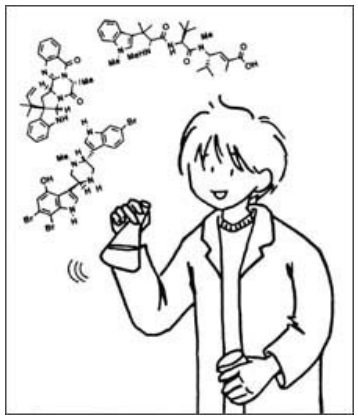
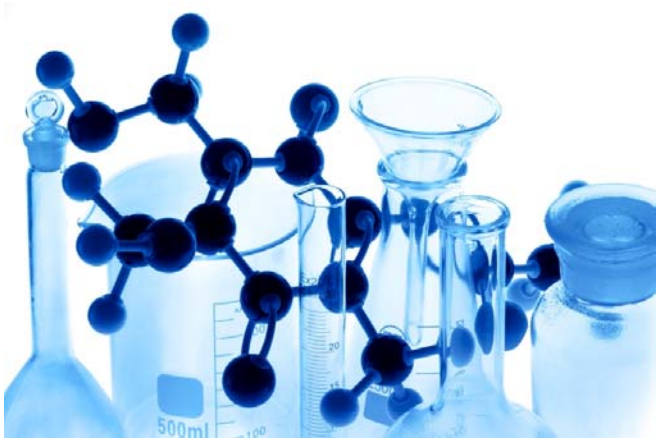




Physicochemical Properties

NEPHAR 305
Pharmaceutical Chemistry I

Assist.Prof.Dr. Banu Keşanlı

NEPHAR 305 Pharmaceutical Chemistry I
Fall 2014 Syllabus

1. Introduction to pharmaceutical-medicinal chemistry
2. Physiochemical Properties
3. Metabolism of Drugs
4. Central nervous system, general and local anasthetics
5. Sedative, hypnotic drugs
6. Tranquilizer, neuroleptics drugs
7. Antidepressant, antiepileptic drugs
8. Muscle relaxant, analeptic drugs
9. Antiparkinson agents, analgesics
10. Analgesics
11. Antitussive, expectorant, mucolytic drugs

Text Books for NEPHAR 305 Pharmaceutical Chemistry

- Principles of Medicinal Chemistry, William O. Foye, 6th Ed
  Lippincott Williams & Wilkins

- An Introduction to Medicinal Chemistry, Graham L. Patrick, 4th Ed
  Oxford University Press

- Farmasötik Kimya

Hülya Akgün, Ayla Balkan, A.Altan Bilgin, Ünsal Çalış, Sevim Dalkara, Dilek Demir Erol
Hakkı Erdoğan, Mevlüt Ertan, Nesrin Gökhan, Fügen Özkanlı, Erhan Palaska, Selma Saraç
Cihat Şafak, Birsen Tozkoparan
2. Baskı, 2004, Hacettepe Üniversitesi Yayınları, Ankara

Pharmaceutical chemistry - Medicinal chemistry

Medicinal chemistry mainly deals with the identification, synthesis and development of new chemical entities suitable for therapeutic use. Studies in pharmacology, toxicology, microbiology, biochemistry, biophysics, molecular biology etc. are necessary

Pharmaceutical chemistry is to do with the discovery and development of new and better drugs through organic synthesis, analytical study and some physical characterization. It involves organic synthesis, complete analytical characterization including spectroscopy, identification of physical and chemical properties, computational analysis, combinatorial approach etc.

- ✓ Synthesis of compounds which could show biological activity as a drug
- ✓ Structural identification
- ✓ Study of structure activity relationship
- ✓ Mechanism of action of a drug molecule

Drug Discovery, Design and Development

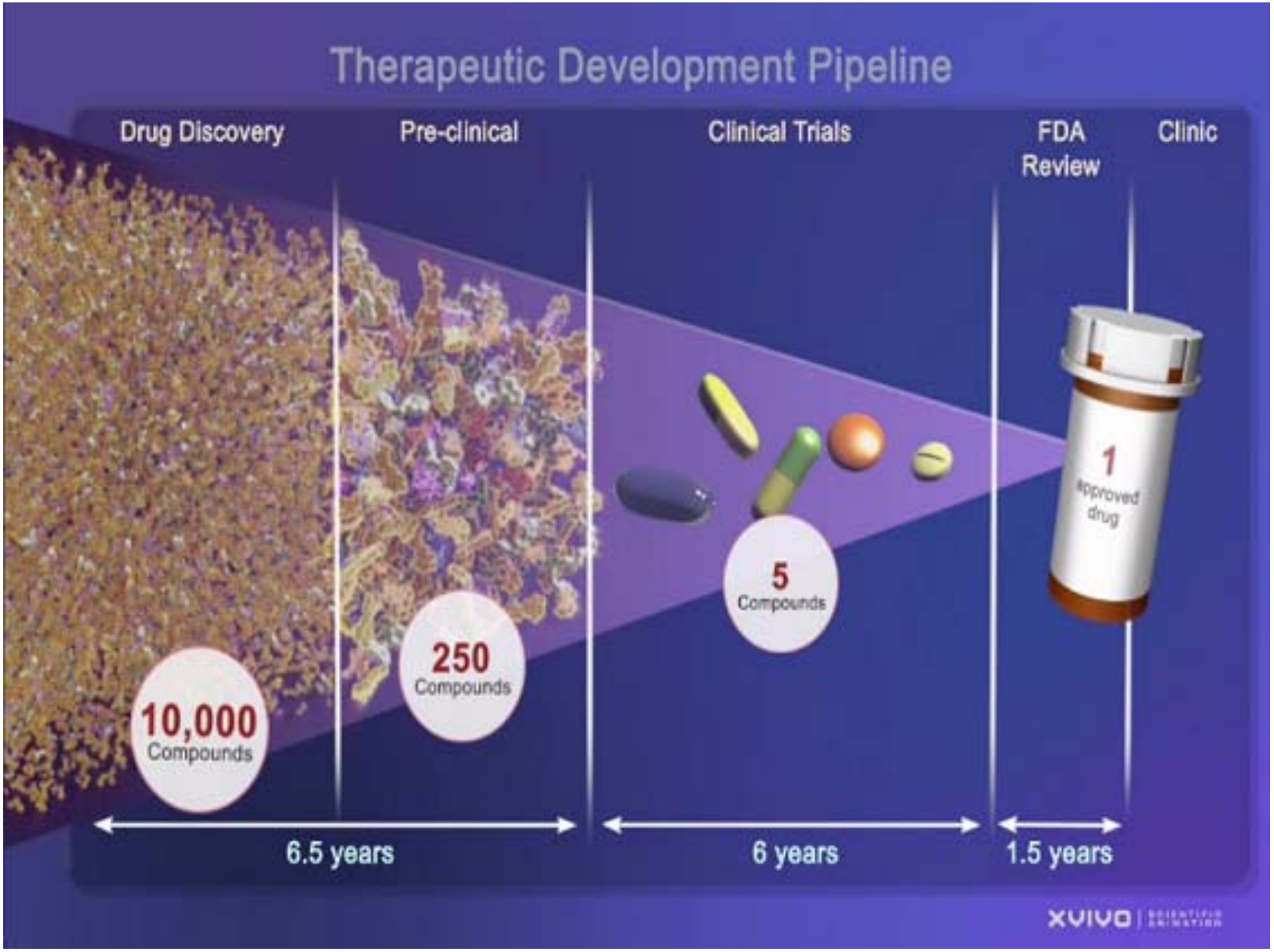
Pure organic compounds are the chief source of agents for the cure, reduction or the prevention of disease.

