Drug Design:
Functional groups / Pharmacological Activity

Structure - Mechanism of action
(Interaction with target)

Structure - Physiochemical properties (Bioavailability etc)

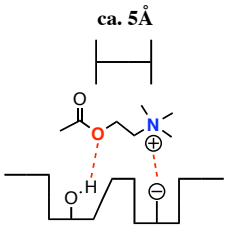
- Acid / base properties
- Water solubility
- Partition coefficient
- (Crystal structure)
- Stereochemistry

} ADME

Absorbtion. **D**istribution, **M**etabolism, **E**xcretion
(ADMET, ADMEtox)

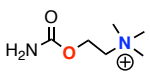
Structure - Mechanism of action

Acetylcholin
(Neurotransmittor)

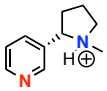


Acetylcholin Agonists

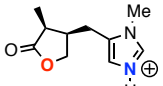
Carbacholin



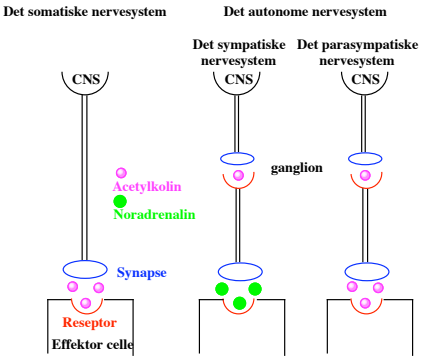
Nicotine



Pilocarpine

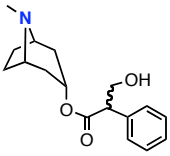


Protonated av phys. pH (pH≈7.4)

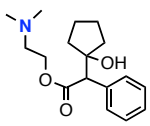


Acetylcholin Antagonists

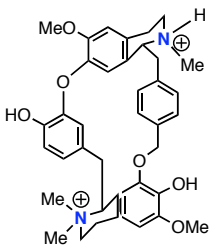
Atropin



Cyclopentolat



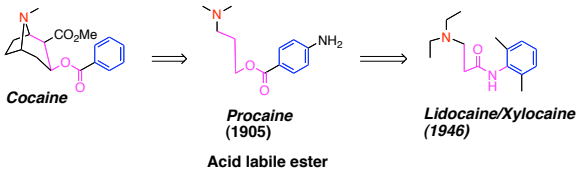
Tubocurarin

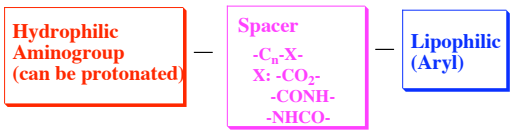


Structure - Mechanism of action

SAR: Structure Activity Relationships

Acetylcholine agonists: Small N-quartenary compds.
Acetylcholine antagonists: Larger N-quartenary compds.





Active compound identified
Target?

Chemistry & Biology, Vol. 11, February, 2004,

Finding Cinderella after the Ball: A Three-Hybrid Approach to Drug Target Identification

Target identified
Ligand?

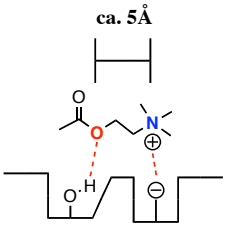
Structure - Physiochemical properties

- **Acid / base properties**
- **Water solubility**
- **Partition coefficient**
- **(Crystal structure)**
- **Stereochemistry**

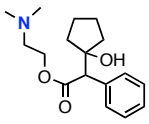
Human body: ca 75% water
pH blood ca 7.4 (physiolog. pH)
pH stomach 1 - 3.5
pH duodenum ca. 4
pH urine ca. 6

Identification of acidic / basic functional groups
pKa determines degree of ionization different places in the body

Acetylcholin (Neurotransmittor)

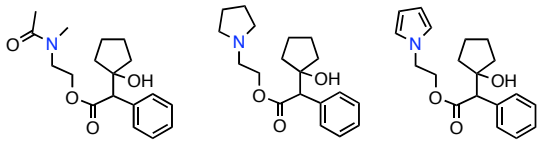


Acetylcholin Antagonists

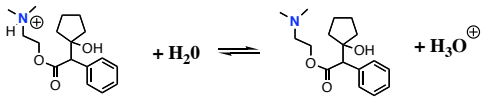


Cyclopentolat

Possible atropine analogs?



