LVA *163.047*
Pharma- u. Agrowirkstoffe
P. Stanetty und U. Jordis

Pharmawirkstoffe

Ulrich Jordis

Lehrbücher 1

- F.D. King., Ed. **Medicinal Chemistry** ***Principles and Practice*** 2nd Ed., The Royal Society of Chemistry 2002
- S. Grabley u. R. Thiericke (Eds.) **Drug Discovery from Nature** Springer 2000
- J.L. McGuire, Ed. **Pharmaceuticals** Classes, Therapeutic Agents, Areas of Application
  Wiley-VCH 2000
  - Vol. 1 Introduction, Cardiovascular Drugs
  - Vol. 2 Neuropharmaceuticals, Gastrointestinal Drugs, Respiratory Tract
  - Vol. 3 Antiinfectives, Endocrine and Metabolic Drugs
  - Vol. 4 Miscellaneous Drugs, Related Technology

- H.-J. Böhm, G. Klebe, H. Kubinyi **Wirkstoffdesign** Spektrum 1996

Lehrbücher 2

- **Silverman, Richard B. : Medizinische Chemie für Organiker, Biochemiker und pharmazeutische Chemiker / Richard B. Silverman. Hrsg. der Übers. Joachim K. Seydel. Übers. von Marion Gurrath und Gerhard Müller . - Weinheim [u.a.] : VCH-Verl.-Ges. , 1995 . - XIV, 440**
- **Textbook of Organic Medicinal and Pharmaceutical Chemistry. Tenth Edition. Edited by Jaime N. Delgado and William A. Remers. Lippincott-Raven, Philadelphia, PA. 1998.**

Software 1

- **Molecular Conceptor 1.0**
  www.molecular-conceptor.com

A DRUG DISCOVERY

1. General Introduction on Drugs
2. Drug Discovery
3. Drug Development

B MOLECULAR BASIS IN DRUG DESIGN

1. Molecular Geometry
2. Molecular Properties
3. Stereochemistry
4. Molecular Energies
5. Conformational Analysis
6. Selected Examples of 3D Analysis

C STRATEGIES & PRINCIPLES IN DRUG DESIGN

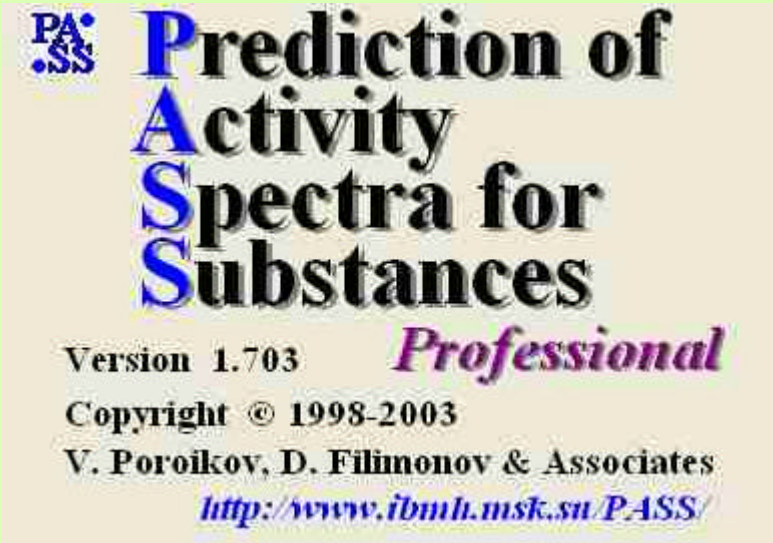
1. Principles of Rational Drug Design
2. Pharmacophore-Based Drug Design : Analysis
3. Pharmacophore-Based Drug Design : Design
4. Pharmacophore-Based Drug Design : Examples
5. Receptor-Based Drug Design : Analysis
6. Receptor-Based Drug Design : Design
7. Receptor-Based Drug Design : Examples

D TOPICS IN DRUG DESIGN

1. Molecular Graphics
2. Peptidomimetism & Molecular Mimicry

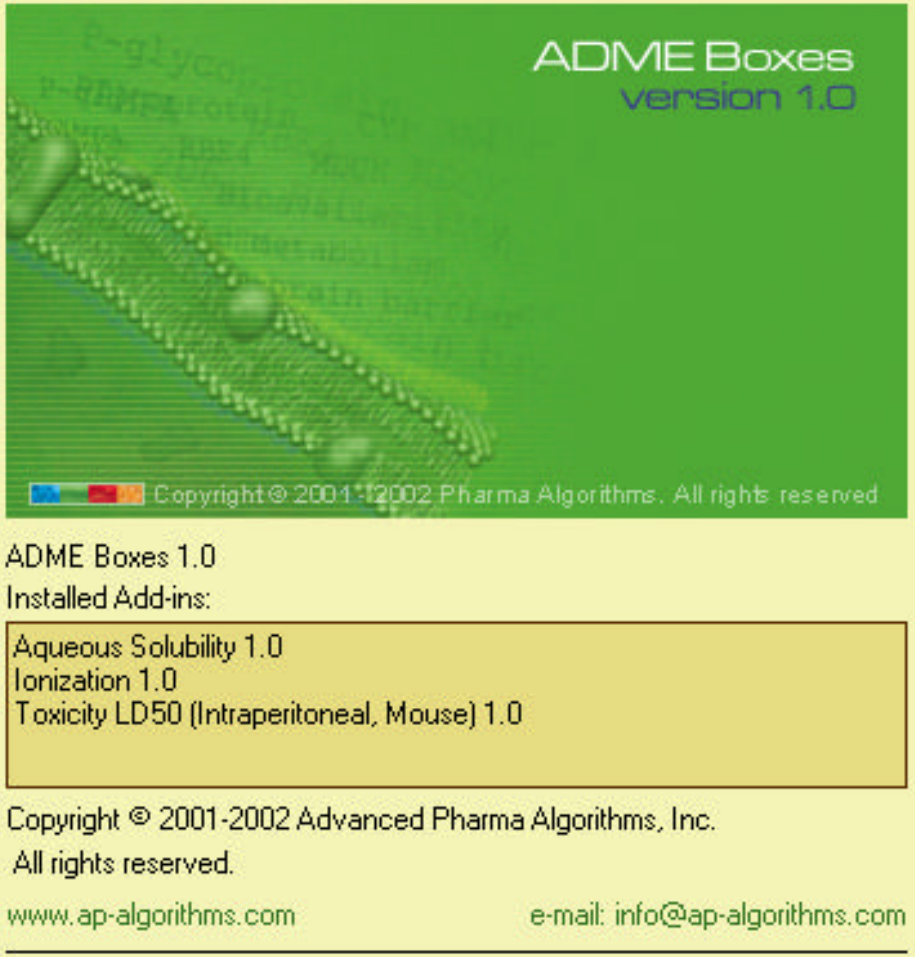
Software 2

- PASS



Software 3

- ADME Boxes von Advanced Pharma Algorithms



Landkarten 1

- **Vorlesung Pharmazeutische Chemie an der Uni:**
- **Inhalt:** Internationale Freinamen, Warenzeichen, Lipide, Neutralfette, Fettverderb, Fettkonservierung, Eicosanoide, Prostaglandine, Thromboxane, Prostacycline, Leucotriene, Blutlipide, Lipidsenker, Lipoide, Wachse, Phospholipide, Glycerophospholipide, Sphingophospholipide, Glycolipide, Isoprenoidlipide, Terpene, Carotine, Carotinoide, A-Vitamine, Retinoide, E-Vitamine, K-Vitamine, Steroide, Gallensäuren, Sterole, 9,10- Secosterine, D-Vitamine, Sexualhormone, Östrogene, Antiöstrogene, Gestagene, Antigestagene, Androgene, Antiandrogene, Anabolica, Corticoidhormone, Steroidglycoside, Herstellung medizinisch verwendeter Steroide.

- B-Vitamine, Thiamin, Riboflavin, Nicotinsäureamid, Pantothensäure, Pyridoxin, Biotin, Folsäure, Cobalamin, Orotsäure, Monosaccharide, Glyconsäuren, Ascorbinsäure, Bioflavonoide, Glycuronsäuren, Glycarsäuren, Glycitole, Inosite, Hexachlorcyclohexane, Zuckeraustauschstoffe, Süßstoffe, Disaccharide, Laxantien, Antacida, Polysaccharide, Homoglucane, Plasmaexpander, Glycosaminoglycane, Hyaluronat, Chondroitinsulfat, Mucoitinsulfat, Heparine, Heparinoide, Aminosäuren, Schilddrüsenhormone, Racemat, Racematspaltung, Peptide, Peptidhormone, HVL-Hormone, HHL-Hormone, Hypothalamische Neurohormone, Pancreashormone, Orale Antidiabetica, Hormone der Schilddrüse und der Nebenschilddrüsen, Gewebshormone, ACE-Hemmer, Reninhemmer, Proteine, Skleroproteine, Sphäroproteine, Blutgerinnung, Fibrinolyse, Cytokine, Erythropoetin.
- Antibiotica, Cycloserin, Chloramphenicol, Beta-Lactam-Antibiotica: Penam-Derivate, Carbapeneme, Oxopename, Cephalosporine, Monobactame, Peptid-Antibiotica, Aminoglycosid-Antibiotica, Tetracycline, Griseofulvin, Fusidinsäure, Actinomycine, Macrolid-Antibiotica, Ansamycine, Fosfomycin, Synthetische Chemotherapeutica, Desinficientia und Antiseptica, Systematische Chemotherapeutica, Antibacterielle Chemotherapeutica, Antituberculotica, Antiprotozoale Chemotherapeutica, Antimycotica, Anthelmintica, Virustatica, Cytostatica, Alpha-Sympathomimetica, Beta-Sympathomimetica, Appetitzügler, Alpha- Adrenozeptorenblocker, Beta-Rezeptorenblocker, Antisympathotonica, Antihypertensiva, Parasympathomimetica, Direkte Parasympathomimetica, Acetylcholinesterasehemmer, Carbaminsäureester, Organ.Phosphorsäureester, Nervengase, Acetylcholinesterasereaktivatoren.

