UNIT-I

INTRODUCTION TO MEDICINAL CHEMISTRY

→ Medicinal chemistry was defined by IUPAC specified commission as "Medicinal chemistry concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level."

→ Explains the design & production of compounds that can be used for the prevention, treatment (or) cure of human & animal diseases.

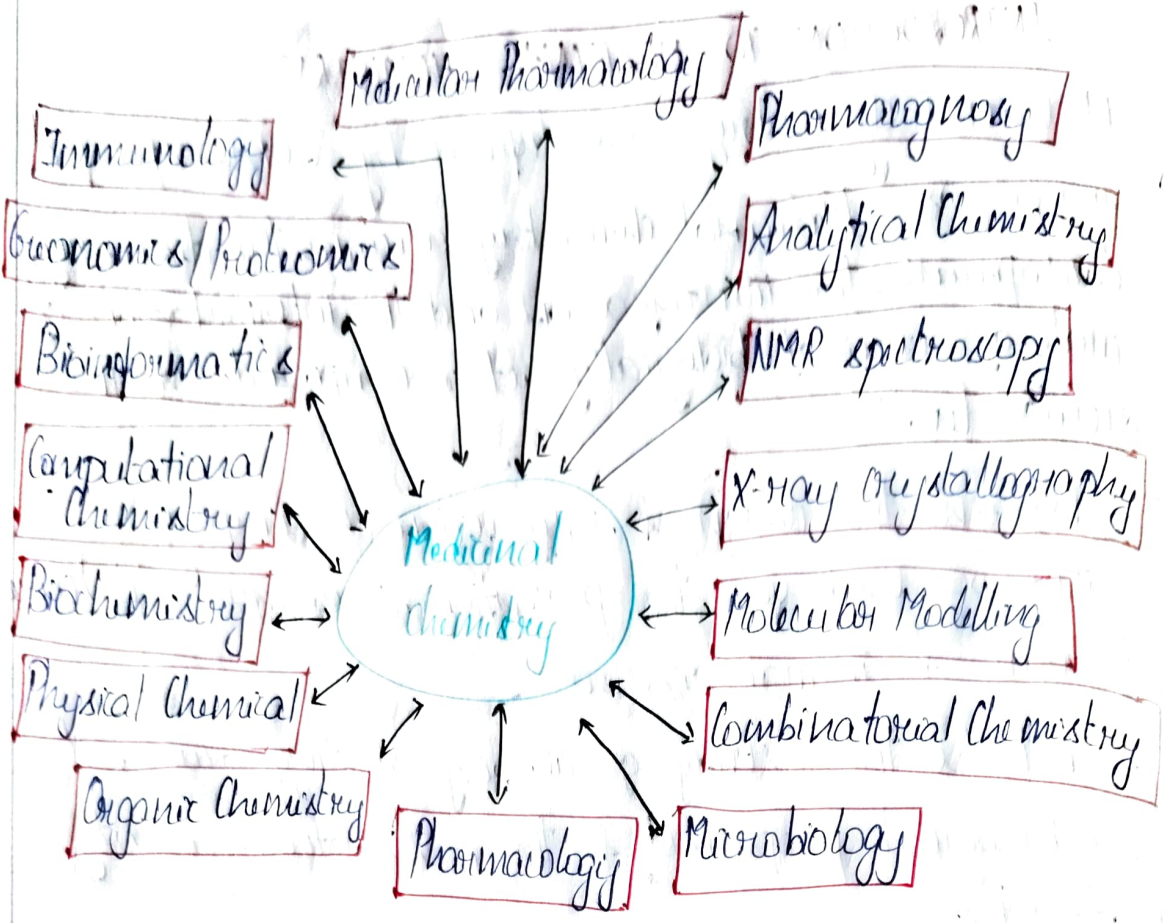
→ Includes the study of already existing drugs, of their biological properties & their structure-activity relationships.

Stages of Medicinal Chemistry:-

* First stage:- New active substances (or) drugs are identified and prepared from natural sources, organic chemical (or) biotechnological processes.
  - They are known as lead molecules.

* Second stage:- Optimization of lead structure to improve potency, selectivity and to reduce toxicity.

* Third stage [Development stage]:- Optimization of synthetic route for bulk production and modification of Pharmacokinetic & pharmaceutical properties of active substance to render it clinically useful.



