INTRODUCTION TO MEDICINAL CHEMISTRY
Medicinal chemistry 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).

In other words, medicinal chemistry is the science, which deals with the discovery and design of new and better therapeutic chemicals and development of these chemicals into new medicines and drugs.

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.
Drug Classification

Pure organic compounds are the chief source of agents for the cure, mitigation or the prevention of disease.

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 penicillins).


Drug Classification

Since there is no certain relation between chemical structure and pharmacological activity therefore, it would be unwise to arrange all drugs on the basis of their structures or origin. Thus, it is better to arrange the drugs according to their medicinal use.

Drugs can be classified according to their medicinal uses into two main classes:

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

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

Drugs can treat different types of diseases:

1- **Infectious diseases**: Born *(transmitted)* from person to person by outside agents, bacteria (pneumonia, salmonella), viruses (common cold, AIDS), fungi (thrush, athletes foot), parasites (malaria)

2- **Non-infectious diseases**: disorders of the human body caused by genetic malfunction, environmental factors, stress, old age etc. (e.g. diabetes, heart disease, cancer, Haemophilia, asthma, mental illness, stomach ulcers, arthritis).

3- **Non-diseases**: alleviation of pain (analgesic), prevention of pregnancy (contraception), anesthesia.
Physico-chemical properties in relation to biological action

Drug action results from the interaction of drug molecules with either normal or abnormal physiological processes. Drugs normally interact with targets (which they are proteins, enzymes, cell lipids, or pieces of DNA or RNA).

The ability of a chemical compound to elicit a pharmacologic/therapeutic effect is related to the influence of its various physical and chemical (physicochemical) properties.

The most pharmacologically influential physicochemical properties of organic medicinal agents (OMAs) are:

1. Solubility
2. Acidity and basicity
3. Reactivity
1- SOLUBILITY OF ORGANIC MEDICINAL AGENTS

Importance of solubility:

(1) Formulation of the drug in an appropriate dosage form and
(2) Bio-disposition: Disposition of OMAs in the living system after administration (absorption, distribution, metabolism, and excretion).

The solubility expression: in terms of its affinity/philicity or repulsion/phobicity for either an aqueous (hydro) or lipid (lipo) solvent.

♣ hydrophilic ....................... water loving
♣ lipophobic ...................... lipid hating
♣ lipophilic ....................... lipid loving
♣ hydrophobic ...................... water hating
Majority of OMAs possess balanced solubility (have some degree of solubility in both aqueous and lipid media).

Because there is a need for OMAs to move through both aqueous (plasma, extracellular fluid, cytoplasm, etc.) and lipid media (biologic membranes) in the biological system.
Solubility of OMAs should be viewed as being on a continuum between high lipophilicity on one end of the spectrum and high hydrophilicity on the other.

In order for a chemical compound to dissolve in a particular solvent/medium the compound must establish attractive forces between itself and molecules of the solvent.
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It is possible to estimate the solubility properties of an OMA (hydrophilic vs. lipophilic) by examining the structure of the OMA and noting whether its structural features promote affinity for aqueous or lipid media.

The most important intermolecular attractive forces (bonds) that are involved in the solubilization process are:
The most important intermolecular attractive forces (bonds) that are involved in the solubilization process are:

1. **Van der Waals Attraction**
   - weakest intermolecular force (0.5-1.0 kcal/mole)
   - electrostatic
   - occurs between nonpolar groups (e.g. hydrocarbons)
   - highly distance and temperature dependent

2. **Dipole-Dipole Bonding**
   - stronger (1.0 to 10 kcal/mole)
   - occurs electrostatically between electron deficient and electron excessive/rich atoms (dipoles)
   - hydrogen bonding is a specific example of this bonding and serves as a prime contributor to hydrophilicity
3. Ionic Bonding

- electrostatic attraction between cations and anions
- common in inorganic compounds and salts of organic molecules
- relatively strong (5 kcal/mole)

4. Ion-Dipole Bonding

- electrostatic between a cation/anion and a dipole
- relatively strong (1-5 kcal/mole)
- low temperature and distance dependence
- important attraction between OMAs and H2O
The relative solubility of an OMA is a function of the presence of both lipophilic and hydrophilic features within its structure, which serve to determine the extent of interaction of the OMA with lipid and/or aqueous phases.

