

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/receptors (which they are proteins, enzymes, cell lipids, or pieces of DNA or RNA).
- The ability of a chemical compound to show a pharmacologic /therapeutic effect is related to the influence of its various physical and chemical (**physicochemical**) properties

Physical-chemical Properties

➤ Physical-chemical properties refer to both physical and chemical properties of the drug molecule that may have an effect on its biological activity

partition coefficient

degree of ionization

surface activity

isosterism

intermolecular forces

oxidation-reduction potentials

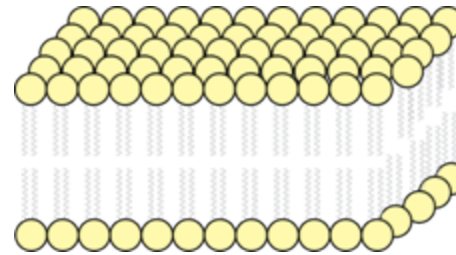
interatomic distances between functional groups

stereochemistry

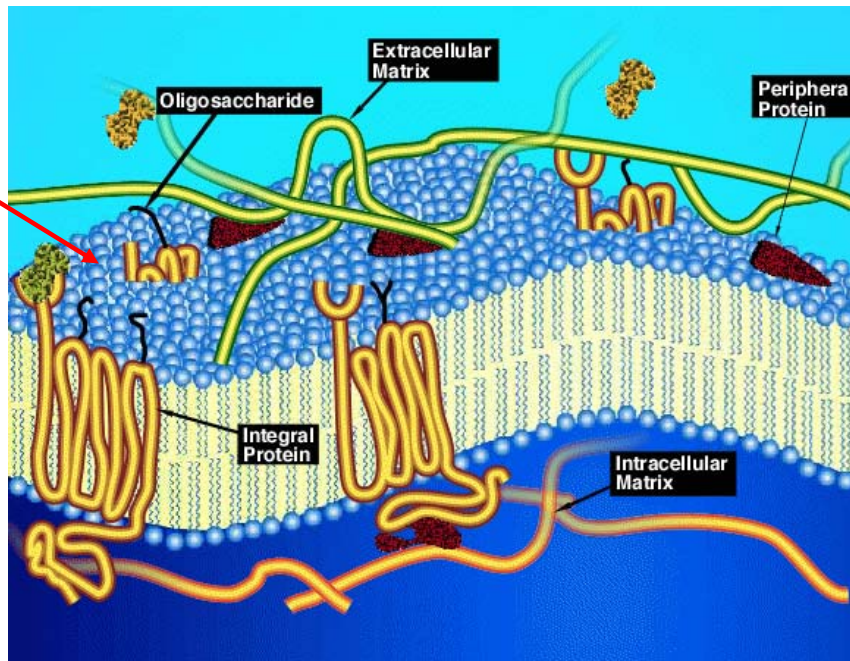
➤ Drug molecules should have the required physicochemical properties to be accessible to active sites
to have favorable drug receptor interaction

Structure of a Cell Membrane

- ✓ amphiphilic lipid molecules form a lipid bilayer



hydrophilic



hydrophobic

Solubility and Chemical Bonding

Lipophilicity ('fat-liking') is the most important physical property of a drug in relation to its absorption, distribution, potency, and elimination.

- If an organic drug molecule dissolves fully or partially in a nonaqueous or lipid solvent, the molecule is said to be **lipophilic** or to have lipophilic character.
- The term lipophilic or lipid loving is synonymous with **hydrophobic** or water hating, and these terms may be used interchangeably.

Hydrophilic**water loving**
Lipophobic**lipid hating**
Lipophilic**lipid loving**
Hydrophobic**water hating**

In order to predict whether a drug will dissolve in water or in lipid solvent, it must be determined whether the molecule and its functional groups can be bond to water or the lipid solvent molecules.

THIS IS THE KEY TO SOLUBILITY.

The hydrophobic effect

- If a compound is too lipophilic, it may
 - be insoluble in aqueous media (e.g. gastrointestinal fluid or blood)
 - bind too strongly to plasma proteins and therefore the free blood concentration will be too low to produce the desired effect
 - distribute into lipid bilayers and be unable to reach the inside of the cell (can go to the other lipophilic sites in the body)

- Conversely, if the compound is too polar, it may not be absorbed through the gut wall due to lack of membrane solubility.

So it is important that the lipophilicity of a potential drug molecule is correct - optimized-.

Partition Coefficient (P)

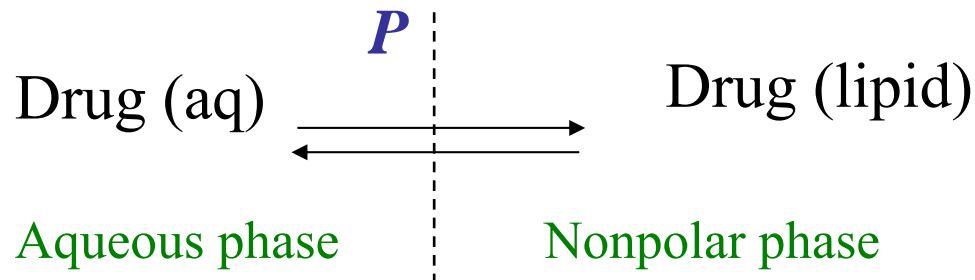
Hydrophobic character of a drug can be measured experimentally by testing drug's relative distribution in octanol/water mixture

- Hydrophobic molecules dissolve in *n*-octanol ($\text{CH}_3(\text{CH}_2)_7\text{OH}$)
- Hydrophilic molecules dissolve in aqueous layer

$$P = \frac{\text{Concentration of drug in octanol}}{\text{Concentration of drug in aqueous solution}}$$

Partition coefficient is the ratio of concentrations of a compound in the two immiscible phases

- a measure of differential solubility of the compound between these two solvents.