DRUG-RECEPTOR AFFINITY

Drug-Receptor:

→ Are Biomacromolecules which are normally membrane bound but are also found in cytoplasm.

→ Contain specific regions [receptor sites] that react with complementary functional groups on their endogenous substance (or) a drug molecule [drug-receptor affinity].

→ Drug-Receptor interactions are often as "ligand-receptor interactions".

→ Allow for physiological messages to be communicated from the drug and/or endogenous substances

a) Affinity:- The Role of Chemical Bonding

→ When a drug interacts with a receptor, the initial affinity [attraction] is based on interactive chemical bonding forces which are * Covalent (or)
* Non-Covalent.

→ Compounds interacting with a drug receptor can be classified as * Agonist
* Antagonist

* Agonist :- A drug / endogenous substance that has affinity for a receptor & producing a biological response [Intrinsic activity]. The response can be full, partial (or) even negative [inverse agonist]

* Inverse Agonist :- Occurs when a receptor has basal activity in the absence of any ligand, so it can produce an effect below the basal level.

* Antagonist :- A drug that has affinity for a receptor but does not activate it to produce a response.

i) Covalent Bond :- [40 - 140 kcal/mol] → Energy

→ strongest drug-receptor interaction.
→ formed when two atoms share a pair of electrons
→ Usually irreversible & drug action terminated only by eventual cleavage (or) receptor turnover.

→ Reactions forming covalent bond include
* Alkylation
* Acylation
* Phosphorylation

i) Ionic Bond :- [5 kcal/mol]

→ Formed when two ions of opposite charge are attracted to each other through electrostatic forces

→ Acidic functional groups on the receptor bind with basic functional groups on the drug molecule

> Eg:- Receptor - Carboxylic acid on the side chain of aspartic acid (or) glutamic acid binds with tertiary amines on the structure of morphine.

iii) Hydrogen Bond :- [1-7 kcal/mole]

→ An electrostatic dipole-dipole interaction between a hydrogen atom on an electronegative atom [-OH] & an electronegative atom [O, N (or) S]

→ Can be * Intramolecular
* Intermolecular [most often in drug-receptor interactions]

→ Not strong enough to support drug-receptor interaction alone.

→ substantial when there are multiple H-bonding interactions.

iv) Reinforced Ionic Bond :- [10 kcal/mol]

→ Formed by the combination of an ionic bond & an additional reinforcing interaction by a hydrogen bond.

v) Ion-Dipole Bond :- [1-7 kcal/mole].
→ Bonding is between an ion & a dipole.
→ Ionic site can be a cation (or) an anion functional group on the drug molecule and the dipole formed by a carbonyl group on a receptor.

vi) Dipole-Dipole Bond :- [1-7 kcal/mole]
→ The interaction between two dipoles, one on the drug molecule & the other on the receptor.

vii) Hydrophobic Bond Interaction :- [0.5-1 kcal/mole]
→ Induced dipoles b/w nonpolar organic molecules as a result of the ability of water molecules to exclude [repel] hydrocarbon molecules.
→ Very weak & increases inversely with the 7th power of the interatomic distance [E = 1/distance^7].
→ Called as Vander-Waals (or) London forces
→ Important contributions to the overall binding of drugs to the receptor.

B) Affinity :- The Role of Conformation
→ Once an Agonist binds to the receptor, it produces a biological response., explained by number of theories which shows how the binding this response.

* Occupancy theory
* Rate Theory
* Induced-fit theory
* Macromolecular Perturbation theory
* Activation-Aggregation theory

i) The Occupancy Theory :-

→ Predicts that the biological response is directly related to the number of Receptors bound [occupied] by the Agonist.

Biological Response ∝ No. of Receptors occupied by the Agonist

→ Response ceases when the drug dissociates from the receptor.

→ Antagonists occupy with high affinity but do not produce a biological response.