- Parasympatholytica, Mydriatica, Anti-Ulcus-Substanzen, Spasmolytica, Neurotrope Spasmolytica, Musculotrope Spasmolytica, Antiparkinsonia, Nicotin, Ganglioplegica, Periphere Muskelrelaxantien, Stabilisierende Muskelrelaxantien, Depolarisierende Muskelrelaxantien, Zentrale Muskelrelaxantien, Histamin, H1-Rezeptorenblocker, H2-Rezeptorenblocker, Mastzellstabilisatoren, Seotonin, 5-HT-Agonisten, 5-HT- Antagonisten, Dopamin, D-Rezeptor-Agonisten, D-Rezeptor-Antagonisten, Lokalanaesthetica, Antiepileptica, Sedativa, Hypnotica, Narcotica, Injections-Narcotica, Inhalations-Narcotica, Aversionstherapie des Alkoholismus, Morphinartige Analgetica, Antitussiva, Expectorantien, Secretolytica, Mucolytica, Secretomotorica, Analgetica-Antipyretica, Antirheumatica, Nichtsteroidale Antirheumatica, Basistherapeutica, Sauerstoff-Abfangreagentien, Chondroprotectiva, Neuroleptica, Tranquillantien, Antidepressiva, Psychostimulantien, Methylxanthine, Gichttherapeutica, Halluzinogene, Cardiaca, Cardiotonica, Antiarrhythmica, Coronartherapeutica, Calciumantagonisten, Diuretica.

Landkarten 2

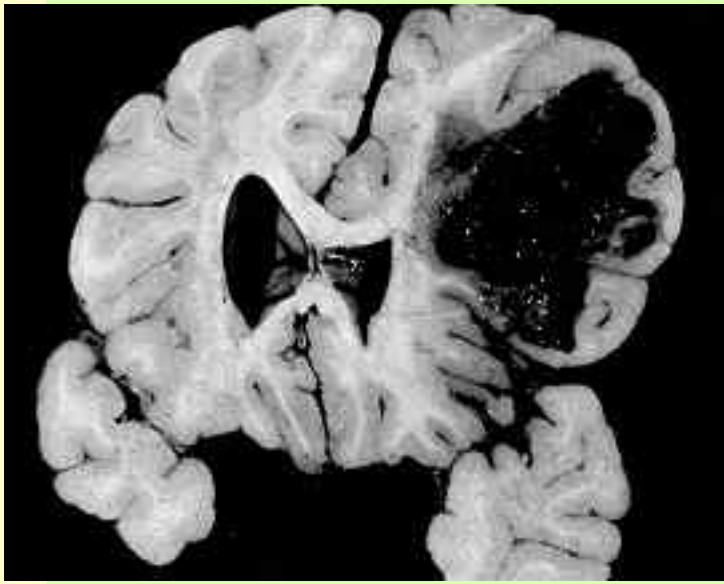
- *learning about the fundamental organic principles that underlie the design of drugs and how they function at the molecular level.*

Major Treatment Categories

- Cardiovascular
- Cancer
- Central Nervous System
- Infection
- Gastrointestinal

Suche nach Lösungen

- Neurodegeneration:
  - Stroke
  - Traumatic brain injury
  - Multiple sclerosis
  - Alzheimer's disease and related dementias
  - Parkinson's disease
- Skeletal degenerative diseases
  - Osteoporosis
  - Arthritis



Suche nach Lösungen 2

- Infection
  - Viral (HIV, HBV, HCV, HSV, SARS)
  - Bacterial resistance
- Metabolic disorders
  - Diabetes
  - Obesity
- Migraine

Some Recent Blockbuster Drugs

VIAGRA (sildenafil)

•Phosphodiesterase type V inhibitor for male erectile dysfunction

•Launched: March 1998; projected sales until end-98: $900 million

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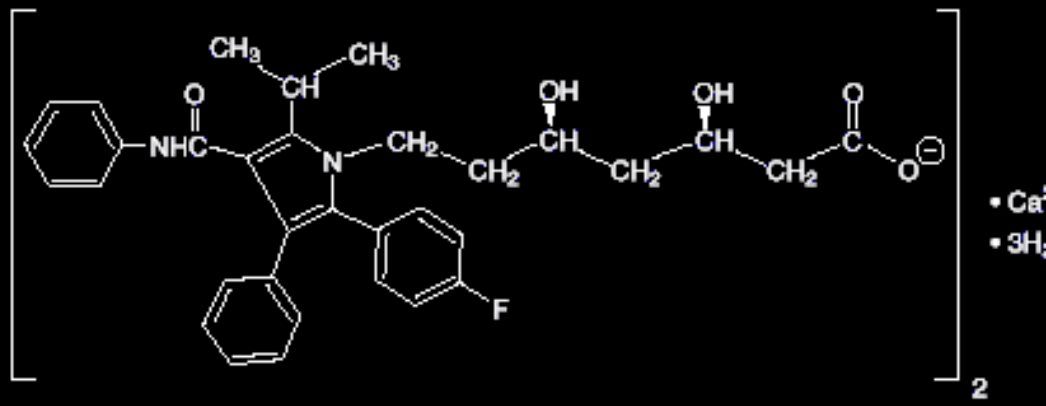
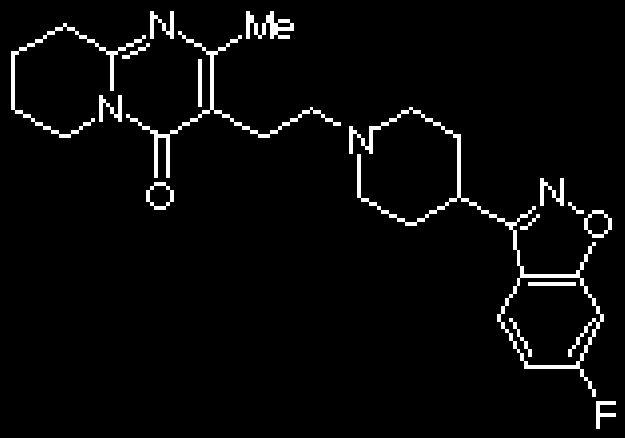
LIPITOR (atorvastatin)

•HMG-CoA reductase inhibitor for hyperlipidaemia

•1997 sales: $865 million



Some Recent Blockbuster Drugs



RISPERDAL (risperidone)

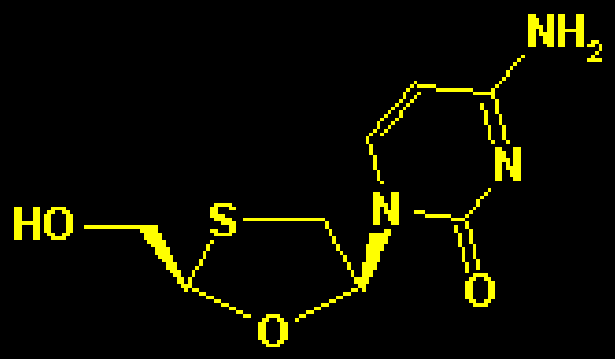
•Serotonin-dopamine antagonist (atypical antipsychotic) for schizophrenia

•1997 sales: $850 million

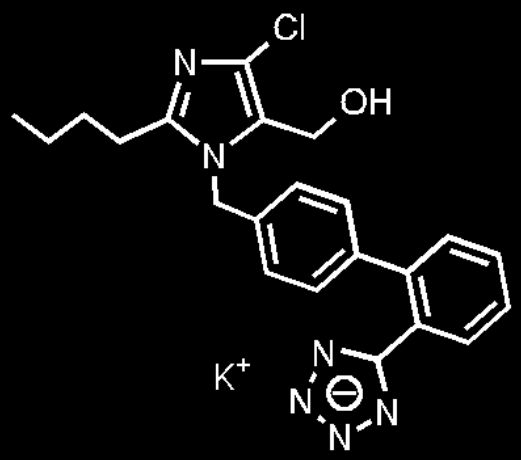
EPIVIR (lamivudine, 3TC)

•Reverse transcriptase inhibitor for antiviral therapy (HBV, HIV)

•1997 sales: $490 million



Some Recent Blockbuster Drugs



COZAAR (losartan)

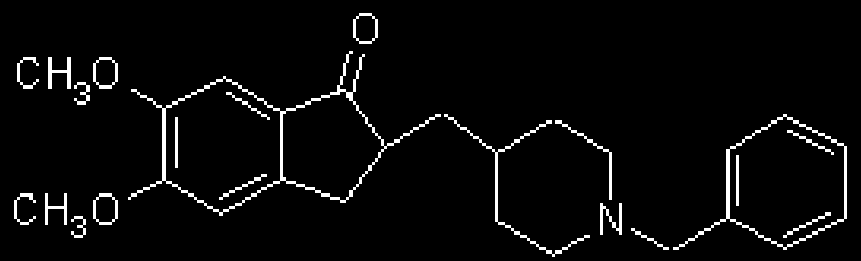
•AT-II receptor antagonist for hypertonia

•1997 sales $605 million

ARICEPT (donepezil)

•Acetylcholinesterase inhibitor for Alzheimer‘s disease

•Projected sales until end-98 $400 million



How Is A Drug Named?