Partition Coefficient (P)

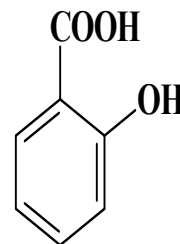
- useful in estimating distribution of drugs within the body
- hydrophobic drugs with high partition coefficients are preferentially distributed to hydrophobic compartments such as **lipid bilayers** of cells
- while hydrophilic drugs (low partition coefficients) preferentially are found in hydrophilic compartments such as **blood serum**
 - * Hydrophobic compounds will **high P** value
 - * Hydrophilic compounds will have **low P** value
- π is a measure of hydrophobicity of a substituent relative to hydrogen

Calculation steps of Log P for Drugs

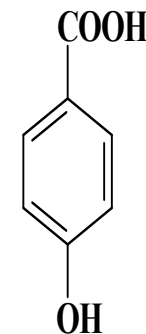
- (i) The molecule is divided into its various groups, functionalities and substituents
- (ii) Appropriate hydrophilic/lipophilic fragment constants are assigned and summed
- (iii) Compounds with **log P_{calc}** values **greater than +0.5** are considered **water insoluble** (lipophilic) and those with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

Calculated log P Values for salicylic acid and *p*-Hydroxybenzoic acid:

Salicylic acid		<i>p</i> -Hydroxybenzoic acid	
Fragment	π Value	Fragment	π Value
Phenyl	+2.0	Phenyl	+2.0
OH	-1.0	OH	-1.0
COOH	-0.7	COOH	-0.7
IMHB*	+0.65	-	-
Sum	+0.95		+0.3
Prediction	Water insoluble	Prediction	Water soluble



Salicylic acid

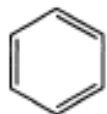


p-Hydroxybenzoic acid

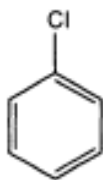
*IMHB: inter molecular hydrogen bonding

Example

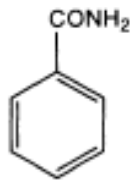
Calculate $\log P$ value for *m*-chlorobenzamide.



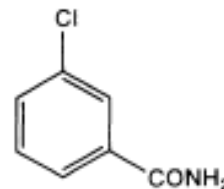
Benzene
(Log P = 2.13)



Chlorobenzene
(Log P = 2.84)



Benzamide
(Log P = 0.64)



