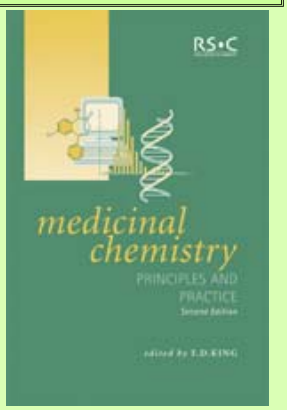
LVA *163.047*
Pharma- u. Agrowirkstoffe
P. Stanetty und U. Jordis

Pharmawirkstoffe
Ulrich Jordis

Lehrbücher 1

- F.D. King., Ed. **Medicinal Chemistry *Principles and Practice*** 2nd Ed.,

  The Royal Society of Chemistry 2002



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**

Lehrbücher 3

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

Chemiebibliothek TU vorhanden

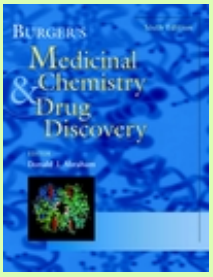
Lehrbücher 4

- 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

5

Lehrbücher 5

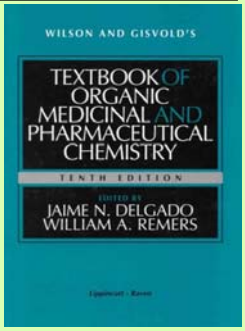
- **Burger's Medicinal Chemistry and Drug Discovery, 6 Volume Set**
  Donald J. Abraham
  ISBN: 0-471-37032-0
  Hardcover
  5568 pages
  February 2003



6

Lehrbücher 6

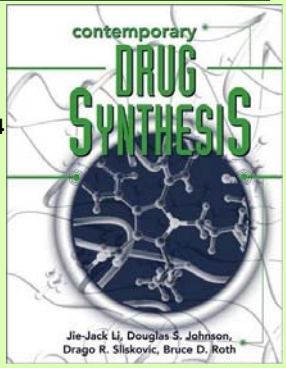
- **Textbook of Organic Medicinal and Pharmaceutical Chemistry. Tenth Edition. Edited by Jaime N. Delgado and William A. Remers. Lippincott-Raven, Philadelphia, PA. 1998.**



7

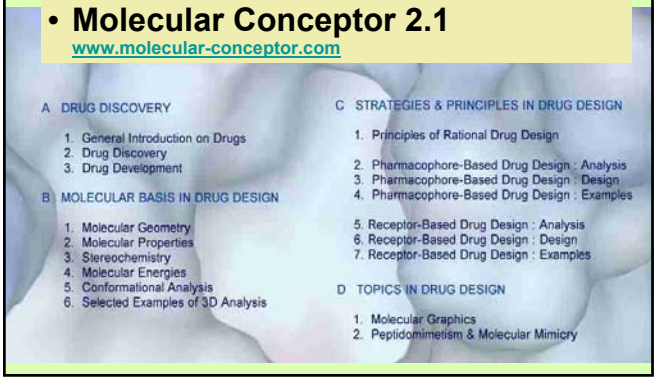
Lehrbücher 7

- **Contemporary Drug Synthesis. Jie-Jack Li, Douglas Johnson, Drago R. Sliskoviv, Bruce D. Roth 2004 John Wiley**
- **(TU-Chemiebibliothek)**

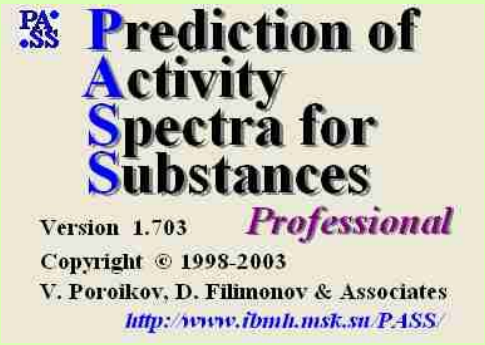


Software 1

- **Molecular Conceptor 2.1**
  www.molecular-conceptor.com

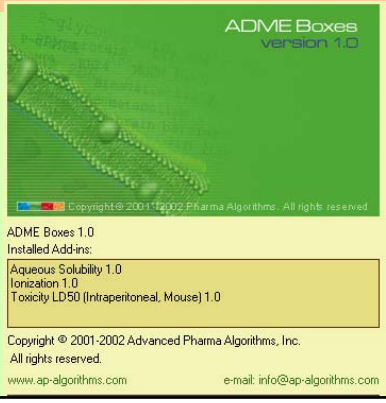


Software 2: PASS



10

Software 3: ADME Boxes



11

Software 4: BIOSTER

12

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

•

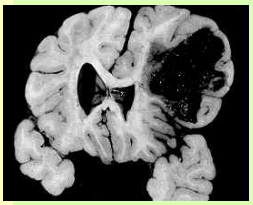
learning about the fundamental organic principles that underlie the design of drugs and how they function at the molecular level.

