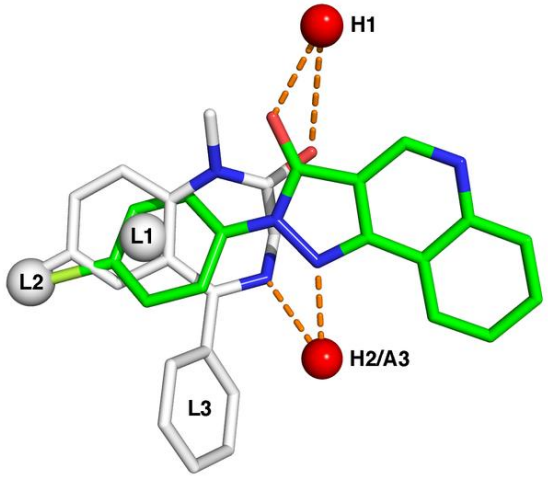
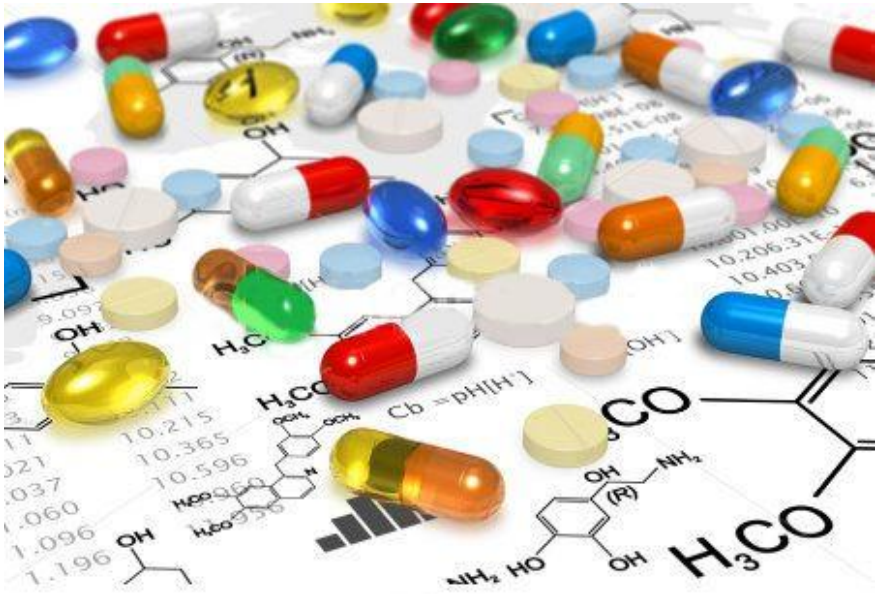
Introduction to Medicinal Chemistry





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Learning Outcomes

At the end of this lesson students will be able to

- Outline the basic concepts of Medicinal Chemistry.
- Describe about drug, targets, roles of medicinal chemistry in drug design and discovery.
- Describe the basic concepts of pharmacokinetics and pharmacodynamics.
- Explain the fundamentals of receptors and drug-receptor interactions.

Introduction to Medicinal Chemistry

- Medicinal Chemistry is the science that deals with the design and development of pharmaceutical agents that has a desired biological effect on human body and other living systems.

- Drug is a compound that interact with a biological target to produce a biological response:-
  - Biological target: Human, bacteria, fungi,….
  - Biological response: desired or undesired.

- Medicinal chemists concern about the synthesis of new molecules to investigate the relationships between the chemical structure of these compounds and their biological activities.

- Medicinal chemistry also involves isolation of compounds from natural sources.

- Ideal drug must be:-
  - Not toxic
  - Effective and potent
  - Selective
  - Easily administered
  - Cheap

- Penicillin: one of the safest and most active antibiotics……**BUT**….. Resistance developed to most of them.

- Morphine: a very effective pain killer….. **BUT**…. May cause tolerance, addiction and respiratory depression.

- Heroin: the best pain killer we know….**BUT**…. addiction developed (still used in terminal cancer).

- Drug might be harmful at higher doses:

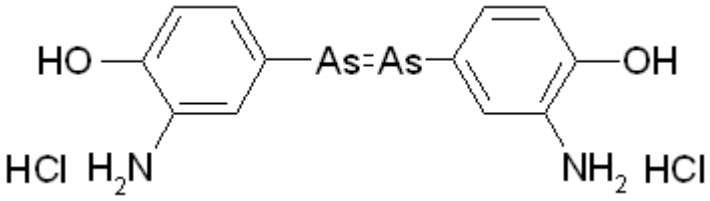
  - Therapeutic index: it is the ratio of the dose leads to toxic effect in 50% of cases to that leads to therapeutic effect in 50% of the cases.