These drugs 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.).

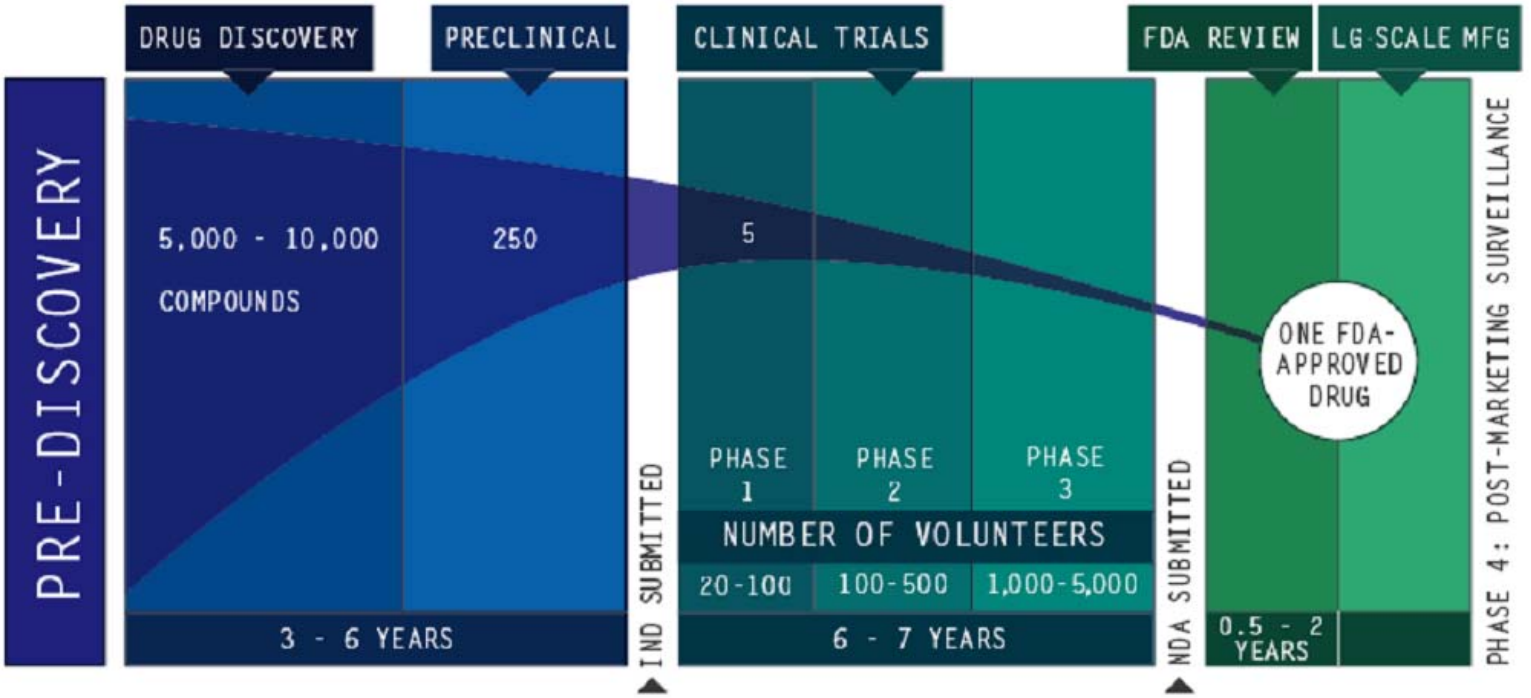
- **Synthetic compounds:** either purely synthetic or synthesis of naturally occurring compounds (e.g. morphine, atropine, steroids and cocaine) to reduce their cost.

- **Semi-synthetic 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).


Therapeutic Development Pipeline
Drug Discovery
Pre-clinical
Clinical Trials
FDA Review
Clinic
10,000 Compounds
250 Compounds
5 Compounds
1 approved drug
6.5 years
6 years
1.5 years
XVIVO

PHARMACEUTICAL RESEARCH & DEVELOPMENT

PROCESS



✓ The average cost to research and develop each successful drug is estimated to be **$800 million** to **$1 billion**. Time it takes is **10-15 years**.

Blockbuster Drugs

Best-selling pharmaceutical products 2002–2004

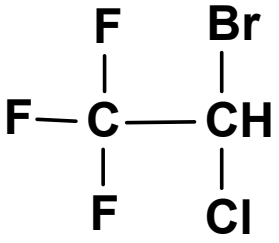
Product Trade (Generic) name	Company		Sales figures for 2004 (US$ billion)	
			Company	IMS
Lipitor (Atorvastatin)	Pfizer	• cholesterol-lowering medication	10.86	12.00
Zocor (Simvastatin)	Merck	• lipid-lowering agent	5.20	5.90
Plavix (Clopidrogrel)	BMS and Sanofi-Aventis	• anti-platelet medication	5.20	5.00
Advair (Fluticasone; Salmetrol)	GSK	• anti-asthma medication	4.50	4.70
Norvasc (Amlodipine)	Pfizer	• blood pressure-lowering agent	4.46	4.80
Zyprexa (Olanzapine)	Eli-Lilly	• anti-depressant	4.42	4.80
Paxil (Paroxetine)	GSK	• anti-depressant	3.90	3.90
Nexium (Esomaprazole)	AstraZeneca	• decreases the amount of acid produced in the stomach	3.88	4.80
Zoloft (Sertraline)	Pfizer	• anti-depressant	3.36	NA
Celebrex (Celecoxib)	Pfizer	• anti-inflammatory drug	3.30	NA
Effexor (Venlafaxine)	Wyeth	• anti-depressant	3.30	3.70
Prevacid (Lansoprazole)	Takeda and Abbott	• decreases the amount of acid produced in the stomach	3.10	3.80
Diovan (Valsartan)	Novartis	• prevents vasoconstriction	3.10	NA
Fosamax (Alendronate)	Merck	• anti-osteoporosis agent	3.10	NA
Risperdal (Risperidone)	J&J	• antipsychotic medication	3.00	NA

Global pharma market IMS US$550 billion; global biotechnology market valued at US$55 billion; global generic market US$62 billion.
Table lists top 15 Medicines in 2004 with sales of over US$3 billion.
Abbreviations: BMS, Bristol-Myers Squibb; GSK, GlaxoSmithKline; J&J, Johnson and Johnson; NA, not available.

