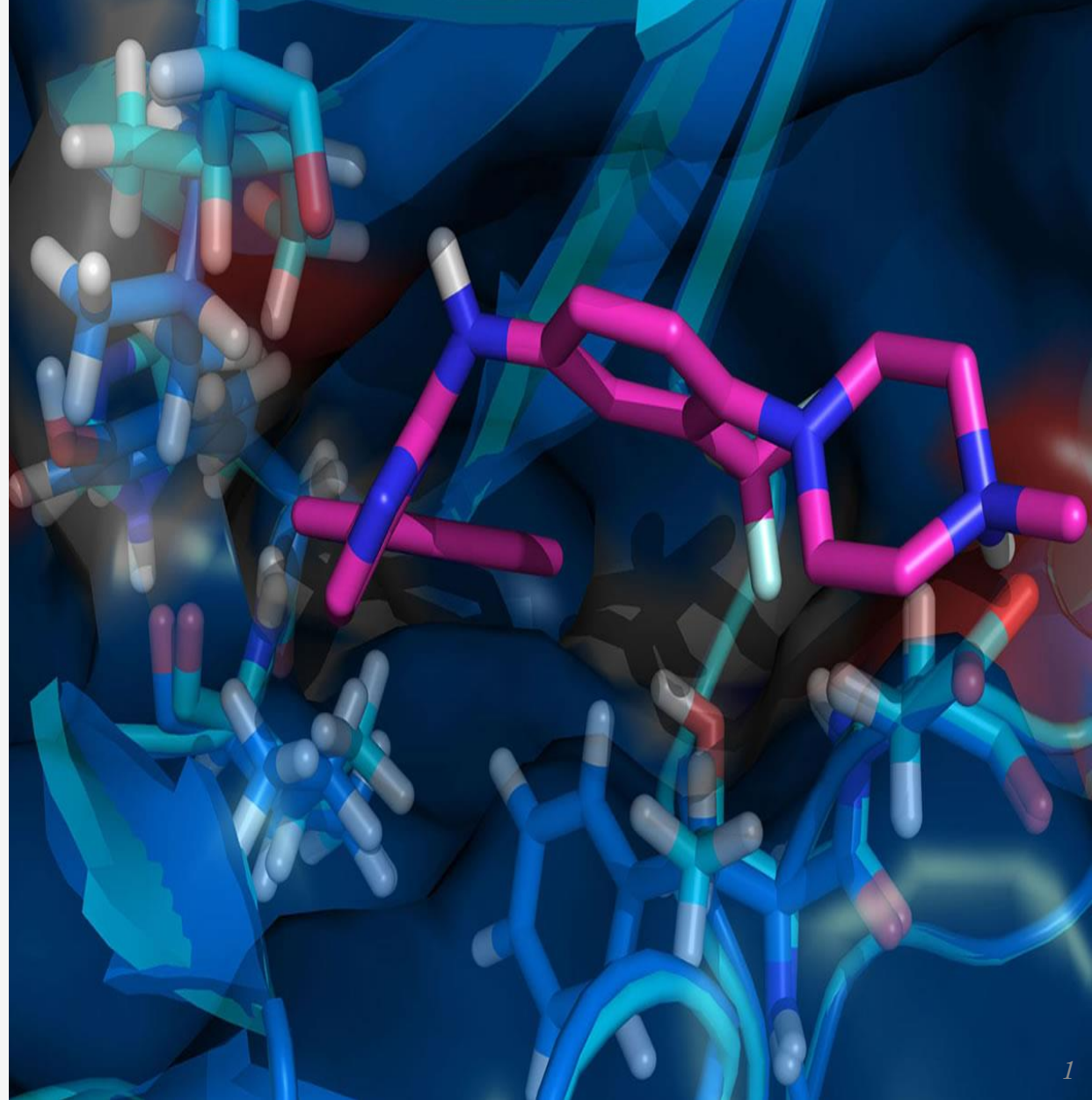# An Introduction to Medicinal Chemistry

Special Topics in Organic Chemistry
Chem-439

**Dr. Wafa Bawazeer,
Fall, 2017**

Course Evaluation & Assessments

أستاذة المـاده/ د. وفاء أبوبكر باوزير

قسـم / الكيمياء

مبنى7 ,مكتب رقم 8 , الدور الأول

البريد الإلكتروني:

Wbawazeer@kau.edu.sa

عدد الوحدات	الرمز	اسم المقرر
2	Chem-439	مقدمة في الكيمياء الطبية
	Chem-332	متطلبات سابقة

Course Evaluation & Assessments

The final course grades will be based on a total of 100 points with:

➢ (2 x25 points) for the midterm exams,
➢ 10 points for the in-class (presentation/paper/essay)
➢ and 40 points for the final paper.

There are **NO MAKEUP MIDTERM EXAMS**!

Evaluation	Mark	Date
1st Mid	25	1st Nov
2nd Mid	25	27 Nov
Assignment	10	TBA
Final	40	25 Dec
	100	

References

- ***An introduction to medicinal chemistry*, Patrick, G.L., 2013. Oxford university press.**

- ***Principles of organic medicinal chemistry* ,Nadendla, R.R., 2007.. New Age International.**

Medicinal chemistry

It is best to be **defined** as an interdisciplinary research area incorporating different branches of chemistry and biology in the research for better and new drugs (Drug Discovery).