- Systematic chemical name, CAS code
- Research Code: [originator]-[identifier]
- U.S. Adopted Name (USAN)
- International Non-Proprietary Name (INN)
- Trademark name

INHALT

- *Optimierung der Leitstruktur*
  - *Isosterie*
  - *Wirkoptimierung*
  - *Agonist/Antagonist*
  - *Rationales Design*
- *Der Einfluß von Naturstoffen*
  - *Klassische Naturstoffe*
  - *Antibiotika*
  - *Immunsuppressiva*
  - *Statine*
    - *Eigene Synthesen*
- *DrugMatrix (Iconix)*
- *Case Studies*
  - *5-HT2c Rezeptor Antagonisten*
  - *Die Identifizierung des HIV- Proteasehemmers Saquinavir*
  - *Die Entdeckung von Vioxx (Rofecoxib)*

Sir Karl Popper

- *„Die Wahrheit ist objektiv und absolut. Aber wir können niemals sicher sein, daß wir sie gefunden haben. Unser Wissen ist immer Vermutungswissen. Unsere Theorien sind Hypothesen. Wir prüfen auf Wahrheit, indem wir das Falsche ausscheiden“*

(Objective Knowledge, 1972)

Optimierung der Leitstruktur

- Änderung der Lipophilie & elektronischen Eigenschaften
- Variation der Substituenten
- Einführung oder Eliminierung von Heteroatomen
- Variation der Substitution
- Stabilisierung von Konformationen
- Änderung der Ringgröße
- Eliminierung von Chiralitätszentren zur Vereinfachung
- Einführung von Chiralität zur Erhöhung der Selektivität

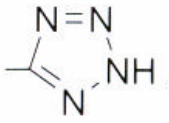
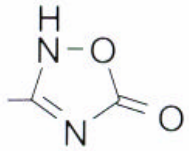
Optimierung der Leitstruktur: Isosterie

Substituenten: F, Cl, Br, I, CF_3, NO_2
Methyl, Ethyl, Isopropyl, Cyclopropyl, t-Butyl,
-OH, -SH, $-NH_2$, OMe, $N(Me)_2$

Brückenglieder: $-CH_2-$, -NH-, -O-
$-COCH_2-$, CONH-, -COO-
>C=O, >C=S, >C=NH, >C=NOH, >C=NOAlkyl

Atome und Gruppen in Ringen: -CH=, -N=
$-CH_2-$, -NH-, -O-, -S-,
$-CH_2CH_2-$, CH_2-O-, -CH=CH-, -CH=N-

Größere Gruppen: $-NHCOCH_3$, $-SO_2CH_3$

-COOH, -CONHOH, $-SO_2NH_2$,  , 

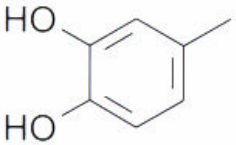
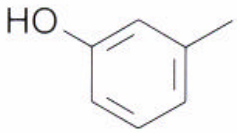
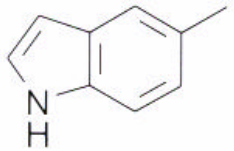
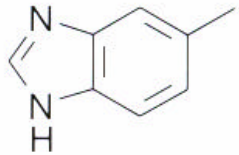
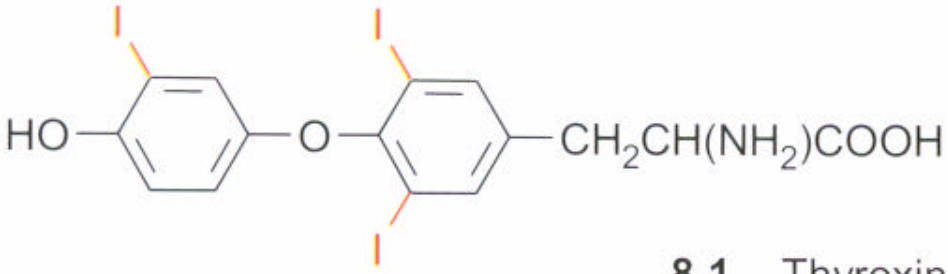
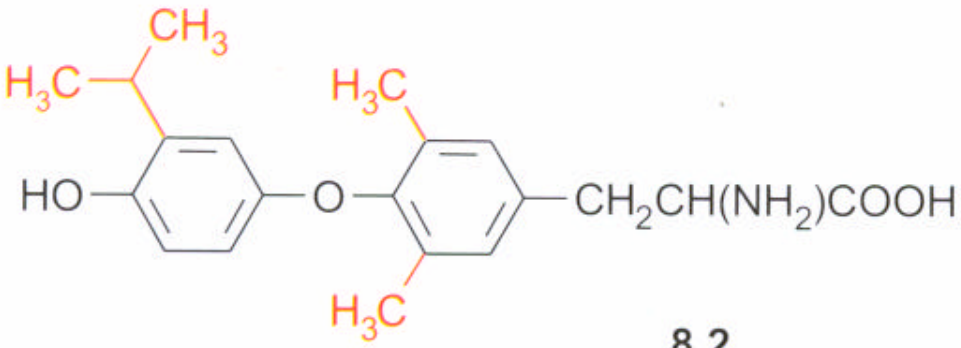





Abb. 8.1 Einige Beispiele für Möglichkeiten zum isosteren Austausch von Atomen bzw. Gruppen.