Major Treatment Categories

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

In need of solutions

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



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Suche nach Lösungen 2

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

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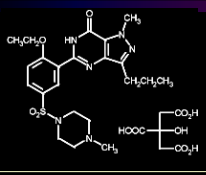
Some Recent Blockbuster Drugs



VIAGRA (sildenafil)
•Phosphodiesterase type V inhibitor for male erectile dysfunction
•Launched: March 1998; projected sales until end-98: $900 million

LIPITOR (atorvastatin)
•HMG-CoA reductase inhibitor for hyperlipidaemia
•1997 sales: $865 million

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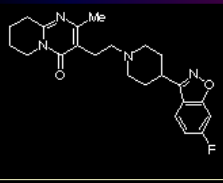
Some Recent Blockbuster Drugs



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

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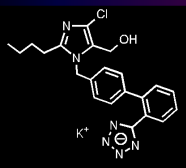
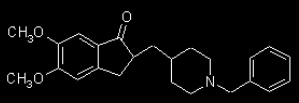
Some Recent Blockbuster Drugs



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



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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

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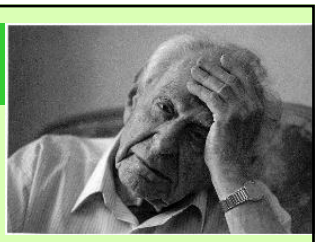
INHALT der Vorlesung

- ***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)

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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

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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, $-SO_2NH_2$,

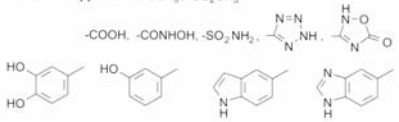

Abb. 8.1 Einige Beispiele für Möglichkeiten zum isosteren Austausch von Atomen bzw. Gruppen.

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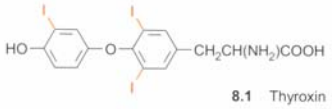
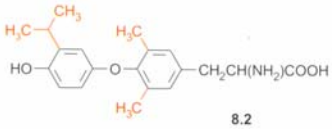
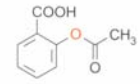
Isosterer Ersatz



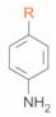
8.1 Thyroxin



8.2



8.3 Acetylsalicylsäure



8.4 R = -COOH
oder $-SO_2NH_2$

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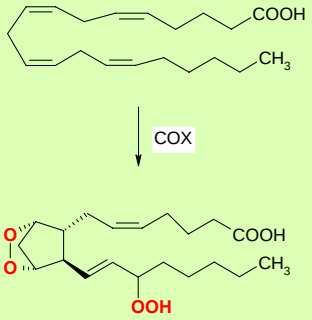
COX Wirkung



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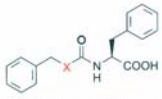
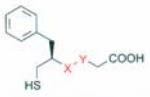
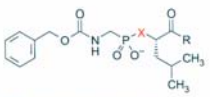
Isosterer Austausch



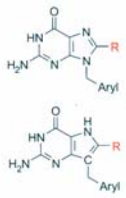
8.5 Thermolysininhibitoren
X = -O- oder $-CH_2-$



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

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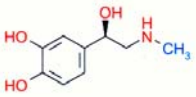
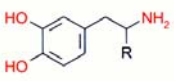
Wirkungsspektren

polare Moleküle:

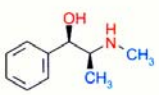


8.9 Adrenalin



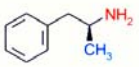
8.10 Dopamin, R = H
L-Dopa, R = COOH

mittlere Polarität:

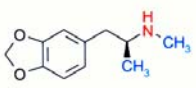


8.11 Ephedrin

unpolare Moleküle:

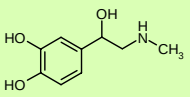


8.12 Amphetamin

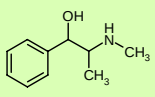


8.13 MDMA

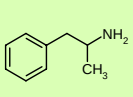
Wirkungsspektren



Strongest pKa(Acid):10±0.5
Strongest pKa(Base):8.6±0.5
Number of ionizable groups:3
AB/LogP:-0.41
Molecular Weight:183.20
No. of Hydrogen Bond Donors:4
No. of Hydrogen Bond Acceptors:4
TPSA:72.72
No. of Rotatable Bonds:3



No acid pKa.
Strongest pKa(Base):9.2±0.5
Number of ionizable groups:1
AB/LogP:0.93
Molecular Weight:165.23
No. of Hydrogen Bond Donors:2
No. of Hydrogen Bond Acceptors:2
TPSA:32.26
No. of Rotatable Bonds:3



No acid pKa.
Strongest pKa(Base):9.7±0.5
Number of ionizable groups:1
AB/LogP:1.66
Molecular Weight:135.21
No. of Hydrogen Bond Donors:2
No. of Hydrogen Bond Acceptors:1
TPSA:26.02
No. of Rotatable Bonds:2

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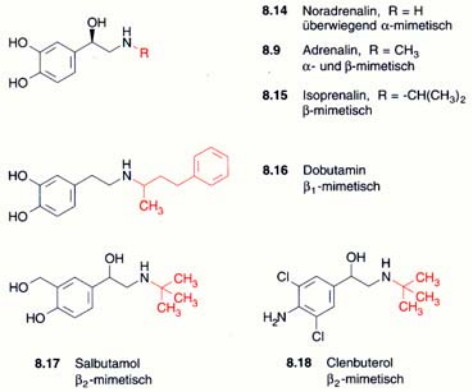
Selektivität von Catecholaminen



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

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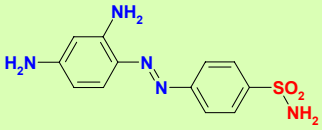
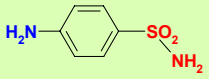
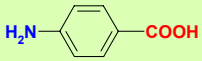
Sulfonamide



Sulfachrysoidin



Sulfanilamid



p-Aminobenzoesäure

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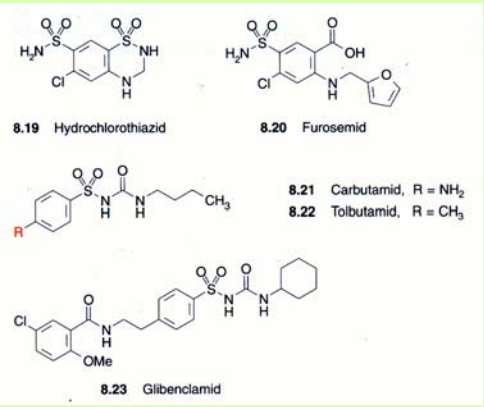
Sulfonamide – Optimierung von Leitstrukturen



8.19 Hydrochlorothiazid

8.20 Furosemid

8.21 Carbutamid, R = NH_2
8.22 Tolbutamid, R = CH_3

8.23 Glibenclamid

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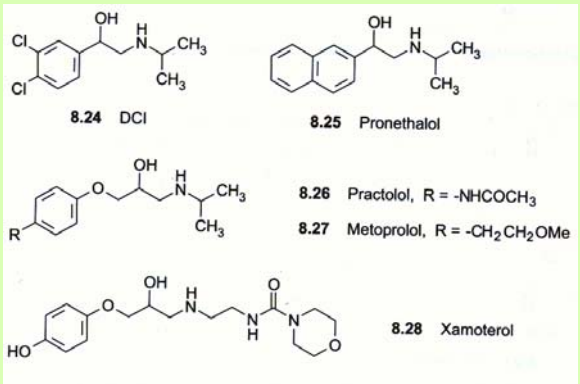
INHALT

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

Agonisten vs. Antagonisten



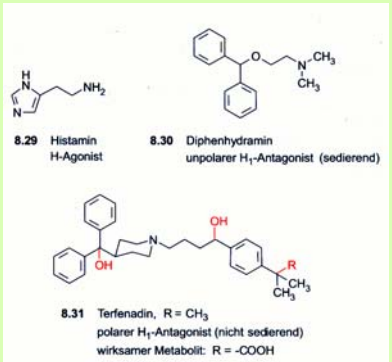
8.24 DCI

8.25 Pronethalol

8.26 Practolol, R = $-NHCOCH_3$
8.27 Metoprolol, R = $-CH_2CH_2OMe$

8.28 Xamoterol

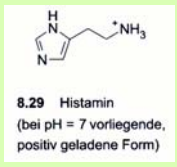
Einführung hydrophober Reste bzw. polarer Gruppen