Cyclopentolate - tertiary amine, pKa ca. 10



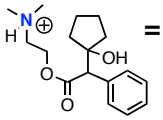
acid form **baseform**

$$pKa = pH + \log \frac{[\text{acid form}]}{[\text{base form}]}$$ **Henderson Hasselbach**

pH=pKa; [acid]= [base]
pH<pKa; acid form dominates
pH>pKa; basic form dominates

At pH 7.4

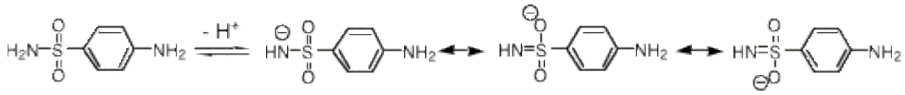
$$10 = 7.4 + \log \frac{[\text{acid form}]}{[\text{base form}]} \Rightarrow \log \frac{[\text{acid form}]}{[\text{base form}]} = 2.6 \Rightarrow \frac{[\text{acid form}]}{[\text{base form}]} = 398;$$ **99.75% acid form**



= active form

Antibacterial sulfonamides

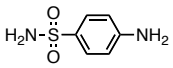
Old compound



Sulfanilamid
pKa 10.4

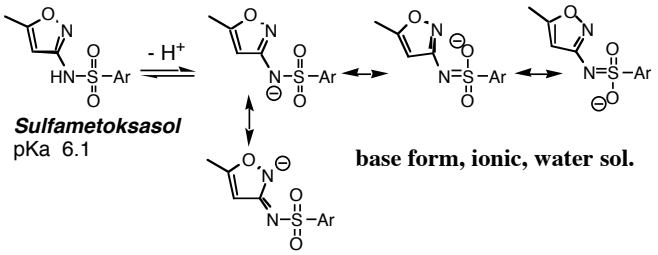
At pH 6 (urine)

$$10.4 = 6 + \log \frac{[\text{acid form}]}{[\text{base form}]} \Rightarrow \frac{[\text{acid form}]}{[\text{base form}]} \approx 25000$$



Acid form - neutral
Low watersol. - crystals -
Kidney damage

Modern compound



Sulfametoksasol
pKa 6.1

base form, ionic, water sol.

At pH 6 (urine)

$$\frac{[\text{acid form}]}{[\text{base form}]} \approx 1$$

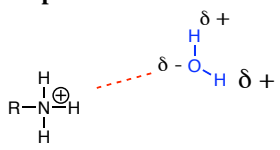
Structure - Physiochemical properties

- **Acid / base properties**
- **Water solubility**
- **Partition coefficient**
- **(Crystal structure)**
- **Stereochemistry**

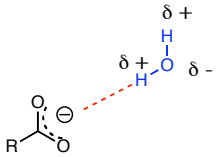
Ionisation -permanent charge
-acid / base properties

Hydrogen bonds

Ion - dipole bonds

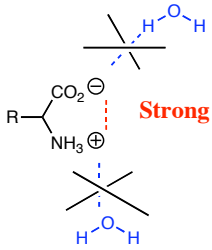


Acidic form of amines



Basic form of carboxylic acid (carboxylate)

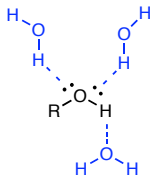
Intramoleculare interact. reduce water sol.

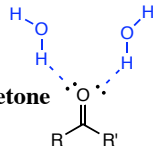


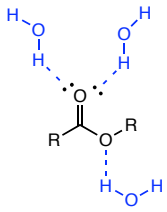
Strong intramolec interact.

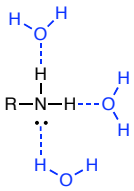
Salts between weak organic acids and weak organic bases does not dissolve well in water

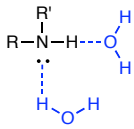
The more H-bonds possible - the more water sol.

