Medicinal Chemistry/ CHEM 458/658

Chapter 2- Drug Structure and Solubility

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Structure

- Overall chemical structure

  - possible binding groups

  - size

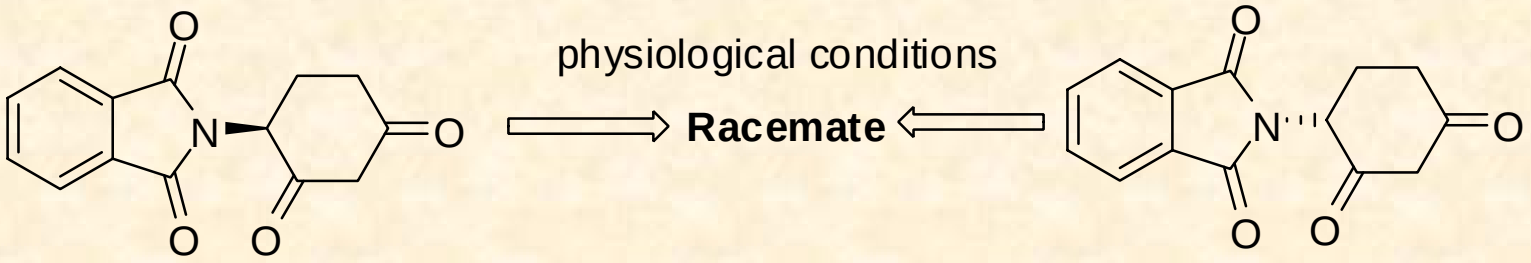
  - shape

  - stereochemical features (flexibility, conformation, configuration)

  - electronic features

Stereochemistry and Drug Design

- The Thalidomide Failure

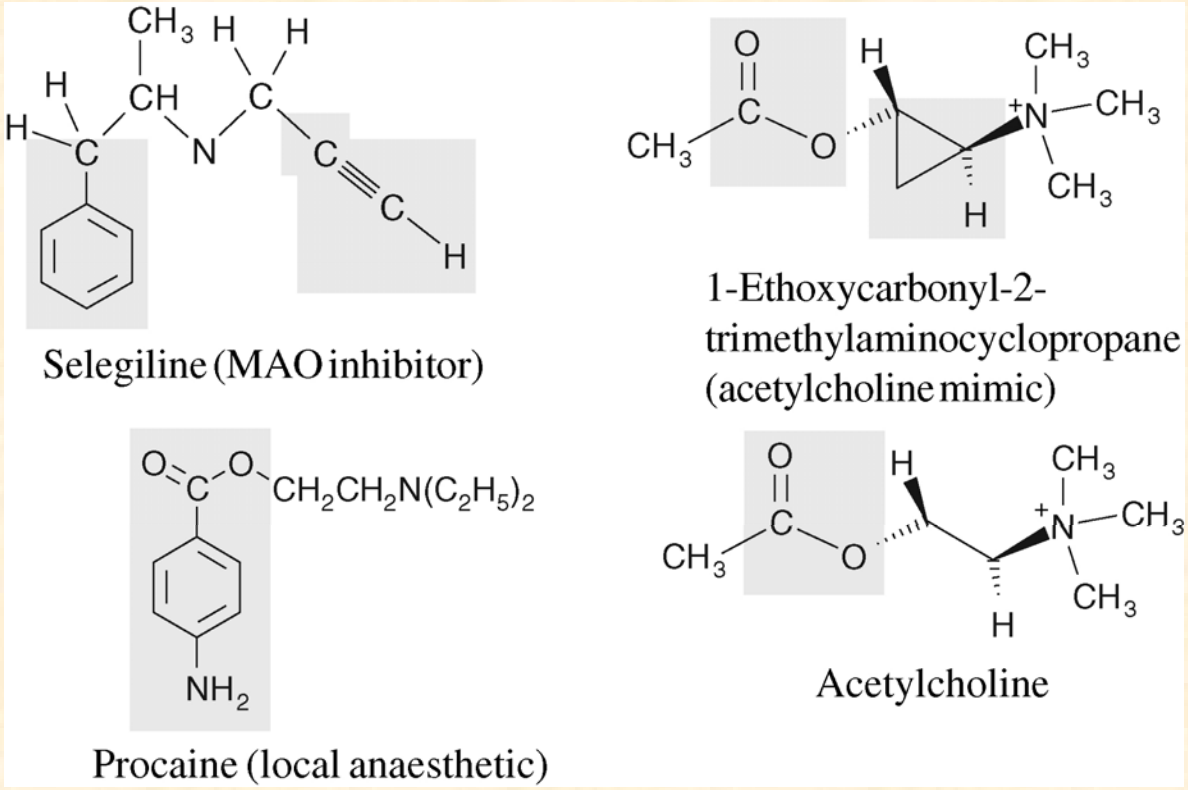


(*S*)-Thalidomide
(sedative + teratogenic)

(*R*)-Thalidomide
(sedative)

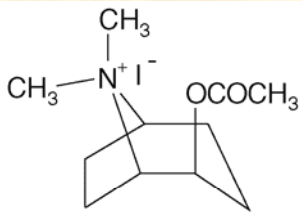
Stereochemistry and Drug Design

- Structurally Rigid Groups

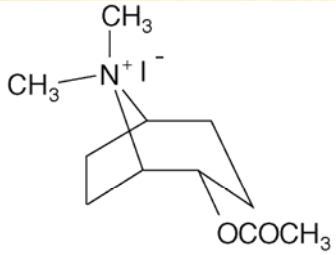


Stereochemistry and Drug Design

- Conformation



2β-Tropanyl ethanoate methiodide



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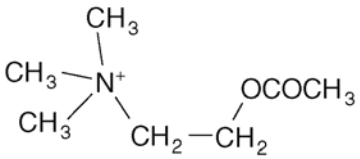
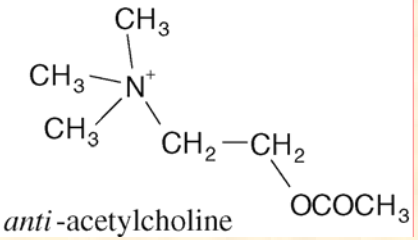
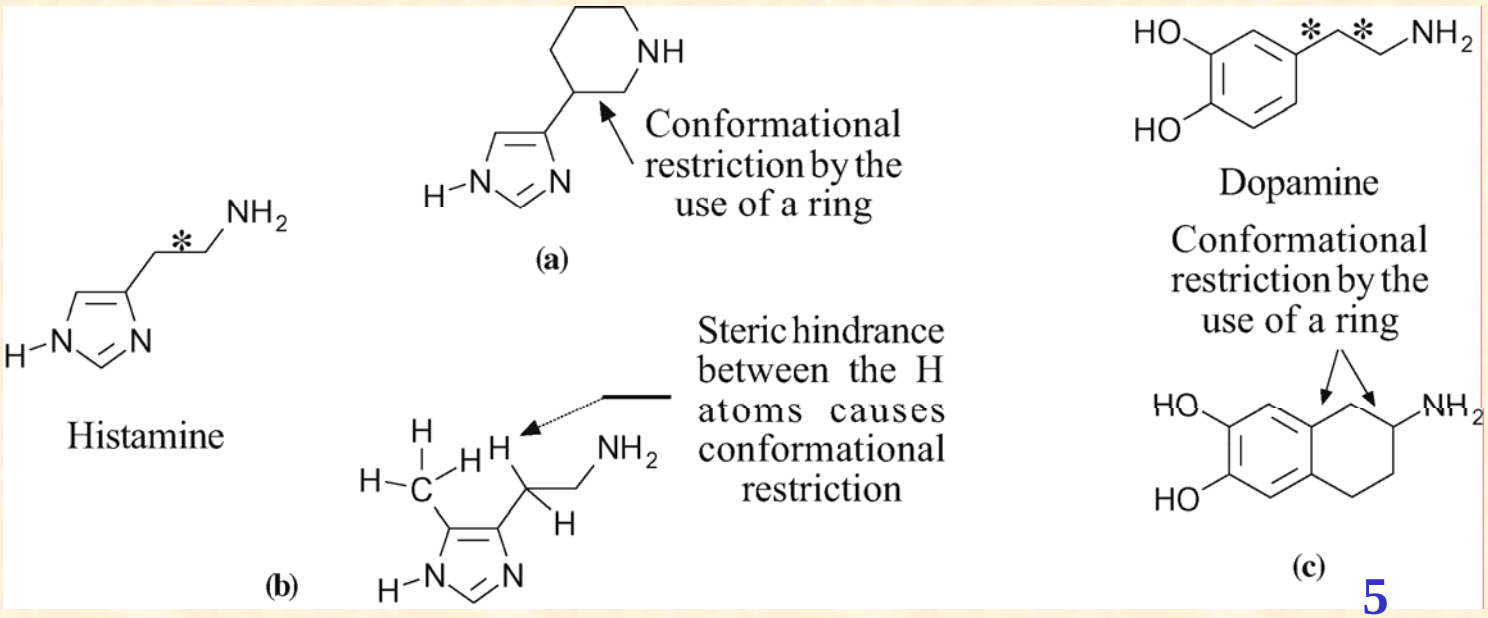