The relative solubility of an OMA can be determined in the laboratory, i.e. the partition coefficient \( P \); the ratio of the solubility of the compound in an organic solvent to the solubility of the same compound in an aqueous environment (i.e., \( P = \frac{[\text{Drug}]_{\text{lipid}}}{[\text{Drug}]_{\text{aqueous}}} \)). \( P \) is often expressed as a log value.
**Solubility Prediction**

A mathematical procedures also have been developed to estimate the relative solubility of an organic molecule based upon differential contributions of various structural features to overall solubility.

For example, the relative solubility of an OMA is the sum of the contributions of each group and substituent to overall solubility.

**Example:**
Examination of the structure of chloramphenicol (indicates the presence of both lipophilic (nonpolar) and hydrophilic (polar) groups and substituents.)
The presence of oxygen and nitrogen containing functional groups usually enhances water solubility. While lipid solubility is enhanced by nonionizable hydrocarbon chains and ring systems.
Solubility Prediction

1. Laboratory Estimation of Relative Solubility

The relative solubility of an organic compound is measured by determining the extent of its distribution into an aqueous solvent (usually pH 7.4 buffer) and a lipid solvent (usually n-octanol). These experiments generate a value, $P$, the partition coefficient for that particular compound.

$$\text{Partition coefficient} = \frac{\text{Conc. of compounds in } C_8H_{16}OH}{\text{Conc. of compounds in } H_2O}$$
2- Mathematical Estimation of Relative Solubility

Solubility contributions (groups and substituents) are expressed as hydrophilic (negative value) or lipophilic (positive value) fragment constants.

\[
\text{Log } P_{\text{calc}} = \Sigma \pi
\]

*Where:* \( \text{Log } P_{\text{calc}} = \log \text{ of partition coefficient and } \Sigma \pi = \text{sum of hydrophilic-lipophilic constants.} *

### Hydrophilic-Lipophilic constants.

<table>
<thead>
<tr>
<th>Fragment</th>
<th>( \pi ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C (aliphatic)</td>
<td>+0.5</td>
</tr>
<tr>
<td>( \text{C}_6\text{H}_5^- )</td>
<td>+2.0</td>
</tr>
<tr>
<td>Cl</td>
<td>+0.5</td>
</tr>
<tr>
<td>( \text{O}_2\text{NO} )</td>
<td>+0.2</td>
</tr>
<tr>
<td>Intramolecular hydrogen bonding (IMHB)</td>
<td>+0.65</td>
</tr>
<tr>
<td>S</td>
<td>+0.5</td>
</tr>
<tr>
<td>O=\text{C-O}</td>
<td>-0.7</td>
</tr>
<tr>
<td>O=\text{C-N}</td>
<td>-0.7</td>
</tr>
<tr>
<td>O(hydroxyl, phenyl, ether)</td>
<td>-1.0</td>
</tr>
<tr>
<td>N (amine)</td>
<td>-1.0</td>
</tr>
<tr>
<td>( \text{O}_2\text{N} ) (aliphatic)</td>
<td>-0.85</td>
</tr>
<tr>
<td>( \text{O}_2\text{N} ) (aromatic)</td>
<td>-0.28</td>
</tr>
</tbody>
</table>
Calculation steps of Log P for OMA

(i) The molecule is dissected into its various groups, functionalities and substituents
(ii) Appropriate hydrophilic/lipophilic fragment constants are assigned and summed
(iii) Compounds with log P_{calc} values greater than +0.5 are considered water insoluble (lipophilic) and those with log P_{calc} values less than +0.5 are considered water soluble (hydrophilic).

