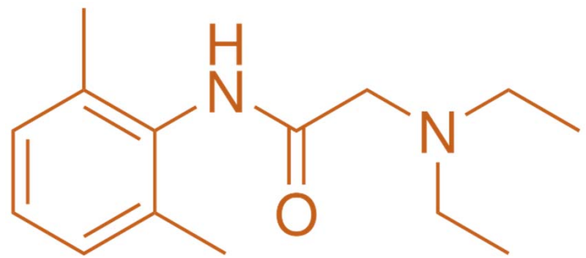


procaine

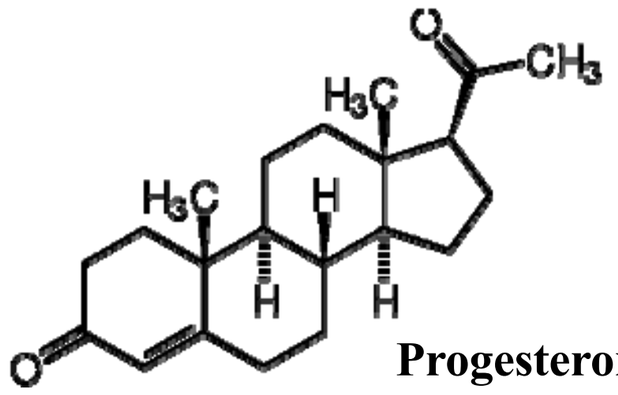
- **Disadvantages:** Not all compounds with similar chemical structure have the same biological action, vice versa about the compounds that have the same biological effects but in differents chemical skeleton.



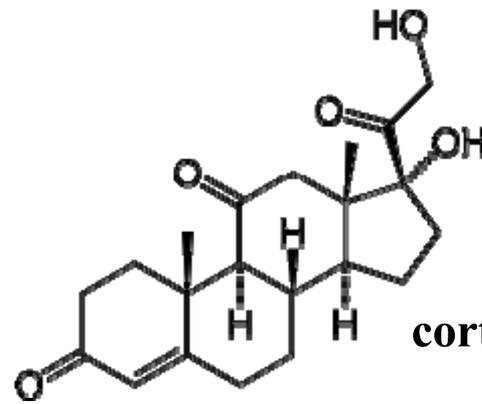
procaine



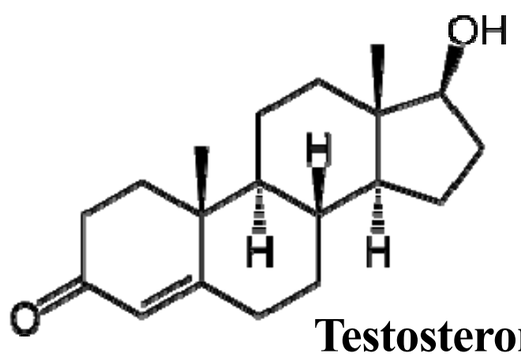
lidocaine



Progesterone



cortisol



Testosterone

3. Target system:

- These are compounds which are classed according to whether they affect a certain target system in the body

- **Advantage**: This classification is a bit more specific than the first, since it is identifying a system with which the drugs interact.

- **Disadvantage**: there are still several different targets with which drugs could interact in order to interfere with the system

- So the drugs included in this category are to be quite varied in structure due to different mechanisms of action that are involved.

4. Target molecule or site of action:

- These are compounds grouped according to the molecular target with which they interact such enzymes and receptors.

- For exmple, anticholinesterases they inhibition the enzyme acetylcholinesterase.

- this is a more specific classification since we have now identified the precise target at which the drugs act.

- We expect some structural similarity between the agents involved and a common mechanism of action.

❖ Naming of drugs and medicine

- The vast majority of chemicals that are synthesized in medicinal chemistry research never reach the market so it is **impractical** to name them all.

- Research groups label them with a code which consists of **letters and numbers**.

- the **letters** are specific to the research group undertaking the work and the **number** is specific for the compound.

- Ro31-8959, ABT-538 and MK-639 were compounds prepared by Roche, Abbott, and Merck pharmaceuticals respectively.

- If the compounds concerned show promise as therapeutic drugs they are taken into development and named. E.g. the above compounds showed promise as anti-HIV drugs and were named **saquinavir, ritonavir and indinavir**, respectively.

- If the drugs prove successful and are marketed as medicines, they are given a proprietary, brand or trade name which only the company can use.

- E.g. the previous compounds were marketed as **Fortovase®, Norvir® and Crixivan®** respectively "note that brand names always start with a capital letter & have the symbol ® or ™ to indicate that they are registered brand names".

- The proprietary names are also specific for the preparation or formulation of the drug.

- E.g. Fortovase® is a preparation containing 200 mg of saquinavir in a gel filled, beige colored capsule. If the formulation is changed then a different name is used. Roche sell a different preparation of saquinavir called Invirase ® which consists of a brown/green capsule containing 200 mg of saquinavir as the mesilate salt.

- When a drug's patent has expired, it is possible for any pharmaceutical company to produce and sell that drug as a generic medicine.

- It is not allowed to use the trade name used by the company that originally invented it.

- European law requires that generic medicines are given a rINN, which is usually identical to the name of the drug.

{ same suffix for same class: Acamol, Paramol, PB Tamol }

Drug's name can be used to denote the active ingredient, such as Viagra, to denote sildenafil, so a list was attached containing the names of the drugs and the active ingredients - List 1 - and another list of the active ingredients and their list of drugs 2.

Attachments:

1. Book Chapter

http://u.pc.cd/BLX7

List 1 Trade names and drugs

http://u.pc.cd/7oVrtalK

List 2 Drugs and their trade names:

http://u.pc.cd/21G

Please click here for all attachments

http://u.pc.cd/Jea

Home Work 1

Please answers 1,6 and 8 of the end chapter questions “ deadline 26.9.2020