syn-acetylcholine

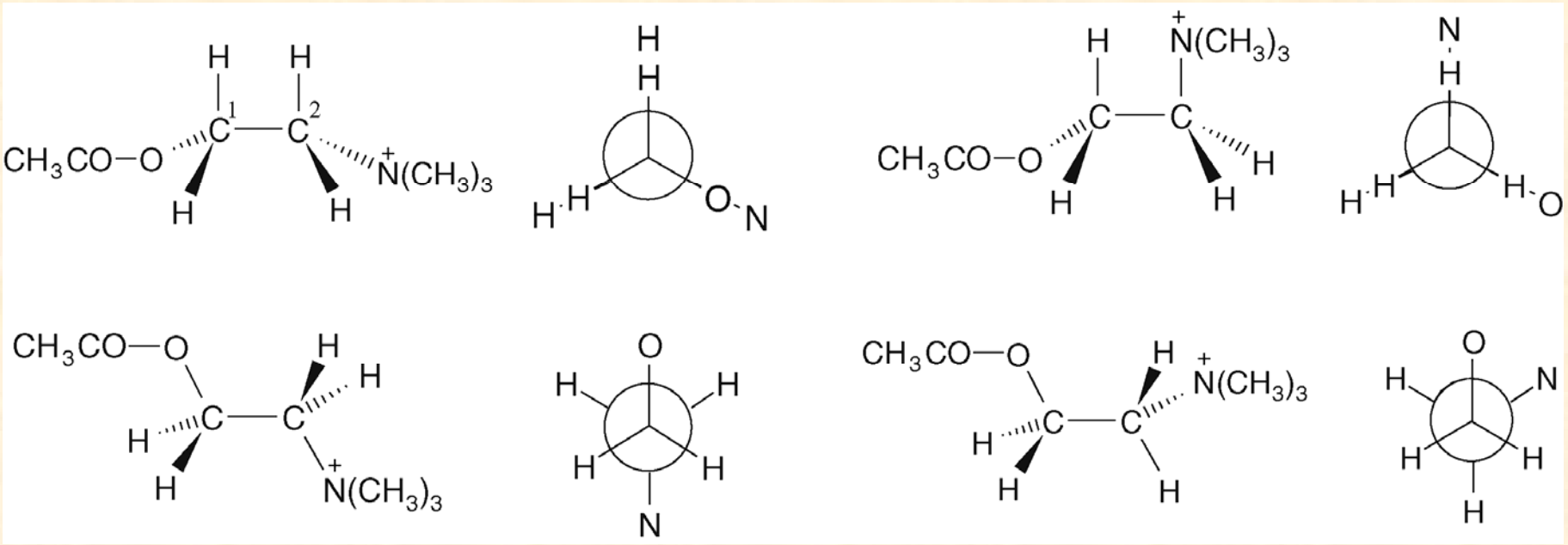


anti-acetylcholine



Stereochemistry and Drug Design

- Conformation



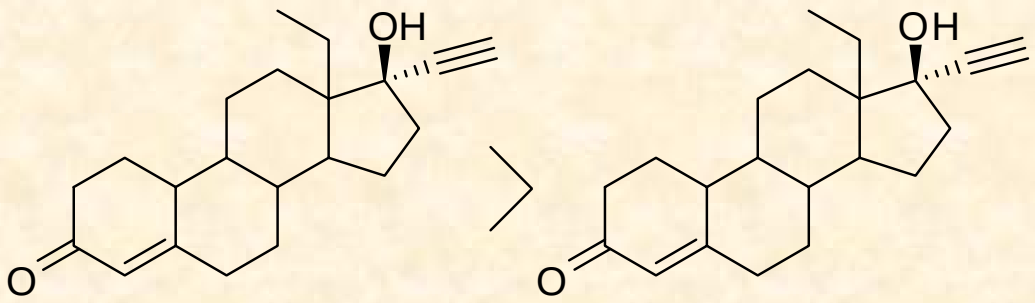
Stereochemistry and Drug Design

- Configuration

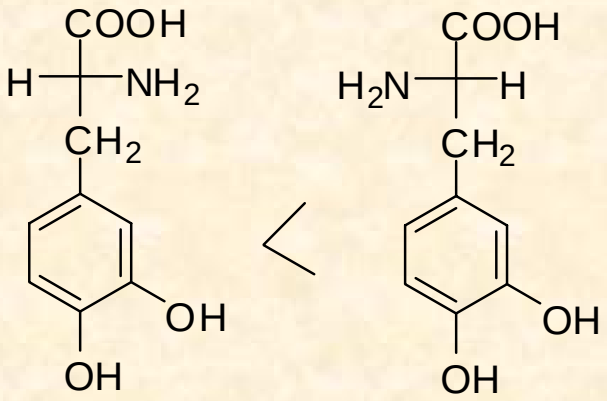
  - almost identical activities, but significantly different potencies
  - completely different activities (one maybe only inactive)
  - the behavior of enantiomers will be different to that of the racemate

Effect on ADME properties

Absorption



(-)-Norgestrel (+)-Norgestrel



D-Dopa L-Dopa

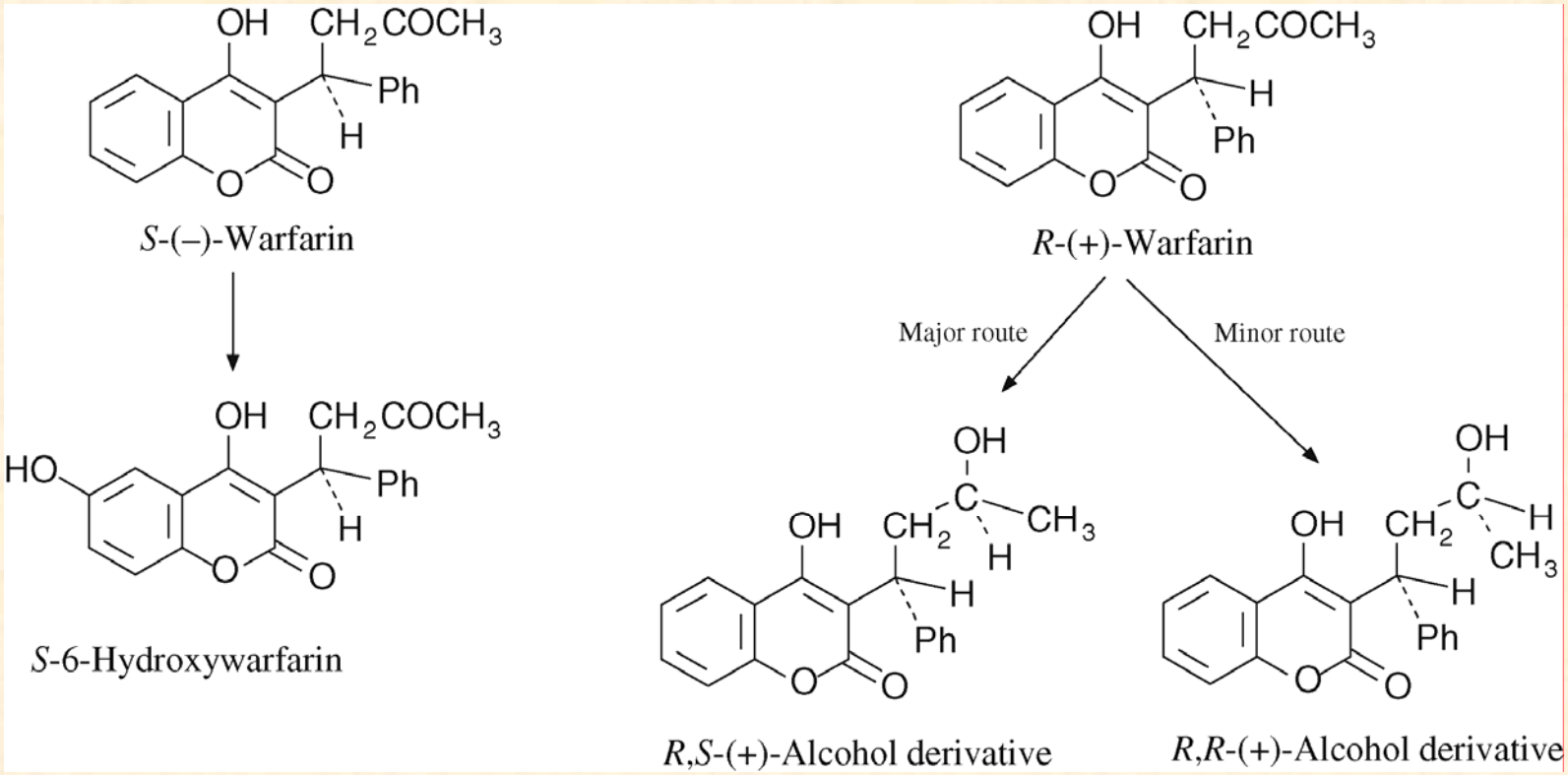
Stereochemistry and Drug Design

- Configuration

  Effect on ADME properties

  Distribution ⟹ little influence

  Metabolism



Excretion ⟹ little influence

Solubility

- Physical Nature of the Solute

Solubility product (C_xA_y)