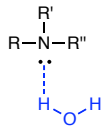
Alchohol  **3 H-Bonds**

Aldehyde / ketone  **2 H-Bonds**

Ester  **3 H-Bonds**

Primary amine  **3 H-Bonds**

Secondary amine  **2 H-Bonds**

Secondary amine  **1 H-Bonds**

Prediction of water solubility - Empirical

Water solubilization of functional groups

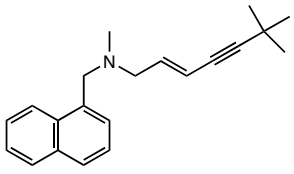
Functional group	Monofunctional comp.	Polyfunctional comp.
Alchohol	5 – 6 carbons	3 – 4 carbons
Phenol	6 – 7	3 – 4
Ether	4 – 5	2
Aldehyde	4 – 5	2
Ketone	5 – 6	2
Amine	6 – 7	3
Carboxylic acid	5 – 6	3
Ester	6	3
Amide	6	2 - 3

Charge: 1 charge - 20-30 C

Ex. monofuctional comp.

methanol - pentanol/hexanol are solubile

Terbinafine
Antifungal agent



21 C-atom, tertiary amine solubilize 6 - 7 C atoms

⟹ **Insolubile (neutral form)**

Corresponding acid (cationic) solubile

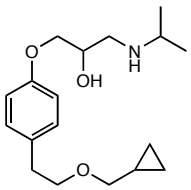
(solubile: >10 mg/mL)

Water solubilization of functional groups

Functional group	Monofunctional comp.	Polyfunctional comp.
Alchohol	5 – 6 carbons	3 – 4 carbons
Phenol	6 – 7	3 – 4
Ether	4 – 5	2
Aldehyde	4 – 5	2
Ketone	5 – 6	2
Amine	6 – 7	3
Carboxylic acid	5 – 6	3
Ester	6	3
Amide	6	2 - 3

Ex. polyfunctional comp.

Betaxolol
Betablokker



18 C-atomer

Ether: 2
Ether: 2
Alchohol: 3-4
Amine 2
Tot: 9 - 10
(not solubile)

Charge: 1 charge - 20-30 C

Structure - Physiochemical properties

- **Acid / base properties**
- **Water solubility**
- **Partition coefficient**
- **(Crystal structure)**
- **Stereochemistry**

logP P: Partition coefficient between *n*-octanol and water

Experimental: MlogP or $logP_{meas}$

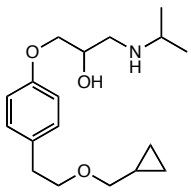
logP ∝ Rt (HPLC, TLC reverse phase)

Calcd: ClogP

π-value: hydrophilic - lipophilic value

Fragment	π-value
C (aliphatic	+0.5
Phenyl	+2.0
-Cl	+0.5
$-ONO_2$	+0.2
-S-	0.0
O=C-O- (carboxyl)	-0.7
O=C-N- (amide)	-0.7
-O- (hydroxyl, ether)	-1.0
N (amine)	-1.0
$-NO_2$ (aliphat.)	-0.85
$-NO_2$ (aromat.)	-0.28

Betaxolol
Betablokker



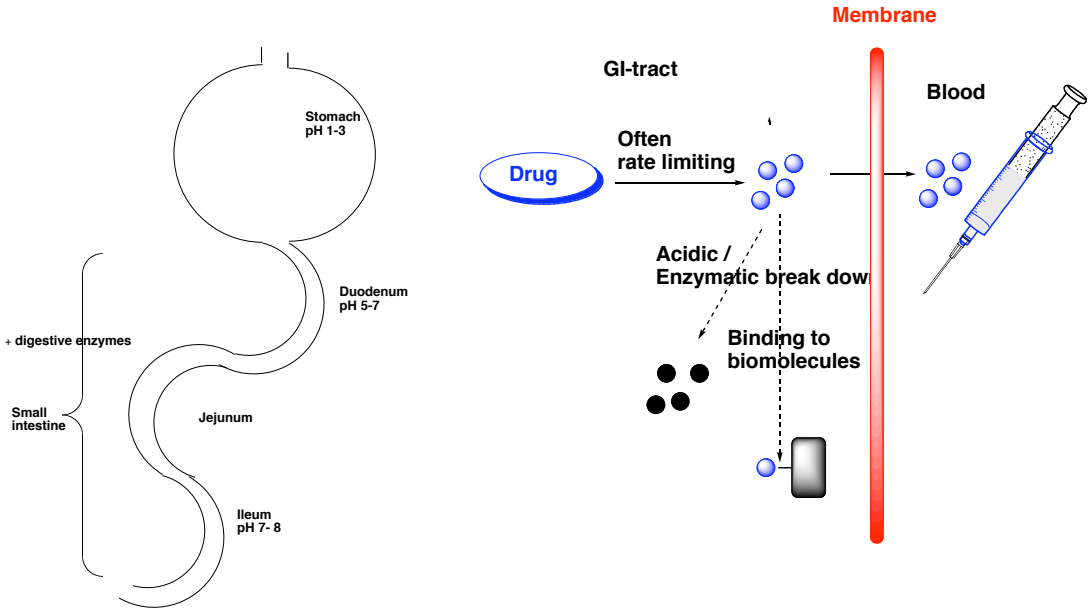
12 x C aliphat: +6.0
Ph: +2.0
3 x O: -3.0
N: -1.0
logP +4.0

