MEDICINAL CHEMISTRY I

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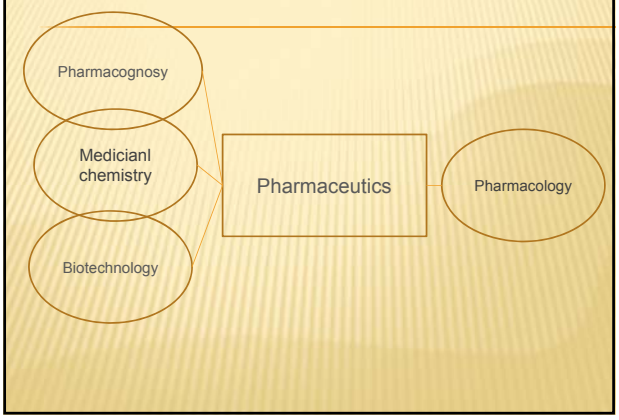
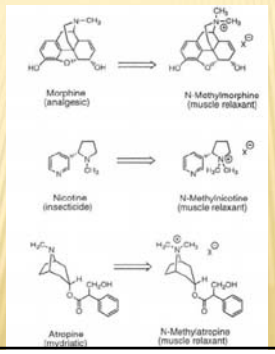
MEDICINAL CHEMISTRY

- **Medicinal chemistry** and **pharmaceutical chemistry** are disciplines at the intersection of chemistry, especially synthetic organic chemistry, and pharmacology and various other biological specialties, where it is involved with design, chemical synthesis and development for market of pharmaceutical agents (drugs).

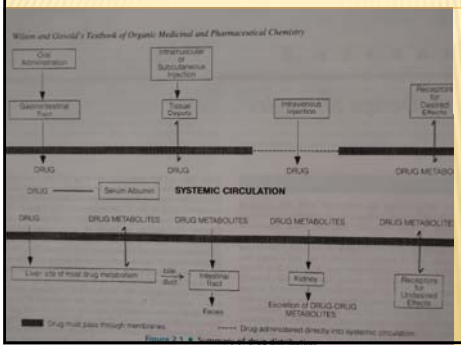
(From Wikipeida)



- Medicinal chemistry : **Relationship Between Molecular Structure and Biologic Activity**
- Crum Brown Fraser (1869)



D + R ⟺ D-R : Pharmacodynamic

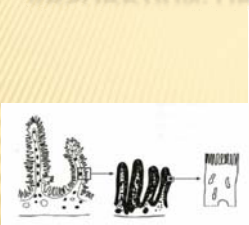


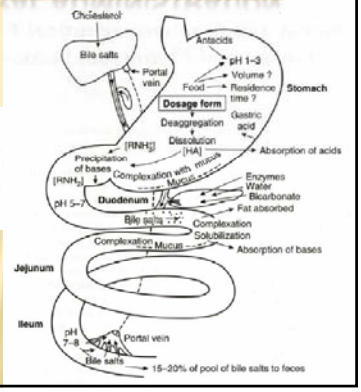
: Pharmacokinetic

PHYSICOCHEMICAL PROPERTIES

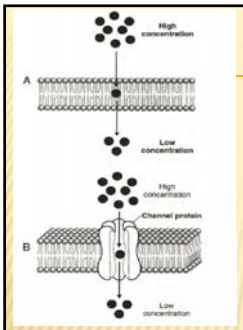
- **physicochemical properties**: influence of the organic functional groups on acid/base properties, water solubility, partition coefficient, crystal structure, stereochemistry
- All of these properties influence the absorption, distribution, metabolism and excretion (ADME)of the molecule