$$K_{sp} = [C^+]^x [A^-]^y$$

Henry's Law

$$C_g = K_g P_g$$

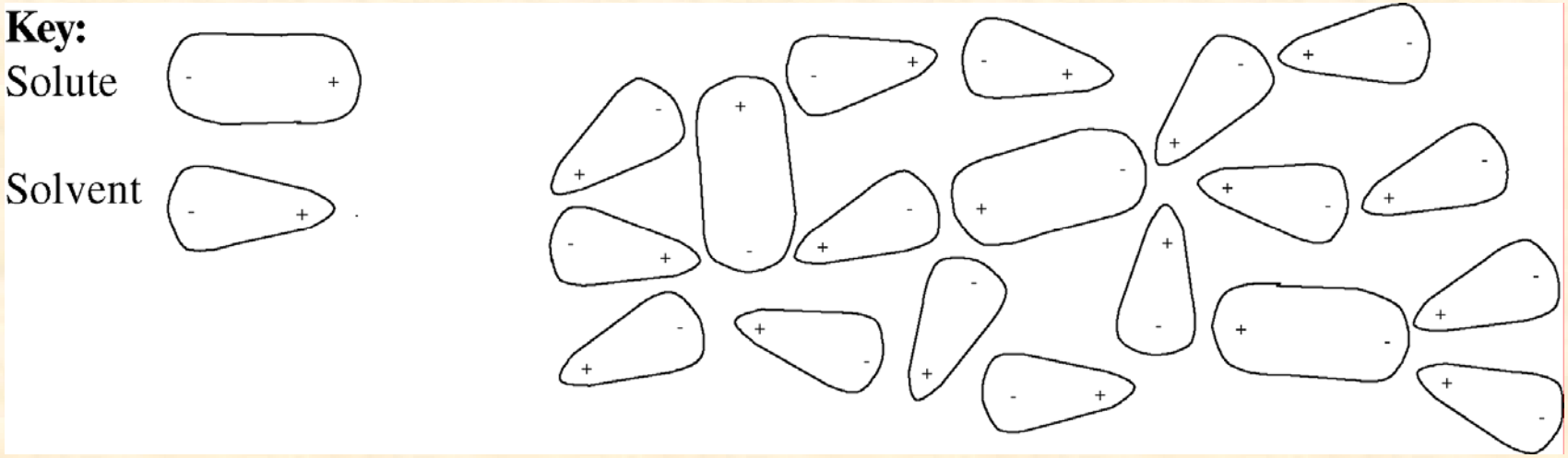
Solutions

- Solubility

  Solvation - lipophilic vs. hydrophilic character of the solute

  ⇩

  polar – hydrophilic; non-polar – lipophilic *like dissolves like*



- Importance of Water Solubility

  cells (65% water!), gastric fluid

Solubility and Structure of the Solute

- Role of polar and non-polar groups

water solubility

lipid solubility

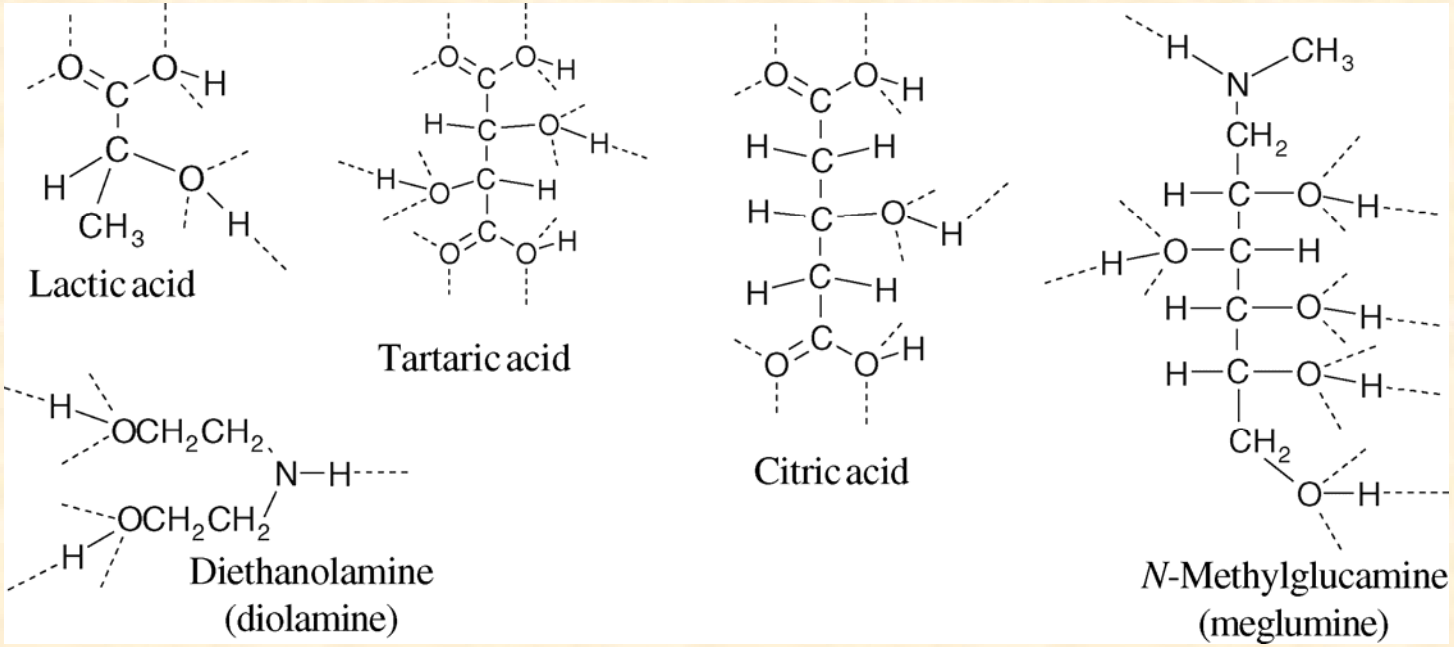
salt formation
incorporation of water solubilizing groups
special dosage forms

Salt Formation

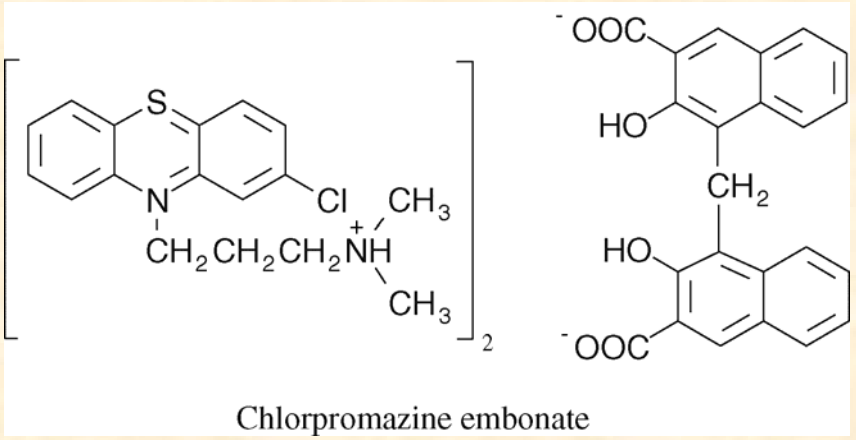
Most common sources:

Anions: $(H)Cl^-$, $(H_2)SO_4^{2-}$, HSO_4^-

Cations: Na^+, Ca^{2+}, Zn^{2+}, diethanolamine, N-methylglucamine



water solubility taste



Incorporation of Water Solubilizing Groups

- The type of group
  polar groups: alcohol, amine, amide, acid, sulfonic acid, etc.

- Reversible and irreversible groups
  irreversible: C-C, C-N, C-O
  reversible: ester, amide phosphate, sulfate, glycosidic links

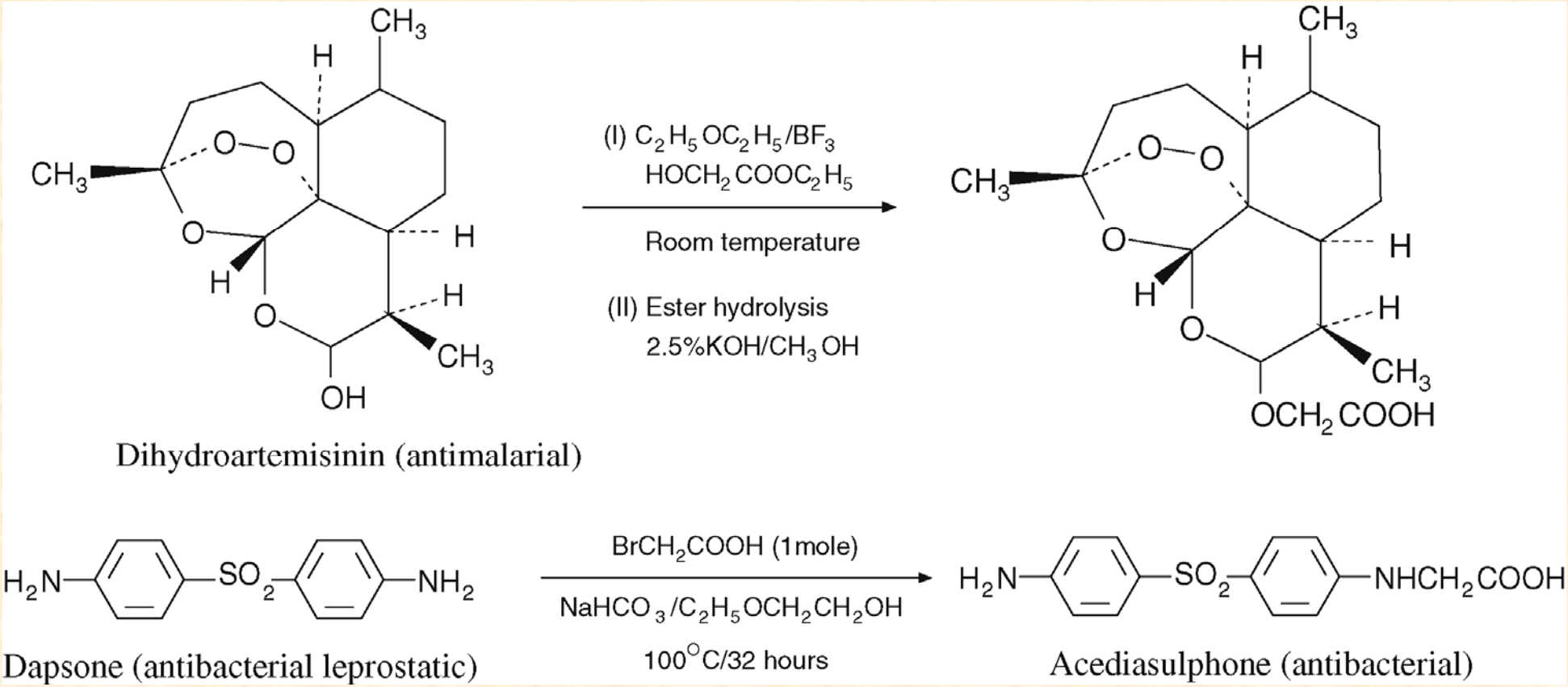
- The position of the water solubilizing group
  depends on the reactivity and the position of the pharmacophore (e.g. aromatic groups, or aldehyde etc.)