Medicinal Chemistry

- It's the design and synthesis of novel drugs, based on an understanding of how they work at the molecular level.
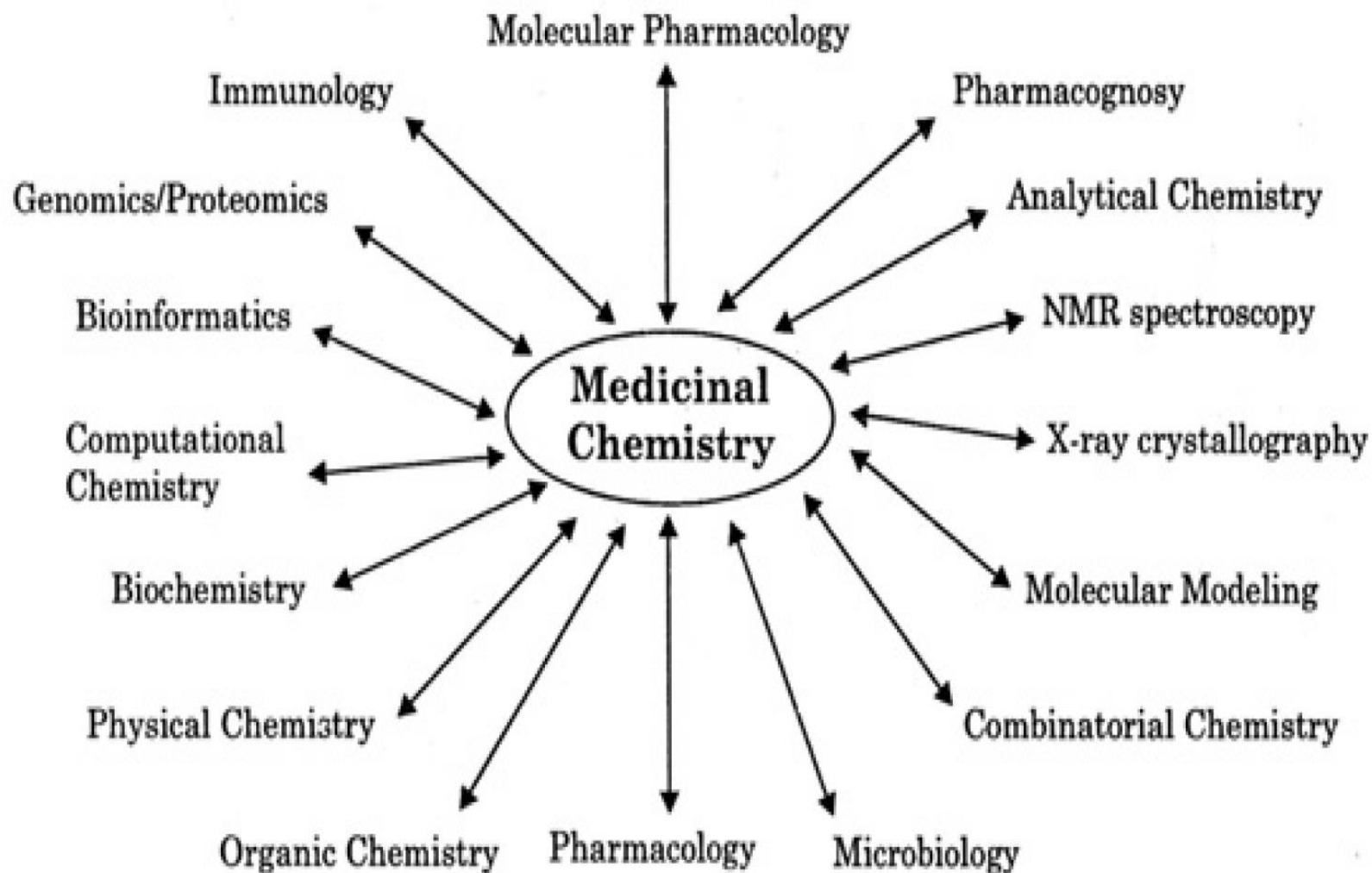
The Medicinal Chemist

- Is skilled in the fields of organic synthesis, molecular modelling and drug design, should have a basic knowledge of relevant subjects such as biochemistry and pharmacology.

Drugs

- Are normally low molecular weight chemicals that interact with macromolecular targets in the body to produce a pharmacological effect

Generally Medicinal Chemists can:

➤ Make new compounds

➤ Determine their effect on biological processes.

➤ Alter the structure of the compound for optimum effect and minimum side effects.

➤ Study uptake, distribution, metabolism and excretion of drugs.

Molecular Pharmacology

Immunology

Pharmacognosy

Genomics/Proteomics

Analytical Chemistry

Bioinformatics

NMR spectroscopy

Medicinal Chemistry

Computational Chemistry

X-ray crystallography

Biochemistry

Molecular Modeling

Physical Chemistry

Combinatorial Chemistry

Organic Chemistry

Pharmacology

Microbiology

Modern Medicinal Chemistry

Penicillin

Year: 1928
Alexander Fleming

Inventor: Alexander Fleming

Year: 1928

What Happened: Halfway through an experiment with bacteria, Alexander Fleming up and went on vacation. Slob that he was, he left a dirty petri dish in the lab sink.
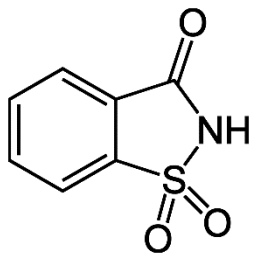
Big Discovery: When he got back, he found bacteria had grown all over the plate, except in an area where mold had formed.