Important Functional Groups on Drugs

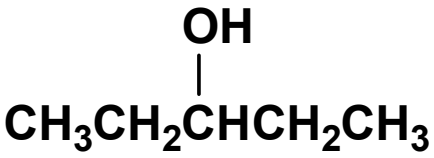
1. **Alkanes** (C_2H_{2n+2}) and **Alkenes** (C_{2H2n})
   - Cannot form ionic, hydrogen or ion-dipole bonds with itself or water, only van der Waals is possible
   - They are not water soluble
   - The larger or more branched the alkyl chains the less hydrophilic or more lipophilic the group becomes
   - Halogenated hydrocarbons (CH_3F, CCl_4 etc) are generally less hydrophilic than the alkyl form due to lack of electron deficient region of the halide that prevents water bonding

Example: Halotane

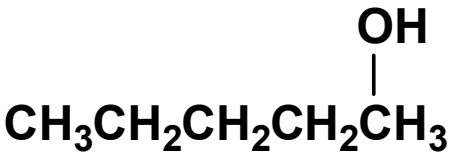


Alcohols

- OH Group participates in intramolecular hydrogen bonding due to electronegative oxygen and positive hydrogen result in permanent dipole
- OH also forms hydrogen bonds with water via dipole-dipole interactions.
- Alcohol solubility decreases with length of hydrocarbon and position of OH on molecule also influences solubility



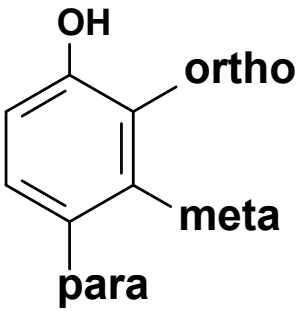
More soluble



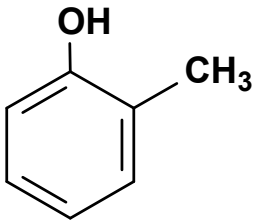
Less soluble

Phenols

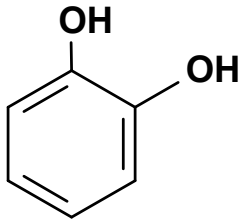
- Hydroxyl group attached directly to the aromatic ring



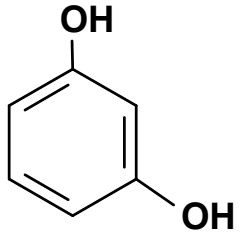
Phenol (carbolic acid)



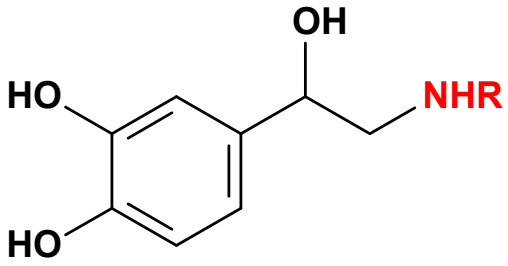
o-cresol



catechol



resorcinol



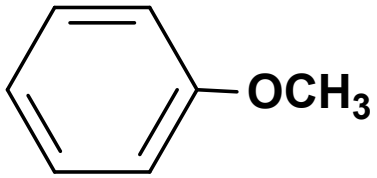
R = H, Noradrenaline

R = CH_3 Adrenaline

Ethers

$CH_3OCH_2CH_3$ Ethylmethylether

$CH_3CH_2OCH_2CH_3$ Diethylether (Ether U.S.P.)



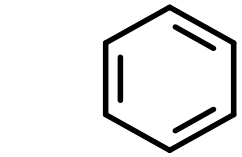
Methylphenylether (Anisole)

Solubility ($g/100g H_2O$)

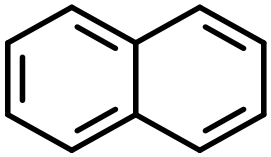
Diethylether……8.4
Diisopropylether……0.002

Aromatic Hydrocarbons

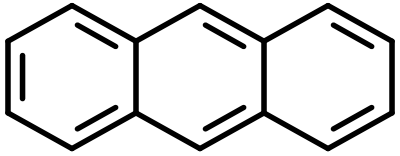
- Not isolated single, double bonds but electron clouds above and below the plane of the ring
- Plays significant role in binding to biological proteins via van der Wall's bonding
- Tend to form the back bone of drug molecules and their solubility is influenced by the functional group attached



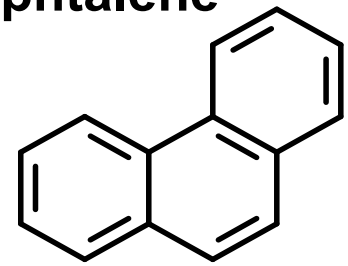
Benzene



Naphtalene



Anthracene



Phenanthrene

What are drugs and why do we need new ones?

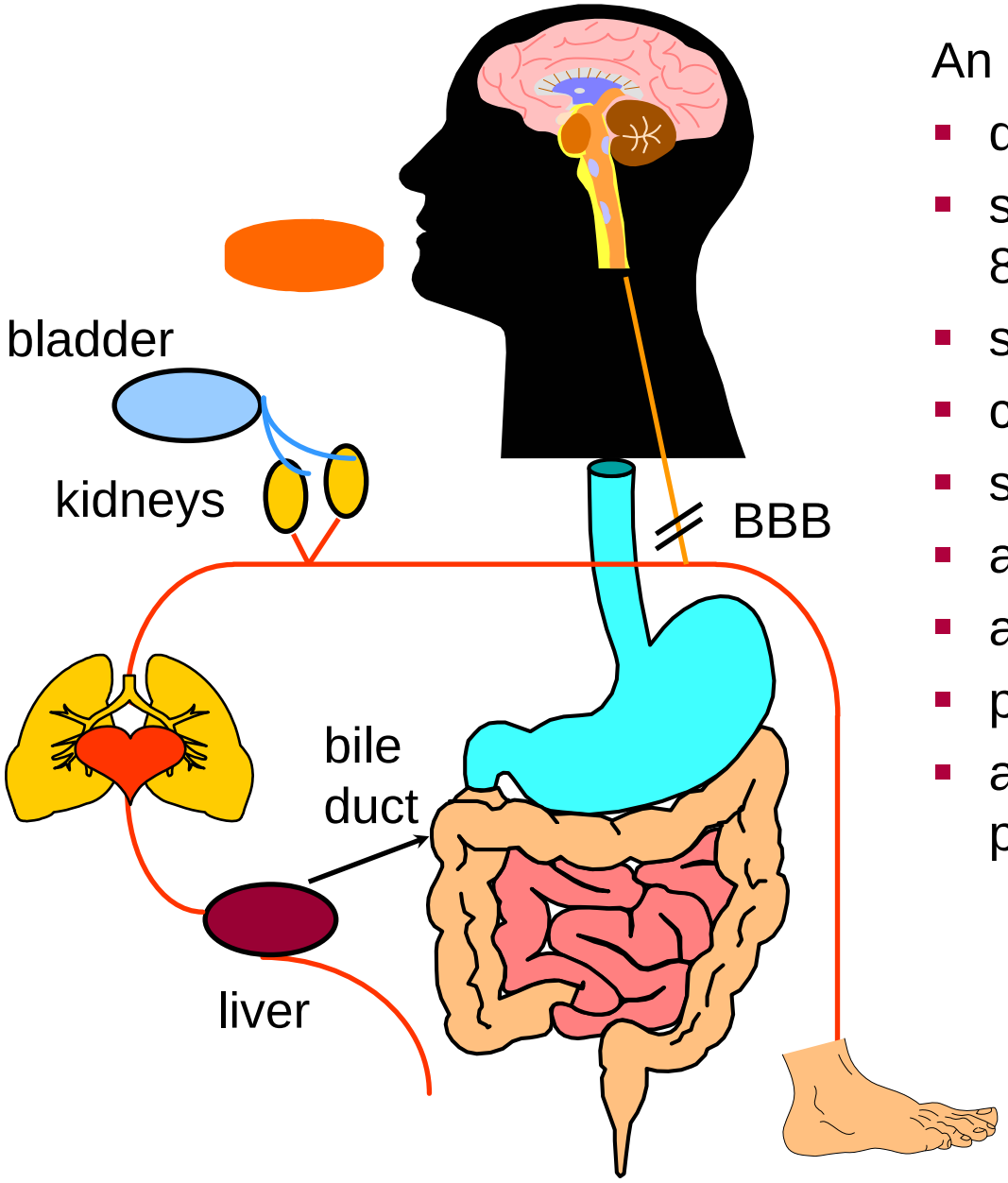
- **Drug** is any substance presented for treating, curing or preventing disease in human beings or in animals. It may also be used for making a medical diagnosis or for restoring, correcting, or modifying physiological functions.