  We should avoid modifying the part that is responsible for the drug-receptor interaction.

Incorporation of Water Solubilizing Groups

- Methods of introduction

  Carboxylic acid by alkylation



Incorporation of Water Solubilizing Groups

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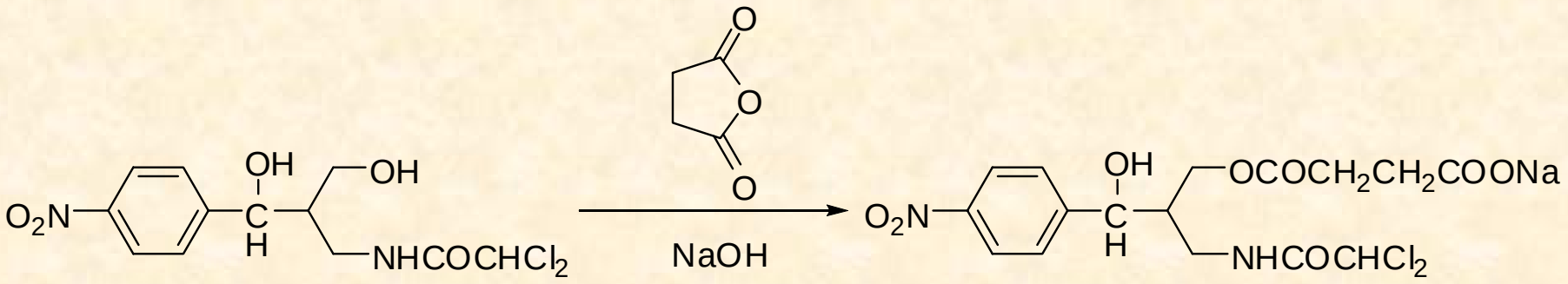
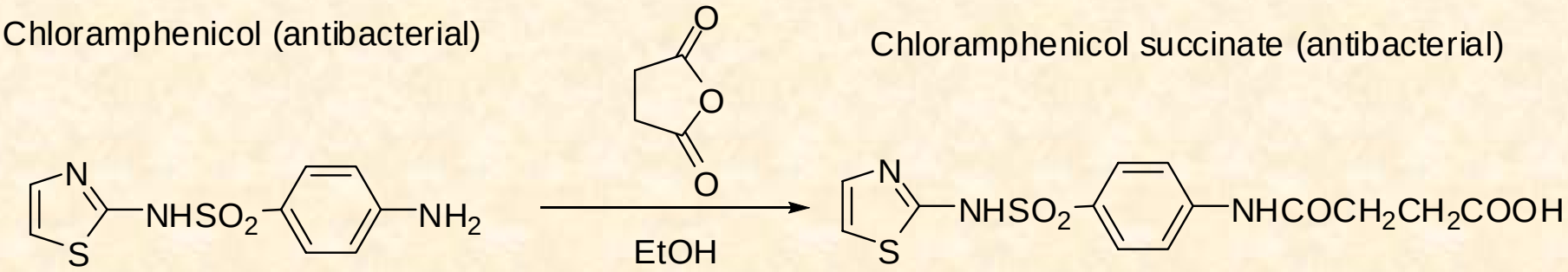


Chloramphenicol (antibacterial)

Chloramphenicol succinate (antibacterial)

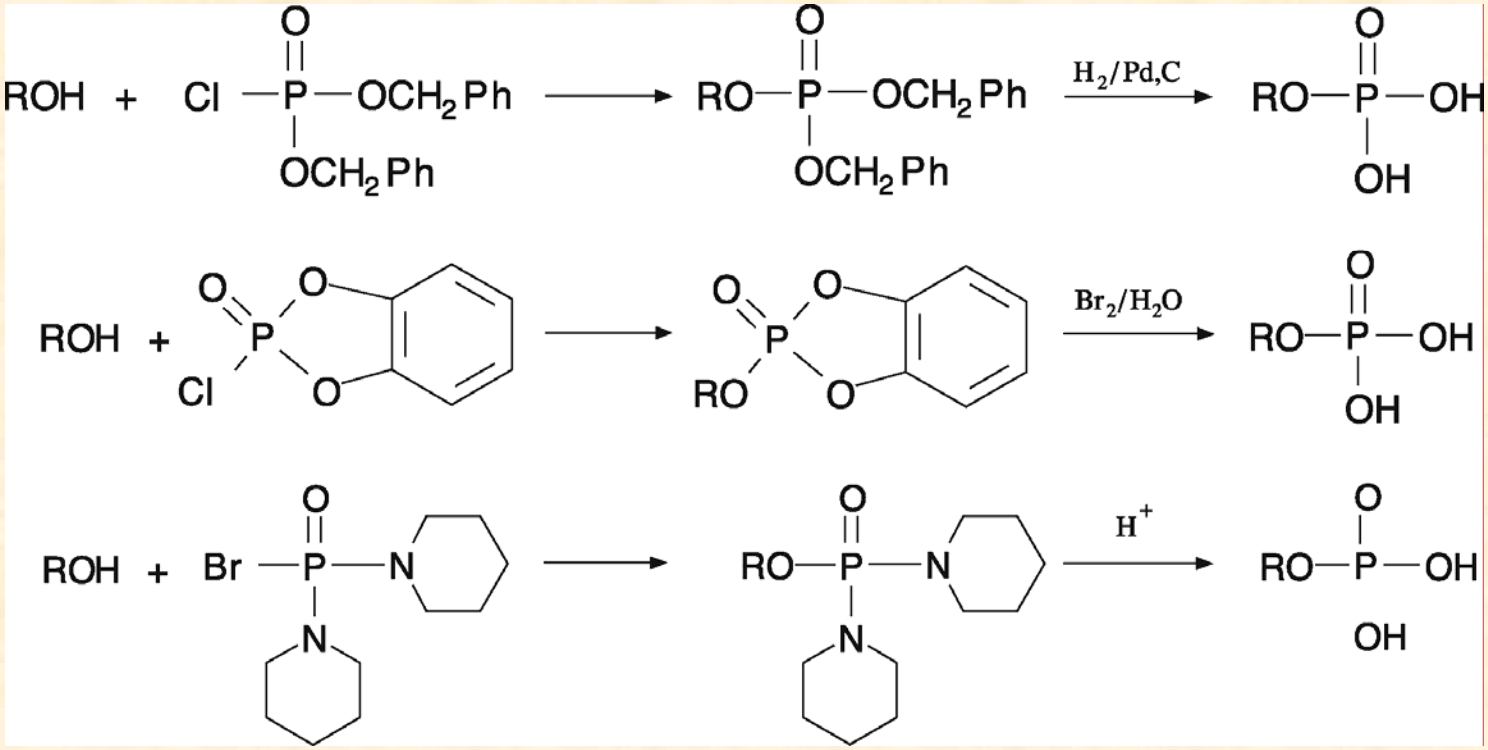


Sulfathiazole (antibacterial)

Succinyl Sulfathiazole (antibacterial)

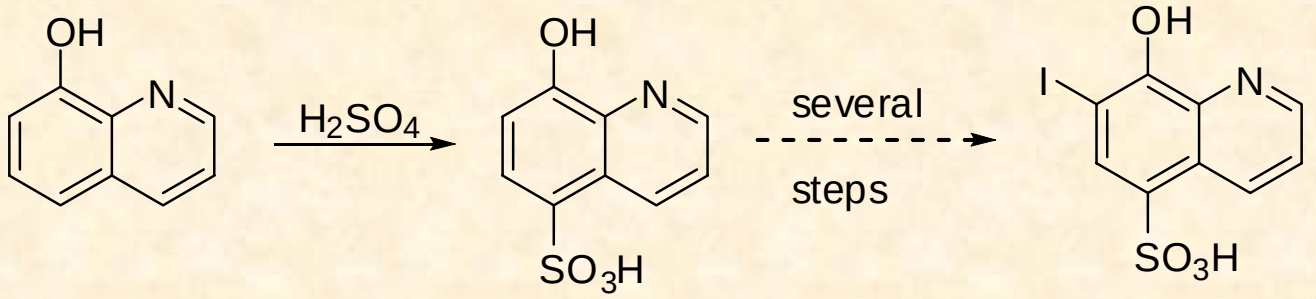
Incorporation of Water Solubilizing Groups

- Methods of introduction
  Phosphate groups



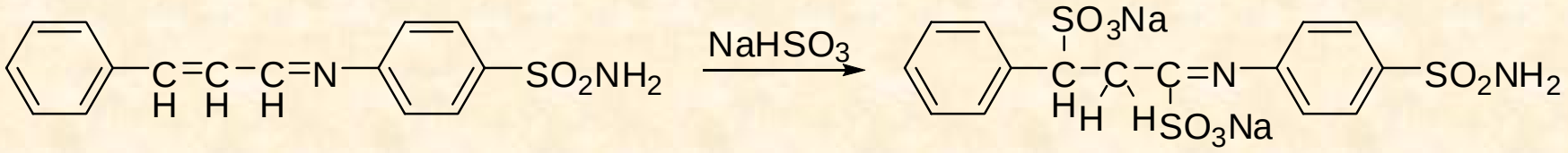
Incorporation of Water Solubilizing Groups

- Methods of introduction
  Sulfate groups



8-hydroxyquinoline

8-hydroxy-7-iodo-5-quinolinesulfonic acid
(topical antiseptic)



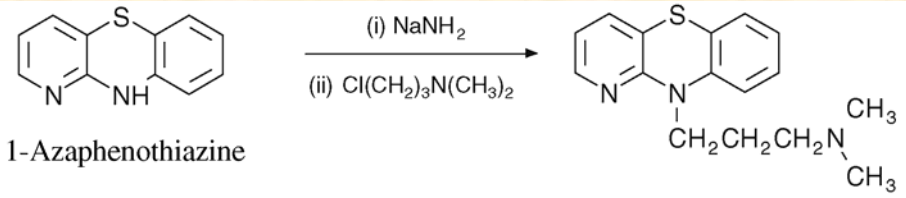
N^4-cinnamylidenesulfanilamide

noprylsulfamide (antibacterial)