Calculated log P Values for salicylic acid and ρ-Hydroxybenzoic acid:

<table>
<thead>
<tr>
<th></th>
<th>Salicylic acid</th>
<th>ρ-Hydroxybenzoic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragment</td>
<td>π Value</td>
<td>Fragment</td>
</tr>
<tr>
<td>Phenyl</td>
<td>+2.0</td>
<td>Phenyl</td>
</tr>
<tr>
<td>OH</td>
<td>-1.0</td>
<td>OH</td>
</tr>
<tr>
<td>COOH</td>
<td>-0.7</td>
<td>COOH</td>
</tr>
<tr>
<td>IMHB</td>
<td>+0.65</td>
<td></td>
</tr>
<tr>
<td>Sum</td>
<td>+0.95</td>
<td></td>
</tr>
<tr>
<td>Prediction</td>
<td>Water insoluble</td>
<td>Prediction</td>
</tr>
</tbody>
</table>
Quantitative Structure Activity Relationship (QSAR)

As shown we can estimate the relative solubility of drugs on the basis of the structure features.

However, there is a relationship between the quantity of the drug that binds to the active site and its structure and thus, the biological activity.

This relationship is called *quantitative structure activity relationship* (QSAR).

QSAR can be used:

1- To predict the design of new compounds and
2- To reduce the types of chemical process involved in the biological activity.

Because, the biological activity of substances is related to oil water distribution coefficient (distribution of the compound between the aqueous and the lipid phases of the tissue), which is an important parameter for solubility and thus the quantity of the drugs that binds to the active site.
2- Acidity and Basicity

Acidic and/or basic properties of OMAs are important in both:

1- Pharmaceutical phase (dosage formulation, etc.) and
2- Pharmacological phases (disposition, structure at target site, etc.).

The three aspects of acid-base chemistry:

(1) Definitions
(2) Recognition of acidic or basic organic functional groups and
(3) An estimation of the relative acid/base strength of these groups.

Definitions:

**Acid**: An organic compound containing a functional group that can donate a proton (H+)

**Base**: An organic compound that contains a functional group that can accept a H+.
2- Recognition of acidic or basic organic functional groups

1- Common acidic organic functional groups

- Carboxylic acid (-COOH)
- Phenol (Ar-OH)
- Sulfonamide (R-SO2NH2)
- Imide (R-CO-NH-CO-R)
- β-Carbonyl group (-CO-CHR-CO-)

\[
\begin{align*}
\text{Carboxylic acid} & : R-C^\text{II}O - H_2O & \rightarrow & R-C^\text{II}O^- + H_3O^+ \\
\text{Phenol} & : R-OH + H_2O & \rightarrow & \text{Phenolate} + H_3O^+ \\
\text{Anilinium cation} & : R-NH_3^+ + H_2O & \rightarrow & R-NH_2 + H_3O^+
\end{align*}
\]
2-Recognition of acidic or basic organic functional groups (cont)

2- Common basic organic functional groups

- Aliphatic 1º (R-NH2), 2º (R2NH) and 3º (R3N)-amines
- Heterocyclic amines
- Aromatic amines (Ar-NH2)
Estimation of the Relative Acid/Base Strength

The ionization constant (\(k_a\)) indicates the relative strength of the acid or base.

An acid with a \(k_a\) of \(1 \times 10^{-3}\) is stronger acid (more ionized) than one with a \(k_a\) of \(1 \times 10^{-5}\).

A base with a \(k_a\) of \(1 \times 10^{-7}\) is weaker (less ionized) than one with a \(k_a\) of \(1 \times 10^{-9}\).

The negative log of the ionization constant (\(p_{k_a}\)) also indicates the relative strength of the acid or base.