meta-Chlorobenzamide

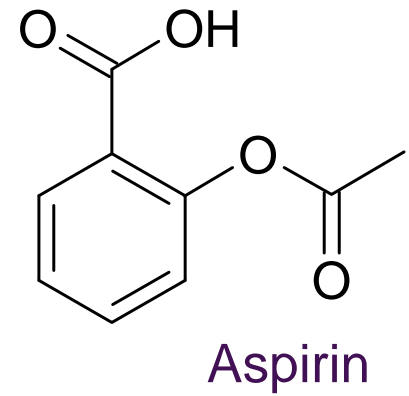
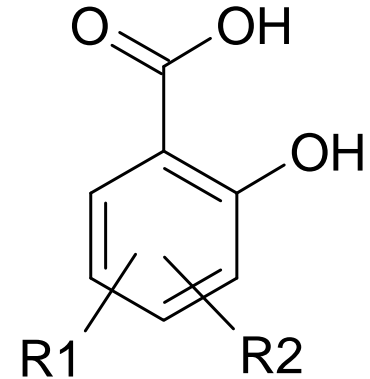
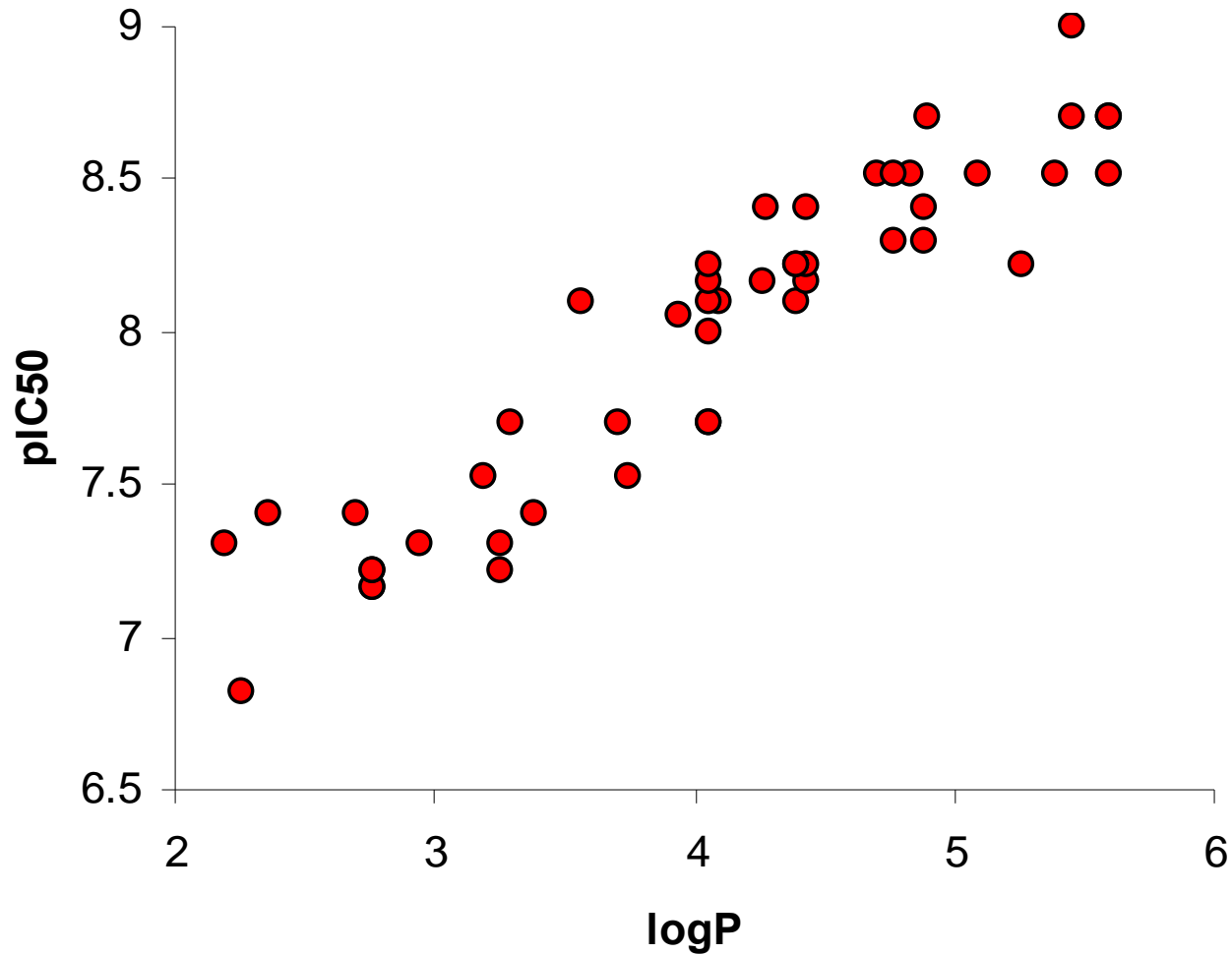
$$\pi_X = \log P_X - \log P_H$$

$$\pi_{\text{Cl}} = 2.84 - 2.13 = 0.71$$

$$\pi_{\text{CONH}_2} = 0.64 - 2.13 = -1.49$$

$$\begin{aligned} \log P_{(\text{chlorobenzamide})} &= \log P_{(\text{benzene})} + \pi_{\text{Cl}} + \pi_{\text{CONH}_2} \\ &= 2.13 + 0.71 + -1.49 = 1.35 \end{aligned}$$

Blood clot preventing activity of salicylic acids



Hydrophilic Groups

-COO⁻

-COOH

-OH

-N⁺R₃

-CHO

-NH₂

-CONH₂

-CONHR

-CONRR'

-COOR

Lipophilic Groups

-CH₃

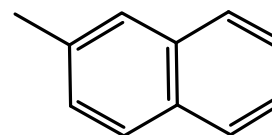
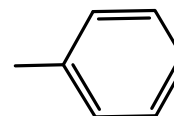
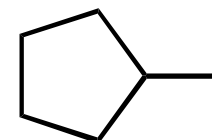
-C₂H₅

-C₃H₇

-CF₃

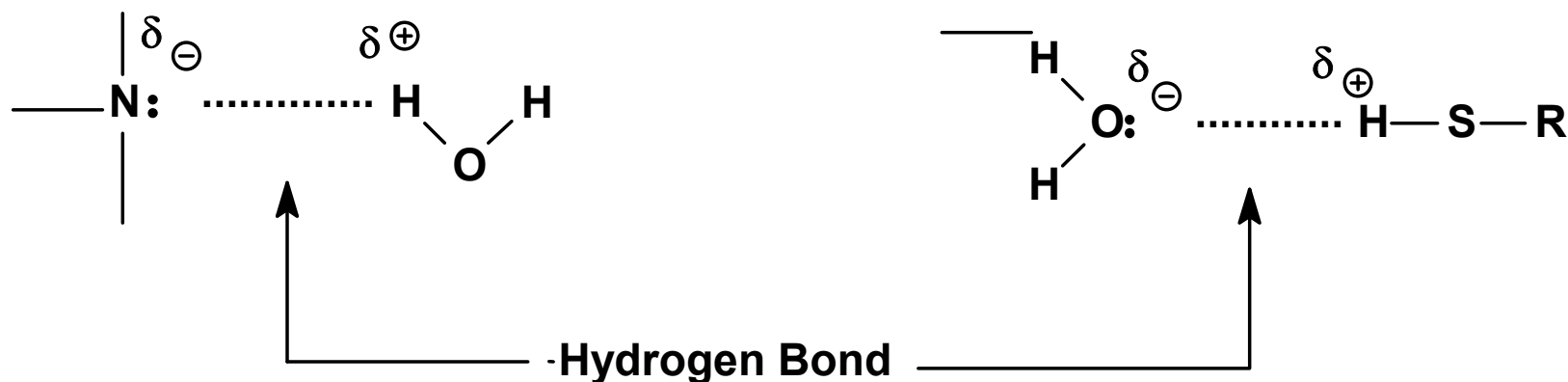
-Cl

-Br



Water Solubility and Hydrogen Bonding

- A stronger and important form of chemical bonding is the dipole-dipole bond, specific example of which is the hydrogen bond.