Incorporation of Basic Groups

- Methods of introduction

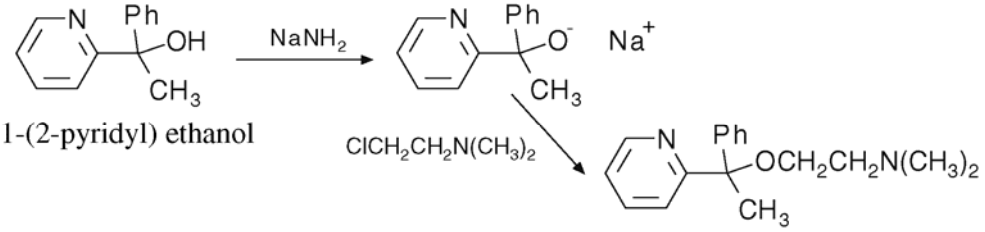
N-Alkylation



1-Azaphenothiazine

Prothipendyl (neuroleptic and psychosedative)

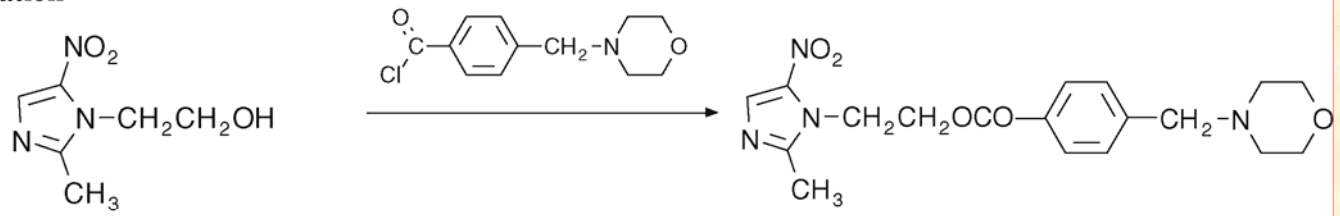
O-Alkylation



1-Phenyl-1-(2-pyridyl) ethanol

Doxylamine (antihistimimic, hypnotic)

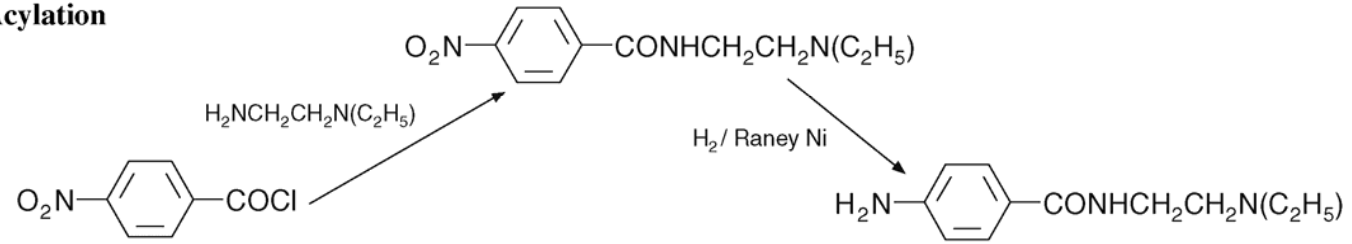
O-Acylation



Metronidazole (antiprotozoal)

Metronidazole 4-(morpholinylmethyl)benzoate (antiprotozoal)

N-Acylation

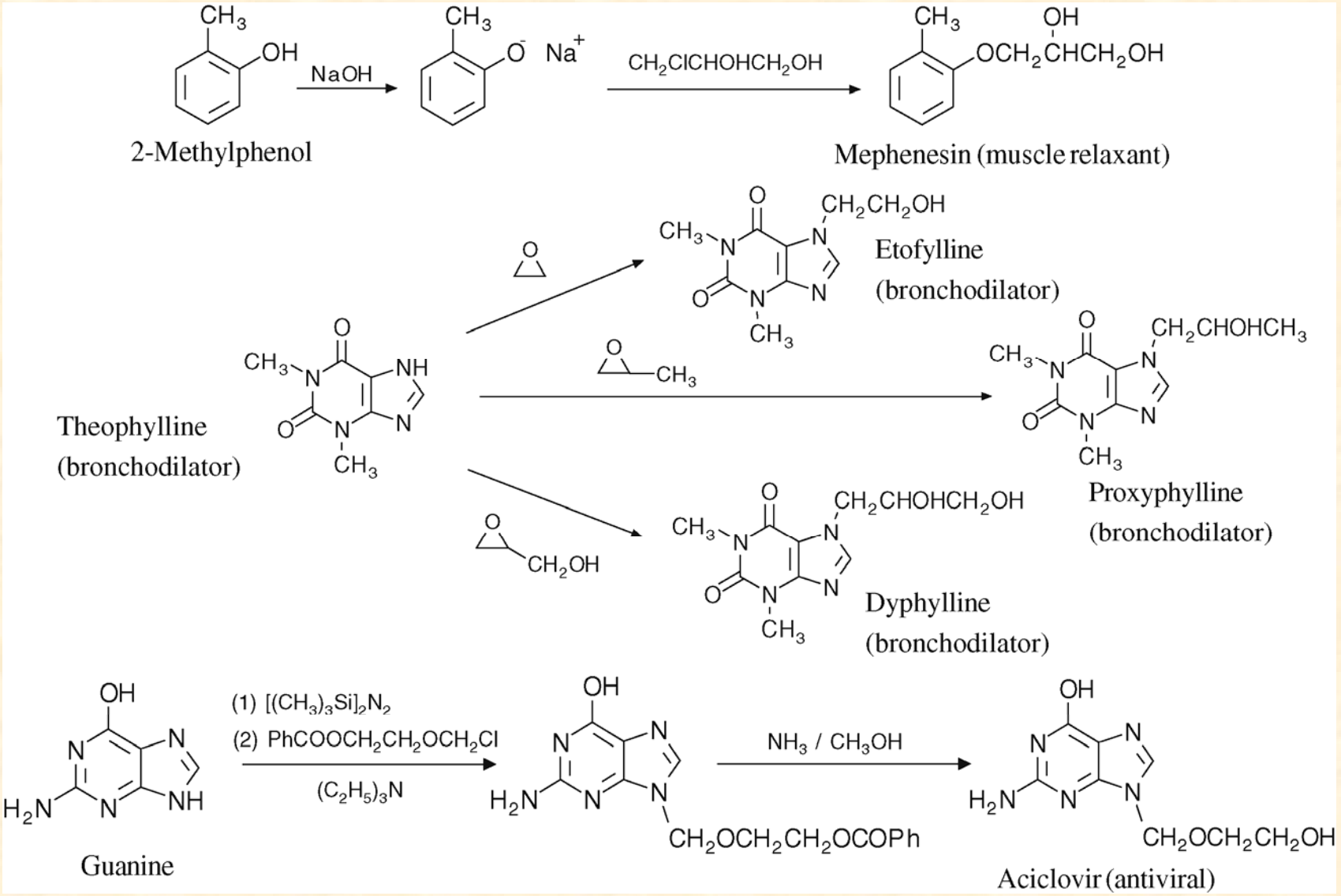


4-Nitrobenzoyl chloride

Procainamide (local anaesthetic)