$$\frac{LD_{50}}{ED_{50}}$$

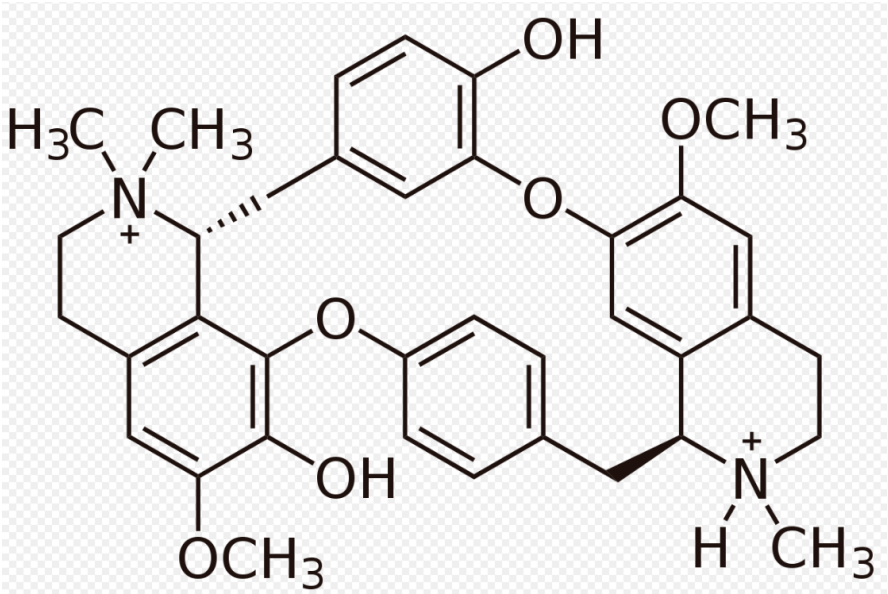
  - **Large therapeutic index…… safer drug.**
  - **narrow therapeutic index…… more toxic drug.**

Poisons can be drugs at lower doses:-

- Arsenicals: very toxic but used as antiprotozoal agents.



- Tubocurarine:- It used as muscle relaxant.



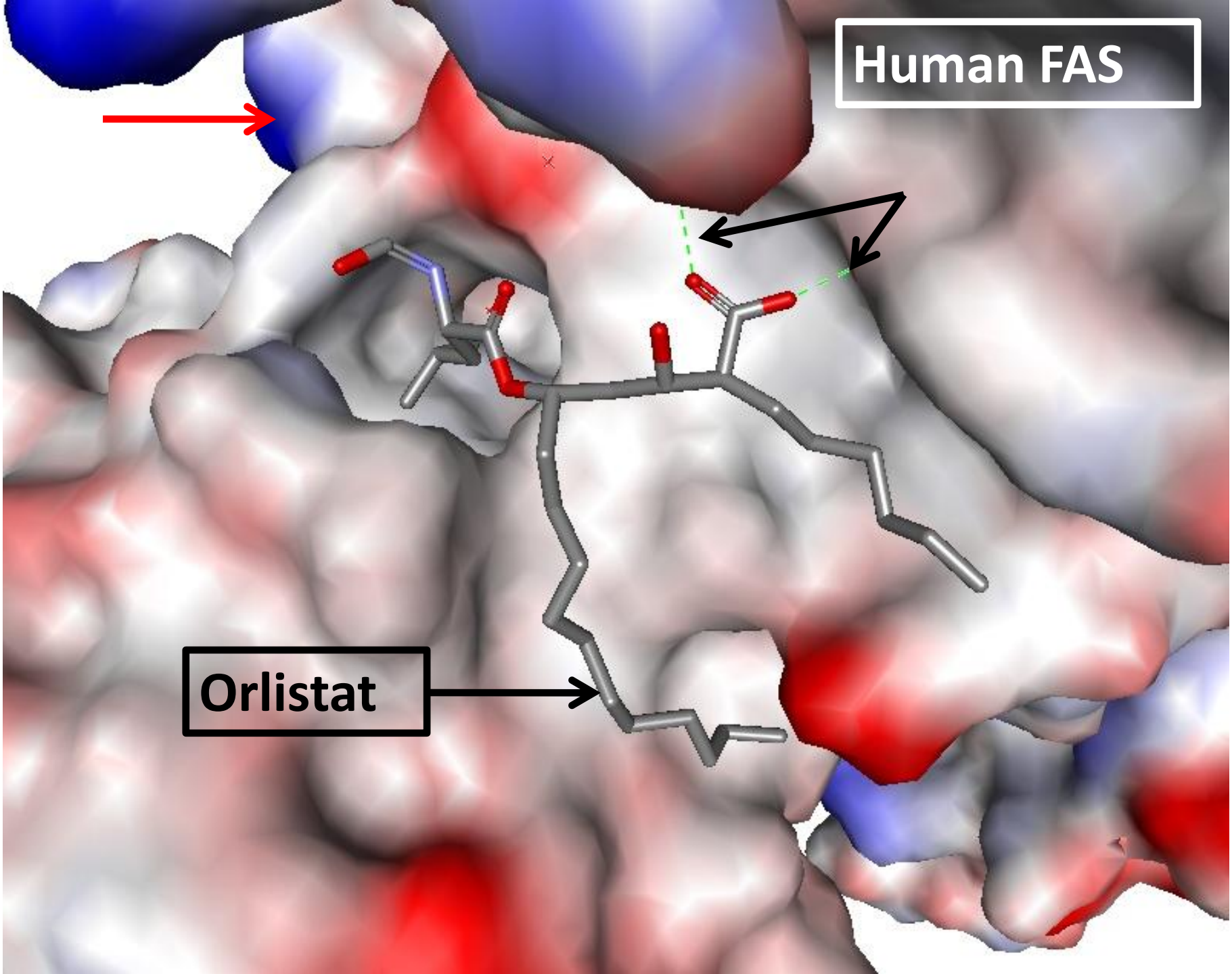
Selective Toxicity

- Selective Drugs: that show toxicity against abnormal cells without affecting normal cells.

- Degrees of selectivity:-
  - No effect on normal host cells.
  - Killing certain microbial strain without affecting others.
  - Targeting certain metabolic pathway without affecting others.

Drug Targets

- They are macromolecules (receptors, enzymes, DNA or transport proteins).
- Drugs interact and bind to the binding sites through intermolecular bonds (ionic, H-bonds, van Der Waals, dipole-dipole and hydrophobic).
- The bonds mainly are weak, therefore in most of the cases this binding is reversible.