ii) The Rate Theory :-

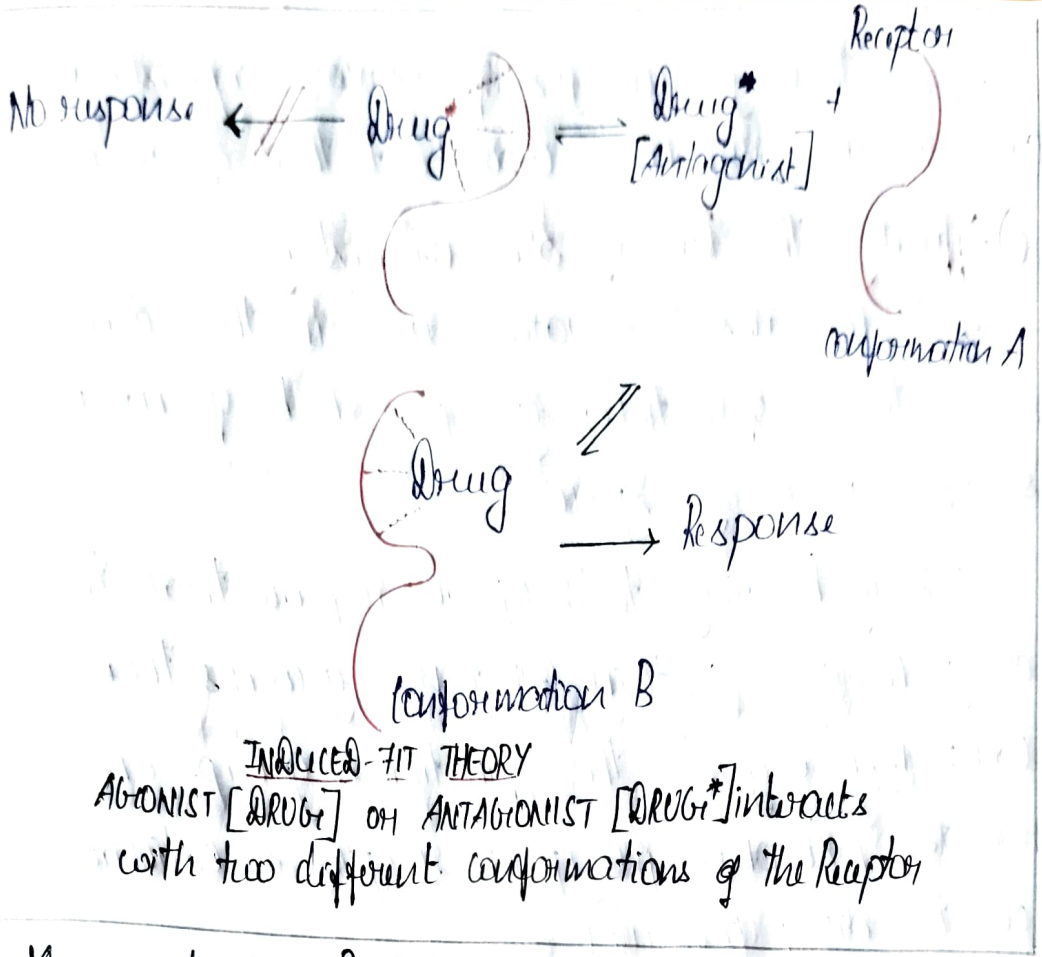
Biological Response ∝ No. of times the drug binds to the receptor per unit of time

→ Drugs rapidly associate & dissociate with the receptor produce the most intense response.

iii) The Induced-fit Theory :-

→ Predicts that as the drug approaches the inactive state of the receptor it induces a specific conformational change [Perturbation] that leads to effective drug binding & to the biological response.

→ Antagonists induce non-specific conformational changes that fail to produce the desired biological response.



INDUCED-FIT THEORY

AGONIST [DRUG] OR ANTAGONIST [DRUG*] interacts with two different conformations of the Receptor

iv) The Macromolecular Perturbation theory :-

→ Combination of induced-fit and rate theory.

→ There are two types of specific receptor conformational perturbations :-

* One leading to the biological Response
* Other to no activity.

→ The rate & ratio of their existence determines the observed biological response.

→ Explains the activity of Partial Agonists.

v) The Activation - Aggregation theory :-

→ The receptor is always in the state of equilibrium blw active & inactive states.

→ Agonists function by shifting the equilibrium to the active

→ Antagonist prevent the active site.

→ This theory accounts for inverse agonists which can produce responses opposite to that of an agonist.