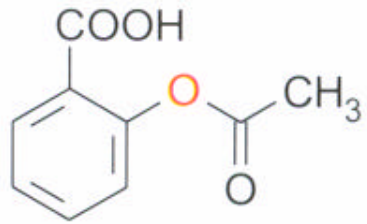
Isosterer Ersatz



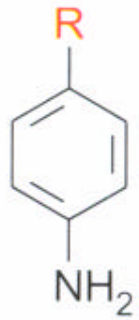
8.1 Thyroxin



8.2



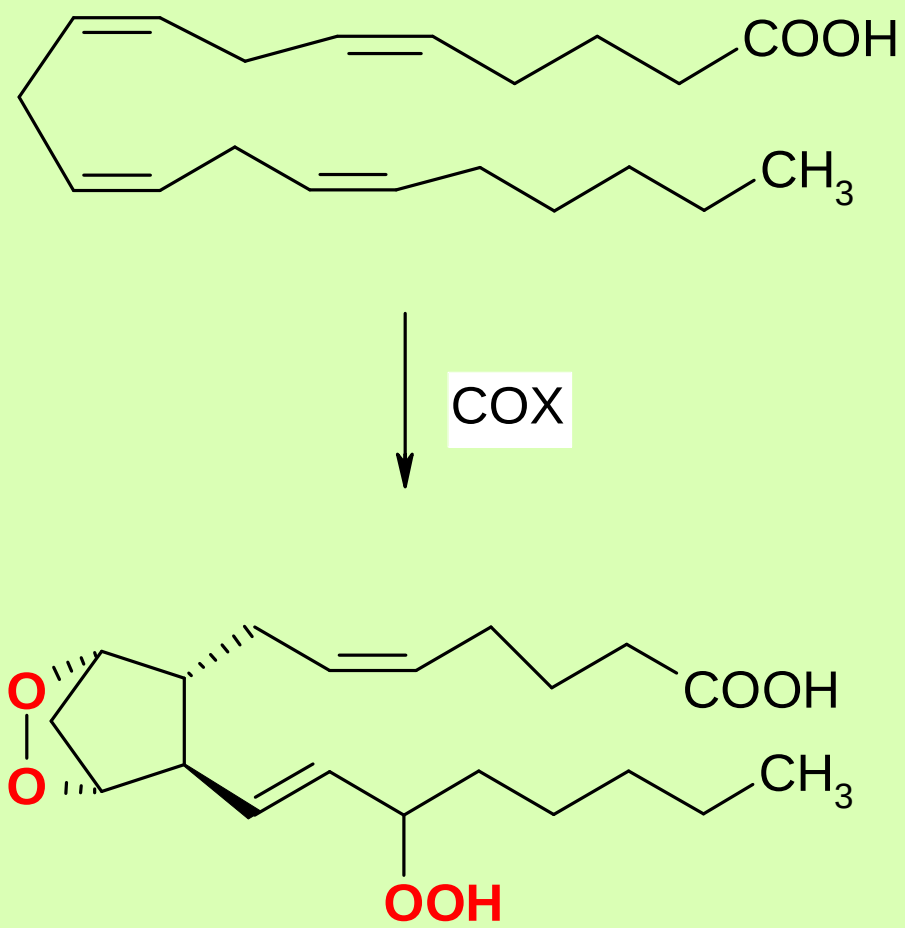
8.3 Acetylsalicylsäure



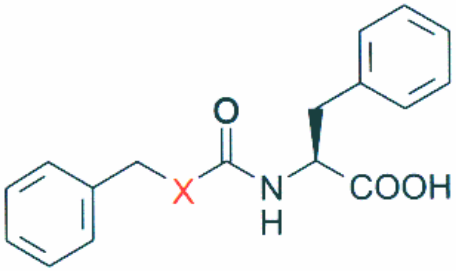
8.4 R = -COOH

oder $-SO_2NH_2$

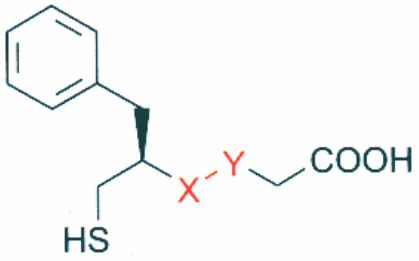
COX Wirkung



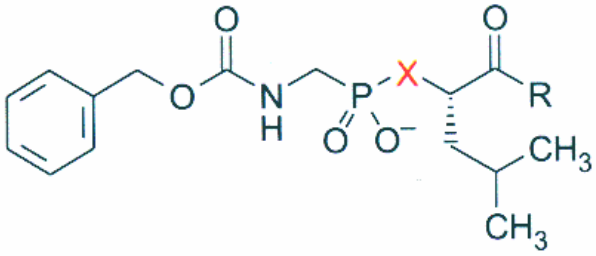
Isosterer Austausch



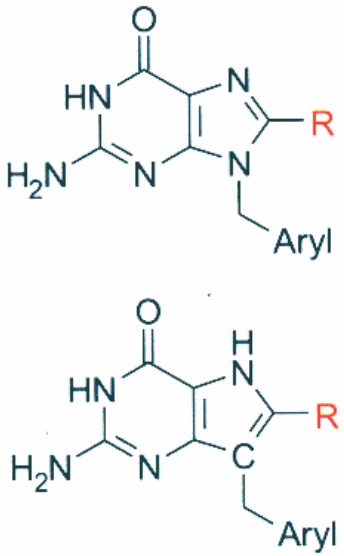
8.5 Thermolysininhibitoren
X = -O- oder -CH_2-



8.6 Thiorphan und *retro*-Thiorphan
X, Y = -CO-NH- bzw. -NH-CO-



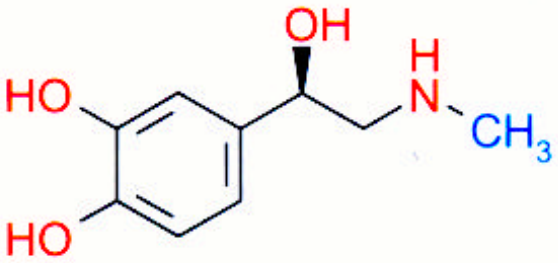
8.7 Thermolysininhibitoren
X = -NH-, -O- oder -CH_2-
R = -OH oder Aminosäurerest



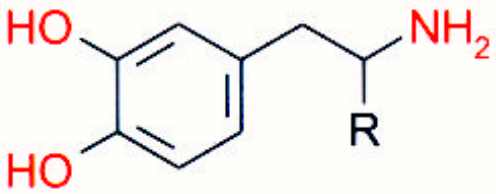
8.8 Purine und Desazapurine
R = H bzw. NH_2

Wirkungsspektren

polare Moleküle:



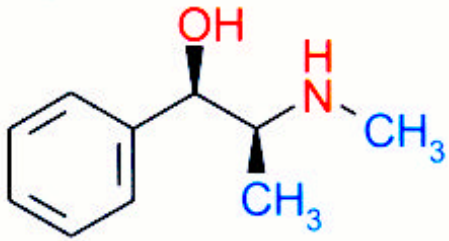
8.9 Adrenalin



8.10 Dopamin, R = H

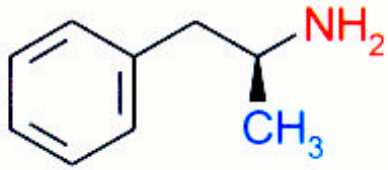
L-Dopa, R = COOH

mittlere Polarität:

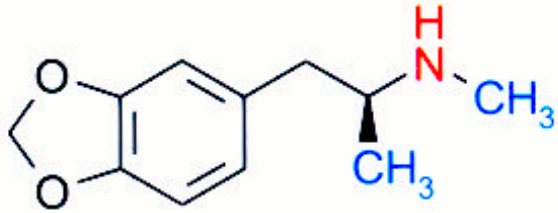


8.11 Ephedrin

unpolare Moleküle:

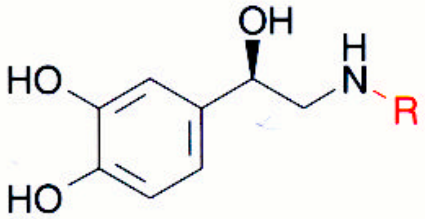


8.12 Amphetamin



8.13 MDMA

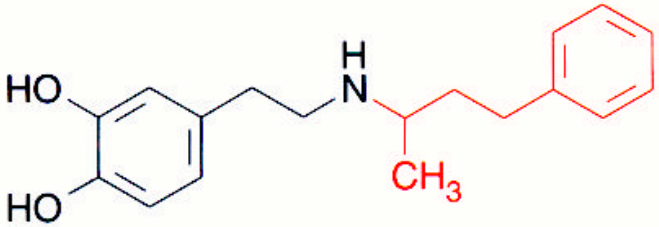
Selektivität von Catecholaminen



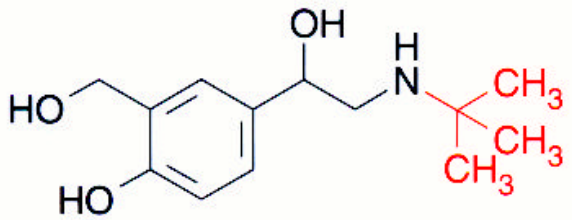
8.14 Noradrenalin, R = H
überwiegend α-mimetisch

8.9 Adrenalin, R = CH_3
α- und β-mimetisch

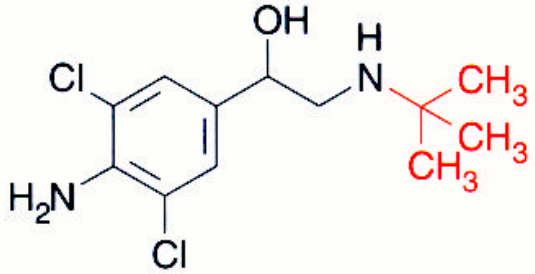
8.15 Isoprenalin, R = $-CH(CH_3)_2$
β-mimetisch



8.16 Dobutamin
β_1-mimetisch

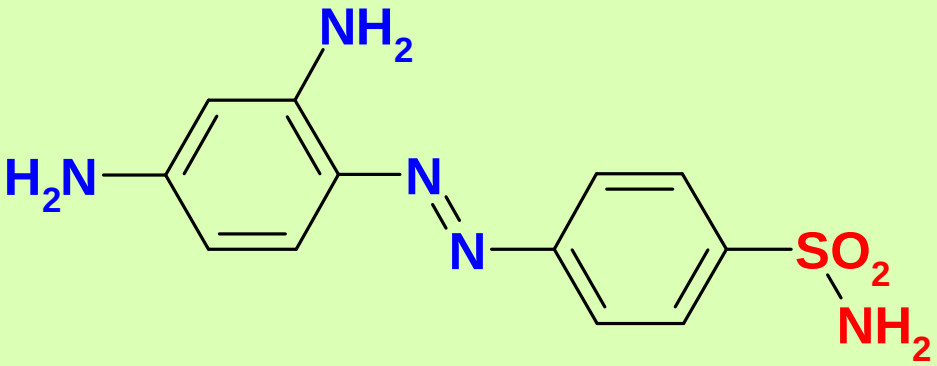


8.17 Salbutamol
β_2-mimetisch

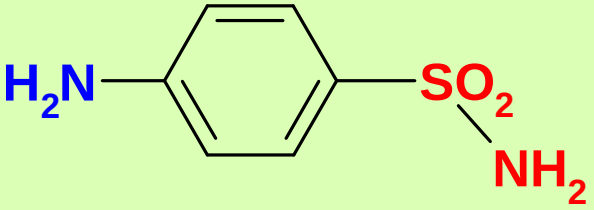


8.18 Clenbuterol
β_2-mimetisch

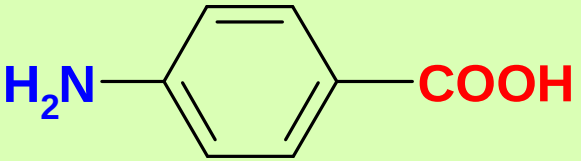
Sulfonamide



Sulfachrysoidin

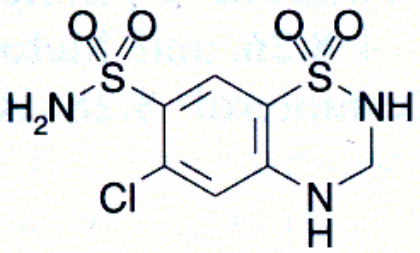


Sulfanilamid

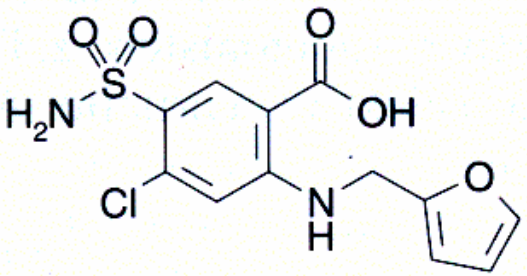


p-Aminobenzoesäure

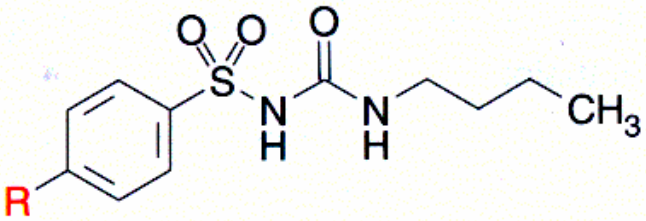
Sulfonamide – Optimierung von Leitstrukturen