An acid with a \(p_{k_a}\) of 5 (\(k_a=1 \times 10^{-5}\)) is weaker (less ionized) than one with \(p_{k_a}\) of 3.

Whereas a base with a \(p_{k_a}\) of 9 is stronger (more ionized) than one with a \(p_{k_a}\) of 7.

E.g. Ionization of weak acid (e.g. acetic acid, \(p_{k_a} = 4.76\)) is as follows:

\[
\text{CH}_3\text{COOH} \rightleftharpoons \text{CH}_3\text{COO}^- + \text{H}^+
\]

\[
\text{NH}_4^+ + \text{H}_2\text{O} \rightleftharpoons \text{NH}_3 + \text{H}_3\text{O}^+
\]
Estimation of the Relative Acid/Base Strength

The following chart is comparing acid/base strengths:

INCREASING ACIDITY

ACIDS: $\text{H}_2\text{SO}_4$, $\text{HCl}$, $\text{HNO}_3$, $\text{H}_3\text{O}^+$, $\text{RCO}_2\text{H}$, ArOH, $\text{RSO}_2\text{NH}_2$, CONHCO

INCREASING BASICITY

BASES: $\text{H}_2\text{O}$, ArNH$_2$, RNH$_2$, NaOH/KOH
The following chart is comparing **acid strengths** of various functional groups

<table>
<thead>
<tr>
<th>ACID</th>
<th>NAME</th>
<th>ACIDITY pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSO₂H</td>
<td>Sulfonic acid</td>
<td>1</td>
</tr>
<tr>
<td>RCOOH</td>
<td>Carboxylic acid</td>
<td>4.5</td>
</tr>
<tr>
<td>ArSO₂,NHR</td>
<td>Aromatic sulfonamide</td>
<td>6-9</td>
</tr>
<tr>
<td>ArOH</td>
<td>Phenol</td>
<td>8-11</td>
</tr>
</tbody>
</table>

The following chart is comparing **base strengths** of various functional groups

<table>
<thead>
<tr>
<th>ACID</th>
<th>NAME</th>
<th>Basicity pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNH₂, R₂NH, R₃N</td>
<td>Aliphatic amines</td>
<td>3-4</td>
</tr>
<tr>
<td>ArNH₂</td>
<td>Aromatic amines</td>
<td>9-13</td>
</tr>
<tr>
<td>Pyridine, piperidine,</td>
<td>Heterocyclic amines</td>
<td>4-12</td>
</tr>
</tbody>
</table>
Ionization of Acidic and Basic Functional Groups

**I-Acids**

- **Carboxylic acids**
  \[ R\text{\small CO}_2\text{H} + \text{H}_2\text{O} \rightleftharpoons R\text{\small CO}_2\text{H}^- + \text{H}_3\text{O}^+ \]

- **Sulfonamides**
  \[ \text{ArSO}_2\text{NH}_2 + \text{H}_2\text{O} \rightleftharpoons \text{ArSO}_2\text{NH}^- + \text{H}_3\text{O}^+ \]

- **Phenols**
  \[ \text{C}_6\text{H}_5\text{OH} + \text{H}_2\text{O} \rightleftharpoons \text{C}_6\text{H}_5\text{O}^- + \text{H}_3\text{O}^+ \]

- **Imides**
  \[ \text{R}-\text{CO}-\text{N}^- + \text{H}_2\text{O} \rightleftharpoons \text{R}-\text{COOH} + \text{H}_3\text{O}^+ \]

**II-Bases**

- **Aliphatic amines**
  \[ \text{R.N}^- + \text{H}_3\text{O}^+ \rightleftharpoons \text{R.N}^- + \text{H}^+ + \text{H}_2\text{O} \]

- **Aromatic amines**
  \[ \text{C}_6\text{H}_5\text{NH}_2 + \text{H}_3\text{O}^+ \rightleftharpoons \text{C}_6\text{H}_5\text{NH}_3^+ + \text{H}_2\text{O} \]