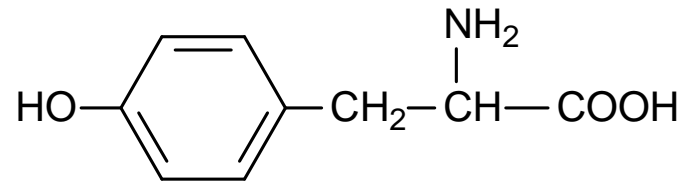
Hydrogen bonding of an amine to water and a thiol to water

Predicting Water Solubility

An excellent example of the importance of intramolecular bonding:

Tyrosine:

- Three functional group present:
 - a phenol
 - an amine
 - and a carboxylic acid group.

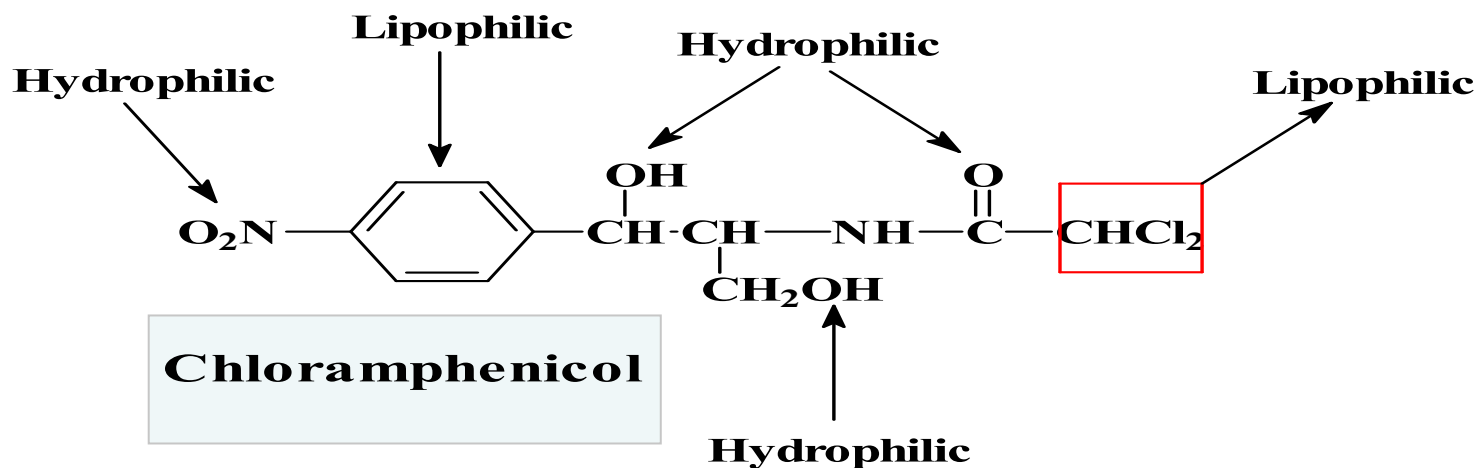


Solubility in H₂O 0.45g/1000ml @ 25° C

Solubility Prediction

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 increases water solubility.

While lipid solubility is enhanced by nonionizable hydrocarbon chains and ring systems.

Acidity and Basicity

Acidic and/or basic properties of drugs 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:

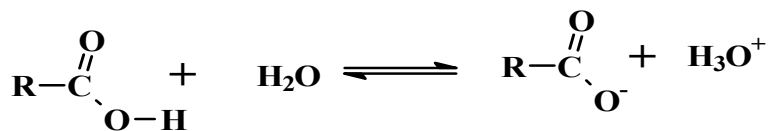
Acid: An organic compound containing a functional group that can donate a proton (H^+)

Base: An organic compound that contains a functional group that can accept a proton (H^+)

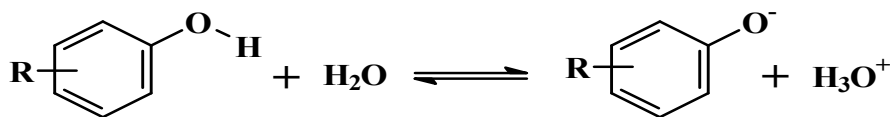
Recognition of acidic or basic organic functional groups

1- Common acidic organic functional groups

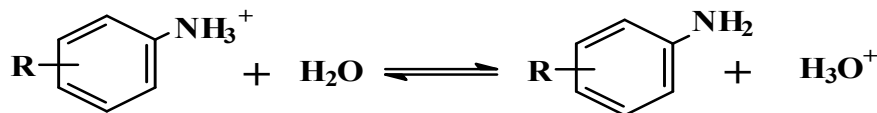
- Carboxylic acid (-COOH)
- Phenol (Ar-OH)
- Sulfonamide (R-SO₂NH₂)
- Imide (R-CO-NH-CO-R)
- β-Carbonyl group (-CO-CHR-CO-)



