Chemistry in the Service of Mankind

PRE-SEMINAR MATERIAL

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Prior knowledge

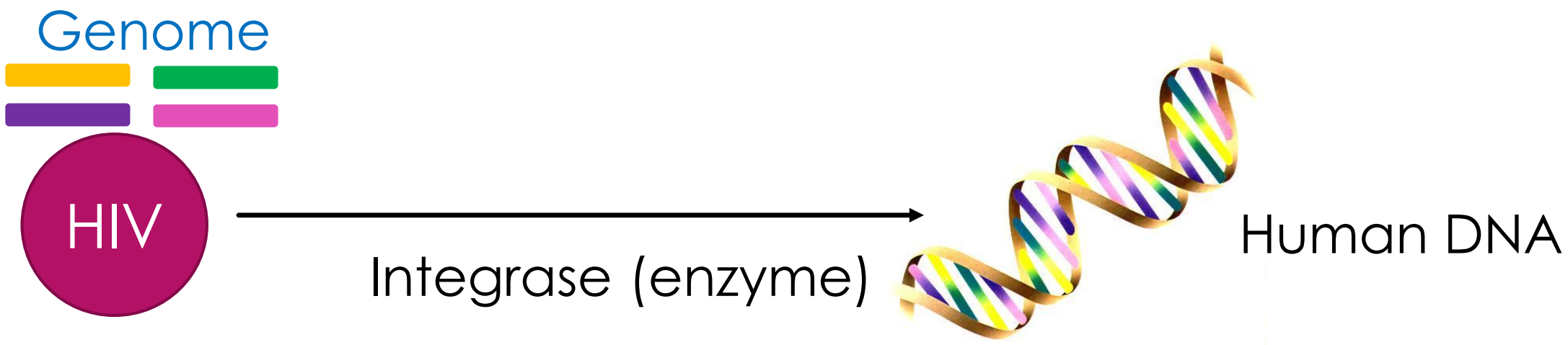
- Please watch the seminar, "Drug Discovery and Organic Chemistry", before watching this seminar. The following ideas from the drug discovery seminar will be applied in this seminar.
  - Lead identification (Slides #24 - #25)
  - Lead optimization (Slide #29)
  - How Tamiflu prevents the spread of the influenza virus (Slide #26)
- The seminar builds on knowledge learnt in the DSE curriculum:
  - Chemistry: Topics V and XI
  - Combined Science (Chemistry): Topic V

HIV (Human Immunodeficiency Viruses)

- HIV is a retrovirus, i.e. a RNA virus that inserts a copy of its genome into humans' DNA upon infection.
- Untreated infection with HIV can lead to AIDS.
- Scientists want to design a drug which can minimize the numbers of replication of HIV in the human body to reduce early death in HIV-infected people.

HIV Integrase

- This seminar focuses on the discovery of a drug called Raltegravir which can stop HIV from inserting a copy of its genome into human's DNA by inhibiting an enzyme called Integrase.
- The role of Integrase is described as follow.



Inhibitor and potency metrics

- A drug is an inhibitor when it works by inhibiting the action of an enzyme.
  - Raltegravir is an inhibitor because it inhibits the action of the enzyme, Integrase.
- We need to set standards to measure the potency of the drug - how well Raltegravir inhibits Integrase.
  - IC50 – The concentration of a drug that is required for 50% inhibition *in vitro*
  - IC95 – The concentration of a drug that is required for 95% inhibition *in vitro*

A low IC value of a drug = High potency of a drug

"in vitro" means "in test tube"

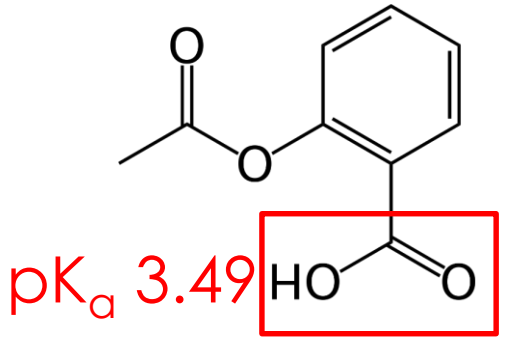
Acid/base properties of drugs

- Roughly speaking, all drug-like molecules can be considered as either acids or bases.
- Acids: $HA\ (aq) + H_2O\ (l) \rightleftharpoons A^-\ (aq) + H_3O^+\ (aq)$
  - $K_a = \frac{[A^-][H_3O^+]}{[HA]}$ (The equilibrium constant for weak acids)
- Bases: $B\ (aq) + H_2O\ (l) \rightleftharpoons HB^+\ (aq) + OH^-\ (aq)$
  - $K_b = \frac{[B][H_3O^+]}{[HB^+]}$ (The equilibrium constant for weak bases)
- By changing the amount of available H_3O^+, the equilibrium positions of the above acid and base equilibria can shift.

pK_a – a measure of acid strength

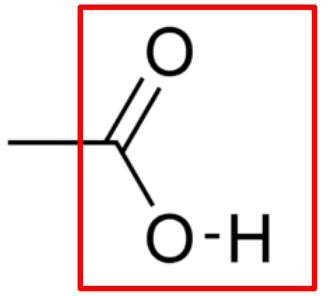
- By definition, $pK_a = -\log_{10}(K_a)$
- pK_a is a measure of acid strength.
  - The lower the pK_a, the stronger the acid is.
  - The higher the pK_a, the weaker the acid is.