8.19 Hydrochlorothiazid

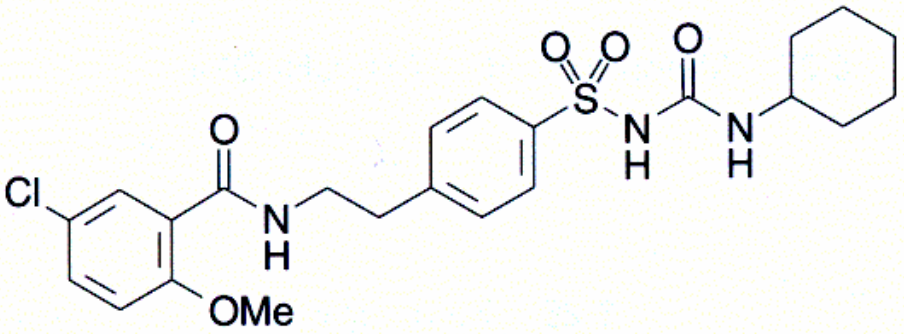


8.20 Furosemid



8.21 Carbutamid, R = NH_2

8.22 Tolbutamid, R = CH_3

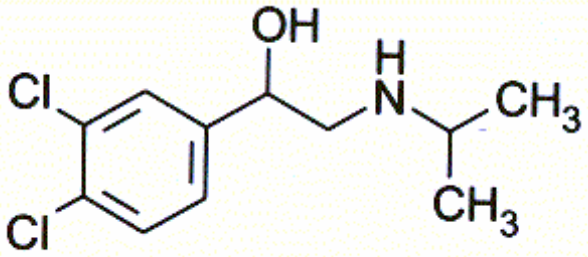


8.23 Glibenclamid

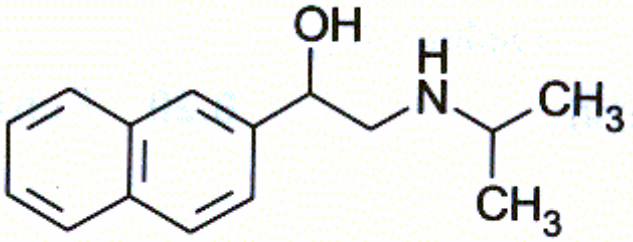
INHALT

- *Optimierung der Leitstruktur*
  - *Isosterie*
  - *Wirkoptimierung*
  - ***Agonist/Antagonist***
  - *Rationales Design*
- *Der Einfluß von Naturstoffen*

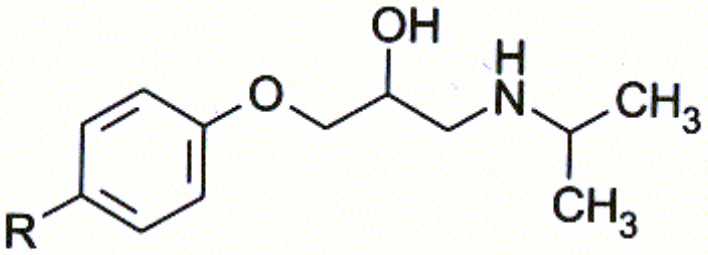
Agonisten vs. Antagonisten



8.24 DCl

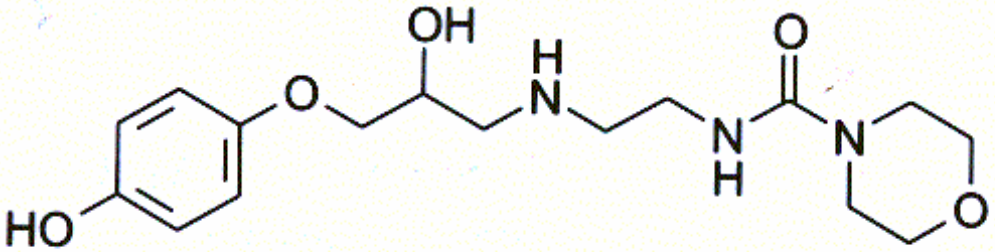


8.25 Pronethalol



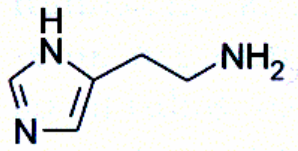
8.26 Practolol, R = $-NHCOCH_3$

8.27 Metoprolol, R = $-CH_2CH_2OMe$

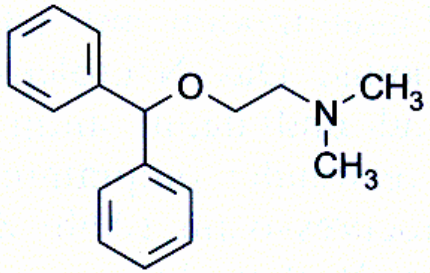


8.28 Xamoterol

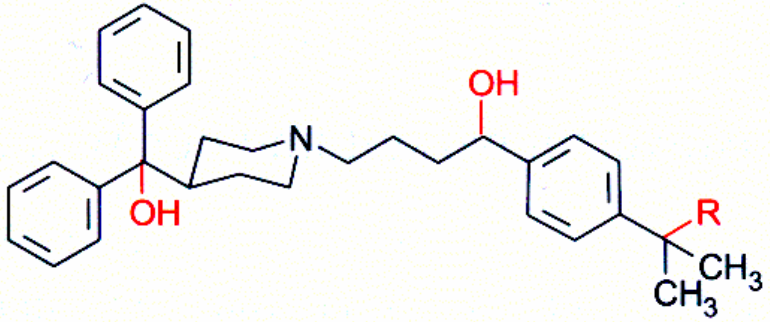
Einführung hydrophober Reste bzw. polarer Gruppen