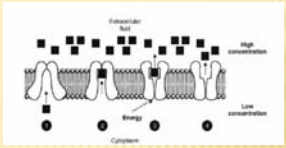
ABSORPTION: ORAL ADMINISTRATION





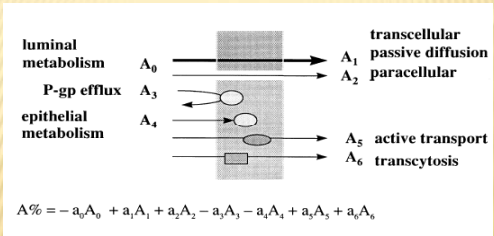
Mechanism of drug absorption



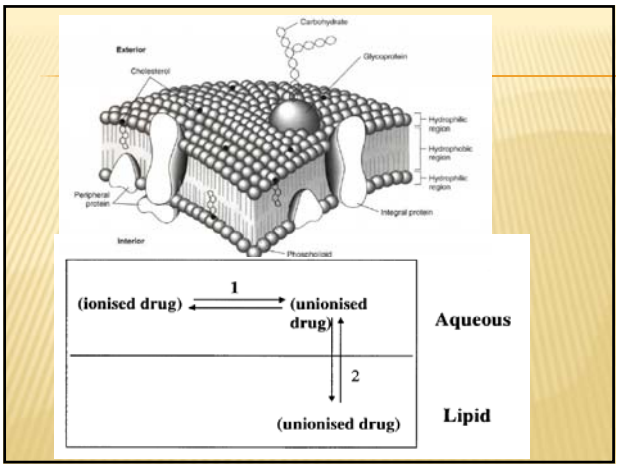


1- Passive diffusion
2- Active transport
3- Convective absorption
4- Ion pair absorption

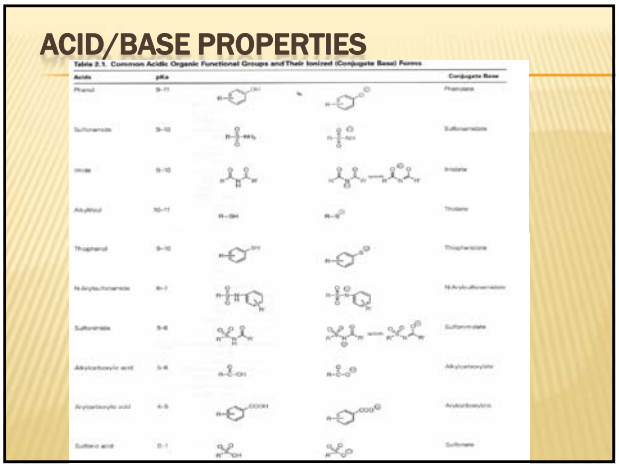
Transcellular vs Paracellular



$$A\% = -a_0A_0 + a_1A_1 + a_2A_2 - a_3A_3 - a_4A_4 + a_5A_5 + a_6A_6$$



ACID/BASE PROPERTIES



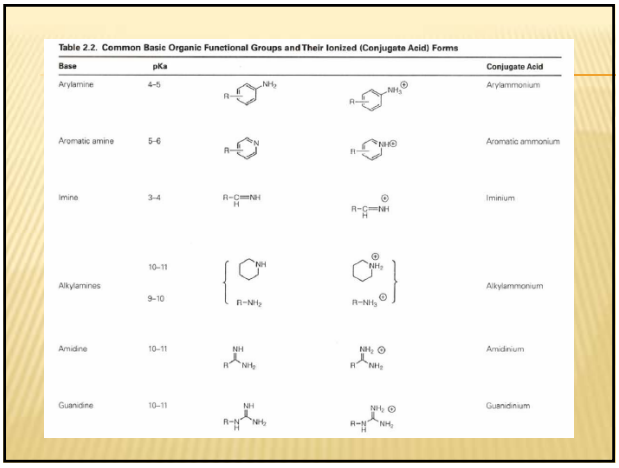
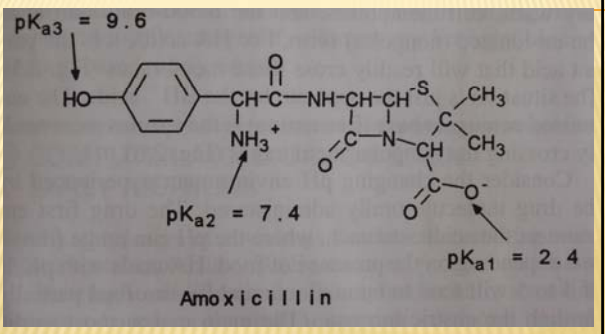
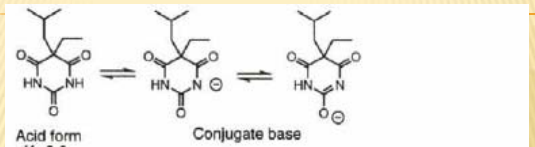