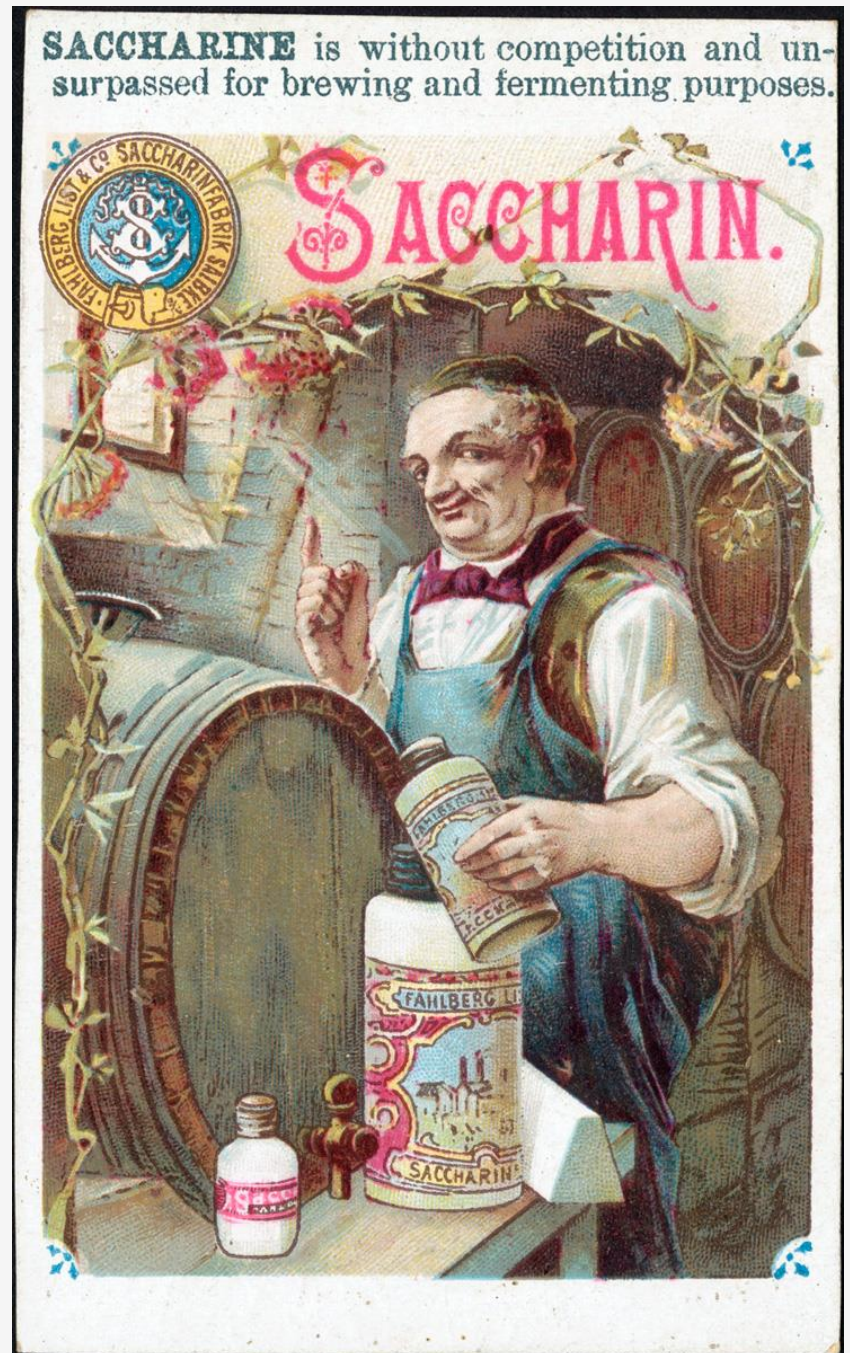**As a Result:** That discovery led to two things: 1) penicillin and 2) Mrs. Fleming hiring a maid.

Saccharin

Year: 1879
by Constantine Fahlberg

anhydroorthosulphaminebenzoic acid

SACCHARINE is without competition and unsurpassed for brewing and fermenting purposes.

SACCHARIN.

Post-it Notes

Year: 1968
By: Spencer Silver.

Year: 1974
By Arthur Fry

Drug Classification

What are drugs and why do we need new ones?

Drugs

..are strictly defined as chemical substances that are used to prevent or cure diseases in humans, animals and plants.

Drugs are chemicals that are normally of low molecular weight (~100-500), which interact with macromolecular targets to produce a biological response.

Drug Classification-I

**Natural compounds**

Synthesis compounds

Semi-synthesis compounds

Drug Classification -I

These remedial agents could be **classified according to their origin:**

- **Natural compounds:** materials obtained from both plant and animal, e.g. vitamins, hormones, amino acids, antibiotics, alkaloids, glycosides…. etc.).

- **Synthesis compounds:** either pure synthesis or synthesis naturally occurring compounds (e.g. morphine, atropine, steroids and cocaine) to reduce their cost.

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

Paclitaxel total synthesis
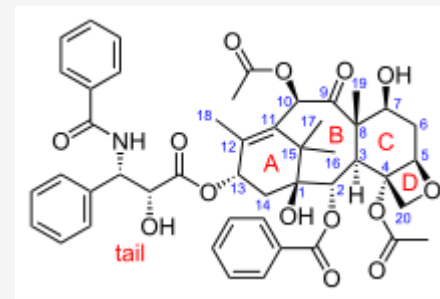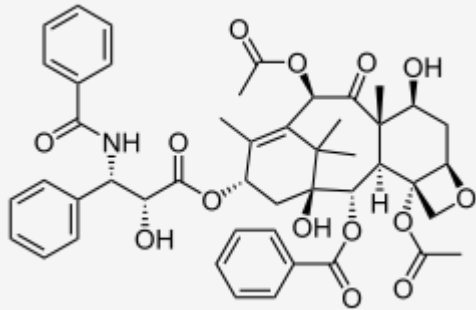
Drug Classification -II

Drugs can be classified according to their **pharmacological effects** into two main classes:

I-Pharmacodynamic agents: Drugs that act on the various physiological functions of the body (e.g. pain killers, general anesthetics, hypnotic and sedatives, analgesic etc.).