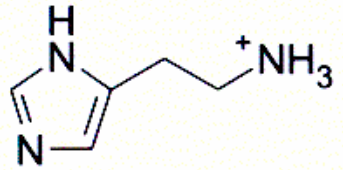
8.29 Histamin
H-Agonist



8.30 Diphenhydramin
unpolarer H_1-Antagonist (sedierend)

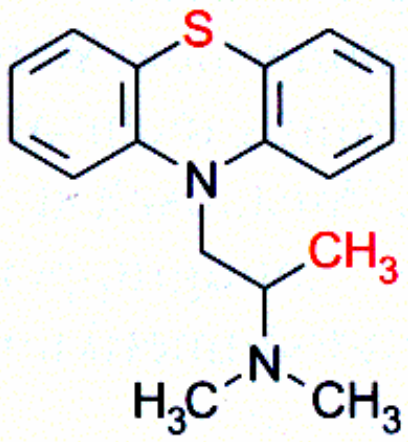


8.31 Terfenadin, R = CH_3
polarer H_1-Antagonist (nicht sedierend)
wirksamer Metabolit: R = -COOH

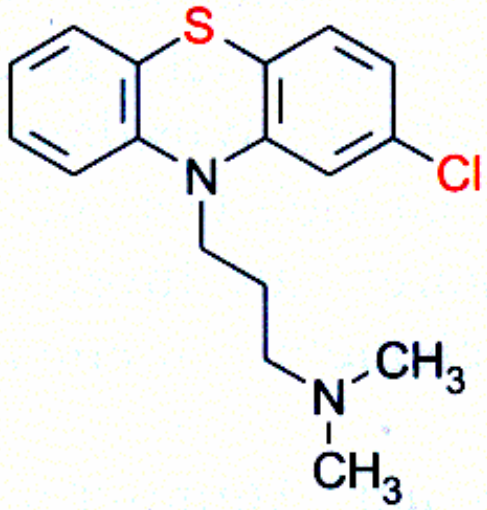


8.29 Histamin
(bei pH = 7 vorliegende, positiv geladene Form)

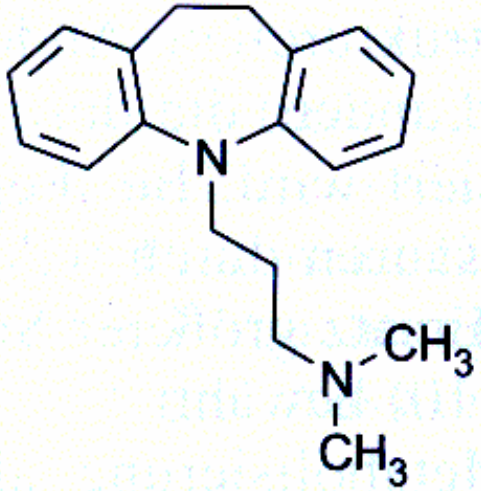
Ähnliche Struktur ? Ähnliche Wirkung



8.32 Promethazin
H_1-Antagonist

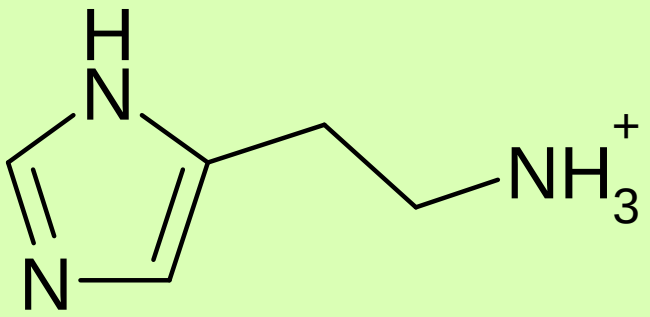


8.33 Chlorpromazin
Neuroleptikum

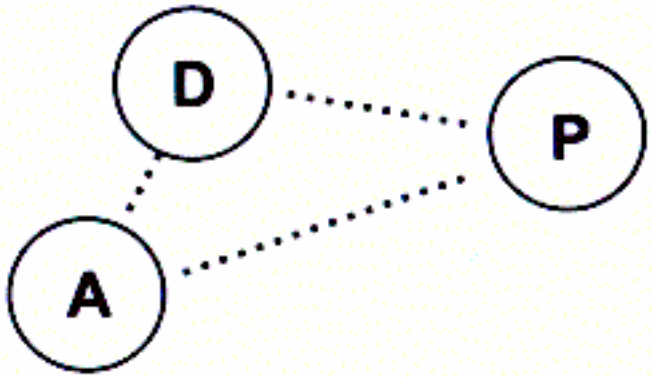


8.34 Imipramin
Antidepressivum

Rationales Drug Design



HISTAMIN



Pharmakophor

Abb. 8.10 Der Wirkstoff Histamin und der dieser Struktur entsprechende Pharmakophor (A = Akzeptor, D = Donor, P = positiv geladene Gruppe).

The rule of five - formulation

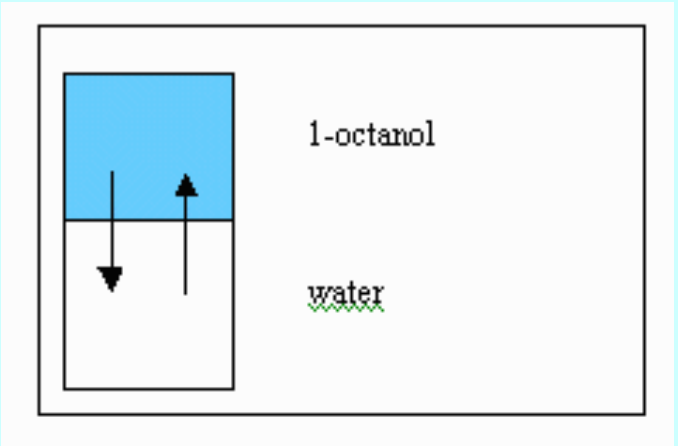
Poor absorption or permeation are more likely when:

- *There are more than **5** H-bond donors.*
- *The molecular weight is over **500**.*
- *The LogP is over **5**.*
- *There are more than **10** H-bond acceptors.*

Partition coefficient Definition

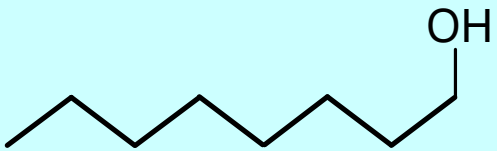
The ratio of the equilibrium concentrations of a dissolved substance in a two-phase system containing two largely immiscible solvents (water and n-octanol)

$$P = \frac{C_{(water)}}{C_{(oct.)}}$$

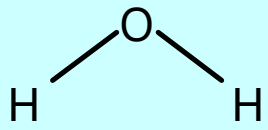


Partition coefficient (cont.)

1-octanol

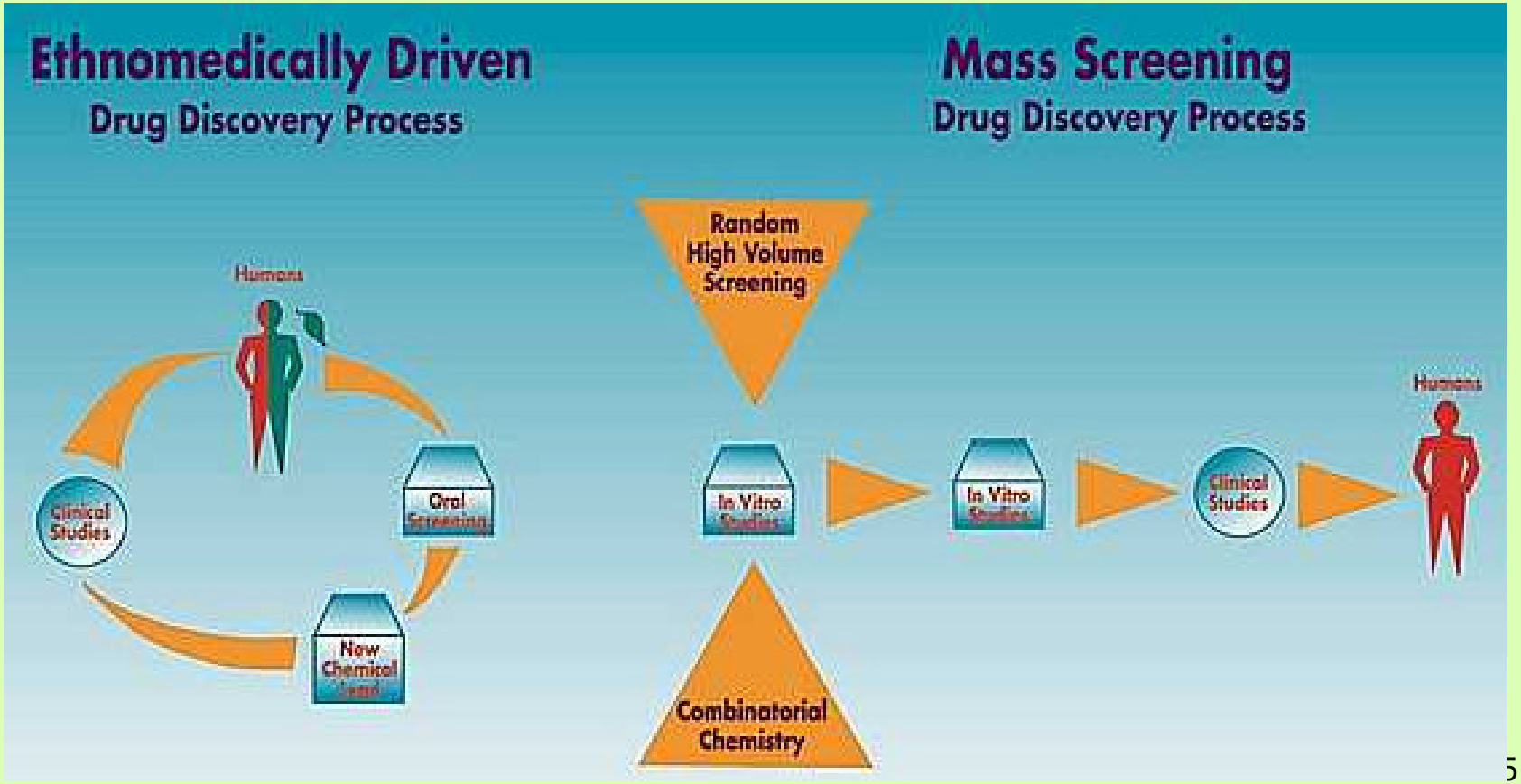


water



Since the differences are usually on a very large scale, $Log_{10}(P)$ is used.