Table 2.3. Common Organic Functional Groups That Are Considered Neutral Under Physiologic Conditions

R–CH_2–OH Alkyl alcohol	 Ether	 Ester	 Sulfonic acid ester
 Amide	 Diarylamine	R–C≡N Nitrile	 Quaternary ammonium
 Amine oxide	 Ketone & Aldehyde	 Thioether	 Sulfoxide  Sulfone



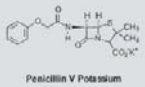


Question: At a pH of 7.4, what is the percent ionization of amobarbital?

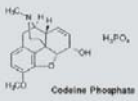
$$pK_a = pH + \log \frac{[\text{acid form}]}{[\text{base form}]}$$

Acid Base Chemistry/Compatibility Cases

The IV technician in the hospital pharmacy gets an order for a patient that includes the two drugs drawn below. She is unsure if she can mix the two drugs together in the same IV bag and isn't sure how water-soluble either of the agents are.



Penicillin V Potassium



Codeine Phosphate

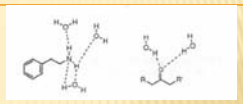
PH AT THE ABSORPTION SITE

Table 7.2. Comparison of Intestinal Absorption of Acids and Bases in the Rat at Several pH Values (13)

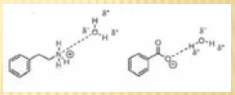
		Percent Absorbed from Rat Intestine			
	pK_a	pH 4	pH 5	pH 7	pH 8
Acids					
5-Nitrosalicyclic acid	2.3	40	27	0	0
Salicylic acid	3.0	64	35	30	10
Acetylsalicylic acid	3.5	41	27	—	—
Benzoic acid	4.2	62	36	35	5
Bases					
Aniline	4.6	40	48	58	61
Amiopyrine	5.0	21	35	48	52
p-Toluidine	5.3	30	42	65	64
Quinine	8.4	9	11	41	54

WATER SOLUBULITY

- Hydrogen bonds

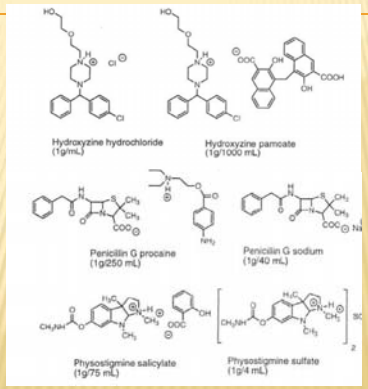


- Ionization

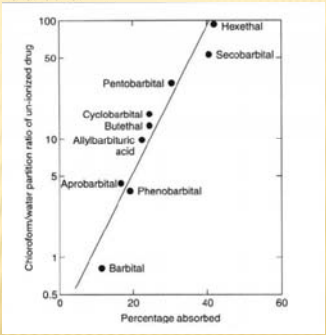


Dissolution ↓ Absorption ↓

Dosage forms → Drug in solution → Drug in general cyclization



LIPID SOULUBILTY



PARTITION COEFFICENT

$$P = \frac{[\text{drug}]\text{organic}}{[\text{drug}]\text{aqueous}}$$

1-octanol: common organic phase

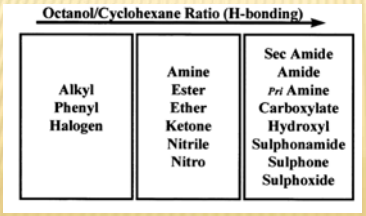
$$D = [HA]_{organic}/([HA]_{aqueous} + [A^-]_{aqueous})$$

$$K_a = [H^+][A^-]/[HA] \longrightarrow \log D = \log P - \log(1 + 10^{pH - pK_a})$$

Limitations in the Use of 1-Octanol

- Octanol, contains 4% v/v water at equilibrium.
-Hydrogen bonding due to hydroxyl group