II-Chemotherapeutic agents: Those drugs which are used to fight pathogenic used to cure infectious diseases and cancer (e.g. sulphonamides, antibiotics, antimalarial agents, antiviral, anticancer etc.).
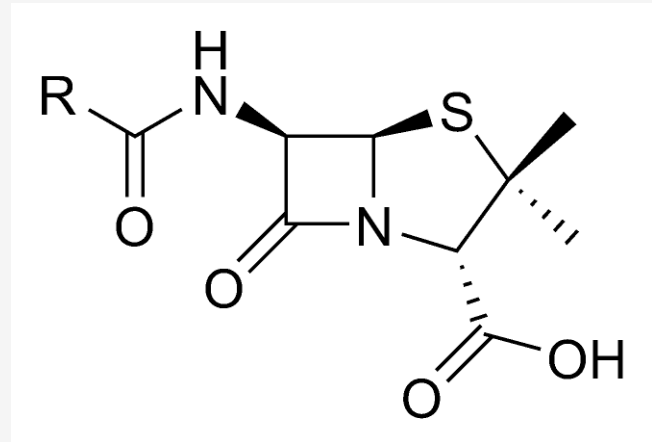
Drug Classification -III

*A third method by which **Drugs can be classified by its chemical structure.***

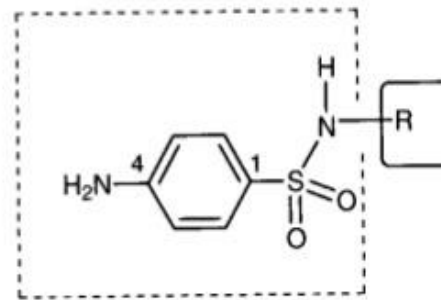*Common structural feature often share a similar pharmacological activity, For example:*

1-Penicillins:

all contain β-lactam ring and kill bacteria by the same mechanism.

2-Sulfonamides:

*have similar structure and are mostly antibacterial, and treatment of diabetes.*

Basic Structure of sulfonamide

The chemical modification of this part of the molecule increases activity and modifies some pharmacological properties.

This part of the molecule cannot be modified chemically without loss of antibacterial activity.

Sulfisoxazole R =

Sulfamethoxazole R =
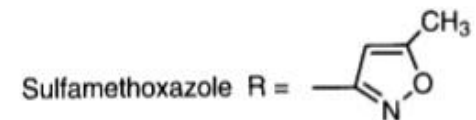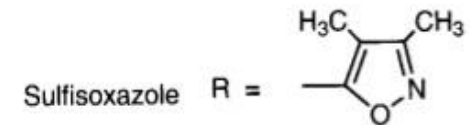
Drug Classification -IV

Drugs classification according to **their molecular target considered** as the most useful classification as far as medicinal chemist is concerned.

It allows comparison of the structure involved.

For example: **anticholinesterases** are compounds inhibit an enzyme called acetylcholinesterase. They have the same mechanism of action and so it is valid to compare various structures
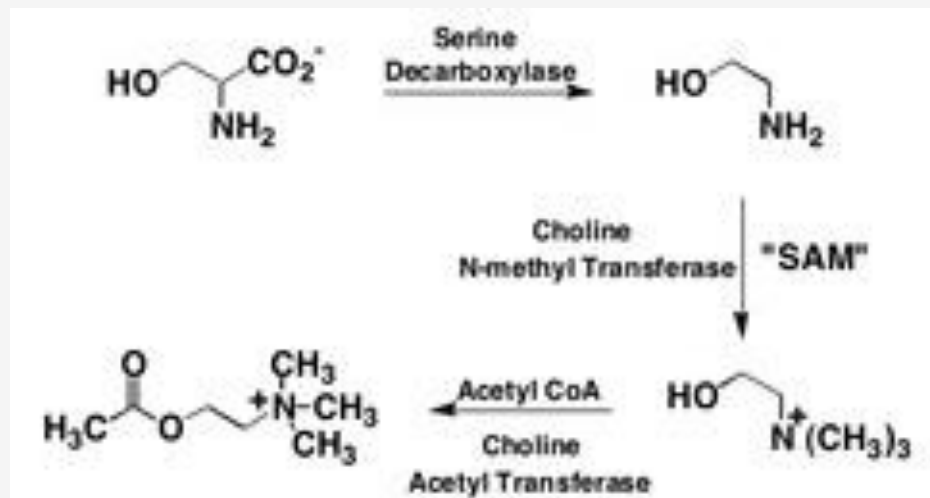
LECTURE- II

Characteristics of Different Routes of Drug Administration

➢ **A route of administration in pharmacology and toxicology**
Is the path by which a drug, fluid, poison, or other substance is taken into the body.

➢ Routes of administration are generally classified by the location at which the substance is applied.

The choice of appropriate route in a given situation depends both on **drug** as well as **patient** related factors.