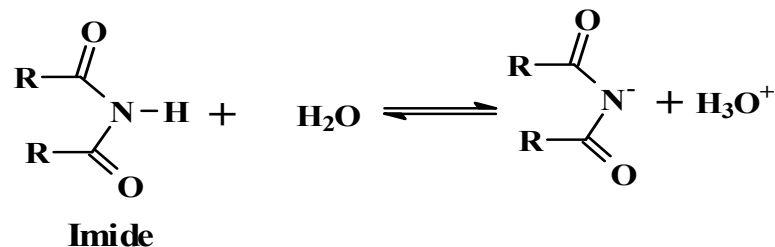
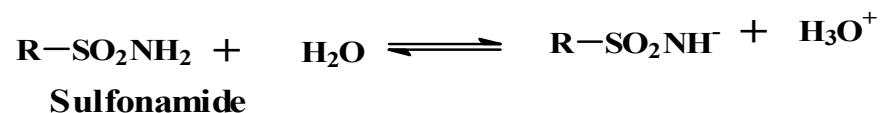
Carboxylic acid



Phenol



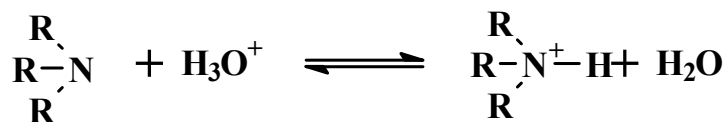
Anilinium cation



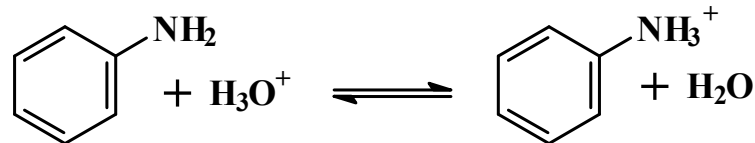
Recognition of acidic or basic organic functional groups (cont)

2- Common basic organic functional groups

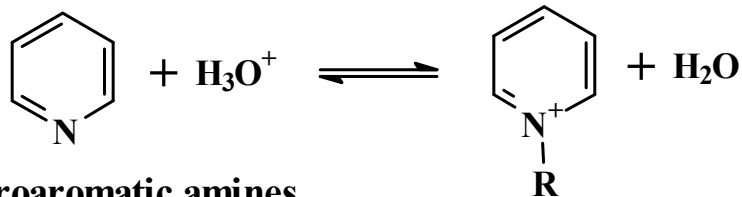
- Aliphatic 1° (R-NH₂), 2° (R₂NH) and 3° (R₃N)-amines
- Heterocyclic amines
- Aromatic amines (Ar-NH₂)



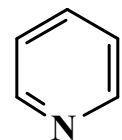
Aliphatic amines



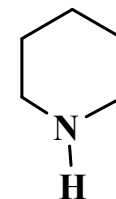
Aromatic amines



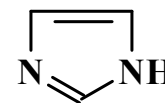
Heteroaromatic amines



Pyridine



Piperidine



Imidazole

Ionization

- **Ionization** = protonation or deprotonation resulting in charged molecules
- About 85% of marketed drugs contain functional groups that are ionized to some extent at physiological pH (pH 1.5 – 8).

The acidity or basicity of a compound plays a major role in controlling:

- Absorption and transport to site of action
 - Solubility, bioavailability, absorption and cell penetration, plasma binding, volume of distribution
- Binding of a compound at its site of action
 - un-ionised form involved in hydrogen bonding
 - ionised form influences strength of salt bridges or H-bonds
- Elimination of compound
 - Biliary and renal excretion
 - CYP P₄₅₀ metabolism

How does pH vary in the body?

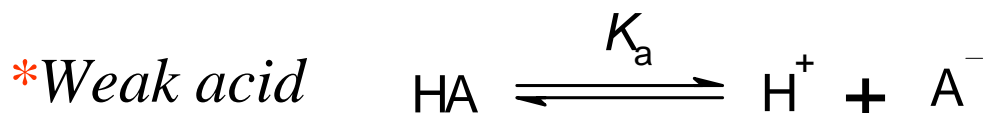
Fluid	pH
Aqueous humour	7.2
Blood	7.4
Colon	5-8
Duodenum (fasting)	4.4-6.6
Duodenum (fed)	5.2-6.2
Saliva	6.4
Small intestine	6.5
Stomach (fasting)	1.4-2.1
Stomach (fed)	3-7
Sweat	5.4
Urine	5.5-7.0

The same compound will be ionised to different extents in different parts of the body.

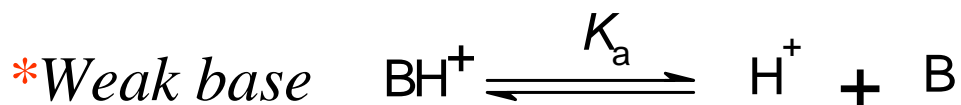
This means that, for example, basic compounds will not be so well absorbed in the stomach than acidic compounds since it is generally the unionised form of the drug which diffuses into the blood stream.