3) Affinity - The Role of Stereochemistry:

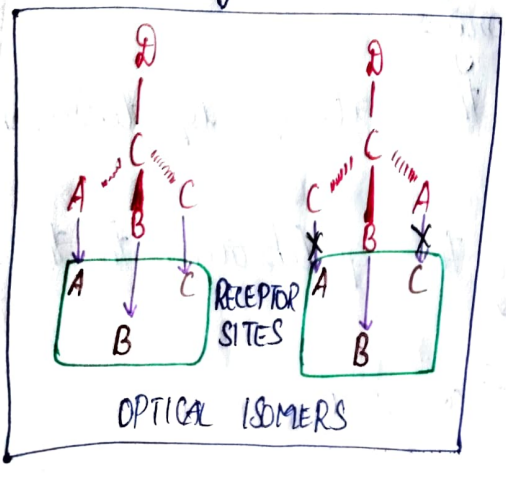
→ All molecules in nature exist in three dimensions & as their functional groups will be found in specific areas of space.

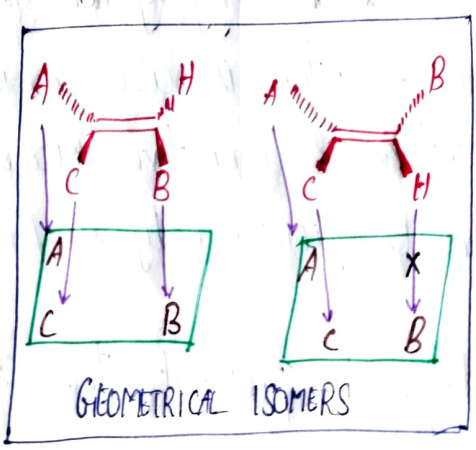
→ Drug binding to receptors require that the drug molecule contain functional groups that are complementary to the functional groups on the receptor [Anionic group on receptor & cationic group on the drug molecule]

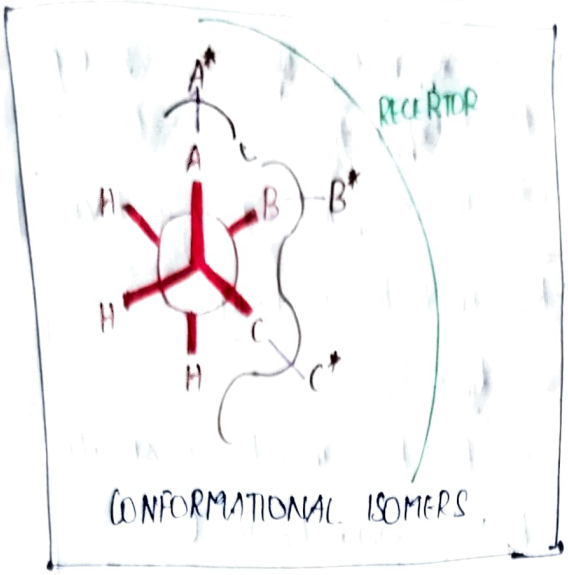
→ For the complementary functional groups to bind, they must also have the proper complementary spacial orientation.

* Optical Isomers
* Geometric Isomers
* Conformational Isomers

→ The Asymmetry of the drug molecule must be complimentary to the asymmetry of the receptor.

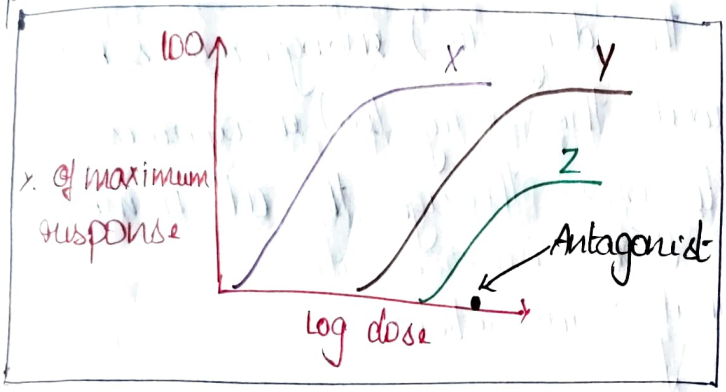






DOSE-RESPONSE RELATIONSHIPS

→ Dose-response curves are a representation to explain the different types of drug effects once a drug is bound to its receptor.



→ Drug X is equally effective as drug Y, but drug X is more potent.

→ Drug Z is less potent than either drug X (or) Y & less effective as well.

→ Antagonists would not give any dose response curve even if drug X is subsequently administered.