Characteristics of Different Routes of Drug Administration

1. Oral/swallowed
2. Oral/sublingual
3. Rectal
4. Topical
5. Inhalation
6. Parenteral Route
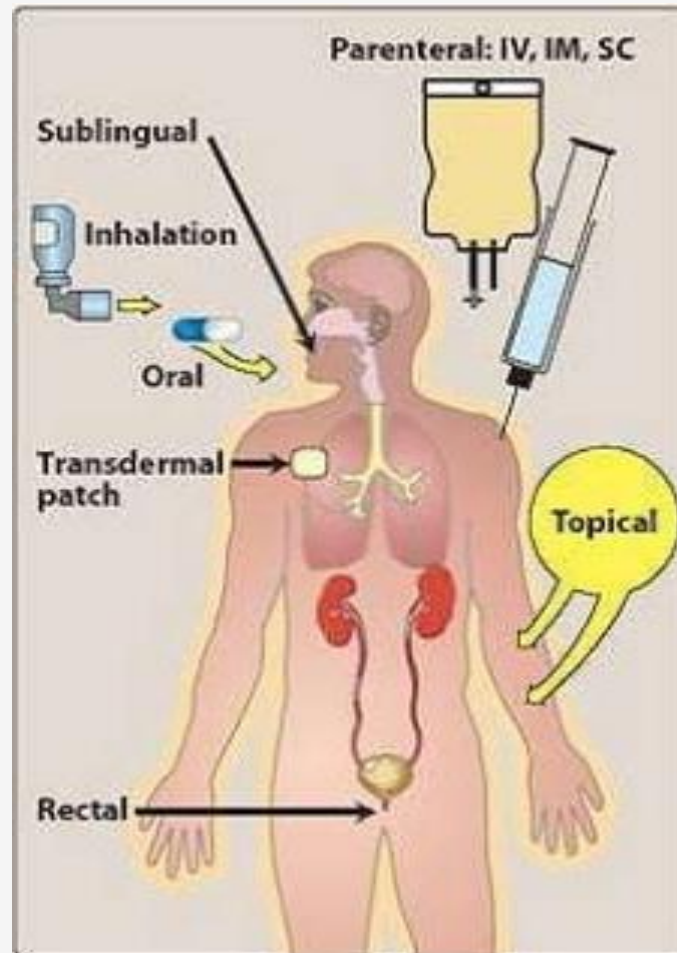
Characteristics of Different Routes of Drug Administrations

- **1. Oral/swallowed. Oral ingestion is the oldest and commonest mode of drug administration.**

- Most drugs in this route of administration are absorbed in small intestine. Full stomach delays absorption.

- Several drugs may subject to first-pass metabolism by liver

- It is safer, more convenient, noninvasive, often painless, the medicament need not be sterile and so cheaper. Both solid dosage forms and liquid dosage forms can be given orally.

Common dose forms for *oral administration*

- tablets
- capsules
- liquids
- solutions
- suspensions
- syrups
- elixirs

Characteristics of Different Routes of Drug Administrations

2. Oral/sublingual. The tablet or pellet containing the drug is placed under the tongue

- or crushed in the mouth and spread over the buccal mucosa. In this mode of administration

- fast systemic absorption is observed which, bypass gastrointestinaltract entry.

- It avoids absorption and first-pass metabolism in the liver and is useful for those likely to vomit from swallowed medication.

3. Rectal. Here the drugs are absorbed directly from the rectum.

- It partially avoids first-pass metabolism by liver and also for those likely to vomit and lose swallowed medication.

- Certain irritant and unpleasant drugs can be put into rectum as suppositories or retention enema for systemic effect.

- Ex: Aminophylline, indomethacin, paraldehyde, diazepam, and few other drugs.

4. Topical. In this technique drugs are absorbed through the skin.

- This route is useful for those likely to vomit (e.g. nicotine patch, ..). Highly lipid soluble drugs can be applied over the skin for slow and prolonged absorption.

- The drug bypasses the liver by this route of administration.

- The drug can be incorporated in an ointment and applied over specified area of skin.

Estrogen

nicotine
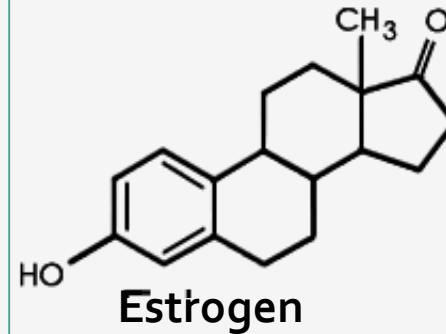
Characteristics of Different Routes of Drug Administrations

5. Inhalation.

- Volatile oils and gases are given by inhalation ex: general anesthetic, amylnitrite.

- The drugs enter the bloodstream very rapidly from the lungs.