Handerson Hasselbalch Equation

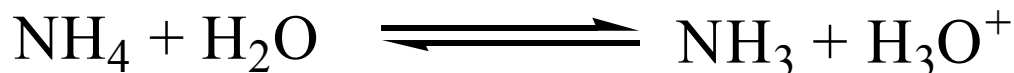
➤ For calculating the percentage of drug existing in ionized or unionized form at a given pH



$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$



$$pH = pK_a + \log \frac{[B]}{[BH^+]}$$

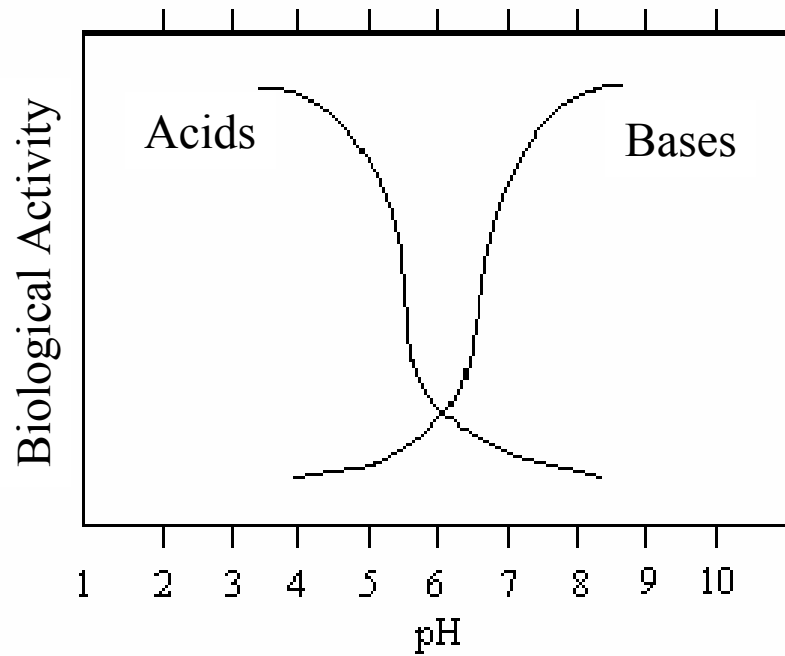


Weak acids: $pH > pK_a$; $[A^-] > [HA]$, (ionized > unionized)

Weak bases: $pH > pK_a$; $[HA] > [A^-]$, (unionized > ionized)

➤ $pH = pK_a$; $[HA] = [A^-]$, (unionized = ionized)

Biological Activity vs. pH



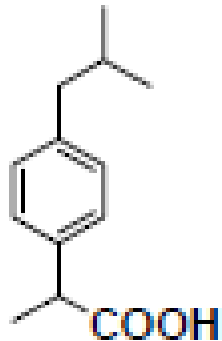
$pK_a < 2$: strong acid; conjugate base is insignificant in water

pK_a 4-6: weak acid; weak conjugate base

pK_a 8-10: very weak acid; stronger conjugate base

$pK_a > 12$: essentially no acidic properties in water;
strong conjugate base

Example



Ibuprofen

pKa = 4.5

- In the stomach

$$2.5 = 4.5 + \log B/A$$

$$-2 = \log B/A$$

$$1/100 = B/A$$

- How about in the small intestine?

$$7.5 = 4.5 + \log B/A$$

$$3 = \log B/A$$

$$1000/1 = B/A$$

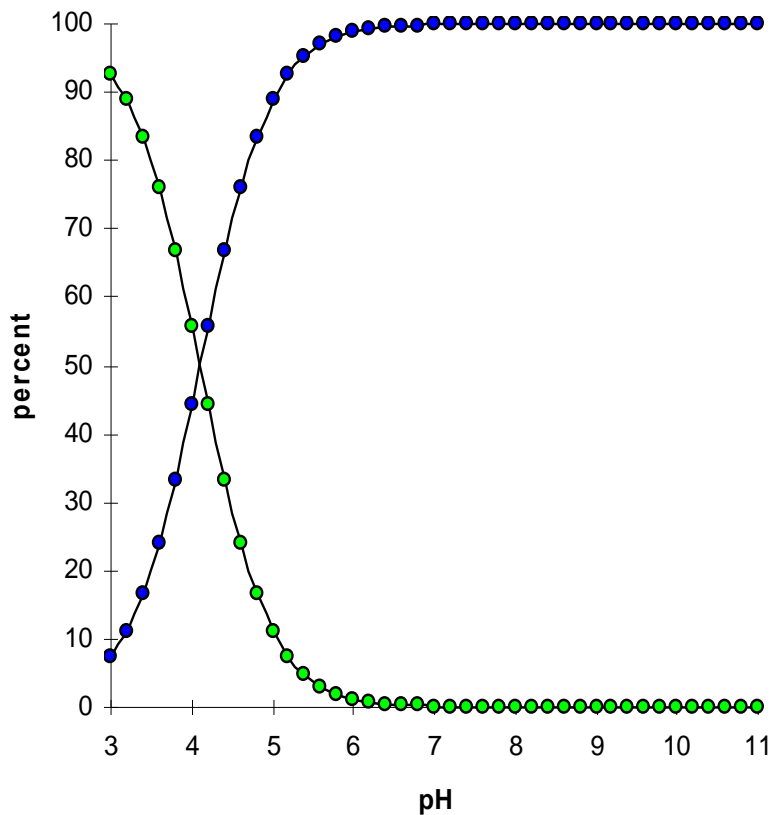
Conclusion: in the stomach, ibuprofen will mainly be in the acid form, which is less polar compared with its base form (charged mode), therefore, it is easier to be absorbed. On the other hand, in the small intestine, it is the opposite.