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)

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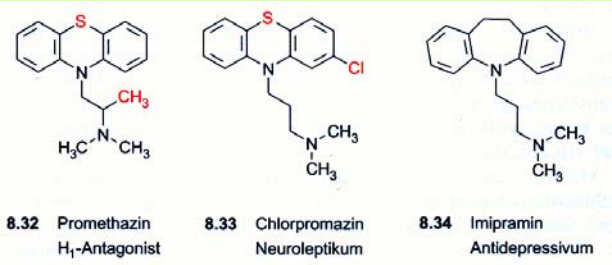
Ähnliche Struktur ≠ Ähnliche Wirkung



8.32 Promethazin
H_1-Antagonist

8.33 Chlorpromazin
Neuroleptikum

8.34 Imipramin
Antidepressivum

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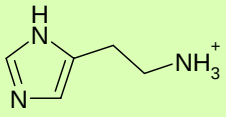
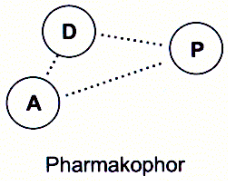
Rationales Drug Design



HISTAMIN



Pharmakophor

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

Objectives

Experimental and computational approaches for estimation of solubility and permeability of new candidate compounds.

This review deals only with solubility and permeability as barriers to absorption

(the 'A' part of ADME)

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Main sources of drug leads 1970's and 1980's

- Around 1970 – large empirically based screening programs.
- From then on – knowledge base grew for rational drug design.
- Most leads had already been in a range of physical properties previously known to be consistent with oral activity.

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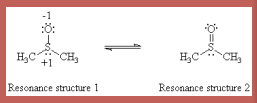
Main sources of drug leads 1989 and on

- HTS enabled screening of hundreds of thousands of compounds across in-vitro assays.
- Soon after – combinatorial chemistry.
- Rapid progress in molecular genetics – expression of receptors.
- Drugs were dissolved in DMSO (dimethyl sulfoxide)



Solubility of leads

- In DMSO, even very insoluble drugs could be tested.
- As a result – in vitro activity could be detected in compounds with very poor thermodynamic solubility properties.
- The physico-chemical profile of leads does not depend on compound solubility

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Solubility of leads (cont.)

- A reliable method to improve in-vitro activity – incorporating properly positioned lipophilic groups that can occupy a receptor pocket
- Adding a polar group that is not required for binding can be tolerated if it does not add to receptor binding.
- Therefore – compounds are more easily detected in HTS if they are larger and more lipophilic.

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Goal

Identifying calculable parameters of the selected compound library, related to absorption and permeability.

Target dataset with good absorption properties

- *Compounds that entered clinical Phase II stage.*
- *Poorly soluble compounds or compounds with poorer physical and chemical properties, as well as insoluble and non-permeable compounds would have been filtered out at earlier stages.*

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Target database

- Data taken from World Drug Index (WDI) – a computerized database of about 50000 drugs.
- USAN – United States adopted name
- INN – International Non-proprietary name
- These names are applied upon entry to phase II
- Database size – about 2500 compounds

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Selected parameters for testing

- *Molecular weight – known relationship between poor permeability and high molecular weight.*
- *Lipophilicity (ratio of octanol solubility to water solubility) – measured through LogP.*
- *Number of hydrogen bond donors and acceptors – High numbers may impair permeability across membrane bilayer*

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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.*

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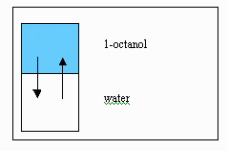
Partition coefficient Definition

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

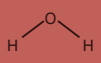
$$P = \frac{C_{(water)}}{C_{(oct.)}}$$



Partition coefficient (cont.)

1-octanol

water



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

MLogP – Moriguchi's correction

Problem – A straightforward counting of lipophilic atoms and hydrophilic atoms account for only 73% of the variance in the experimental LogP.