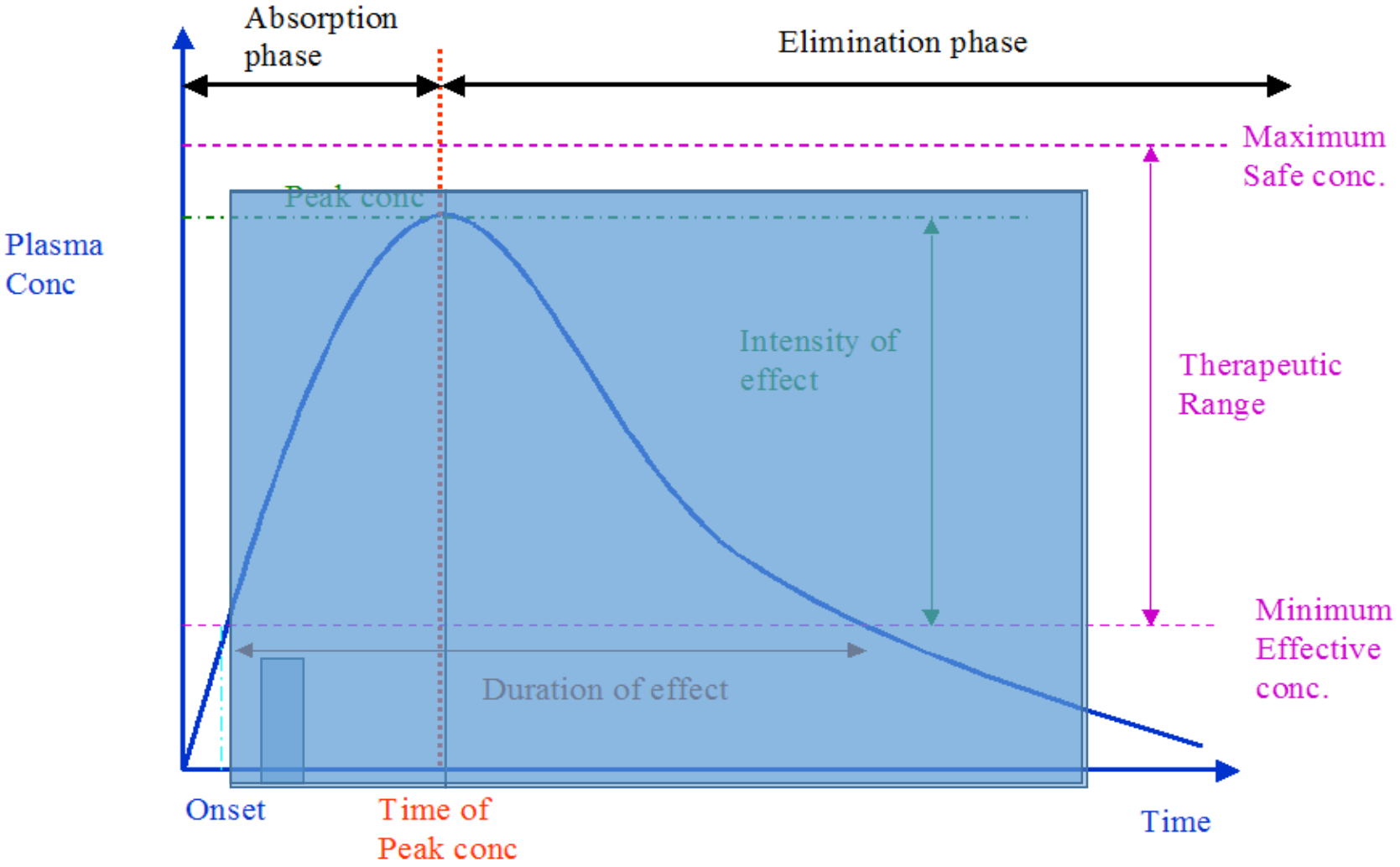

Human FAS
Orlistat

Pharmacokinetics

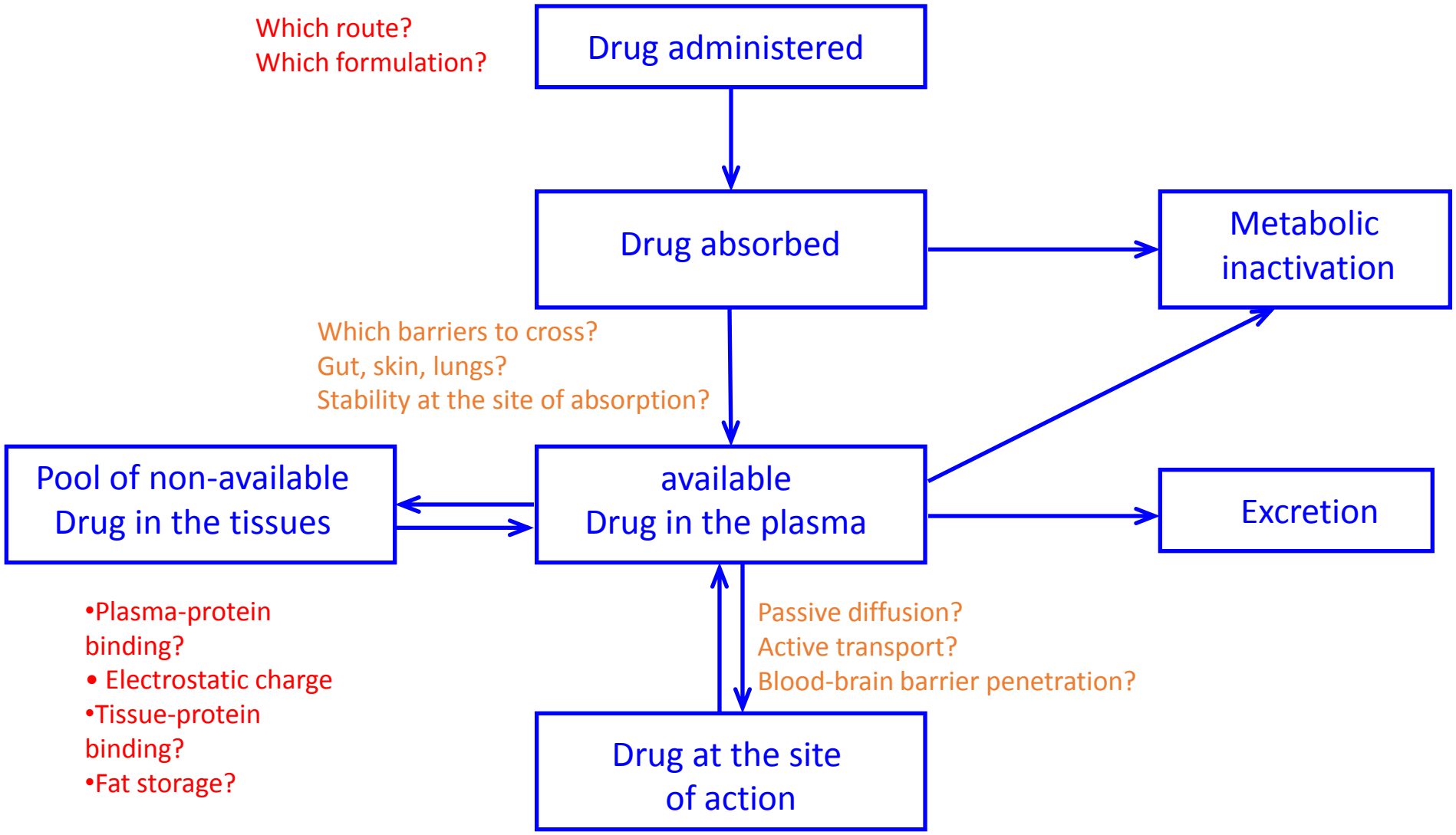
- Pharmacokinetics: How the drug distribute and reach its target (ADME) and what will happen to the drug.

- Pharmacokinetics – what the body does to the drug.
  - How does drug get it into the body?
  - How long does it take to exert its action?
  - How long does it stay in the body?
  - Where does it go to in the body?
  - Is it metabolised to another form?