→ Dose-response relationships can also be expressed by

$$D + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [DR] \xrightarrow{k_3} E$$

Drug-Receptor equation

→ k_1 - Measure of drug affinity for the receptor
k_2 - Measures lack of affinity
k_3 - Measures effectiveness [intrinsic activity]

Agonist ⇒ $k_1 > k_2$ and k_3 is large
Inactive drug ⇒ $k_2 < k_1$
Partial agonist ⇒ $k_1 > k_2$ and k_3 is small
Antagonist ⇒ .. $k_1 > k_2$ and k_3 is 0

DRUG RECEPTORS AND THE BIOLOGIC RESPONSE

→ Binding of a drug (or) endogenous substance to its receptor allows for physiological messages to be communicated from the drug (or) endogenous substance into the cells without the drug (or) endogenous substance having to cross through the cell membrane.

↓ Communication called
Signal Transduction
↓

Involves a sequence of biochemical reactions inside the cell which are carried out by enzymes, proteins & ions [Ca^{2+}] that are linked through second messengers.

Second Messengers
↓
cyclic Adenosine Monophosphate [cAMP]
Inositol 1,4,5 - triphosphate [IP_3]
Diacylglycerol [DAG]

⇒ Four major types of receptors

* Transmembrane ion channels [Voltage / ligand gated]
* Transmembrane G-protein coupled
* Transmembrane catalytic (or) enzyme - coupled
* Intracellular cytoplasmic / Nuclear.

1) Transmembrane Ion channels :-

⇒ Types :-

* Voltage-gated
* Ligand Gated

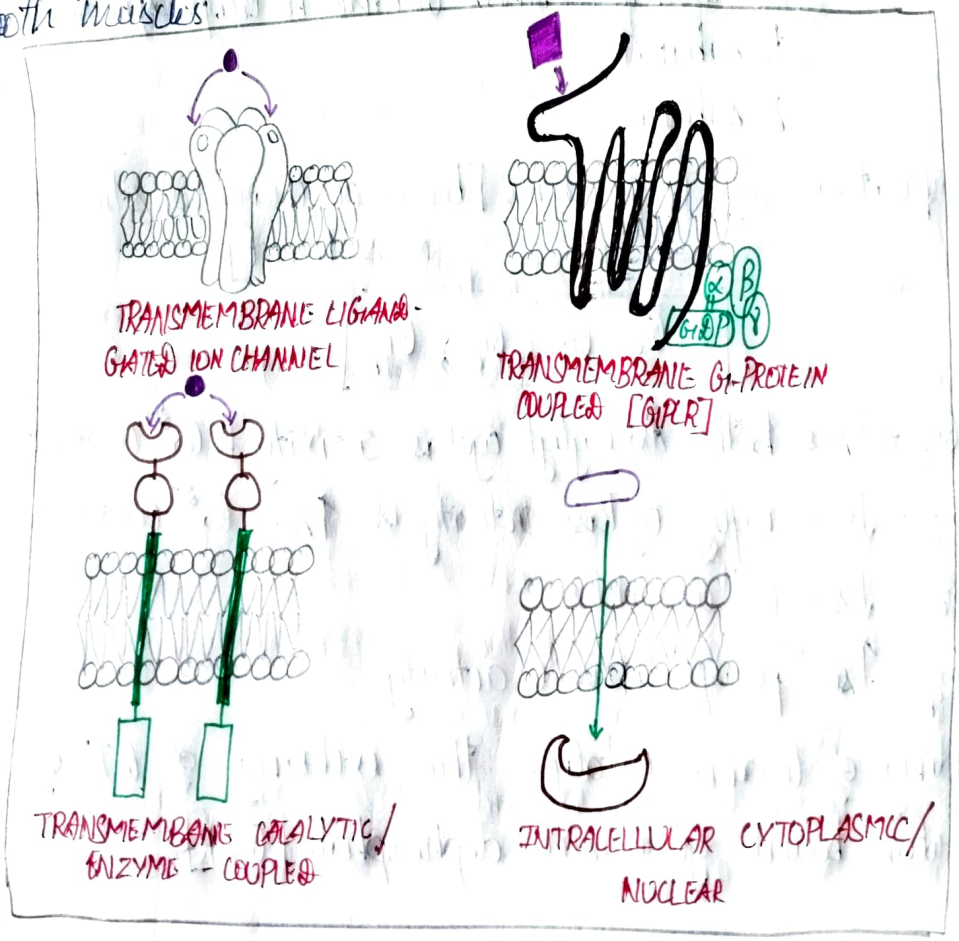
* Voltage - Gated :-

→ Opened & closed by changes in the membrane potential

→ Ions - Na^+, K^+, Ca^{2+} :

Eg :-

* Muscle contraction :- Voltage-dependent calcium channels are found in pacemaker cells and skeletal, cardiac & smooth muscles.