Therefore, corrections should be applied

Exception to the rule of five

Compound classes that are substrates for biological transporters:

- *Antibiotics*
- *Fungicides-Protozoacides - antiseptics*
- *Vitamins*
- *Cardiac glycosides.*

Computational calculations for new chemical entities

- *Applied to entities introduced between 1990-1993*
- *Average values:*
  - *MlogP=1.80*
  - *H-bond donor sum=2.53*
  - *Molecular weight =408*
  - *H-bond acceptor sum=6.95*
- *Alerts for possible poor absorption- 12%*

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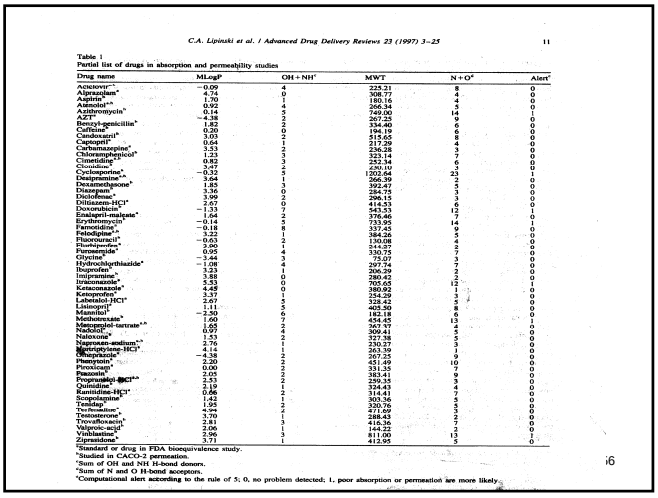

C.A. Lipinski et al. / Advanced Drug Delivery Reviews 23 (1997) 3–25 11

Table 1
Partial list of drugs in absorption and permeability studies

Drug name	MLogP	OH + NH[a]	MWT	N + O[b]	Alert[c]
Acitretin[d,e]	−0.09	4	225.21	8	0
Alprazolam[e]	4.74	0	308.77	4	0
Amiodarone[d]	1.70	1	180.16	4	0
Amrinone[d,e]	0.90	1	189.22	3	0
Azithromycin[e]	0.14	5	749.00	14	2
AZT[e]	−4.38	3	267.25	9	0
Benzyl-penicillin[e]	1.82	2	334.40	6	0
Caffeine[e]	0.20	0	194.19	6	0
Candoxatril[e]	3.03	2	515.65	8	0
Captopril[e]	0.64	1	217.29	4	0
Carbamazepine[e]	1.33	2	236.28	3	0
Chloramphenicol[e]	1.13	3	323.14	7	0
Cimetidine[e]	0.82	3	252.34	6	0
Clonidine[e]	3.67	2	230.10	3	0
Cyclosporine[e]	−0.32	5	1202.64	23	1
Desipramine[d,e]	3.64	1	266.39	2	0
Dexamethasone[e]	1.85	3	392.47	5	0
Diazepam[e]	3.36	0	284.75	3	0
Diclofenac[e]	3.97	2	296.15	3	0
Diltiazem-HCl[e]	2.57	0	450.99	5	0
Doxorubicin[e]	−1.33	7	543.53	12	2
Enalapril-maleate[e]	1.64	2	376.46	7	0
Erythromycin[e]	−0.14	5	733.95	14	1
Famotidine[e]	−0.18	8	337.45	9	0
Felodipine[d,e]	3.22	1	384.26	5	0
Fluorouracil[e]	−0.63	2	130.08	4	0
Flurbiprofen[e]	3.81	1	244.26	3	0
Furosemide[e]	0.95	4	330.75	7	0
Glycine[e]	−3.44	3	75.07	3	0
Hydrochlorothiazide[e]	−1.08	4	297.74	7	0
Ibuprofen[e]	3.23	1	206.29	2	0
Imipramine[e]	3.88	0	280.42	2	0
Irbesartan[e]	5.33	0	705.65	12	1
Isosorbide-dinitrate[e]	0.57	0	380.92	1	0
Ketoprofen[e]	3.37	1	254.29	3	0
Labetalol-HCl[e]	2.67	5	328.42	5	0
Lisinopril[e]	1.11	5	405.50	8	0
Mannitol[e]	−2.50	6	182.18	6	0
Methotrexate[e]	1.60	7	454.45	13	1
Metoprolol-tartrate[d,e]	1.65	2	267.37	4	0
Nadolol[e]	0.95	4	309.41	5	0
Naltrexone[e]	1.71	2	327.38	5	0
Naproxen-sodium[e,f]	2.76	1	252.28	3	0
Nitrofurazone-HCl[e]	4.14	1	263.39	1	0
Omeprazole[e]	−4.38	2	267.25	9	0
Phenytoin[e]	2.20	2	451.49	10	0
Piroxicam[e]	0.00	2	331.35	7	0
Prazosin[e]	2.05	2	383.41	9	0
Propranolol-HCl[d,e]	2.13	2	259.35	3	0
Quinidine[e]	2.57	1	324.43	4	0
Ranitidine-HCl[e]	0.06	3	314.41	6	0
Scopolamine[e]	1.43	1	303.36	5	0
Tenidap[e]	1.95	2	330.76	5	0
Terbutaline[e]	4.74	4	471.69	5	0
Testosterone[e]	3.79	2	288.43	2	0
Trovafloxacin[e]	2.81	3	416.36	7	0
Valproic-acid[e]	2.75	1	144.22	2	0
Vinblastine[e]	2.96	3	811.00	13	1
Ziprasidone[e]	3.71	1	412.95	5	0