The [plasma]-time curve after drug administration



Pharmacokinetics

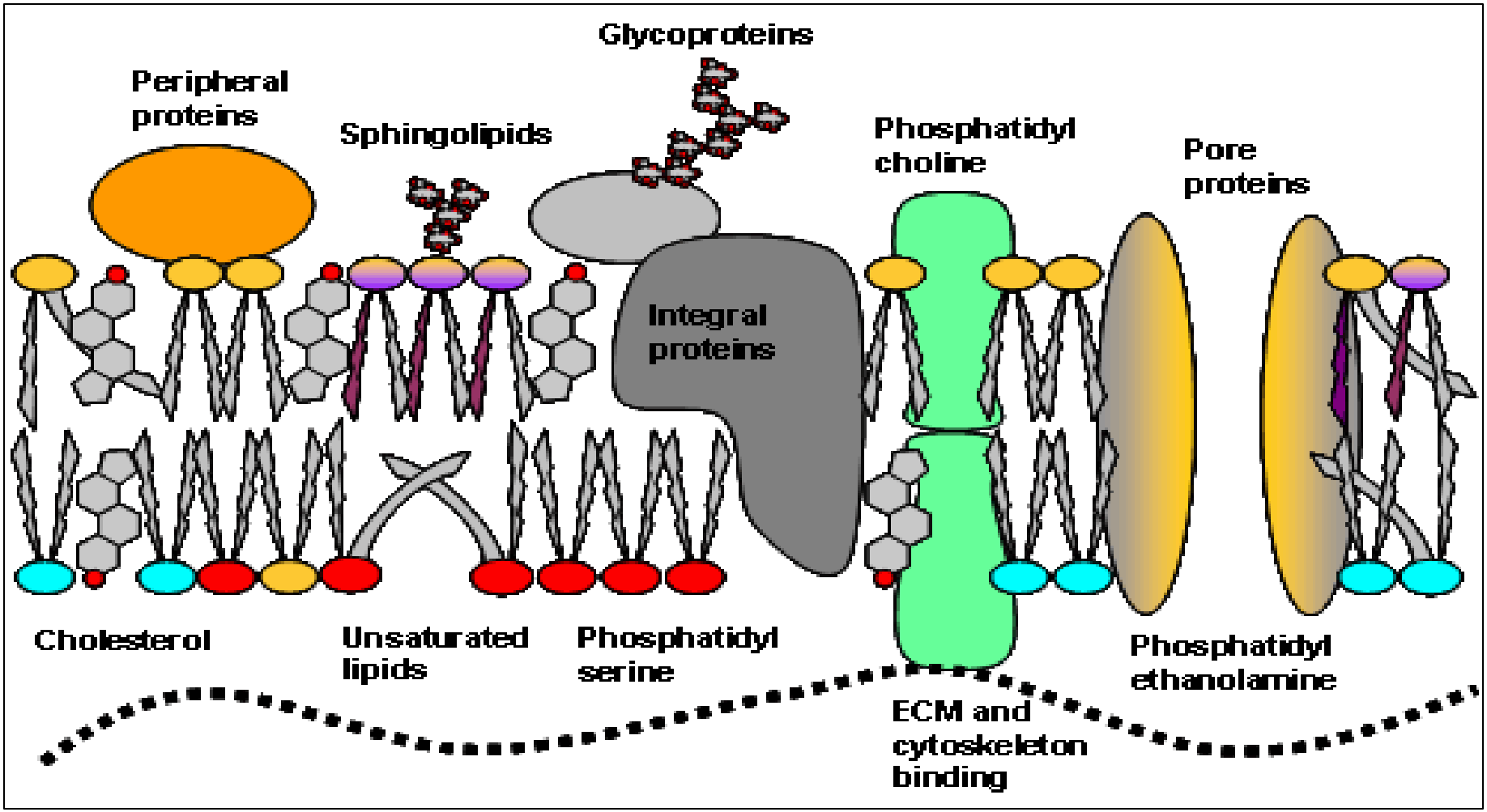


Pharmacokinetics

Drug administration: How is the drug to be formulated? If as an injection, is it soluble in aqueous solution? If as a tablet, will it dissolve when released in the gut?

Drug absorption: can the drug pass through the barrier membranes in the GIT? Can it pass through the skin barriers? These barriers are made up in a large part by lipids, so the drug must be sufficiently lipophilic/ unionized to diffuse through them.

Membranes have phospholipids bilayer that act as barriers to the movement of drugs within the body



Pharmacokinetics

Drug metabolism: Metabolism increases the water solubility of drugs by enzymatically introducing polar functional groups so that they can be excreted. What is the chemistry of the drug? How fast is it inactivated? Is it converted into more active or even toxic components?

Drug excretion: Kidney excretes water-soluble metabolites and the ionized forms of drugs.

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Pharmacodynamics

- **Pharmacodynamics**: How the drug interacts with its target.

- **Pharmacodynamics**: What the drug does to the body.

  - What is the therapeutic effect of the drug?
  - How does it exert its effect?
  - How does the drug interact with the target?
  - Can the effect be modified?

Pharmacodynamics

- More than 90% of drugs have biological targets to bind with in order to exert their pharmacological effects.
- Biological targets: are endogenous macromolecules including DNA, RNA, enzymes, receptors, membrane proteins, etc…

- The nature of drug-receptor binding
  - Either reversible or irreversible.
  - Reversible binding means that the drug-target complex will dissociate to release the free functioning target.
  - Irreversible binding means permanently blocking the binding site of the target… irreversible damage.