- Here no absorption or first-pass metabolism problems occur. This route is potentially dangerous because it is so fast and direct.
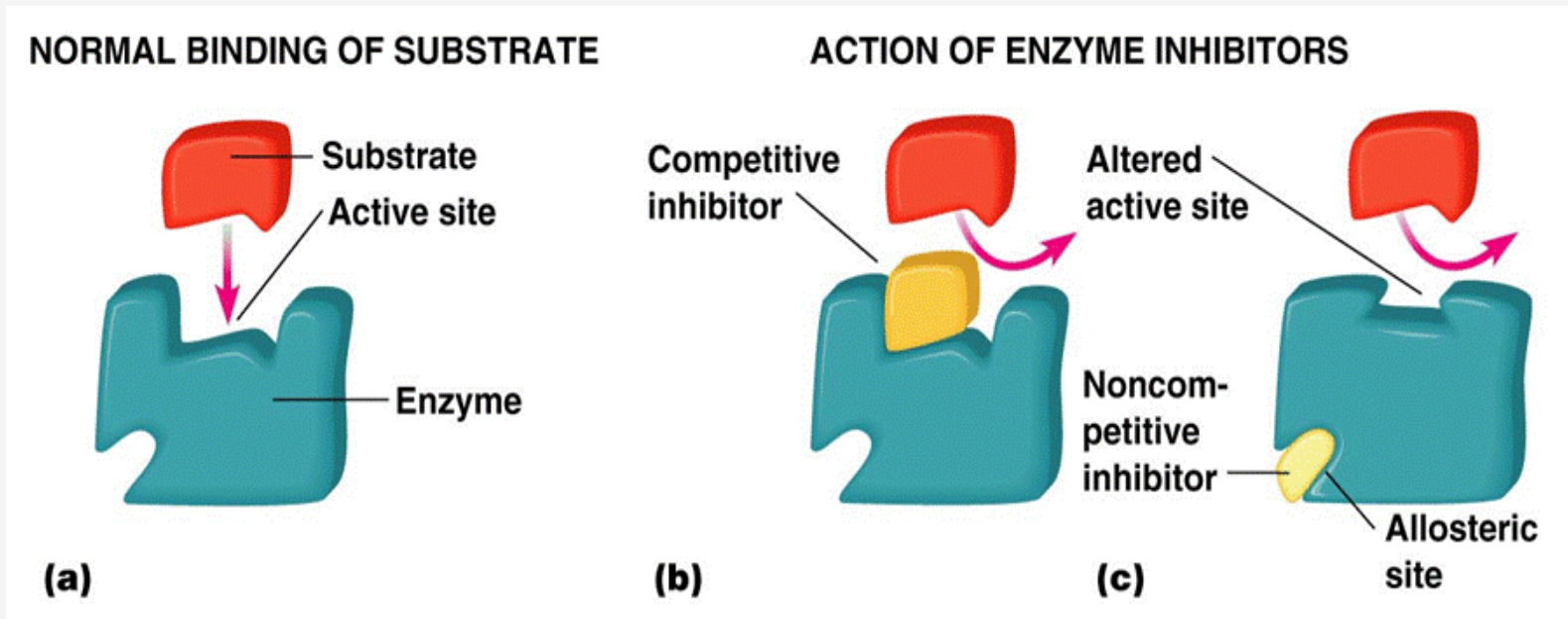
6. Parenteral Route.

- Parenteral administration refers to administration by **injection** into tissue fluid or blood without having to cross the intestinal mucosa.

- This route can be employed even in unconscious, uncooperative or vomiting patient.

- The rate of absorption depends on blood flow through injection site.

Sites of Drug Action

1. Enzyme inhibition

by modifying normal biochemical reactions.

Enzyme inhibition may be reversible or non-reversible

NORMAL BINDING OF SUBSTRATE

ACTION OF ENZYME INHIBITORS

(a) Substrate / Active site / Enzyme

(b) Competitive inhibitor / Altered active site / Noncompetitive inhibitor

(c) Allosteric site

Sites of Drug Action

2. Drug Receptor interaction

- Drugs act on the cell membrane by physical and/or chemical interactions. This is usually through specific drug receptor sites known to be located on the membrane.

Drug **A** binds to receptor
Drug **B** cannot bind to receptor

- **A receptor is** *the specific chemical constituents of the cell with which a drug interacts to produce its pharmacological effects.*

- Some receptor sites have been identified with specific parts of proteins and nucleic acids. In most cases, the chemical nature of the receptor site remains obscure.
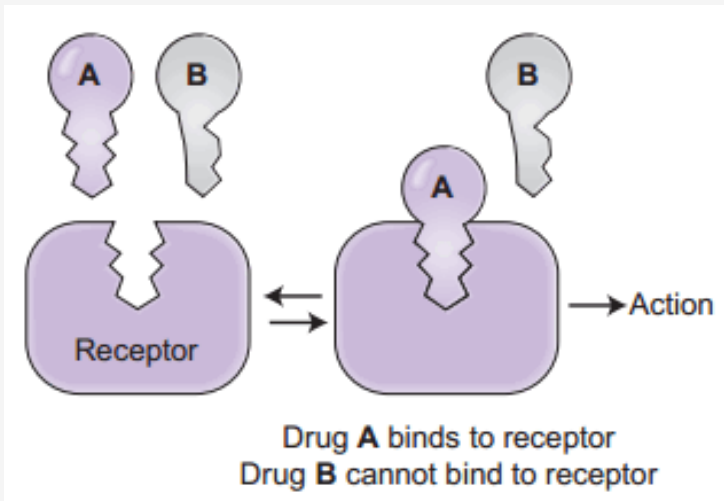
Sites of Drug Action

Antacid

3. Non-Specific interaction

- Drugs act exclusively by physical means outside of cells.

- These sites include external surfaces of skin and gastrointestinal tract.