$$B = A^-$$

$$A = HA$$

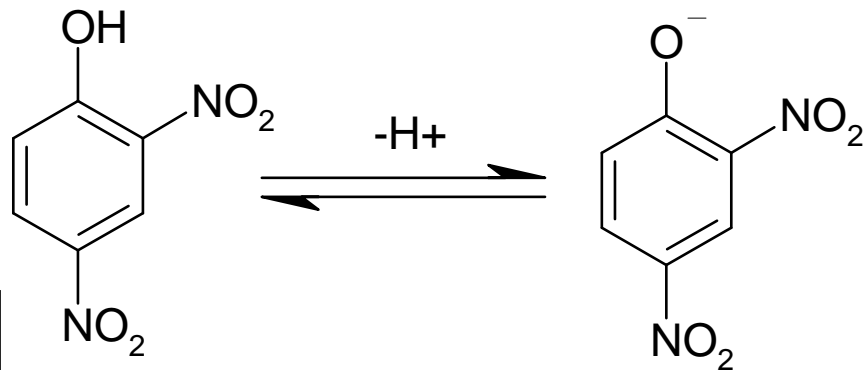
$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

Ionisation of an acid – 2,4-dinitrophenol



—●— % neutral
—●— % anion

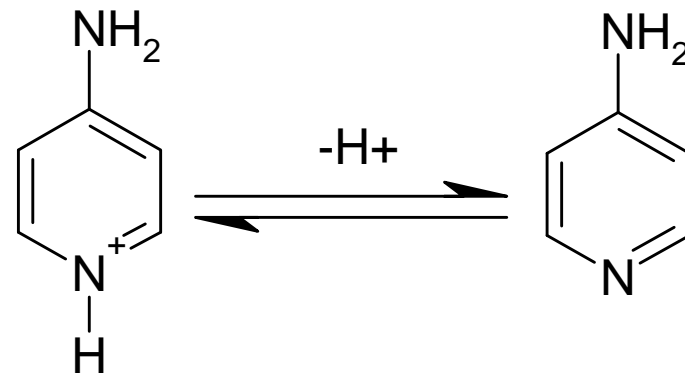
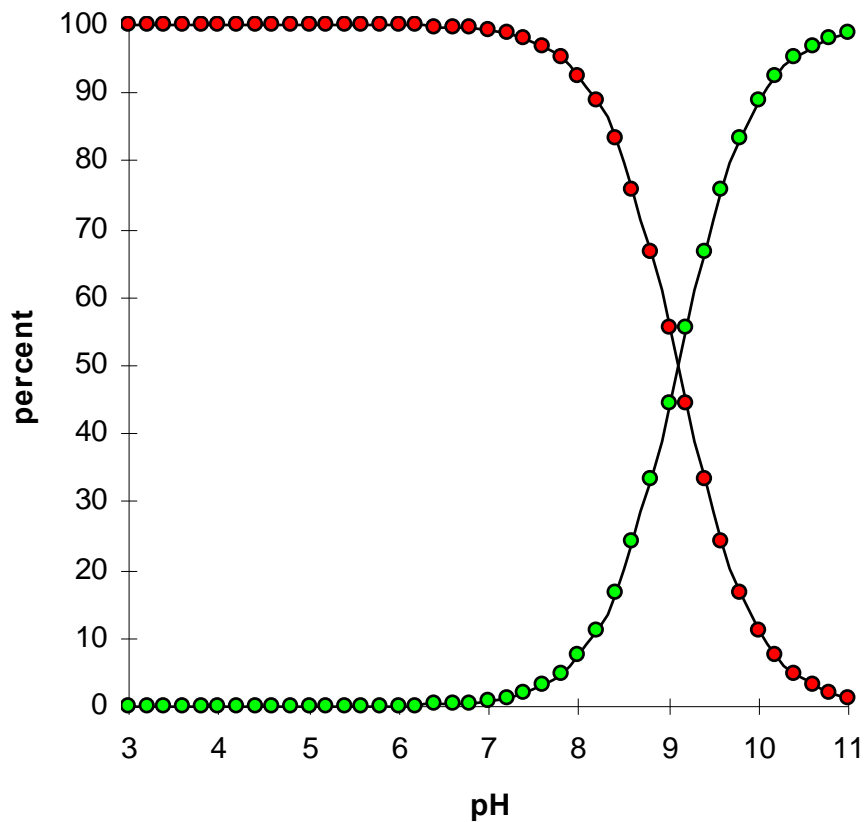
$pK_a = 4.1$



Neutral: unionized

Anion: ionized

Ionisation of an base – 4-aminopyridine



$\text{pK}_a = 9.1$

Steric Factors

- Bulk, size and the shape of a drug have an influence on its interaction with an enzyme or a receptor
- Bulky (large) substituent may shield and hinder the ideal interaction between drug and receptor
- or alternatively may help to orientate a drug for maximum receptor binding, increasing activity
- Difficult to quantify steric properties
 - Taft's steric factor (ES)
 - Molar refractivity (MR)
 - Verloop steric parameter

Structural features of drugs and their pharmacological activity

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

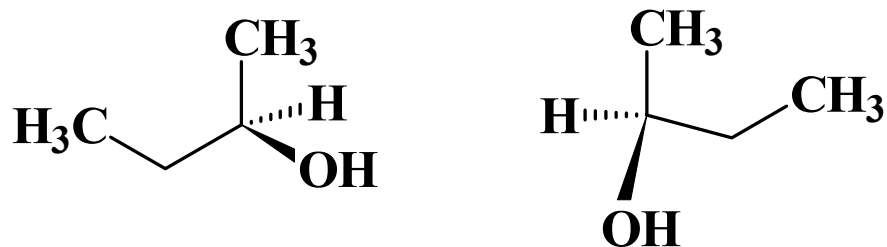
Stereochemistry plays a major role in the pharmacological properties because:

- (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**

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.