Interactions involved between drug and receptor

Covalent bonding — **Irreversible bond**

Ionic (electrostatic) interaction

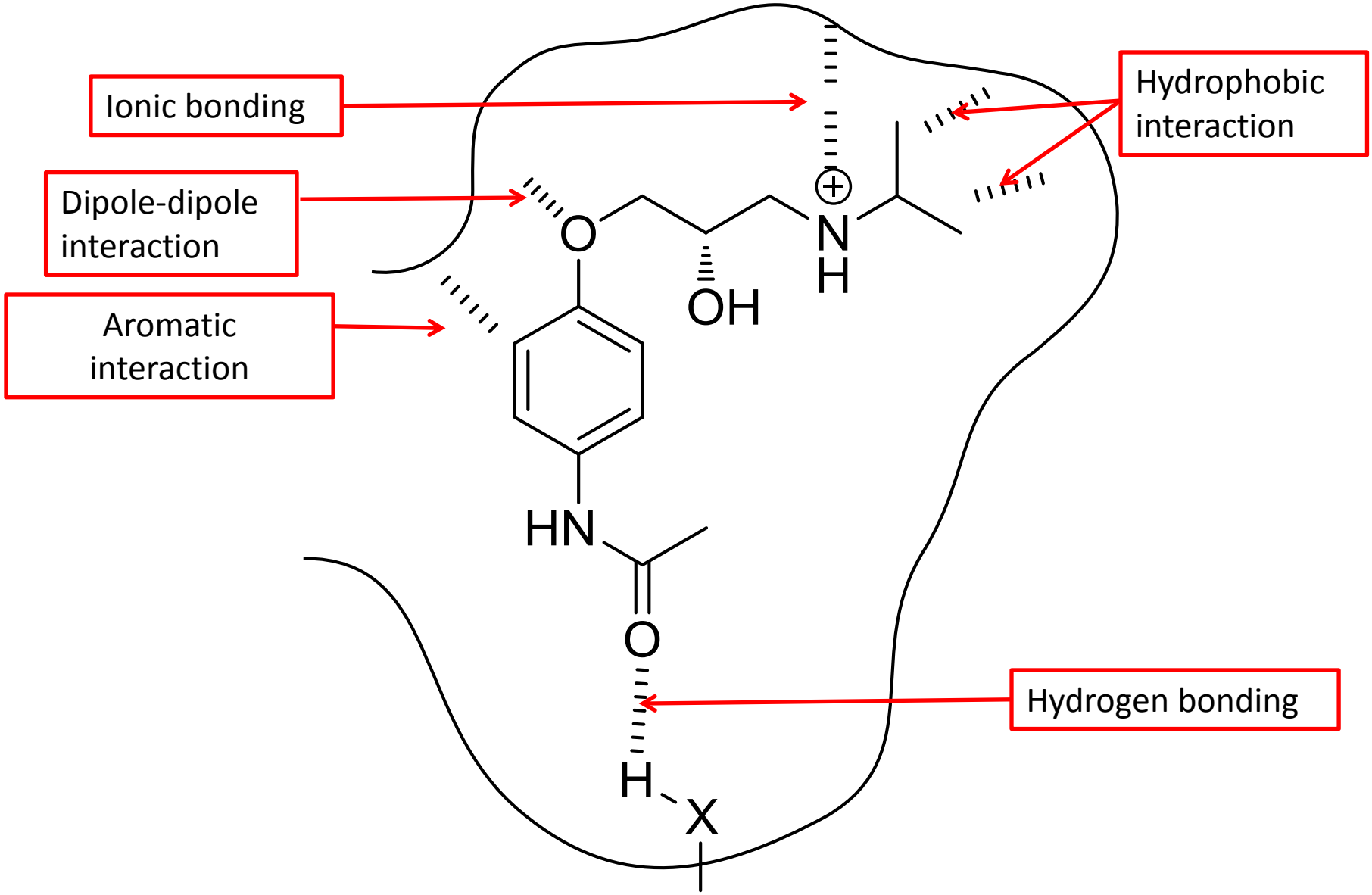
Dipole-dipole interaction

H-bonding

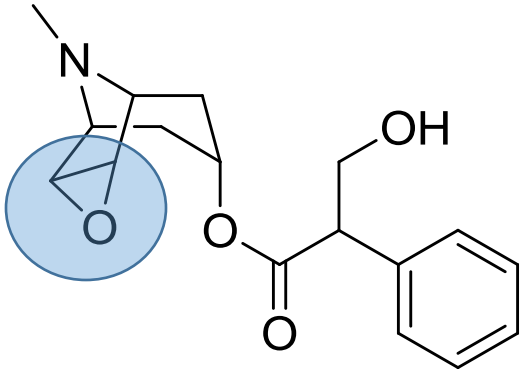
Hydrophobic interaction

Reversible bonds

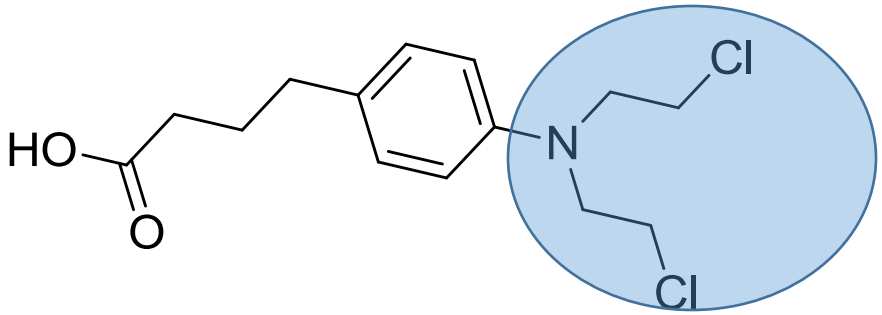
Van der Waals forces



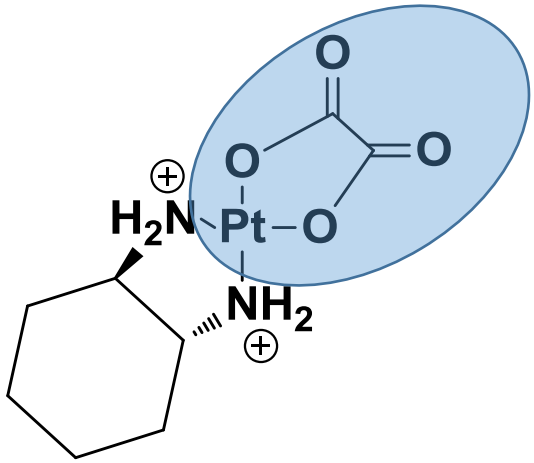
Practolol inside the adrenergic B-receptor