Activity - pharmaceutical/pharmacological effect on the subject, e.g. analgesic or *β*-blocker

Potency - the quantitative nature of the effect

What must a drug do other than bind?



An oral drug must be able to:

- dissolve
- survive a range of pHs (1.5 to 8.0)
- survive intestinal bacteria
- cross membranes
- survive liver metabolism
- avoid active transport to bile
- avoid excretion by kidneys
- partition into target organ
- avoid partition into undesired places (e.g. brain, fetus)

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

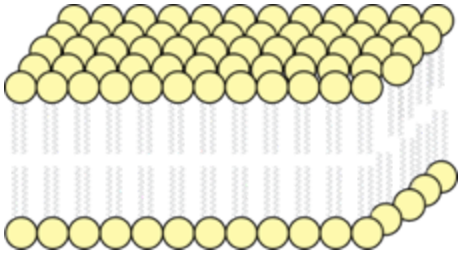
Physical-chemical Properties

- 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

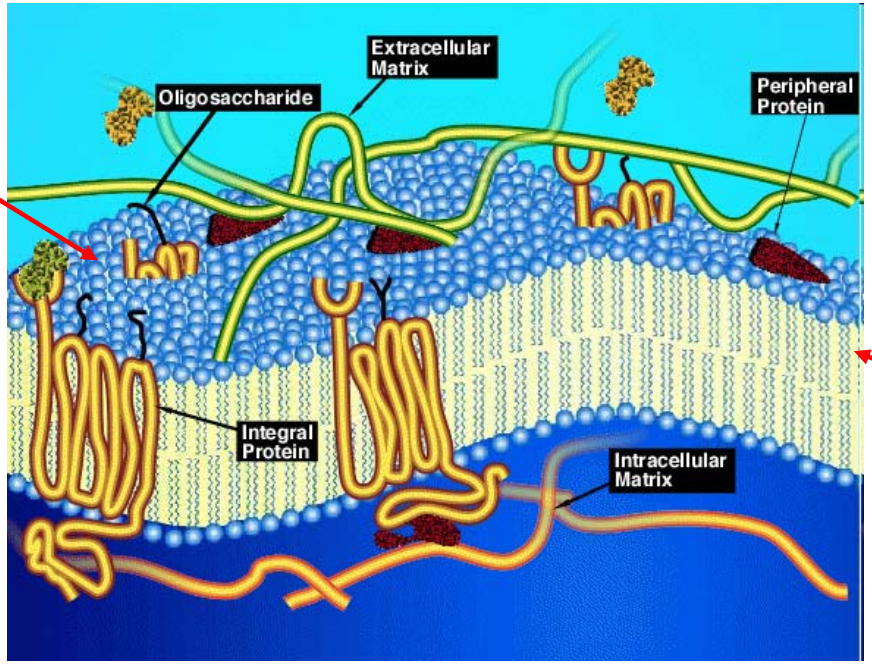
- Drug molecules should have the required physicochemical properties
  - to be accessible to active sites
  - to have favorable drug receptor interaction

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*)

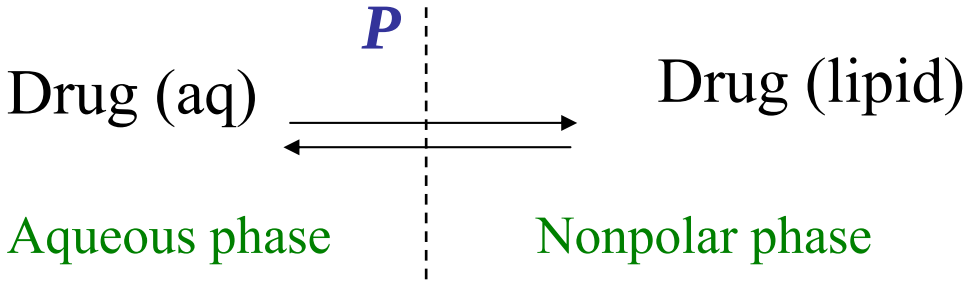
Hydrophobic character of a drug can be measured experimentally by testing drug's relative distribution in octanol/water mixture

- Hydrophobic molecules dissolve in *n*-octanol ($CH_3(CH_2)_7OH$)
- Hydrophilic molecules dissolve in aqeous layer

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

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

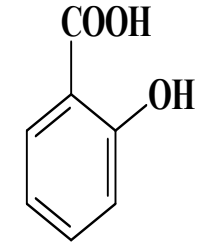
(i) The molecule is divided into its various groups, functionalities and substituents

(ii) Appropriate hydrophilic/lipophilic fragment constants are assigned and summed

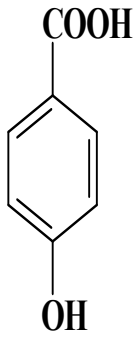
(iii) Compounds with **log Pcalc** values **greater than +0.5** are considered **water insoluble** (lipophilic) and those with **log Pcalc** values **less than +0.5** are considered **water soluble** (hydrophilic).