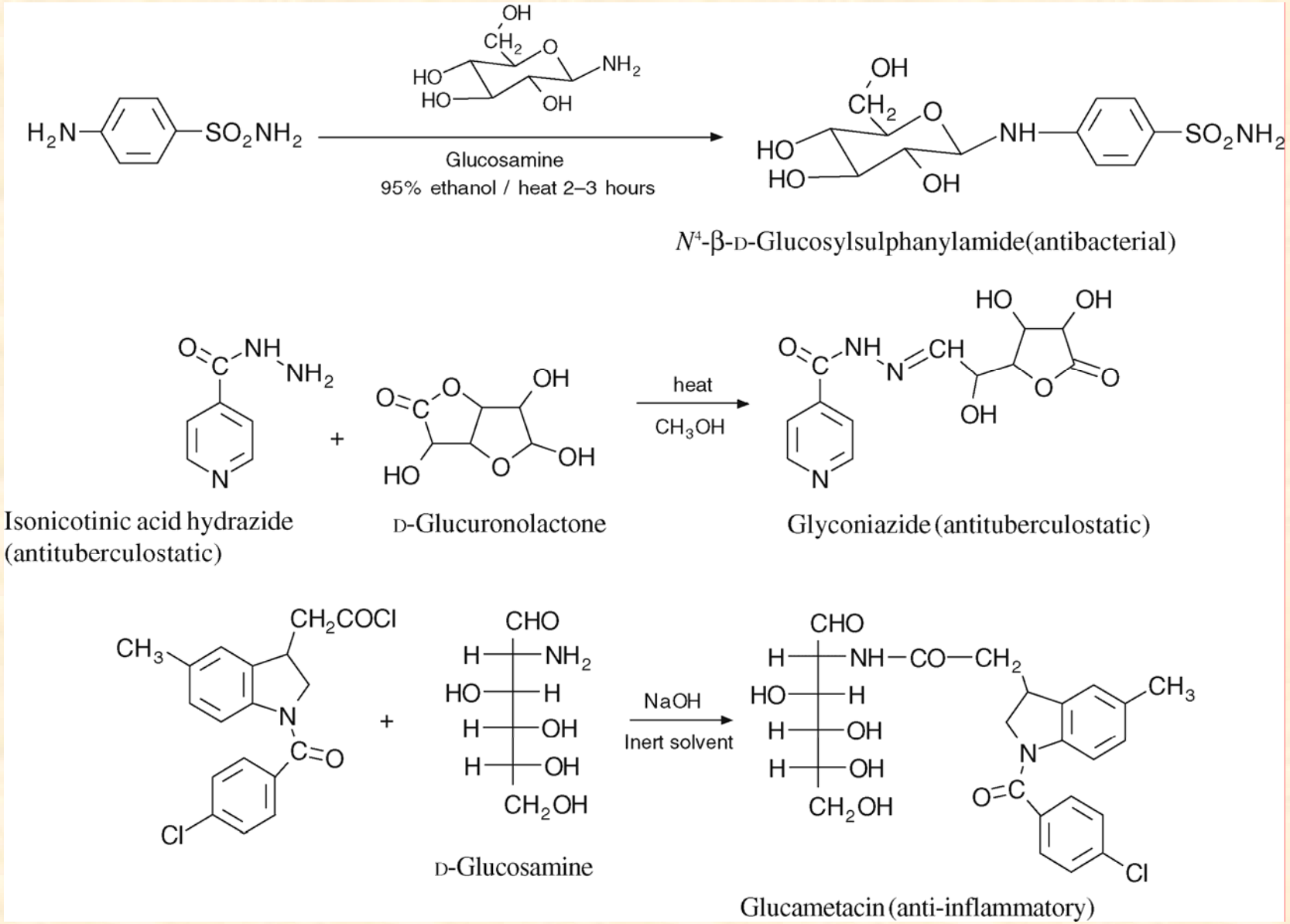
Polyhydroxy and Ether Residues

- Methods of introduction



Polyhydroxy and Ether Residues

- Methods of introduction



Improving Lipid Solubility

- Introduction of

  - methyl, alkyl;
  - fluoro, trifluoro
  - chloro

  groups

Formulation Methods of Improving Water Solubility

- Cosolvents

  non-toxic, inert (toward the drug), water-soluble

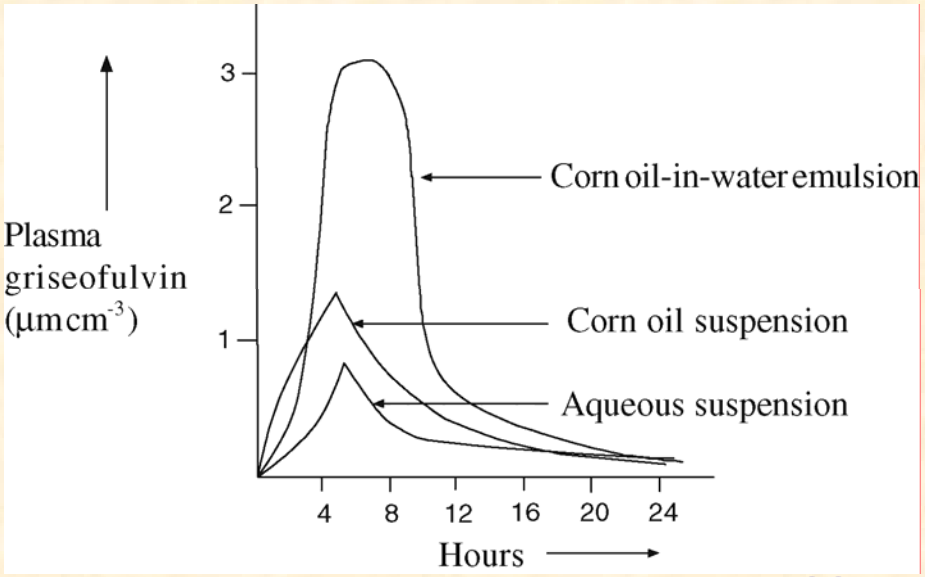
  (ethanol, isopropanol, glycerol, sorbitol, etc.)

- Colloid "Solution" (L/S systems)

  Preparation of colloid particles (1-1000 nm); sols or hydrosols

- Emulsions (L/L systems)

  o/w or w/o emulsions; surfactants



The Effect of pH on the Solubility of Drugs

The pH of the system will either enhance or reduce solubility

- Acidic drugs

$$pK_a = pH + \log \frac{[\text{Non-ionized from}]}{[\text{Ionized form}]}$$

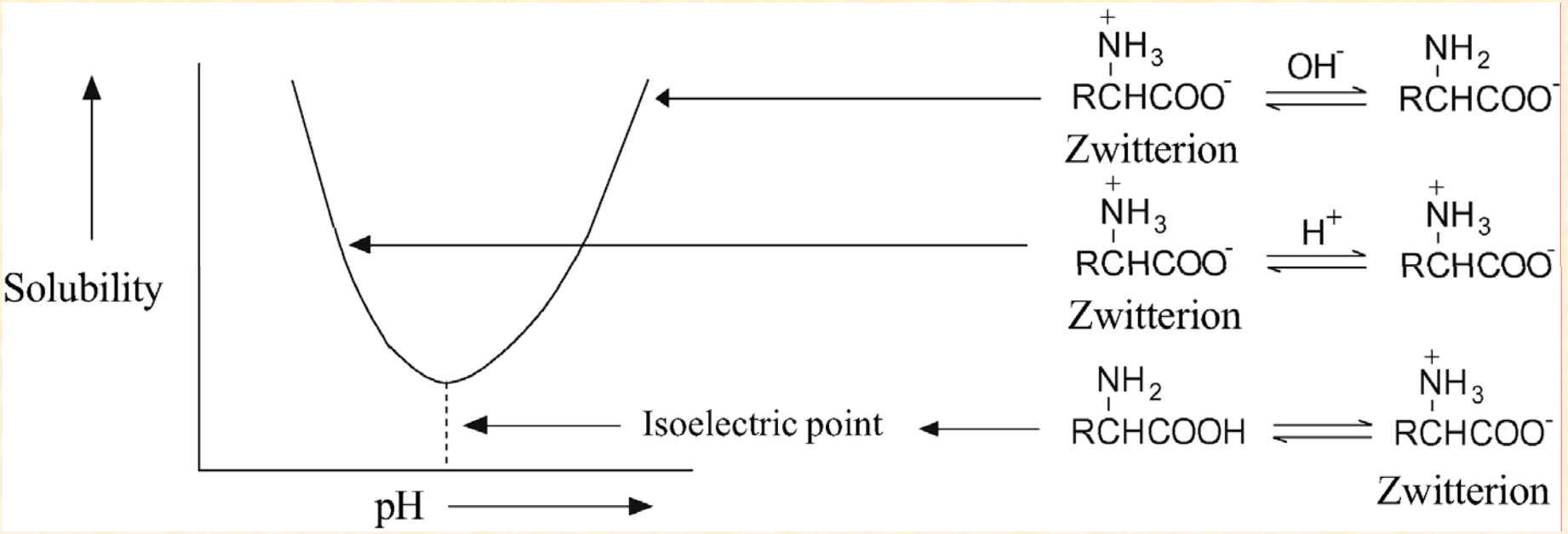
pH is important but not exclusive

- Basic drugs

$$pK_a = pH + \log \frac{[\text{Ionized from}]}{[\text{Non-ionized form}]}$$

The Effect of pH on the Solubility of Drugs

- Dual function molecules – amino acids, peptides



Partition

- Partition coefficient

$$\text{Partition coefficient (P)} = \frac{\text{[Drug in the organic phase]}}{\text{[Drug in an aqueous phase]}}$$

$$\text{Partition coefficient (P)} = \frac{\text{[Non-ionized drug in the organic phase]}}{\text{[Non-ionized drug in an aqueous phase]}}$$

normally: 25 °C or 37 °C
octanol as organic solvent

Practical Determination of P

- Mutual saturation by shaking at constant temperature (traditional)
- HPLC method
- Buffer model (octanol/aqueous)

Theoretical Determination of P

- Producing database by measuring the P of many compounds - statistical analysis

  Rekker and Hansch comtributions from the fragments

- Extrapolation from known $P_{organic/H2O}$ data to other solvents

Surfactants and Amphiphiles

- Amphiphiles – molecules with fragment that likes to dissolve in opposite solvents

- Surfactants – compounds that lower surface tension

Cationic surfactants:

-Sodium stearate ($CH_3(CH_2)_{16}COO^- Na^+$)

Anionic surfactants

- dodecylpyridinium hydrochloride ($C_{12}H_{25}C_5H_5N^+ Cl^-$)
- dodecylamine hydrochloride ($CH_3(CH_2)_{11}NH_3^+ Cl^-$)

Ampholytic surfactants

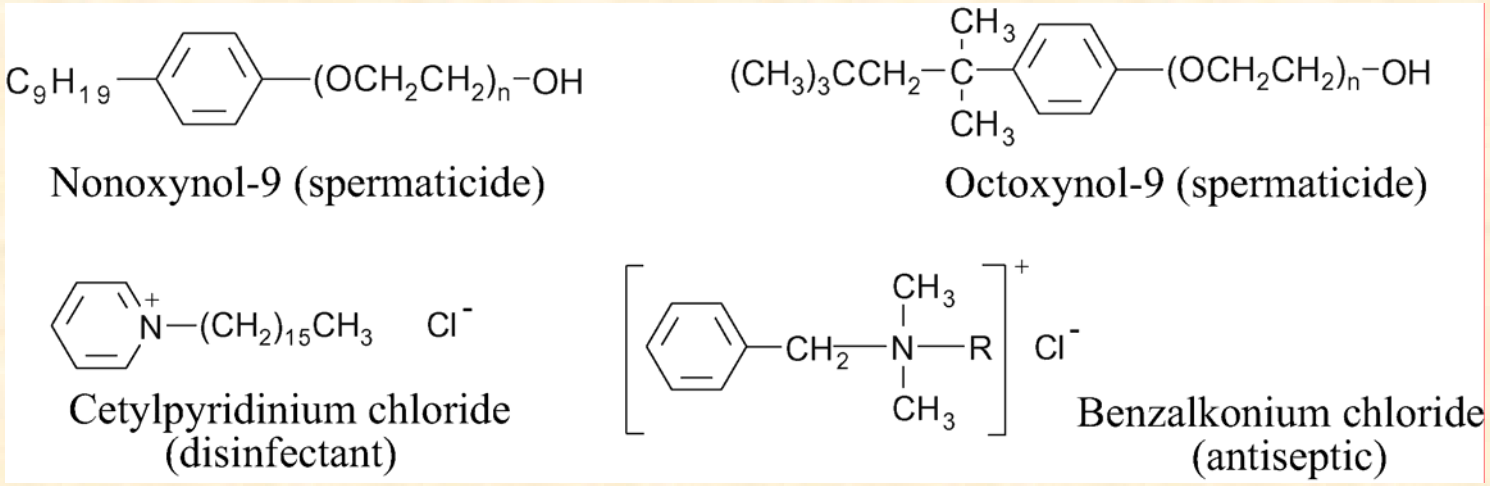
- dodecyl betaine ($C_{12}H_{25}N^+(CH_3)_2CH_2COO^-$)