Acid	pK_a
Carboxylic acid in aspirin	3.49
Acetic acid	4.75
Ammonium	9.2



pK_a 3.49

Aspirin



pK_a 4.75

Acetic acid

Pronation and deprotonation of an acid

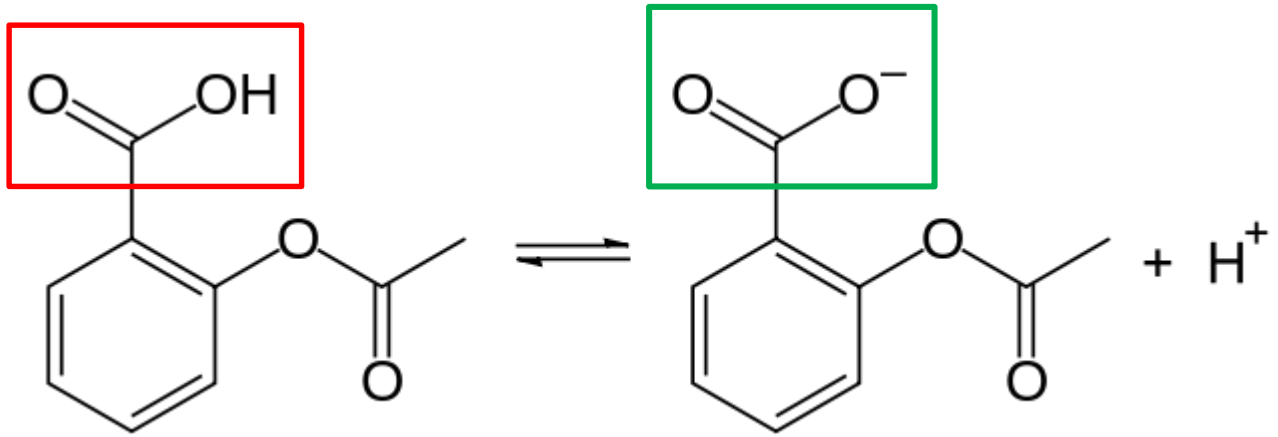
- Terminologies
  - Protonation - the addition of hydrogen ions (H^+) to the molecule
  - Deprotonation - the removal of hydrogen ions (H^+) from the molecule
- Examples
  - Acids: $HCl\ (aq) + H_2O\ (l) \rightleftharpoons Cl^-\ (aq) + H_3O^+\ (aq)$

    [Deprotonation – a H^+ ion is lost from a HCl molecule]
  - Bases: $NH_3\ (aq) + H_2O\ (l) \rightleftharpoons NH_4^+\ (aq) + OH^-\ (aq)$

    [Protonation – a H^+ ion is added to a NH_3 molecule]

Pronation and deprotonation of an acid

- An acid can stay protonated or become deprotonated in different pH environment.
- Acid molecules are deprotonated if the pK_a of the acid is lower than the pH of the environment.
  - E.g.



Aspirin

pK_a 3.49

Deprotonated Aspirin

When pH is higher than 3.49, equilibrium shifts to the product side.

"Deprotonated aspirin" is more favorable in environment of pH 7.2 – 7.4 (e.g. in human cells).

Effect of pK_a on drug delivery

- Since a drug molecule can be protonated or deprotonated in human cells, depending on the pH of the environment. The drug molecule can be electrically neutral or charged.
- Negatively charged drug molecules (e.g. a deprotonated acid molecule) cannot get into the cell membrane because of the negatively charged lipid layer.
- However, the prototype of the Integrase inhibitor is a weak organic acid which is negatively charged in human cell.
- Therefore, medicinal chemists need to find a way so that the drug can be delivered into the cell membrane for action.
- Please watch the seminar to see how medicinal chemists solved this problem.

Coverage of this seminar

- How HIV infects humans
- How scientists discovered the lead compound for the Integrase inhibitor
- How medicinal chemists solved the different problems encountered in the optimization of the lead compound to make it safe for humans

Glossary

英文	中文
Hydrolysis	水解作用
Inhibitor	抑制劑
Aspartic acid	天冬氨酸
Glutamic acid	谷氨酸
Catalytic core	催化核心
Integrase	整合酶
Integration	整合
Pharmacophore	藥效基團
DNA stand	DNA鏈