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

Salicylic acid		***p*-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

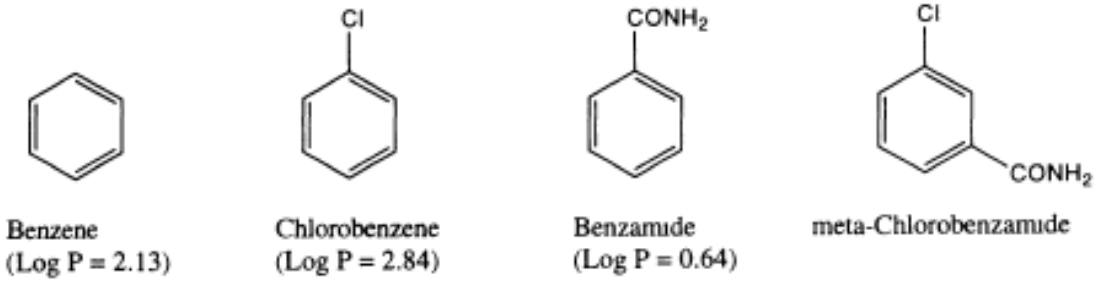


p-Hydroxybenzoic acid

*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

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

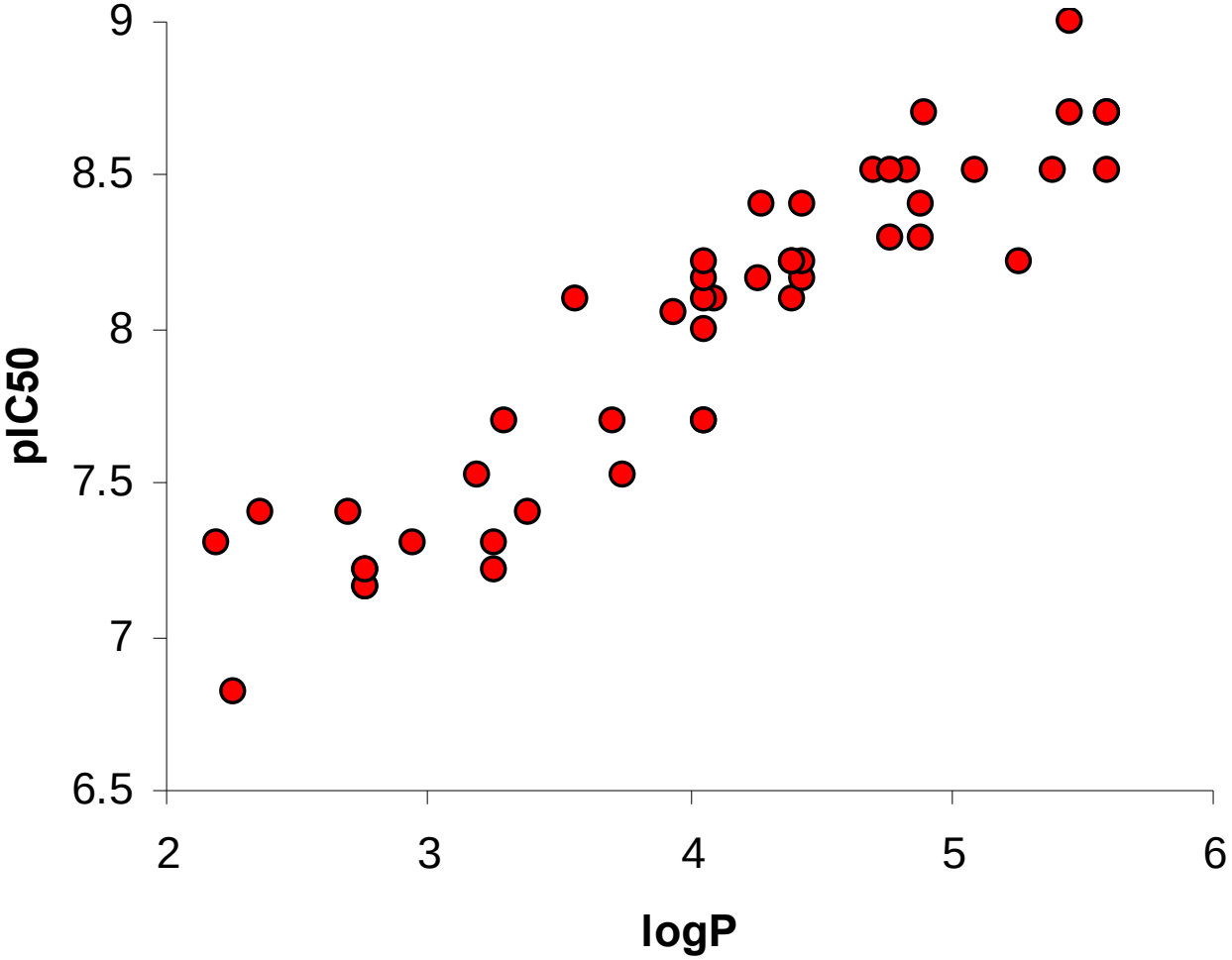
$\pi_{Cl} = 2.84\text{-}2.13 = 0.71$

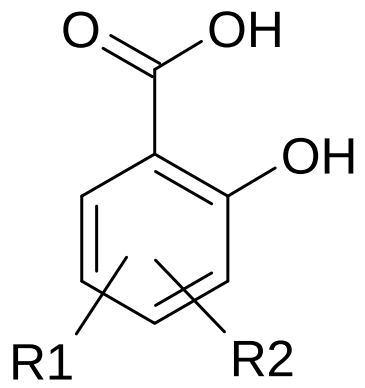
$\pi_{CONH2} = 0.64\text{-}2.13 = -1.49$

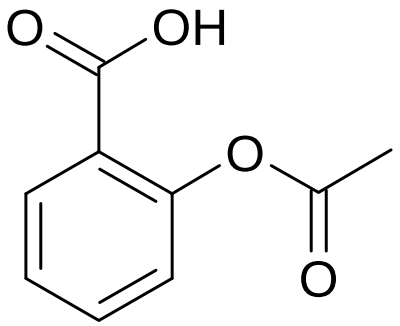
$$\log P_{(chlorobenzamide)} = \log P_{(benzene)} + \pi_{Cl} + \pi_{CONH2}$$

$$= 2.13 + 0.71 + -1.49 = 1.35$$

Blood clot preventing activity of salicylic acids







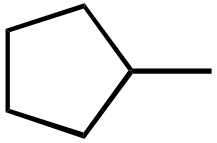
Aspirin

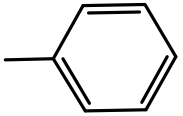
Hydrophilic Groups

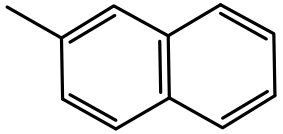
- $-COO^-$
- $-COOH$
- $-OH$
- $-N^+R_3$
- $-CHO$
- $-NH_2$
- $-CONH_2$
- $-CONHR$
- $-CONRR'$
- $-COOR$

Lipophilic Groups

- $-CH_3$
- $-C_2H_5$
- $-C_3H_7$
- $-CF_3$
- $-Cl$
- $-Br$

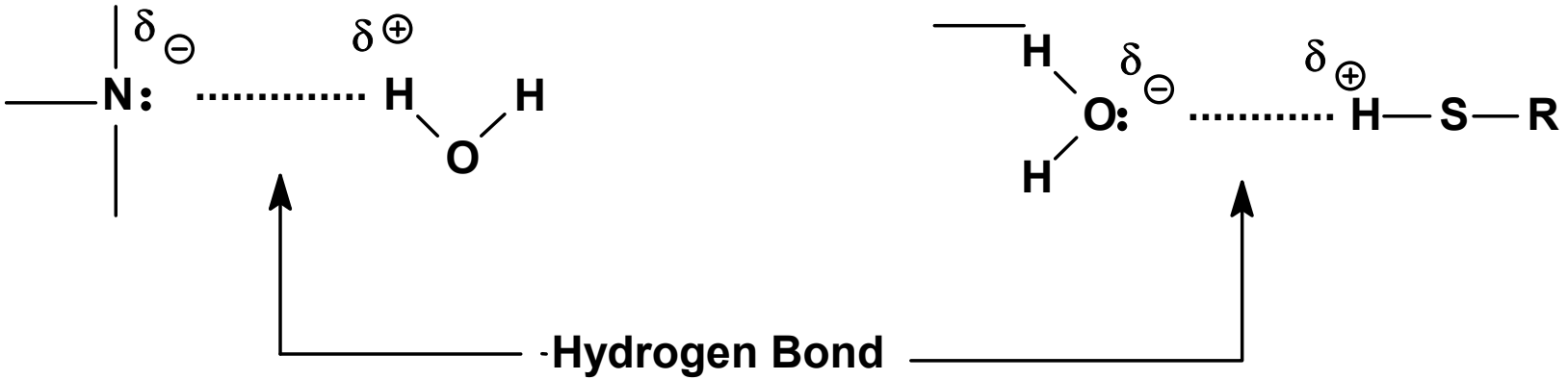






Water Solubility and Hydrogen Bonding

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



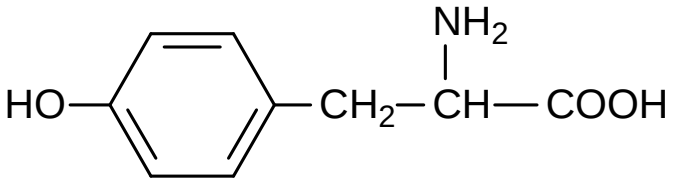
Hydrogen bonding of an amine to water and a thiol to water