Non-ionic surfactants

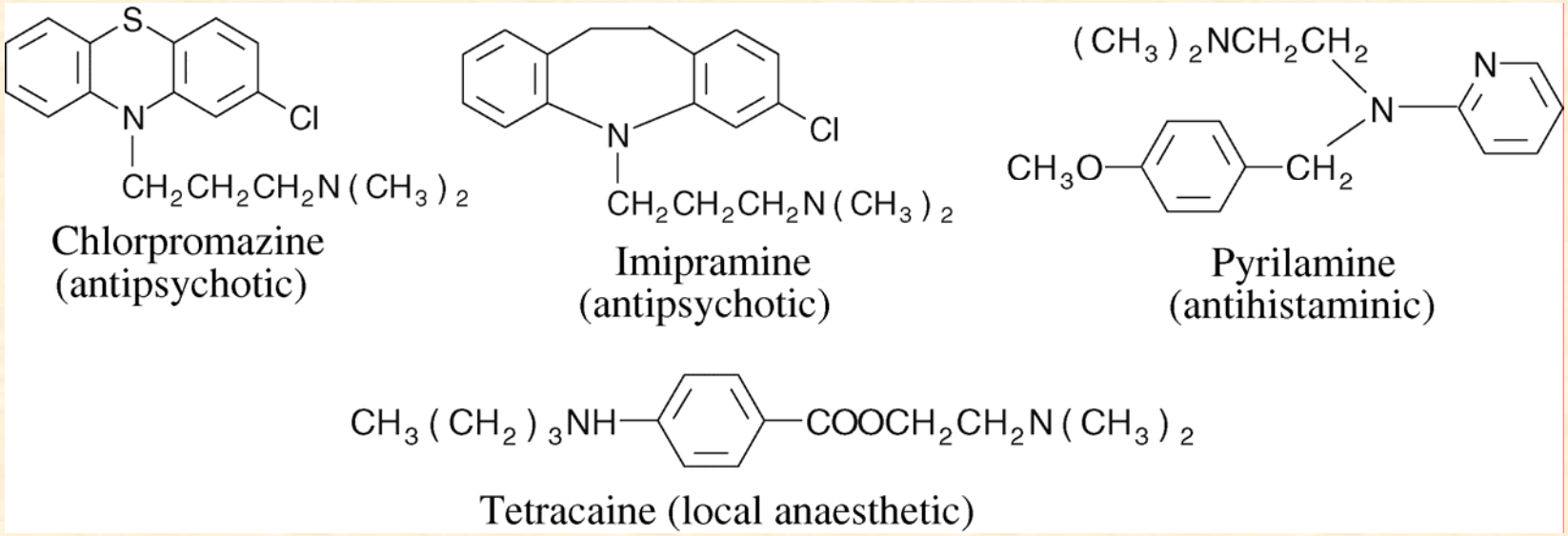
- heptaoxyethylene monohexyldecyl ether
- polyoxyethylene sorbitan monolaurate

Surfactants and Amphiphiles

- Biological systems – at interfaces of the target cell – cell death

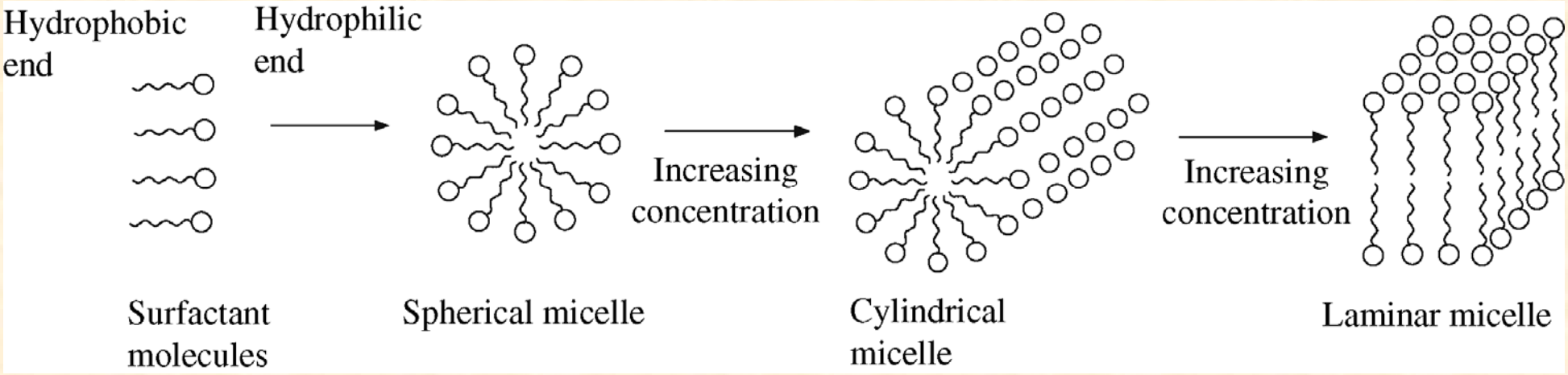


- Natural surfactants and surfactant drugs

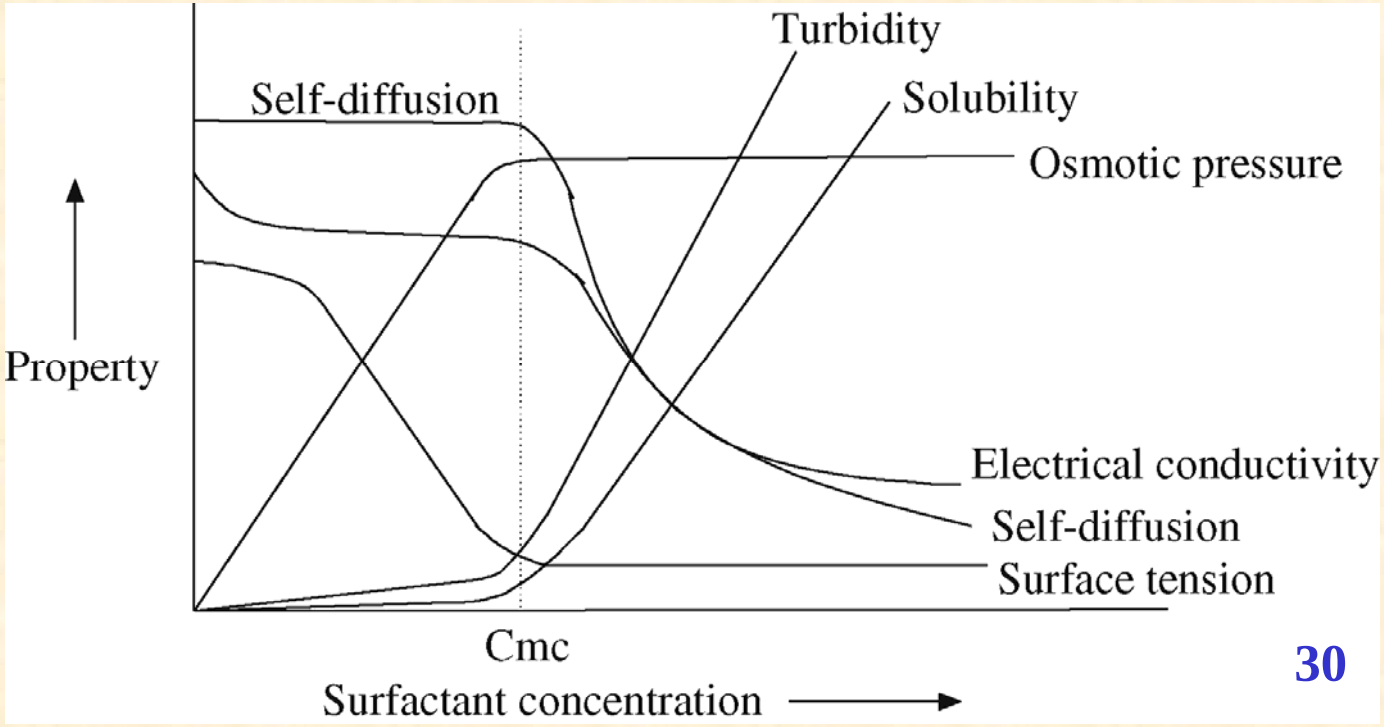


Surfactants and Amphiphiles

- Micelles – *cmc* (critical micelle concentration)