- Drugs also act outside of cell membranes by chemical interactions. Neutralization of stomach acid by antacids is a good example.
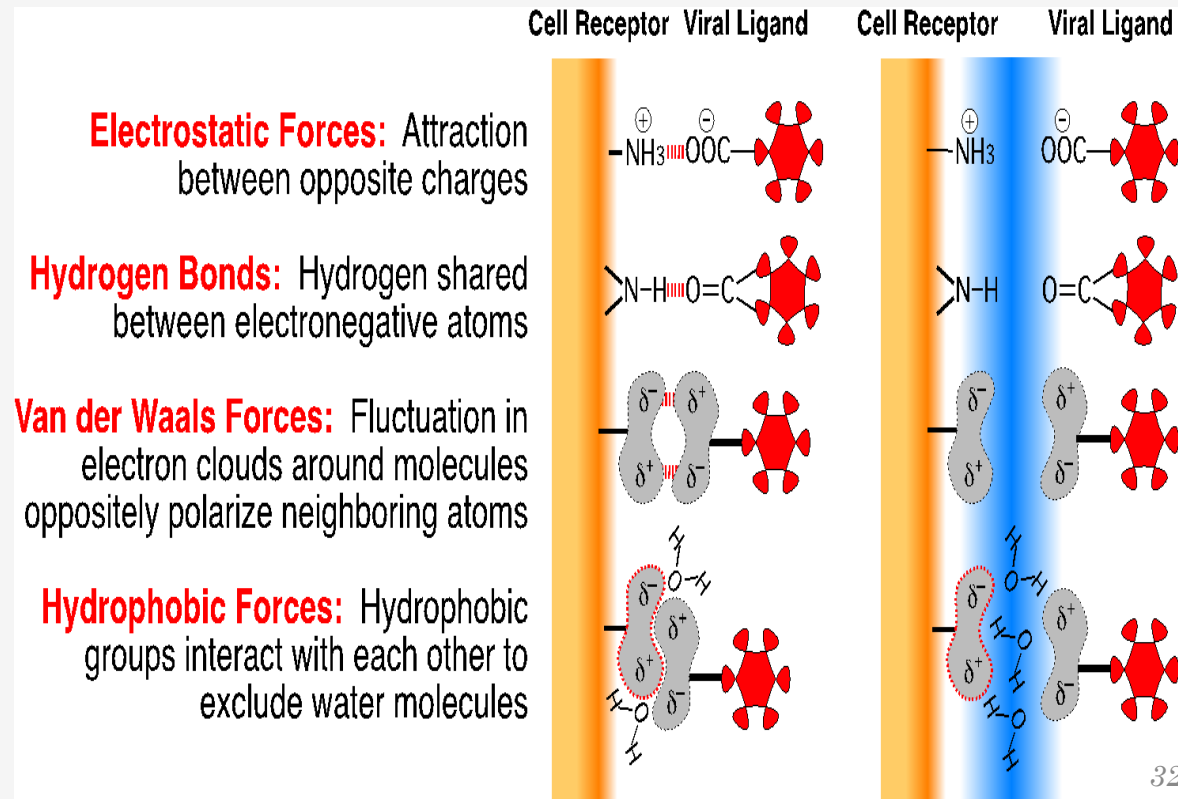
Drug Receptor Interactions

Drug **A** binds to receptor
Drug **B** cannot bind to receptor

- Majority of drugs show remarkably high correlation of structure and specificity to produce pharmacological effects.

- A minimum three-point attachment of a drug to a receptor site is required.

- In most cases specific chemical structure is required for the receptor site and a complementary drug structure.

- Slight changes in the molecular structure of the drug may drastically change specificity.

- To initiate a biological response, the drug must form bond with the receptor surface.

- Different types of binding forces that may exist in drug-receptor interactions are as follows:
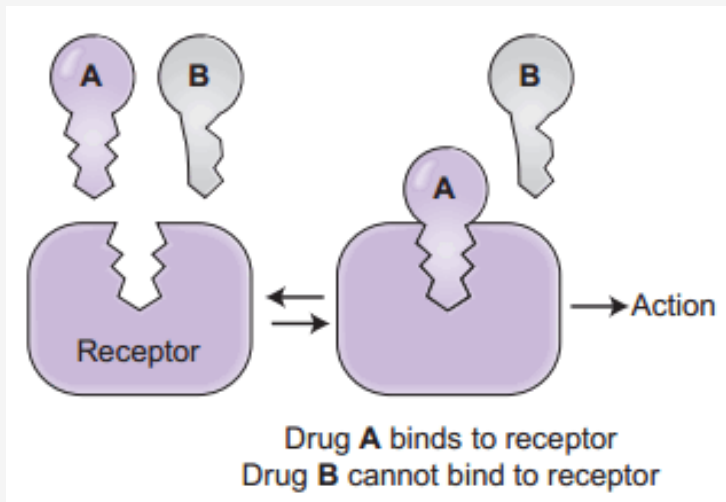
Drug Receptor Interactions

(i) **Covalent interactions.**

(ii) **Ionic interactions.**

(iii) **Hydrogen bonding interactions (non-ionic/neutral).**

(iv) **Vander Waals interaction**

(v) **Hydrophobic/Lipophilic interactions**

Drug Receptor Interactions

(i) Covalent interactions.

These chemical forces may result in a temporary binding of the drug to the receptor.

- Frequently, a covalent bond is firm and described as essentially

- "irreversible" under biological conditions.. Examples:

- (*a*) Antineoplastic or antibiotic drugs act mainly through the formation of covalent bonds

- (*b*) The DNA-alkylating chemotherapeutic agents are chemically highly reactive, forming covalent bonds with DNA functional groups.


D—N—C—R
| ‖
H   O

Covalent
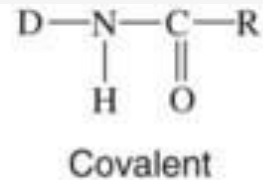
Drug Receptor Interactions

(ii)Ionic interactions.

Since many drugs contain acid or amine functional groups,which are ionized at physiological pH.

- Ionic bonds are formed by the attraction of opposite charges in the receptor site with the ionized groups of the drug molecule.