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.**

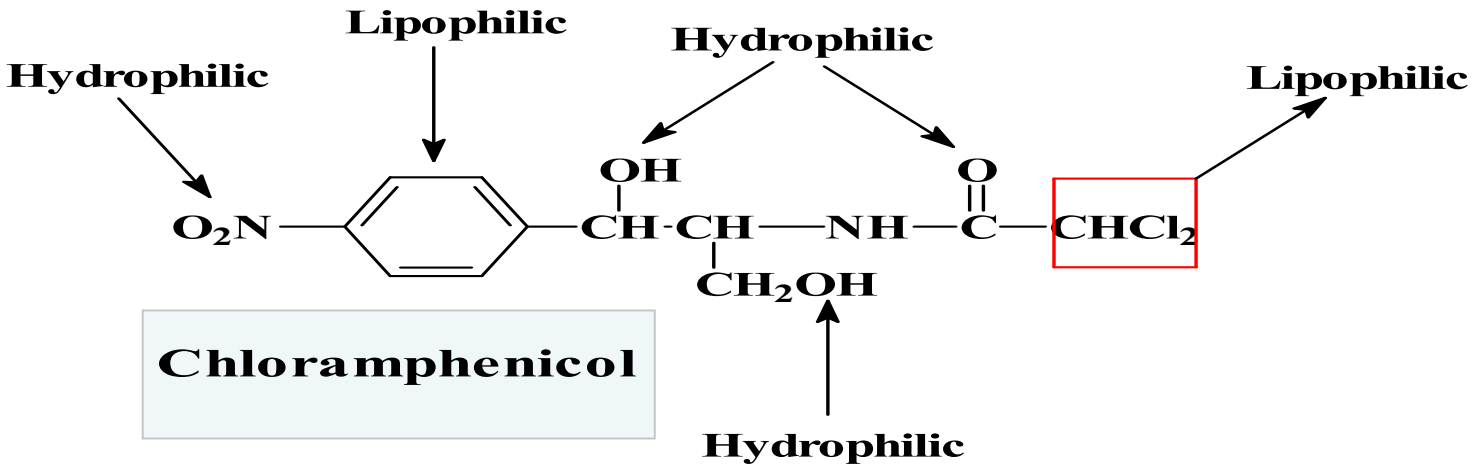


Solubility in H_2O 0.45g/1000ml @ 25° C

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:

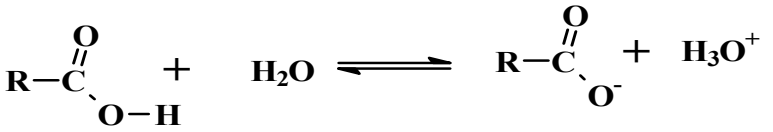
Acid: An organic compound containing a functional group that can donate a proton (H+)

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

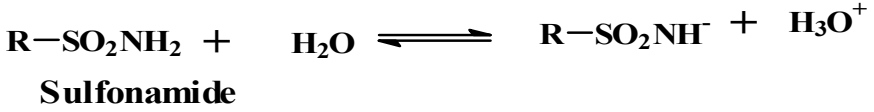
Recognition of acidic or basic organic functional groups

1- Common acidic organic functional groups

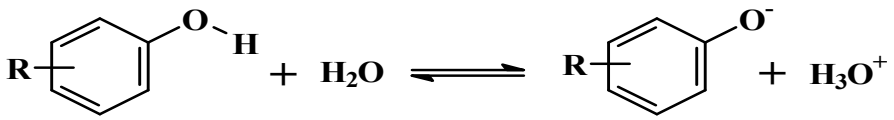
- Carboxylic acid (-COOH)
- Phenol (Ar-OH)
- Sulfonamide (R-SO_2NH2)
- Imide (R-CO-NH-CO-R)
- β-Carbonyl group (-CO-CHR-CO-)



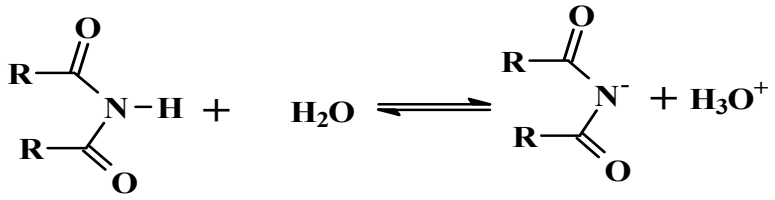
Carboxylic acid



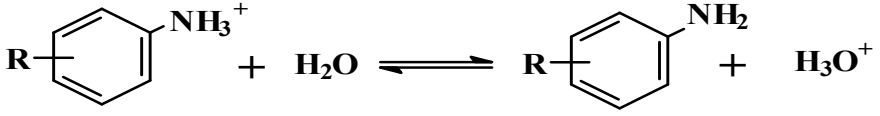
Sulfonamide



Phenol



Imide

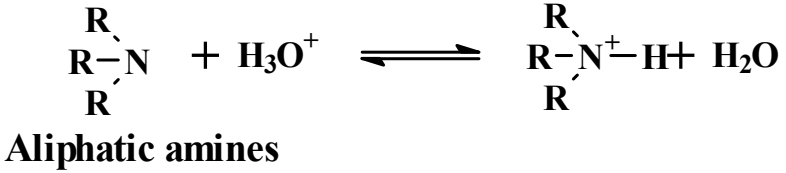


Anilinium cation

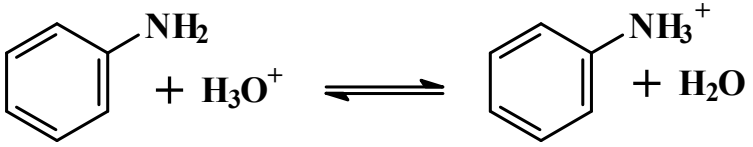
Recognition of acidic or basic organic functional groups (cont)

2- Common basic organic functional groups

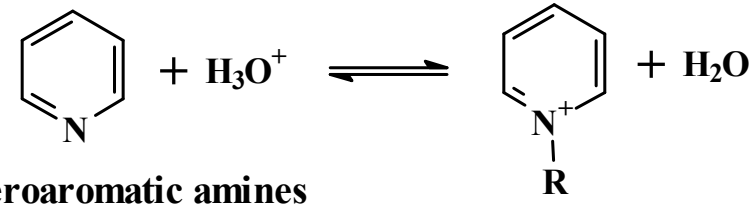
- Aliphatic 1º ($R\text{-}NH_2$), 2º (R_2NH) and 3º (R_3N)-amines
- Heterocyclic amines
- Aromatic amines ($Ar\text{-}NH_2$)



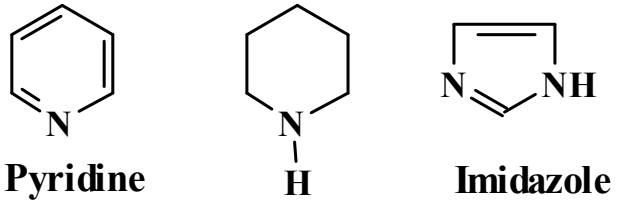
Aliphatic amines



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 P_{450} 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