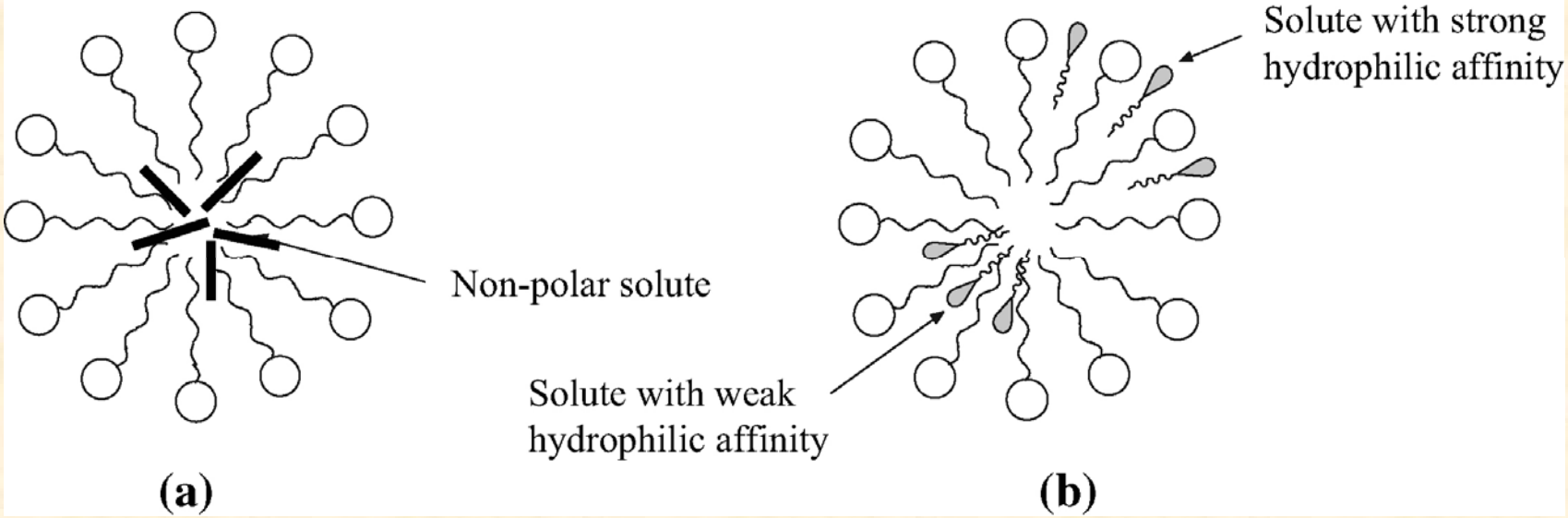


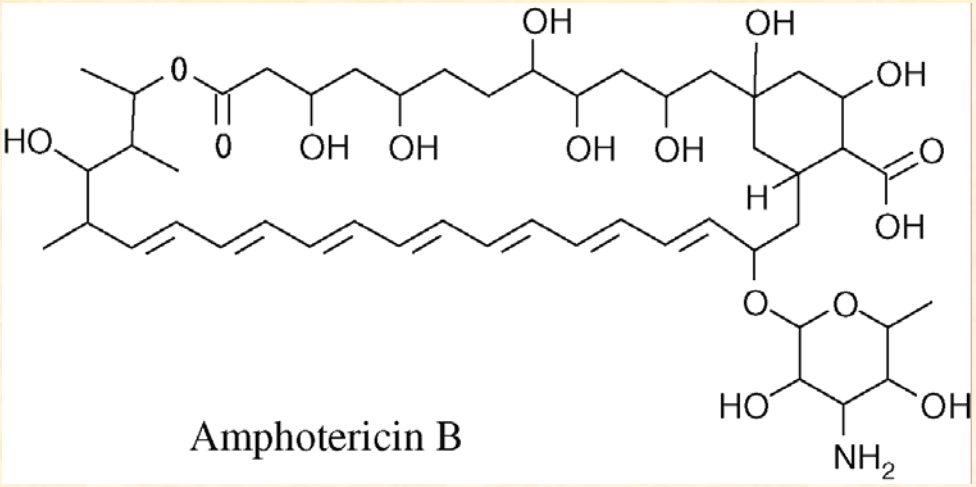
- Effect of micelle formation



Drug Solubilization

- Micelles can help solubilize drugs

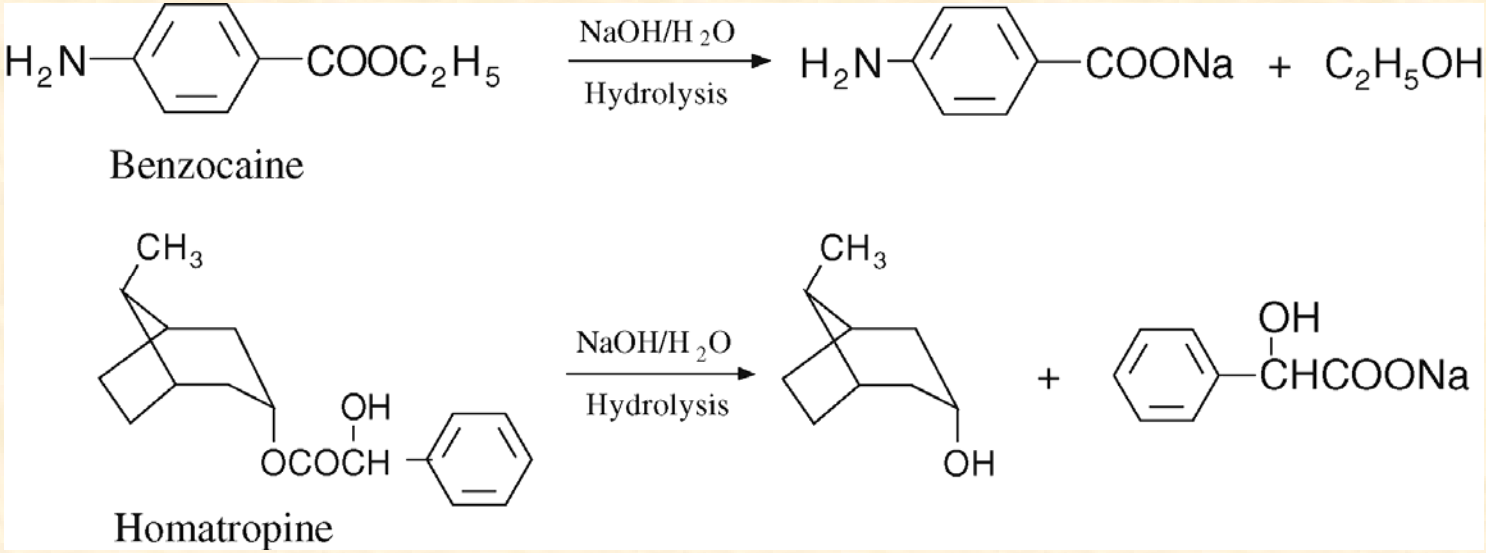




Amphotericin B

Drug Solubilization

- Micelles can help delay metabolitic degradation



- Micelles are also important in the digestion of triglycerides in mammals.

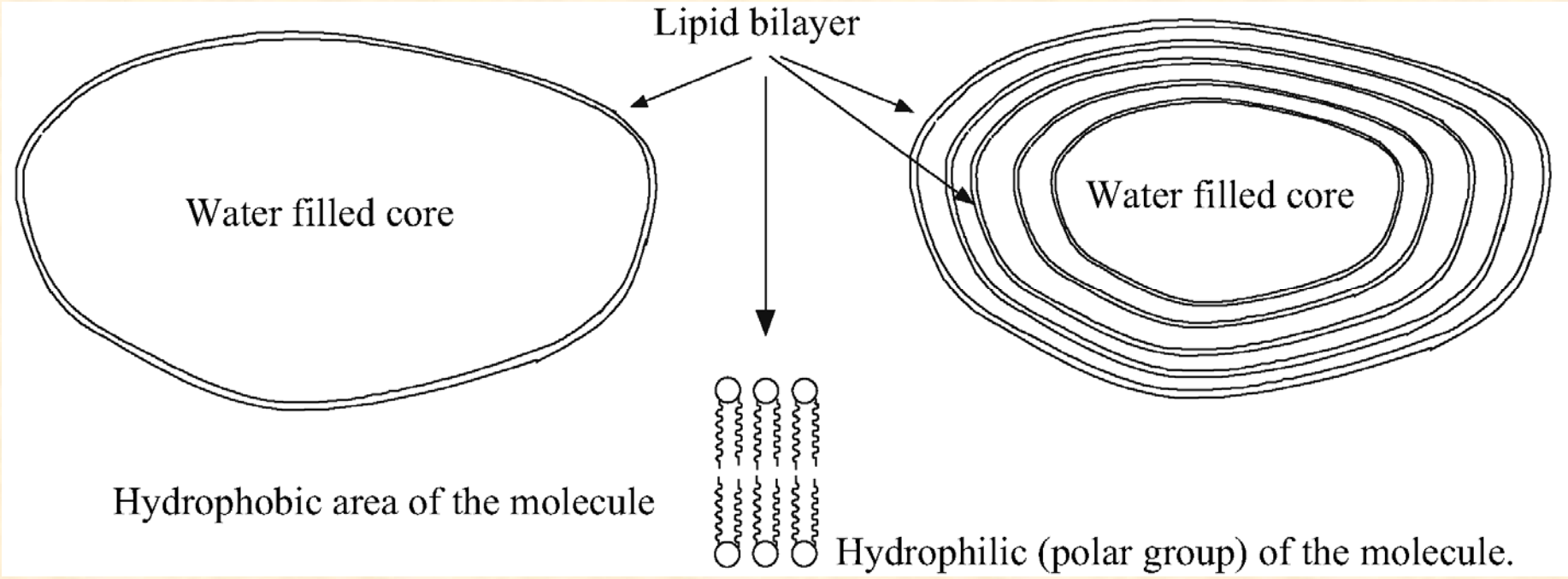
Mixed Micelles as Drug Delivery Systems

- Mixed micelles – mixture of surfactants

  e.g. Diazepam is stabilized by micelles formed by lechitin and sodium cholate

Vesicles and Liposomes

- Vesicles – aggregates formed from spherical bilayers of amphiphiles
- Liposomes – vesicles formed from lipids



- Importance in drug delivery – e.g. amphotericin B. or doxorubicin daunorubicin