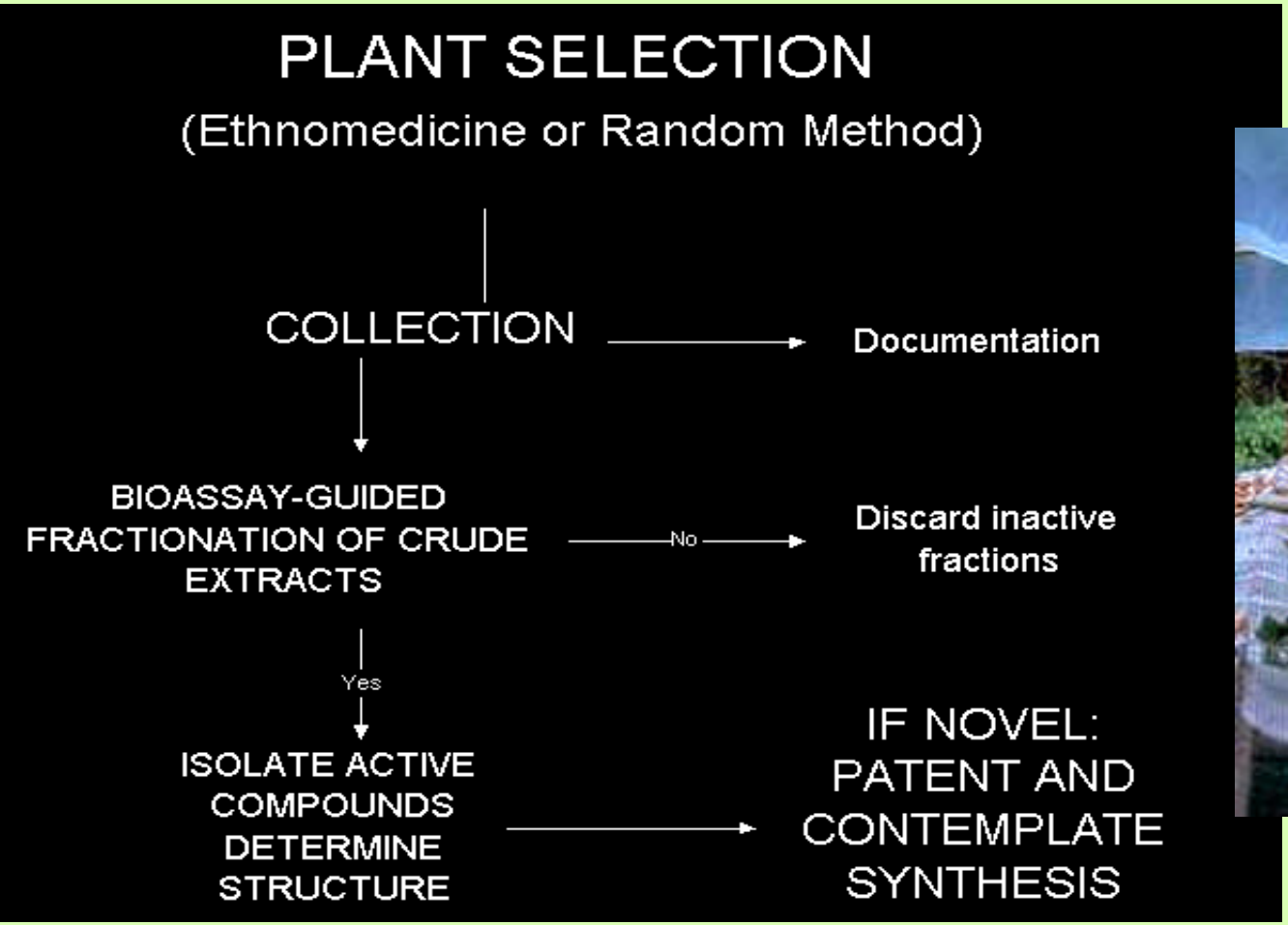
Natural Product-Based Drug Discovery



Natural Product Success Stories

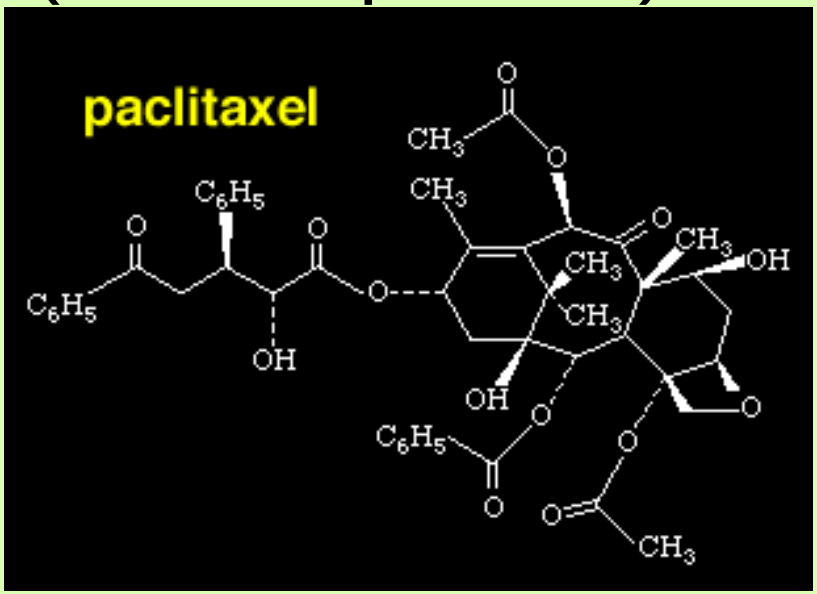
- Microorganisms: Antibiotics
- Plants:
  - Taxoids for cancer
  - Artemisinin for malaria
  - Huperzine A and galanthamine for Alzheimer
- Animals: Conotoxins as ultra-high potency analgetics

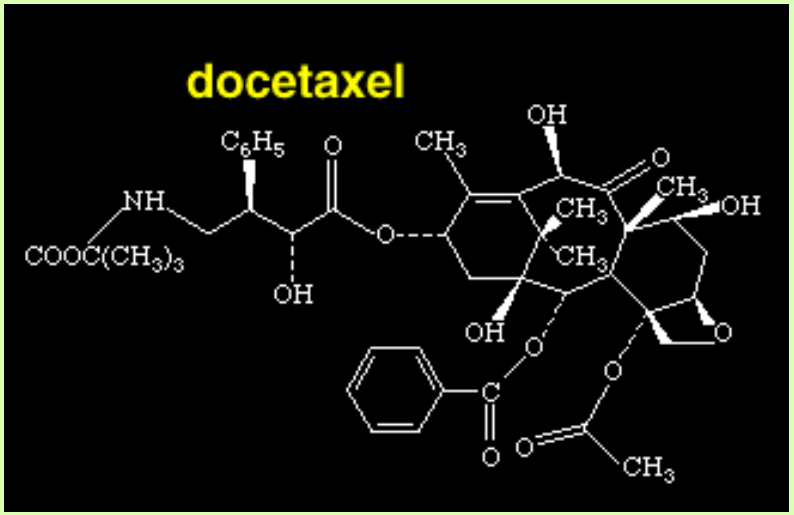
Phytopharmacology: Decision Tree



Phytopharmacology: Taxoids

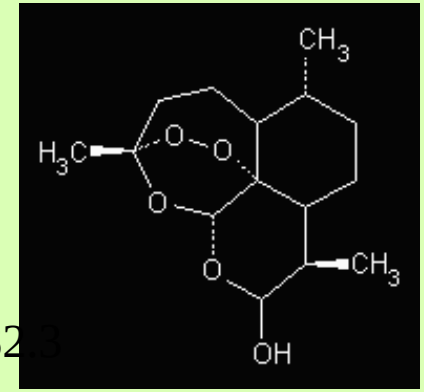
- Diterpene from *Taxus brevifolia*
- Most significant anticancer agent developed in the past two decades ("mitotic poison")





Phytopharmacology: Artemisinin

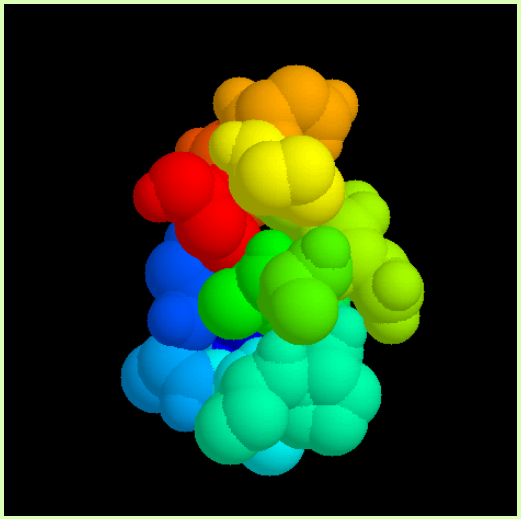
- Unusual sesquiterpene endoperoxide from *Artemisia annua* (Quinghaosu in Chinese traditional medicine)
- Lead compound for new generation of malaria therapeutics (including chloroquine- resistant and cerebral malaria)



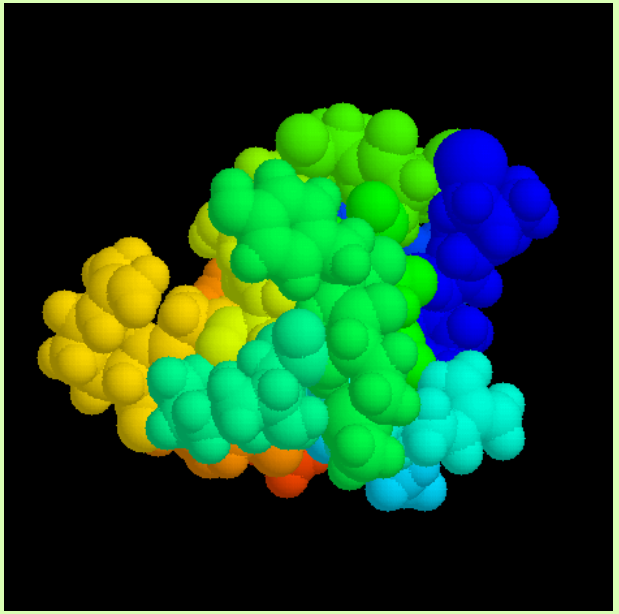
$C_{15}H_{22}O_5$
MW = 282.3

Marine Pharmacology: Conotoxins

- Peptide neurotoxins (receptor channel blockers) from molluscs (snails and shells)