- **Heteroaromatic amines**
  \[ \text{N}^- + \text{H}_3\text{O}^+ \rightleftharpoons \text{N}^+ + \text{H}_2\text{O} \]
Acidic and Basic Functional Group - Salt Formation

Salt: is the combination of an acid and a base
All salts are strong electrolytes (with few exceptions: mercuric and cadmium halides and lead acetate)

The salt form of the drug is more soluble than its parent molecule

Drug salts can be divided into two classes:

1) **Inorganic salts:** are made by combining drug molecules with inorganic acids and bases, such HCl, H₂SO₄, KOH and NaOH. Inorganic salts are generally used to increase the aqueous solubility of a compound

2) **Organic salts:** are made by combining two drug molecules, one acidic and one basic. The salt formed by this combination has increased lipid solubility and generally is used to make depot injections (e.g. procaine penicillin).

Sodium salt formation from carboxylic acid:

\[
\text{RCOOH} + \text{NaOH} \rightarrow \text{RCOO}^-\text{Na}^+ + \text{H}_2\text{O}
\]

Hydrochloric salt formation from an aliphatic amine

\[
\text{R}_3\text{N} + \text{HCl} \rightarrow \text{R}_3\text{NH}^+\text{Cl}^-
\]
Structurally Non-Specific and Specific Activity

Drug activity can be classified as

(a) Structurally non-specific or
(b) Structurally specific

1-Structurally non-specific activity is dependent on physical properties like solubility, partition coefficients and vapour pressure and not on the presence or absence of some chemical group.

Substances such as alkanes, alkenes, alkynes, alcohols, amides, ethers, ketones and chlorine hydrocarbons exhibit narcotic activity and potency of each substance is related to its partition coefficient.

Structurally non-specific action results from accumulation of a drug in some vital part of a cell with lipid characteristics.

The structurally non-specific drugs include general anaesthetics, hypnotics together with a few bactericidal compounds and insecticides.
Structurally Non-Specific and Specific Activity

2-Structurally specific activity is dependent upon factors such as the presence or absence of certain functional groups, intramolecular distance, and shape of the molecules.

Activity is not easily co-related with any physical property and small changes in structure often lead to changes in activity.

Structurally specific activity is dependent upon the interaction of the drug with a cellular receptor.
**Drug-receptor Interaction**

*Receptor* is the site in the biological system where the drug exerts its characteristic effects or where the drug acts.

Receptors have an important regulatory function in the target organ or tissue.

Most drugs act by combining with receptor in the biological system (specific drugs).

1-cholinergic drugs interacts with acetylcholine receptors.

2-synthetic corticosteroids bind to the same receptor as cortisone and hydrocortisone

3-non steroidal anti inflammatory drugs inhibit cyclooxygenase enzyme that will inhibit the formation of prostaglandins which will lead to inflammation symptoms.

Non-specific drugs do not act upon receptors.

The receptor substance is considered mostly to be a cellular constituent. Recent studies, however, indicate that the receptors are proteins or enzymes.

The ability of a drug to get bound to a receptor is termed as the affinity of the drug for the receptor.
Drug-receptor Interaction

The ability of a drug to get bound to a receptor is termed as the affinity of the drug for the receptor.

The receptors are also dynamic in nature and have a special chemical affinity and structural requirements for the drug. Thus, affinity represents kinetic constants that relate to the drug and the receptor.

The drug elicits a pharmacological response after its interaction with the receptor. A given drug may act on more than one receptor differing both in function and in binding characteristics (non-selective drugs).

There are also many factors effect changes in receptor concentration and/or affinity.

A drug, which initiates a pharmacological action after combining with the receptor, is termed agonist. Drugs which binds to the receptors but are not capable of eliciting a pharmacological response produce receptor blockage, these compounds are termed antagonists.
**Structural features of drugs and their pharmacological activity**

**Stereochemistry:** Space arrangement of the atoms or three-dimensional structure of the molecule.

**Stereochemistry** plays a major role in the pharmacological properties because:

(1) Any change in stereospecificity of the drug will affect its pharmacological activity.
(2) The isomeric pairs have different physical properties (partition coefficient, pka, etc.) and thus differ in pharmacological activity.