ClogP (SciFinder): 2.69

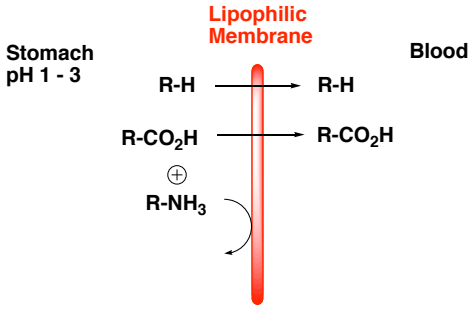
www.molinspiration.com/ : 2.84

Absorbtion of Bioactive Compounds

Absorbtion from GI tract



Most drugs: Passive diffusion



pK_a — pH

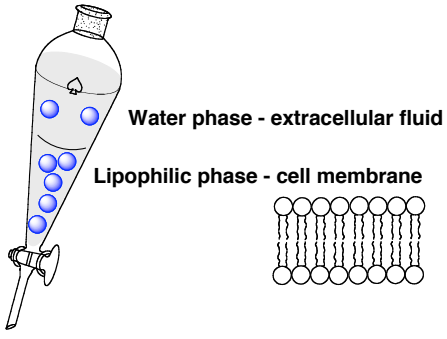
Amount un ionized drug

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

Henderson Hasselbach

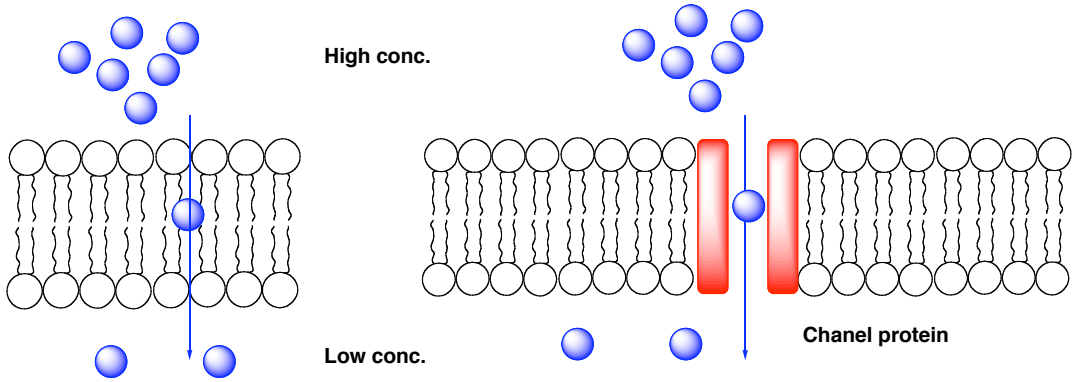
Low lipophilicity unionized form - low absorbtion