-$\Delta \log P = \log P_{(octanol)} - \log P_{(cyclohexane)}$



TRANSPORTATION RATE OF BASIC DRUGS ACROSS CACO-2 MONOLAYERS

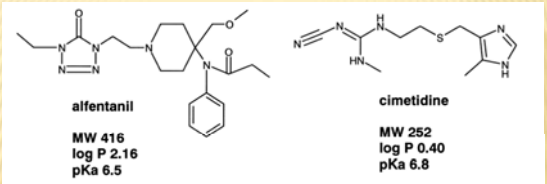
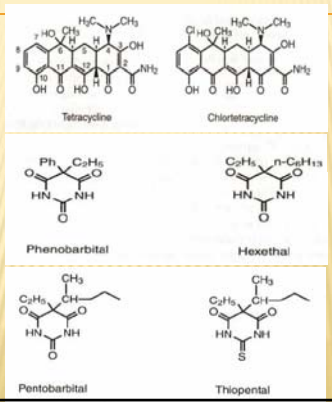


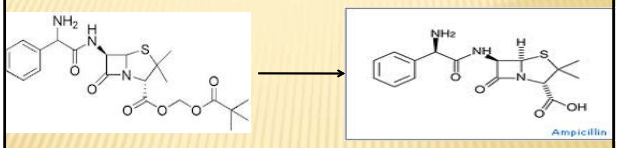
Table 7.3. Comparison of Barbiturate Absorption in Rat Colon and Partition Coefficient (Chloroform/Water) of Undissociated Drug

Barbiturate	Partition Coefficient	Percent Absorbed
Barbital	0.7	12
Apobarbital	4.9	17
Phenobarbital	4.8	20
Allylbarbital	10.5	23
Butethal	11.7	24
Cyclobarbital	13.9	24
Pentobarbital	28.0	30
Secobarbital	50.7	40
Hexethal	>100	44

Modification to improve absorption



PRODRUGS: TO IMPROVE ABSORPTION

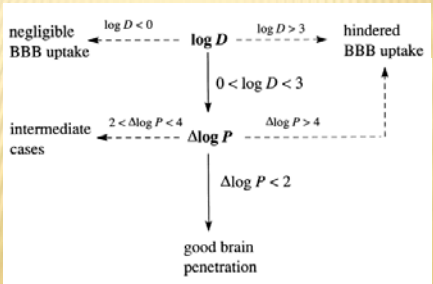


Pivampicillin

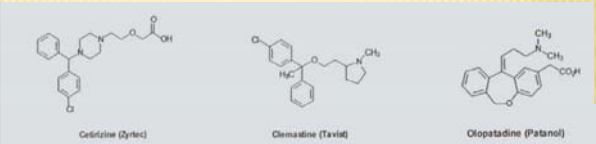
Ampicillin

PERMEABILITY TO BBB

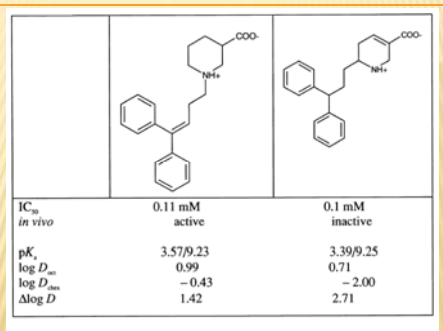
Decision tree for the design of non-sedative H1antihistaminics. Log *D is* measured at pH 7.4



Penetration to BBB



Antiepileptic agents



IC_{50} *in vivo*	0.11 mM active	0.1 mM inactive
pK_a	3.57/9.23	3.39/9.25
$\log D_{ox}$	0.99	0.71
$\log D_{neu}$	−0.43	−2.00
$\Delta \log D$	1.42	2.71

COMPUTAION OF LOGP

$$\text{LogP} = \Sigma\pi \text{ (fragments)}$$

EXPERIMENTAL CALCULATION OF LOGP

-Liquid-liquid partitioning
-RP-HPLC

PARAMETERS AFFECTING LOGP OR LOGD

log *P or log D = a · V – Λ*

- *V :molar volume of the compound*
- *Λ: general polarity descriptor*
- *a: regression coefficient*

BALANCE FOR HYDROPHILYCITY LIPOPHILICITY

Lipinski rule of five:

- Mw < 500
- Log P < 5
- HB donors < 5
- HB acceptors <10

End of session I : Any questions?