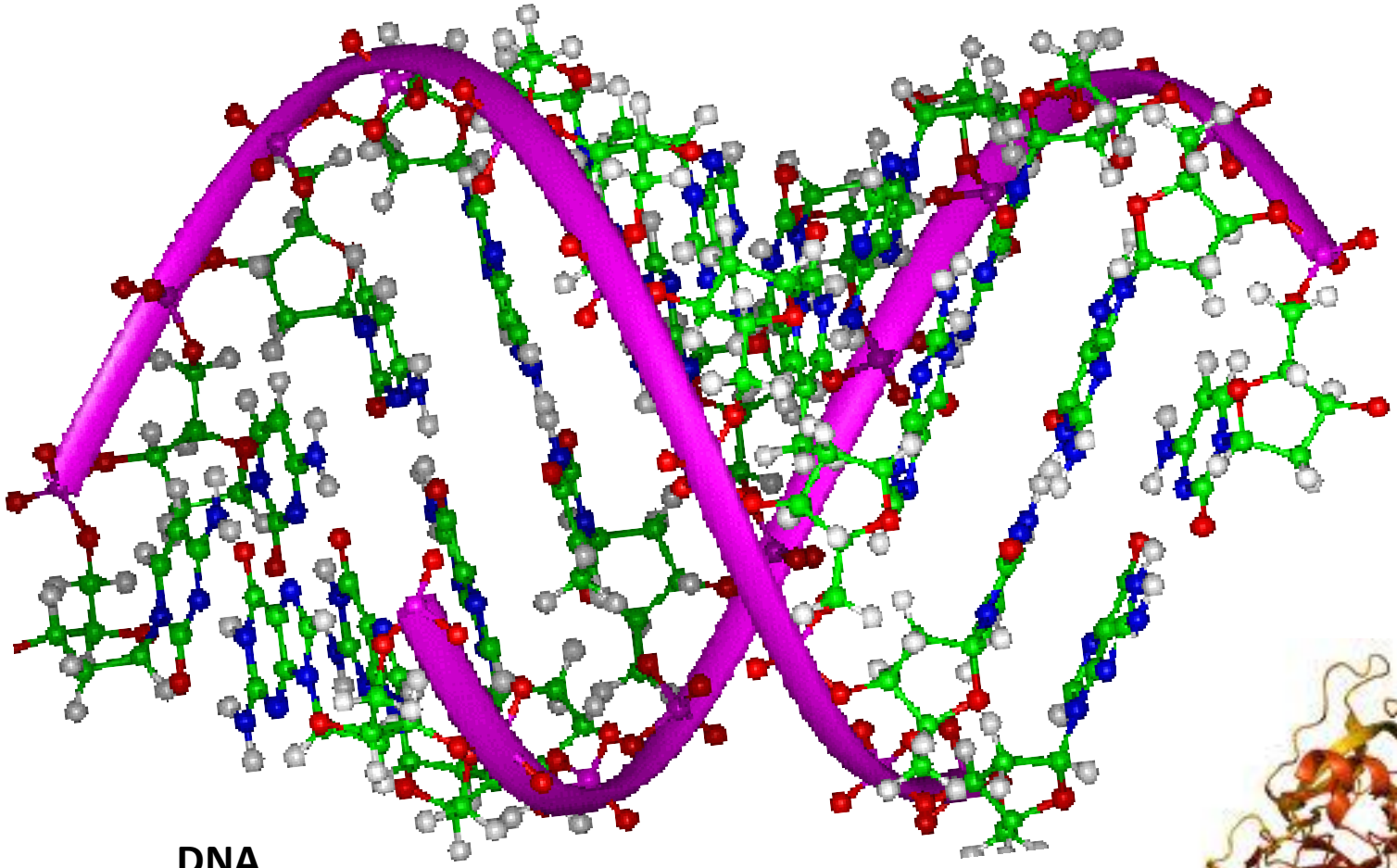
Hyoscine
Anti-cholinergic



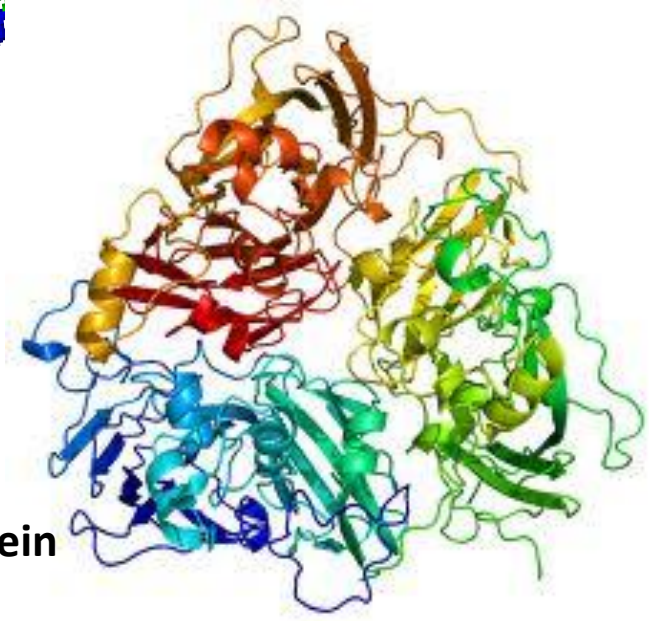
Chlorambucil (Leukeran)
for chronic leukemia