logP - P: Partition coefficient between *n*-octanol and water



Crossing the membrane

Passive transport / diffusion



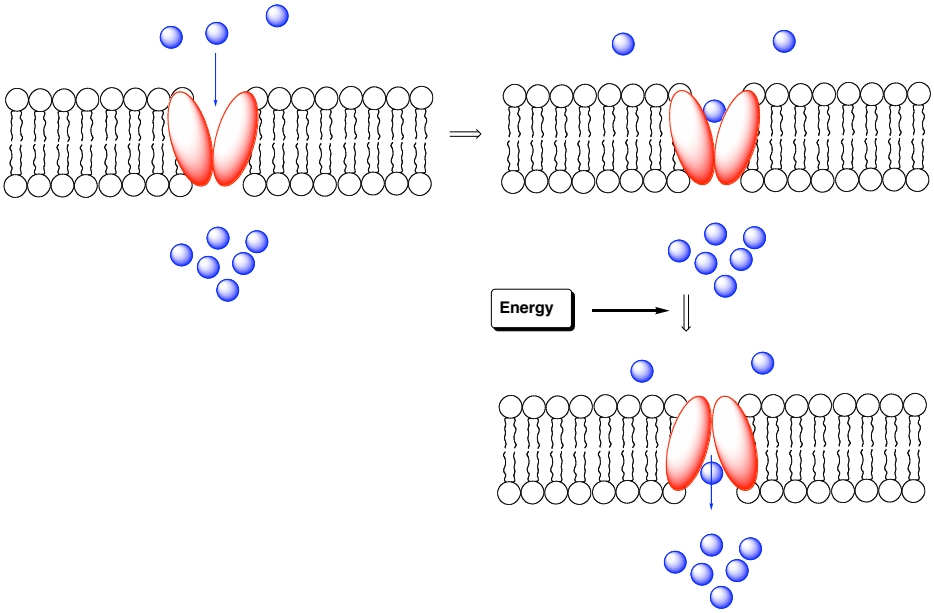
Rate ∝ Conc. absortion site (1. order kinetics)
% Drug absorbed ∝ lipophilicity

Size of molecule

Certain ionic compounds may go thru as ion-pair

Active transport / Carrier mediated transport

- **Less common**
- **Structural recemblanse with for instance nutritional compound**
- **Transport against conc. gradient**
- **Mechanism saturated at high conc.**
- **Competition for carrier molecules, compounds with structural resemblance**



The Lipinski "Rule of Five"

states that compounds are likely to have good absorption and permeation in biological systems and are more likely to be successful drug candidates if they meet the following criteria:

five or fewer hydrogen-bond donors

ten (2 x 5) or fewer hydrogen-bond acceptors } Not too polar

molecular weight less than or equal to 500 Not too big

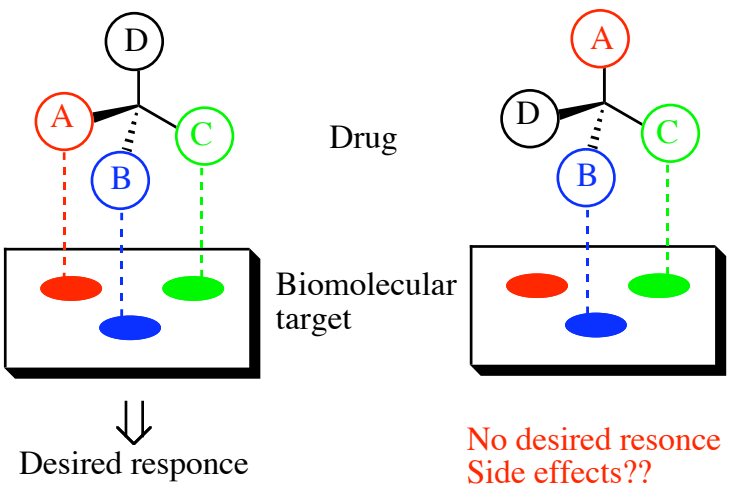
calculated logP less than or equal to 5 Not too hydrophobic

***Compound classes that are substrates for biological transporters are exceptions to the rule.**

Structure - Physiochemical properties

- Acid / base properties
- Water solubility
- Partition coefficient
- (Crystal structure)
- Stereochemistry

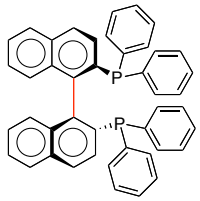
Biomolecules (reseptors, enzymes): Asymmetric



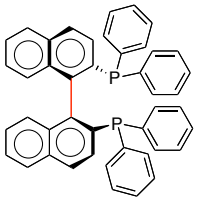
Enantiomers may behave differently:

- **Absorbtion (membrane selectivity)**
- **Metabolism**
- **Binding to other reseptors than target (loss, side effects)**
- **Binding to target reseptor**

Restricted rotation - optically active rotamers

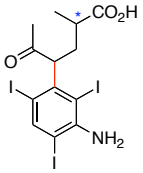


(R)-(+)-BINAP



(S)-(-)-BINAP

X-ray contrast agent



Chiral C-atom

Chiral axis (restrict. tot.)