- They are strong electrostatic interactions (5-10 kcal/mol) and are responsible for relative orientation of the drug to its binding site.
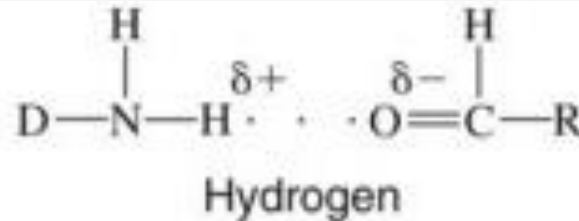

Ionic

34
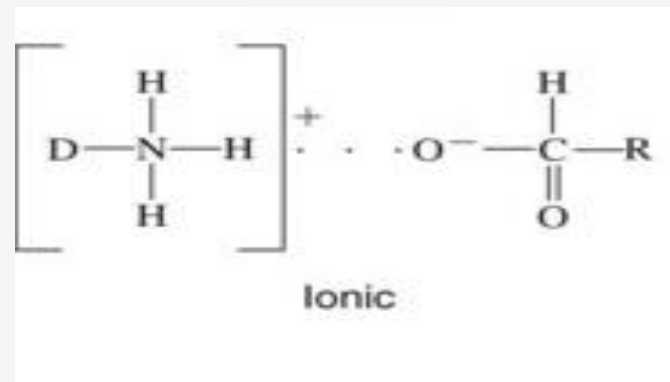
Drug Receptor Interactions

(iii) Hydrogen bonding interactions (non-ionic/neutral).
Polar-polar interactions are the attraction of opposite charges

- The hydrogen bond strength is distance dependent may range from $5-7$ kcal/mol, depending on the binding environment.
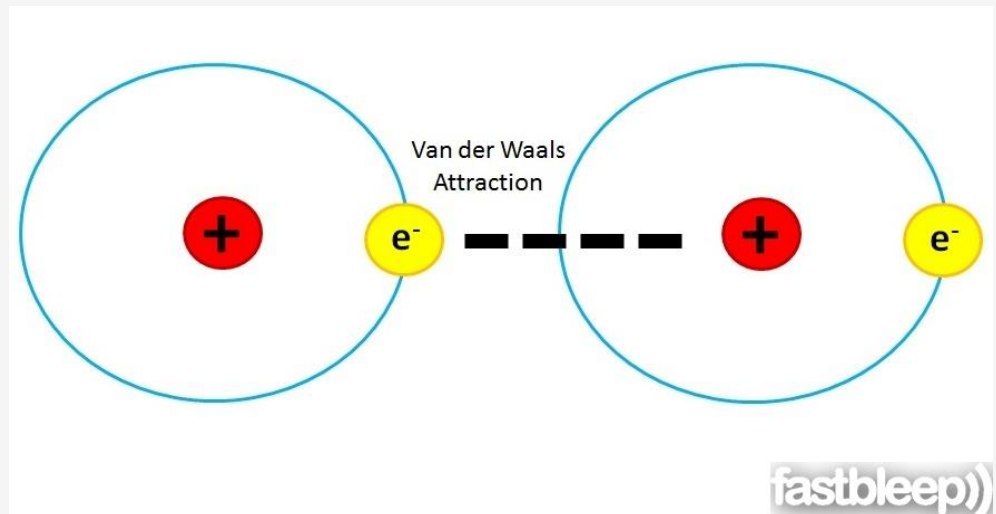

Hydrogen

Drug Receptor Interactions

(*iv*) **Vander Waals interaction.** These forces have the following characteristic feutures:

(*a*) Interactions at a close range

(*b*) The Vander Waals interaction forces occur less frequently than hydrophobic forces

(*c*) Interactions are much weaker (~ 0.5-1 kcal/mol) than other electrostatic interactions
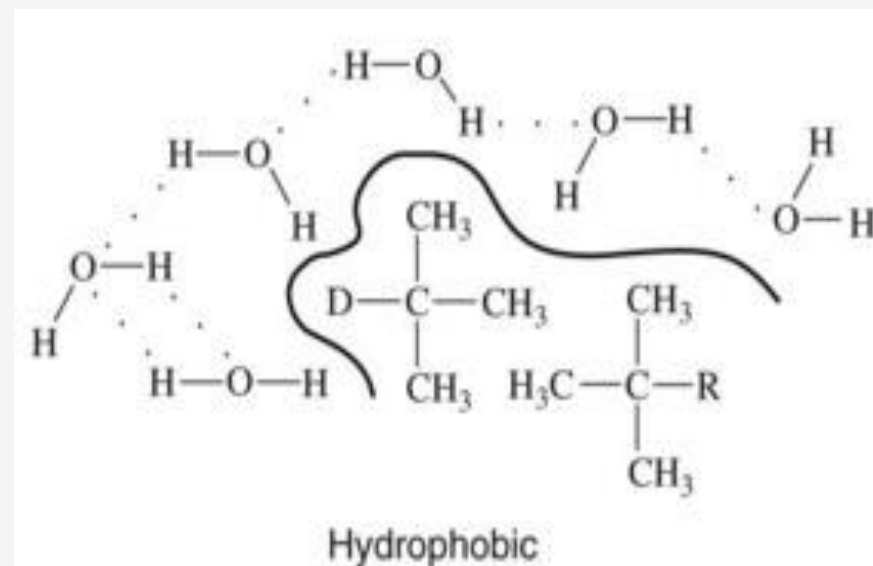
Drug Receptor Interactions

(v) Hydrophobic/Lipophilic interactions

Finally hydrophobic bonds are formed between:

- non-polar hydrocarbon groups on the drug and those in the receptor site.

- These bonds are not very specific but the interactions do occur to exclude water molecules

Hydrophobic

Practice Questions
(Essay and Short Questions)

CHAPTERS 1, 2 & 3

1. Define medicinal chemistry? Explain how medicinal chemistry has interrelationship with other subjects?

2. What are drugs? Explain various routes of drug administration?

3. What are receptors?

4. What are drugs? Explain with examples how drus act?

5. What are drug-receptor interactions? Explain different types of binding forces exist in drug-receptor iteractions   ?

6. Explain different mechanisms of drug actions?

7. Write notes on different sites of drug action?