*Weak acid $HA \overset{K_a}{\rightleftharpoons} H^+ + A^-$

$CH_3COOH \rightleftharpoons CH_3COO + H^+$

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

*Weak base $BH^+ \overset{K_a}{\rightleftharpoons} H^+ + B$

$NH_4 + H_2O \rightleftharpoons NH_3 + H_3O^+$

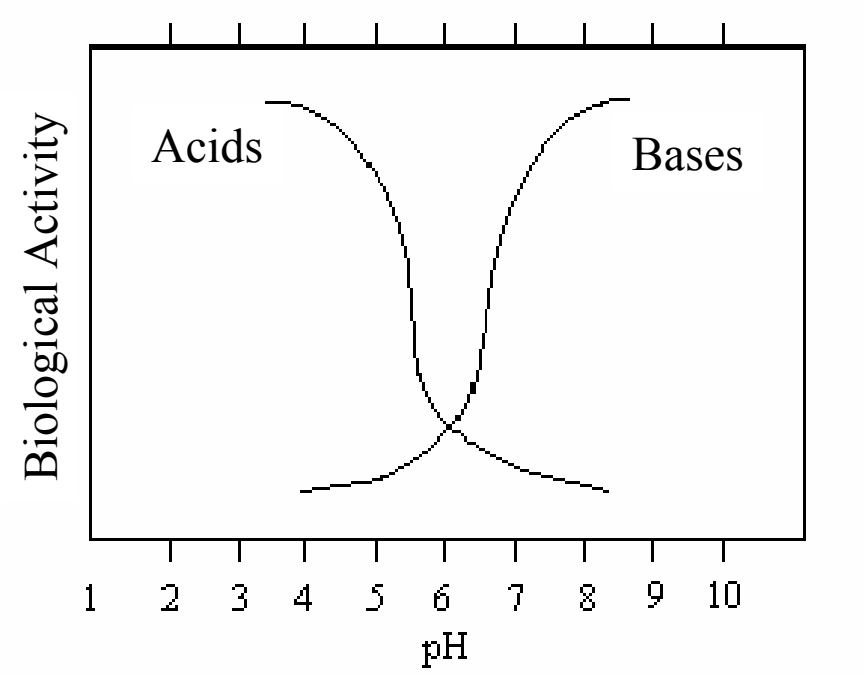
$$pH = pK_a + \log \frac{[B]}{[BH^+]}$$

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

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

➢ pH = pKa ; $[HA] = [A^-]$, (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

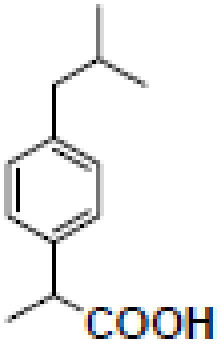
pK_a 8-10: very weak acid; stronger conjugate base

pK_a > 12: essentially no acidic properties in water;

strong conjugate base

Example

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



Ibuprofen

pKa = 4.5

- In the stomach

2.5=4.5+logB/A

-2=logB/A

1/100=B/A

- How about in the small intestine?

7.5=4.5+logB/A

3=logB/A

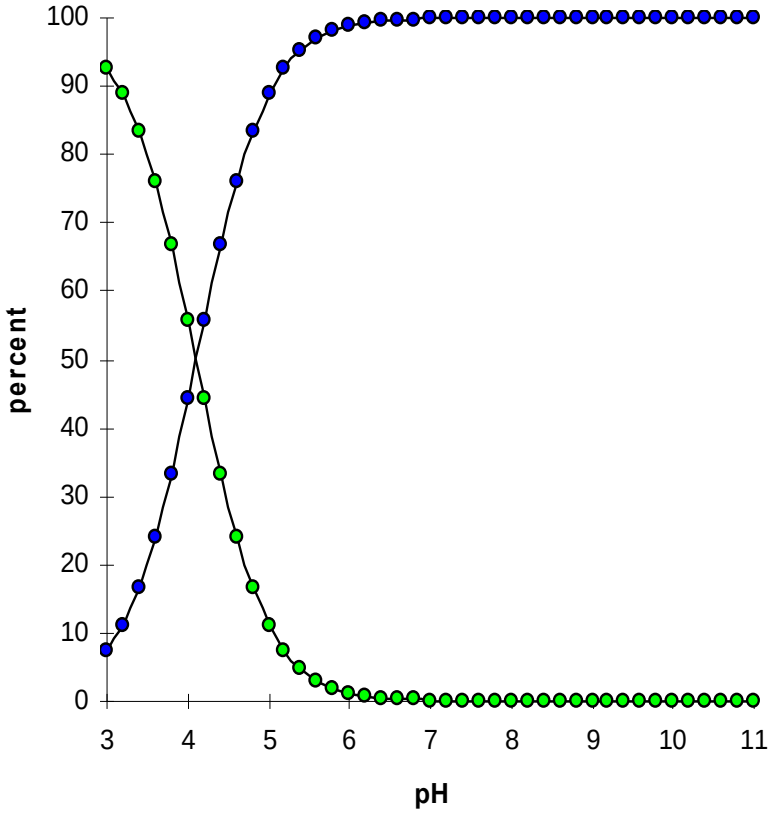
1000/1=B/A

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.