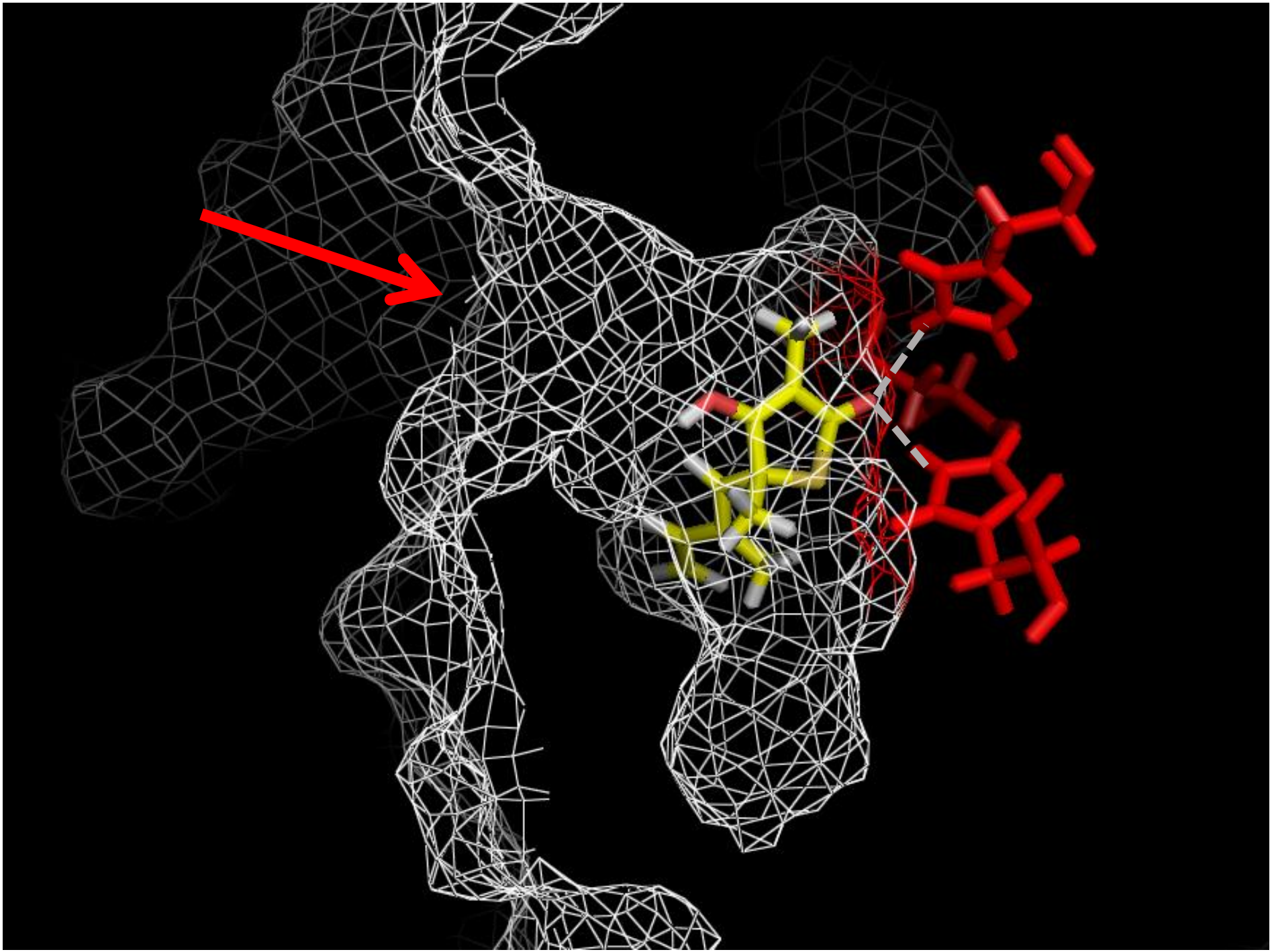
Oxaliplatin

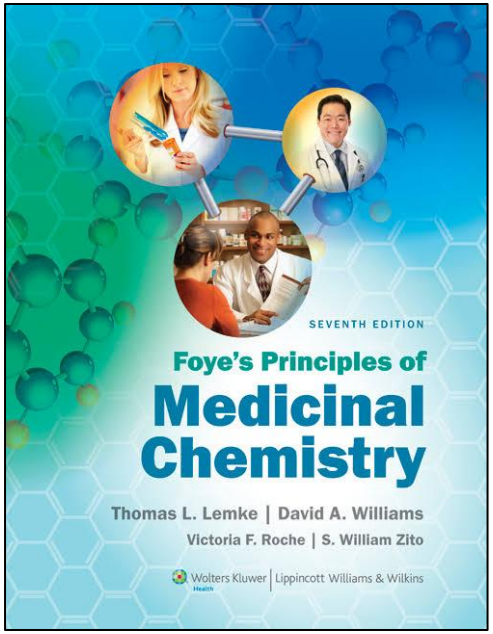


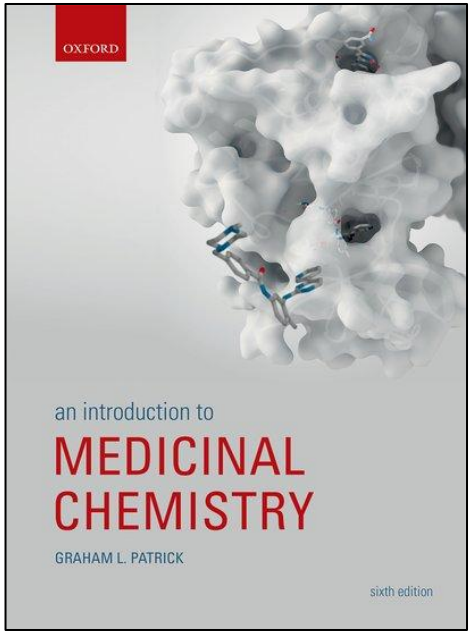
DNA

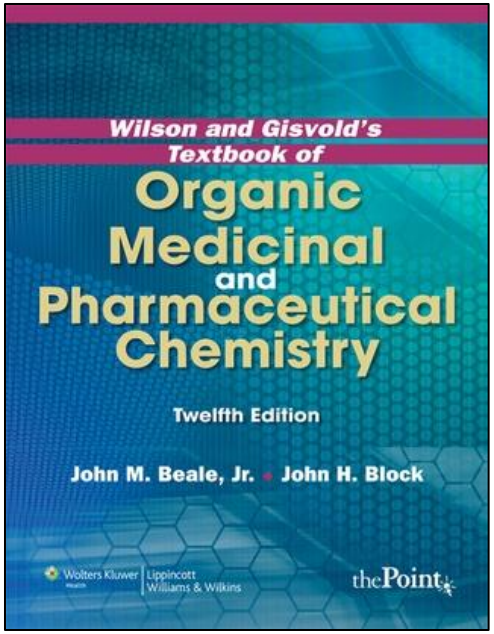


Protein









1. An introduction to Medicinal Chemistry by Graham L. Patrick. 4th edition, Oxford, 2009
2. Wilson and Gisvolds text book of organic medicinal and pharmaceutical chemistry by John H. Black and John M. Beale, jr. 12th edition, Lippincott Williams and Wilkings 2011.
3. Foyes principle of medicinal chemistry by David H. Williams, Thomas L. Leuke, Williams O. Foye. Lippincott William and Wilkins. 7th edition, 2013.


Thank
You