Bioisosterism and pharmacological activity

Bioisosteres are compounds or groups that have near-equal molecular shapes and volumes, approximately the same distribution of electrons, and show similar chemical and physical properties producing broadly similar biological effects.

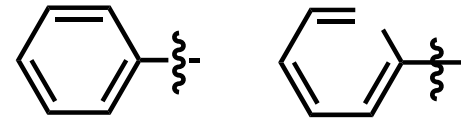
Parameters affected with bioisosteric replacements

Size, conformation, inductive and mesomeric effects, polarizability, H-bond formation capacity, pKa, solubility, hydrophobicity, reactivity, stability

Bioisosteric replacements: Why?

- Greater selectivity
- Less side effects
- Decreased toxicity
- Improved pharmacokinetics (solubility-hydrophobicity)
- Increased stability
- Simplified synthesis

Classical Bioisosteres



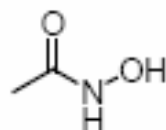
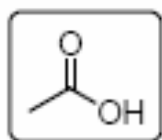
1) Monovalent a

- ✓ Halogen to CN or CF_3 replacements
- ✓ $\text{COCH}_2\text{-R}$ (ketone), -COOR (ester)
- ✓ CONHR (amide) for the carbonyl containing compounds

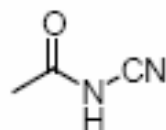
D and H

F and H

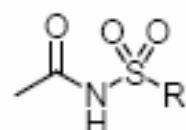
Bioisosterism - Carboxylic acid replacements



hydroxamic
(strong chelating agents)

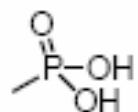


acylcyanamide

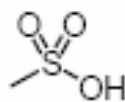


sulfonimide

(similar acidities)

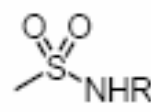


phosphonate



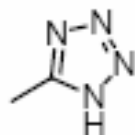
sulfonate

(more acidic;
ionized at physiological pH)

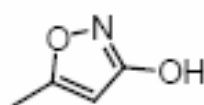


sulfonamide

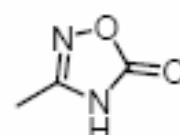
(less acidic)



tetrazole



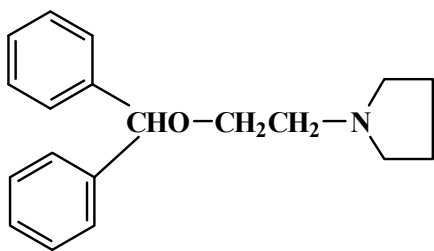
hydroxyisoxazole



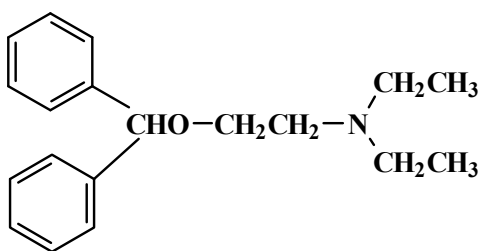
oxadiazolone

Bioisosterism and pharmacological activity

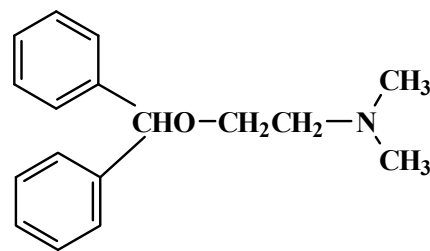
E.g. (Antihistamine; A; B and C)



A



B



C

Compound A has twice the activity of **C**, and many times greater than **B**

What is QSAR ?

QSAR (quantitative structure-activity relationships)

includes all statistical methods, approach attempts to identify and quantify the physicochemical properties of a drug and to see whether any of these properties has an effect on the drug's biological activity

QSAR Models - Hansch model (property-property relationship)

Definition of the lipophilicity
parameter π

$$\pi_X = \log P_{RX} - \log P_{RH}$$

Linear Hansch model



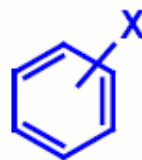
QSAR can be used:

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

Molecular Properties and Their Parameters

Molecular Property	Corresponding Interaction	Parameters
Lipophilicity	hydrophobic interactions	$\log P, \pi, f, R_M, \chi$
Polarizability	van-der-Waals interactions	MR, parachor, MV
Electron density	ionic bonds, dipol-dipol interactions, hydrogen bonds, charge transfer interactions	σ, R, F, κ , quantum chemical indices
Topology	steric hindrance geometric fit	E_S, r_V, L, B , distances, volumes

Hammett equation



$$\rho\sigma = \log k_{RX} - \log k_{RH}$$