*Ligand-Gated:-

→ Action regulated by binding of a ligand to the channel.

→ Ligands include acetylcholine, γ-aminobutyric acid [GABA] & Glutamate.

→ Action modified by many drugs [Benzodiazepines for GABA receptor]

Eg:-

Nicotinic receptors:- Binding of acetylcholine results in Na^+ influx, generation of an action potential & activation of skeletal muscle contraction.

ii) Transmembrane G-Protein Coupled Receptors:-

→ A single peptide with seven membrane-spanning regions linked to a G-Protein.

↓↓ Three sub-units

α-subunit → Binds Guanosine triphosphate [GTP]

β-subunit

γ-subunit

→ Classification of G-proteins [based on characteristics of α-subunit]

↓↓

* G_s, G_i, G_o, G_q

* G_s - ↑ses both Adenylyl cyclase activity & Ca^{2+} currents

* G_i - ↓s Adenylyl cyclase activity & ↑ses Ca^{2+} currents

* G_o - ↓ses Ca^{2+} currents

* G_q - ↑ses phospholipase C activity.

→ Binding of ligand catalyzes the exchange of GTP for G-protein bound guanosine diphosphate [GDP].

→ GTP G-protein interacts with specific secondary messenger systems to elicit a biological response.

Second Messenger pathways:
* Adenylyl cyclase [Messenger = cAMP]
* Phospholipase A_2 [M - Arachidonic acid]
* Phospholipase C [M - IP_3 & DAG]
* Ion channels for Ca^{2+}, K^+ and Na^+

→ eg - β-Adrenergic receptors: When endogenous norepinephrine binds, it causes interaction with Adenylyl cyclase to form cAMP as the secondary messenger which results in intracellular actions that lead to heart muscle contraction, smooth muscle relaxation & glycogenolysis.

iii) Transmembrane Catalytic/Enzyme-coupled receptors:-

→ Has cytosolic enzyme activity as an integral component of its structure.

→ Binding of ligand - either activate / inhibit the cytosolic enzyme activity.

→ Common Enzyme → Tyrosine kinase

↓

Binding of ligand

↓ converts

Inactive kinase to its active form

↓ in turn

Phosphorylates tyrosine residues

↓ Activates

Intracellular effects.

→ Eg:- Insulin receptor :- When insulin binds to its receptor

· Intrinsic tyrosine kinase activity

↓ causes

Autophosphorylation itself

↓ Allows receptor

Phosphorylate insulin Receptor substrate peptides [IRSP]

↓ start

Cascade of intracellular Activations [IP_3 & mitogen-activated Protein kinase system (MAPK)]

↓ Results in

No. of cellular effects

[Translocation of glucose receptor to cell membrane]

iv) Intracellular cytoplasmic / Nuclear Receptors :-

→ Located within the cytoplasm (or) bound to nuclear surface.

→ Are a single polypeptide with three functional domains.

* Amino Terminal
* Carboxy terminal
* Binding site for DNA [in middle]

→ When ligand binds it activates the receptor by causing the release of the heat-shock protein-90.

→ The receptor-ligand complex then dimerizes & translocates into the nucleus & binds to a DNA hormone response element [HRE], which in turn initiates translation of the target gene.

→ Endogenous ligand include nitric oxide, steroid hormones & vitamin D.

Classification of drugs

1) By origin - Sources of Drugs:-
   * Synthetic
   * Natural - Plants
     Animals
     Microorganisms
     Minerals
   * Semisynthetic
   * Biosynthetic
2) By Action
3) By Therapeutic use
4) By site of drug Action
5) By chemical structure

Routes of Drug Administration

1) Oral/Swallowed
2) Oral/Sublingual
3) Epithelial
4) Inhalation
5) Rountoral

Sites of Drug Action

1) Enzyme inhibition
2) Drug-Reupton interaction
3) Non-specific Interaction

Mode of Drug Action

1) Killing foreign Organism
2) Stimulation & Depression
3) Irritation
4) Replacement

Mechanism of Drug Action

1) Physical Properties
   * Taste
   * Mass
   * Adsorption
   * Radioactivity
2) Chemical Properties
3) Through Enzymes
4) Through Receptors