The following steric factors influence pharmacological activity:

- **Optical and geometric isomerism**
- **Conformational isomerism**
- **Isosterism and bioisosterism**
I-Optical and geometric isomerism and pharmacological activity

Optical isomers are compounds that contain at least one chiral carbon atom or are compounds that differ only in their ability to rotate the polarized light.

The (+) or dextrorotatory isomer rotates light to the right (clockwise). The (-) or levorotatory isomer rotates light to the left (counterclockwise).
I-Optical and geometric isomerism and pharmacological activity

2-Hydroxybutane enantiomers (mirror images can not superimposed)

Enantiomers (optical isomers) can have large differences in potency, receptor fit, biological activity, transport and metabolism.

For example, levo-phenol has narcotic, analgesic, and antitussive properties, whereas its mirror image, dextro-phenol, has only antitussive activity.
I-Optical and geometric isomerism and pharmacological activity

**Geometric isomerism** (*cis-trans isomerisms*).

Occur as a result of restricted rotation about a chemical bond, owing to double bonds or rigid ring system in the molecule.

They are not mirror images and have different physicochemical properties and pharmacological activity. Because different distances separate the functional groups of these isomers.

They generally do not fit to the same receptor equally well and if these functional groups are *pharmacophores* the isomers will differ in biologic activity.

For example, *cis*-diethylstilbestrol has only 7% of the oestrogenic activity of *trans*-diethylstilbestrol.
Conformational isomersim is the non-identical space arrangement of atoms in a molecule, resulting from rotation about one or more single bonds.

Almost every drug can exist in more than one conformation and thus the drug might bind to more than one receptor but a specific receptor site may bind only to one of many conformations of a drug molecule.

For example, the trans conformation of acetylcholine binds to the muscarinic receptor, whereas the gauche conformation binds to the nicotinic receptor.
III- Isosterism, Bioisosterism and pharmacological activity

**Isosterism**: Any two ions or molecules having an identical number and arrangement of electrons (e.g. CO and NO2; CO2(O=C=O) and N2O (\(^{\text{N}=\text{N}^{+}=\text{O}} \leftrightarrow \text{N}^{=}\text{N}^{+}\text{O})\); and N-3 and NCO- etc.).

**Bioisosterism** is the procedure of the synthesis of structural analogues of a *lead compound* by substitution of an atom or a group of atoms in the parent compound for another with similar electronic and steric characteristics. Bioisosetres are functional groups which have similar spatial and electronic character, but they retain the activity of the parent.

**Bioisosterism** is important in medicinal chemistry because:
1- Maintain similar biological properties.
2- Resolved biological problems effectively (potency, side effects, separate biologic activities and duration of action)
Friedman defined bio-isosterism as the phenomenon by which compounds usually fit the broadest definition of isosteres and possess the same type of biological activity.

E.g. (Antihistamine; A; B and C)

Compound A has twice the activity of C, and many times greater than B
Classical and non-classical bioisosteres

- for the classical ones, where size equivalence is the key, the replacement should have roughly the same size.
- The key replacements (for example, the C, O, and N replacements are seen for three of the classical isosteres: CH3-, -OH, -NH2 for univalent;
- -CH2-, -O-, and -NH- for divalent;
- and -COCH2-R (ketone), -COOR (ester), and -CONHR (amide) for the carbonyl containing compounds.
- You should also be able to make isosteric replacements for the ring equivalents (single aromatic rings; single aliphatic rings, or the general tricyclic replacement).
- For example we could change the ester alcohol oxygen (not the carbonyl oxygen) with a CH2 (ketone), NH (amide), or S (thioester).