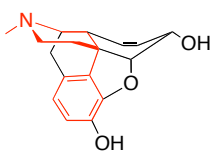
} 4 stereoisomers

- **Screening/Design/Serendipity/Natural products**
- **Lead compound**
- **Structure Optimisation** ⟹ **Refinement of lead structure:**
  - **Determining pharmacophore**
  - **Functional group modification**
- **Actual Drug**

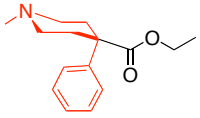
Pharmacophore:

The part of the molecule that contains the functional groups that actually binds to the reseptor

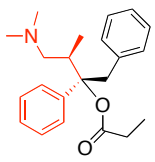
Morfin



Petidine

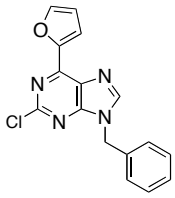


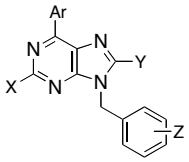
Dextropropoxyphene



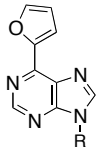
Antimycobacterials

Lead compound

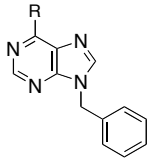




Rel high activity



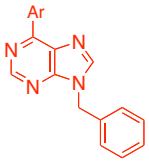
R ≠ CH_2Ph



R=H, alkyl

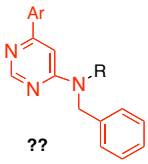
inactive

Pharmacophore??



Azapurines??

Deazapurines??



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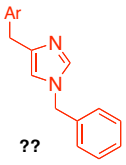

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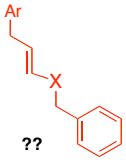

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Improvement of lead by functional group modification

- **Activity**
- **Toxicity**
- **Bioavailability**
- **Metabolism**

Isosters:
Functional groups that results in approx. the same properties
Steric and electronic similarities

bp 81 °C bp 84 °C bp 116 °C

-CH=CH- and -S- are isosters -C= and -N= not isosters

(at least with respect to bp)

Bioisosters:
Functional groups that results in approx. the same biological properties

Classical bioisosters
Steric and electronic similarities

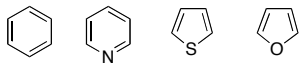
Monovalent
-F, -H
-OH, -NH_2
-H, -F, -OH, -NH_2, -CH_3
-SH, -OH
-Cl, -Br, -CF_3

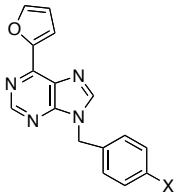
Divalent
-C=S, -C=O, -C=NH, -C=C-

Trivalente
-CH=, -N=

Tetravalente

Rings





-X	π	σ_p	% Inhib at 6.25 µg/mL	MIC (µg/mL)
-H	0.00	0.00	>90	3.13
-F	0.15	0.06	>90	6.25
-Cl	0.70	0.23	>90	6.25
-OH	-0.61	-0.37	79	n.d.
-OMe	-0.04	-0.27	>90	1.56
-NH_2	-1.23	-0.66	23	n.d.
-NMe_2	0.18	-0.83	>90	12.5
-CH_3	0.60	-0.17	>90	3.13
-*t*-Bu	1.98	-0.20	>90	12.5
-SO_2Me	-1.63	0.72	23	n.d.

Bioisosters

σ: electronic effects; σ>0 electron withdrawing, σ<0 electron donating
π: Lipophilicity, π>0 increased lipophil. rel to H

Non-classical bioisosters
Not strong steric or electronic similarities

pKa 14.2 **pKa 10.3** **pKa 9.2** **pKa 4.9** ≈ karboksylsyrer

Angiotensin II antagonists (Hypertention)