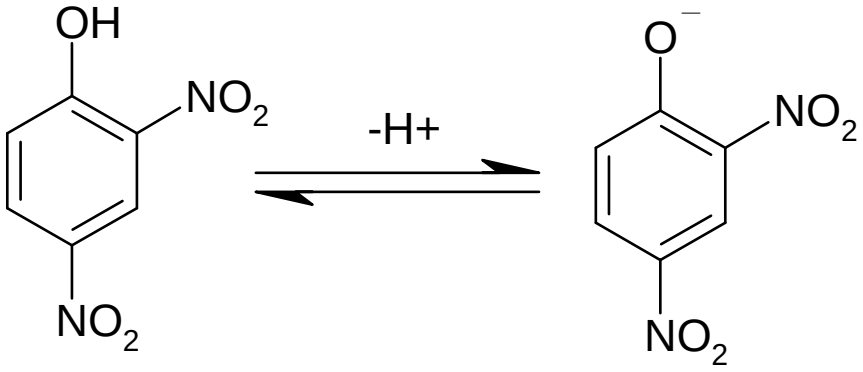
$B = A^-$

$A = HA$

Ionisation of an acid – 2,4-dinitrophenol

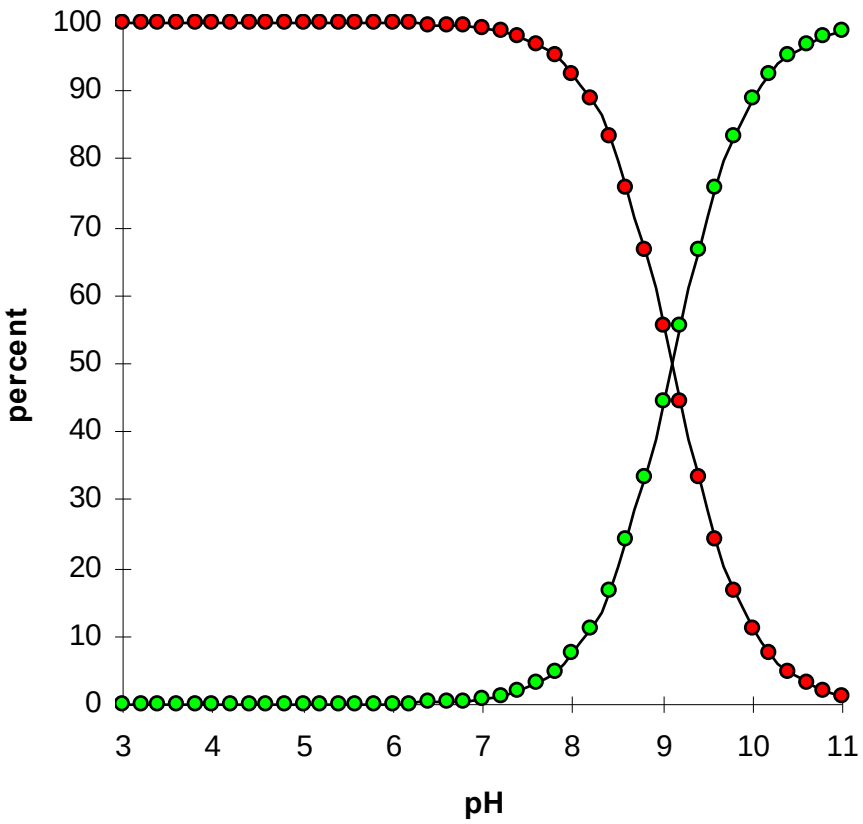


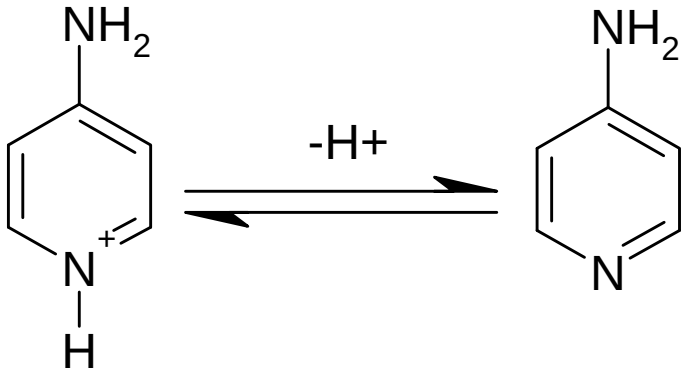
$pK_a = 4.1$



Neutral: unionized
Anion: ionized

Ionisation of an base – 4-aminopyridine





$pK_a = 9.1$

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.

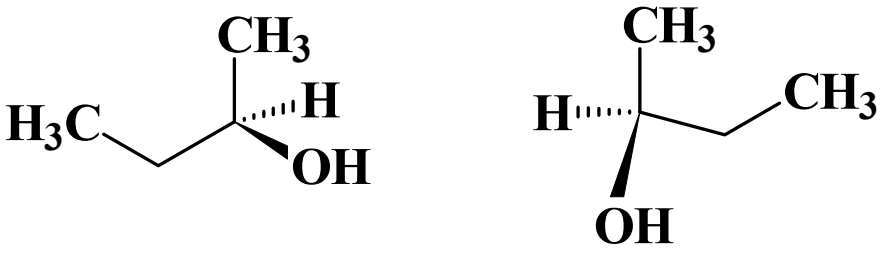
Stereochemistry plays a major role in the pharmacological properties because:

(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.

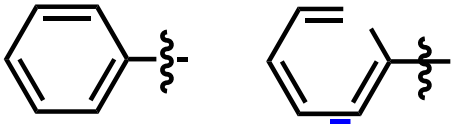
Parameters affected with bioisosteric replacements

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



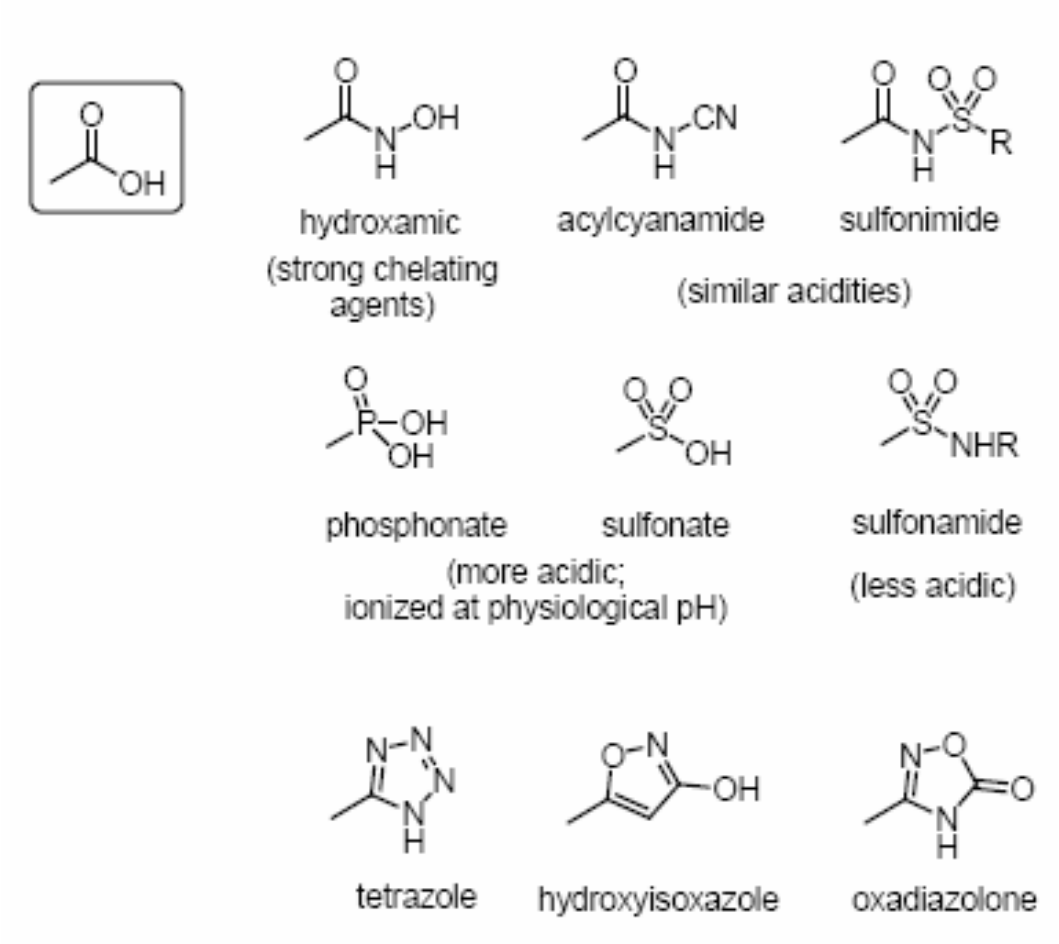
1) Monovalent a

- ✓ Halogen to CN or CF_3 replacements
- ✓ $COCH_2$-R (ketone), -COOR (ester)
- ✓ CONHR (amide) for the carbonyl containing compounds

D and H

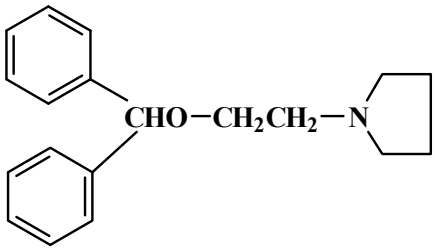
F and H

Bioisosterism - Carboxylic acid replacements

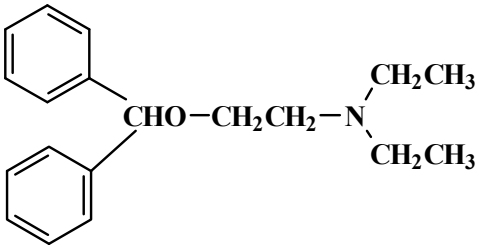


Bioisosterism and pharmacological activity

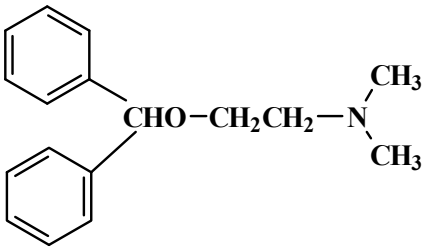
E.g. (Antihistamine; A; B and C)



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

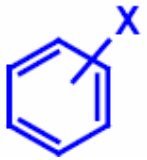
QSAR can be used:

- 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, π, f, R_M, χ
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



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