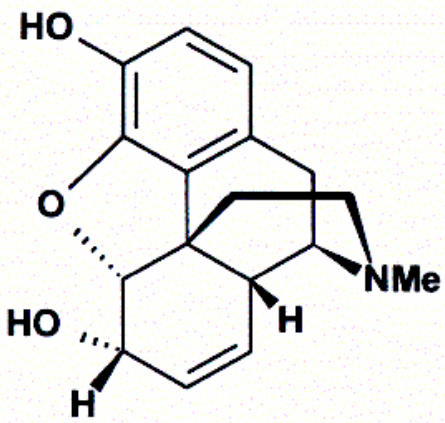


α-conotoxin PnIa:
nicotinic receptor blocker

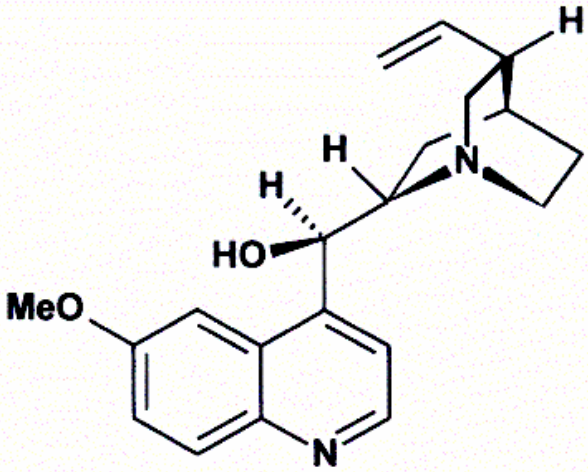


P-type Ca-channel blocker

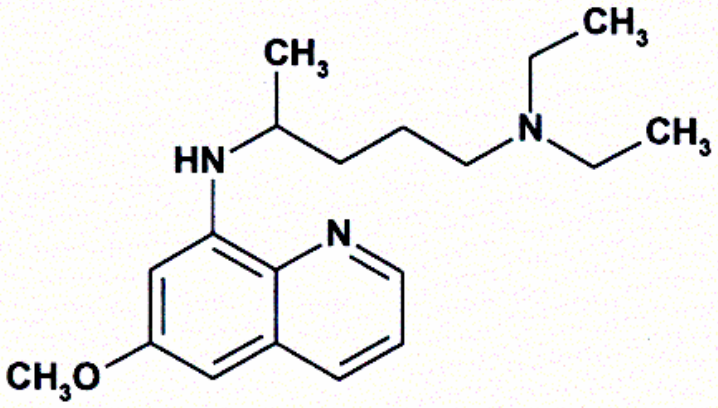
Klassische Naturstoffe



6: Morphine

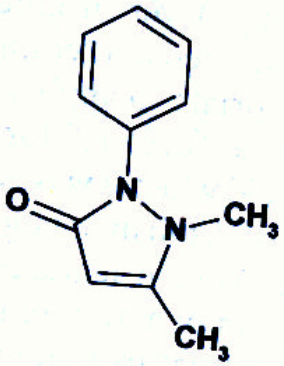


7: Quinine

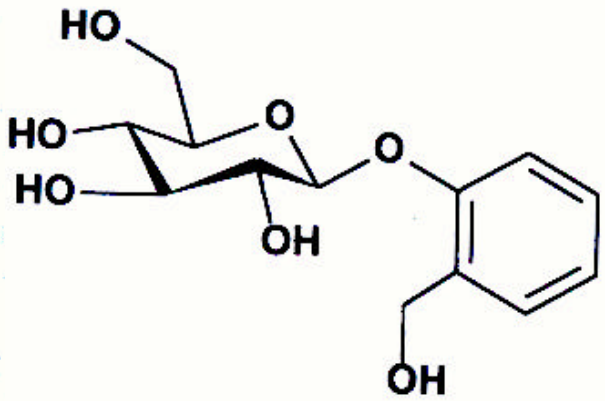


8: Pamaquine

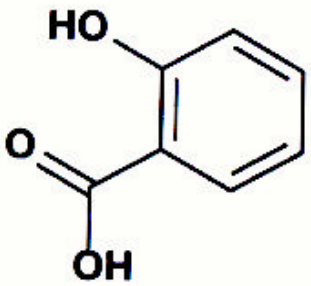
Aspirin



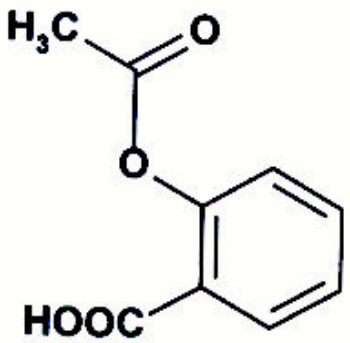
12: Antipyrine



9: Salicin

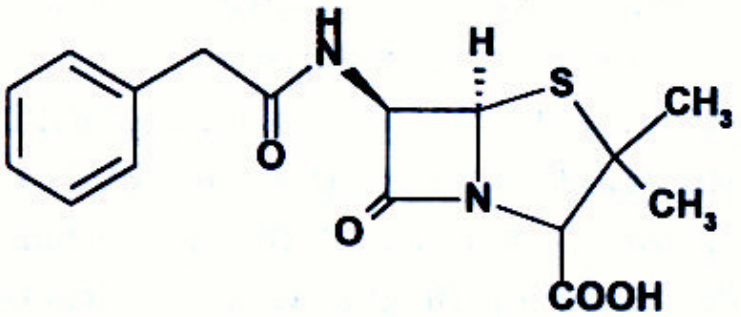


10: Salicylic acid

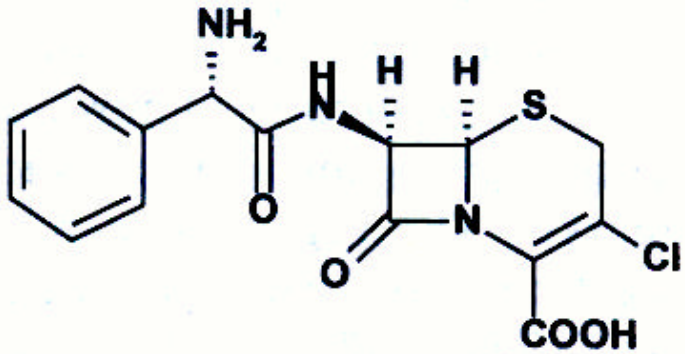


11: Acetylsalicylic acid

Antibiotika

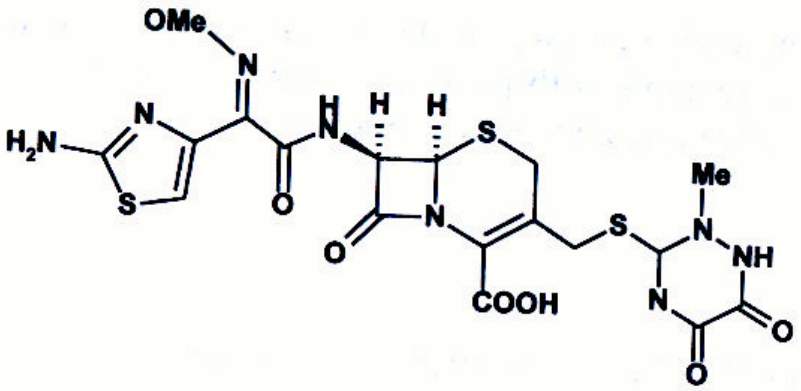


13: Penicillin G

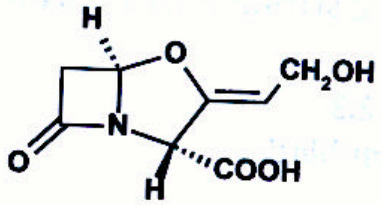


14: Cefaclor

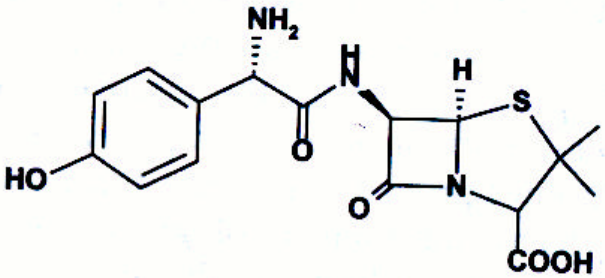
Antibiotika 2



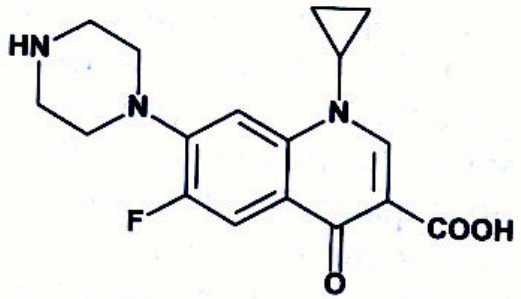
15: Ceftriaxone



16: Clavulanic acid



17: Amoxicillin



18: Ciprofloxacin