[a]Standard or drug in FDA bioequivalence study.
[b]Studied in CACO-2 permeation.
[c]Sum of OH and NH H-bond donors.
[d]Sum of N and O H-bond acceptors.
[e]Computational alert according to the rule of 5; 0, no problem detected; 1, poor absorption or permeation are more likely.

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Validating the computational alert

- *A very coarse filter – discovers compounds whose probability of useful oral activity is very low.*
- *Goal – to shift the chemistry SAR toward the region where oral activity is reasonably possible.*
- *From there – more intensive pharmaceutical and metabolic testing is needed.*

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Conclusions

- The majority of drugs are intended for oral therapy, which is not predictable.
- The in-vitro nature of HTS techniques shifts leads toward lower solubility.
- Therefore – obtaining oral activity may be the rate limiting step.
- Computational methods in the early discovery setting may use as a filter that shifts SAR toward compounds with greater probability for oral activity

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Conclusions (cont)

- Calculations, however imprecise (give only probabilities), may help when choices must be made as to the design or purchase
- Accurate prediction of solubility of complex compound is still an “elusive target”

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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.*

60

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)

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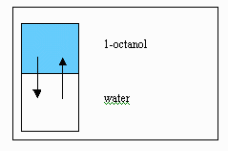
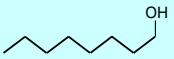


Partition coefficient (cont.)

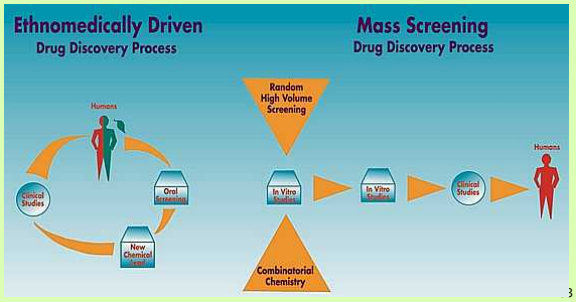
1-octanol



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

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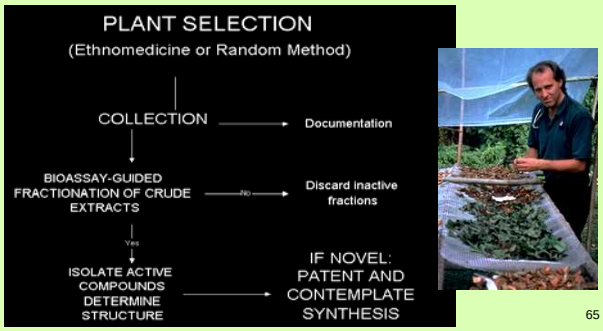
Phytopharmacology: Decision Tree



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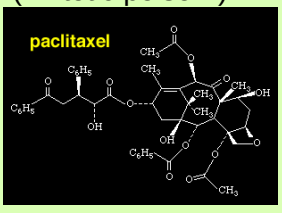
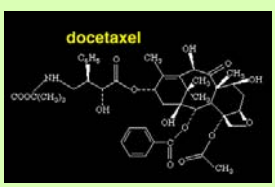
Phytopharmacology: Taxoids

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





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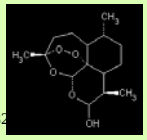
Phytopharmacology: Artemisinin

- 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

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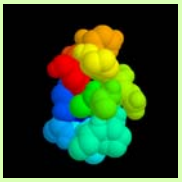
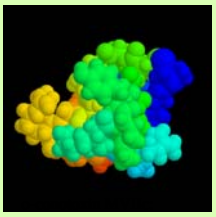
Marine Pharmacology: Conotoxins

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



α-conotoxin PnIa:
nicotinic receptor blocker



P-type Ca-channel blocker

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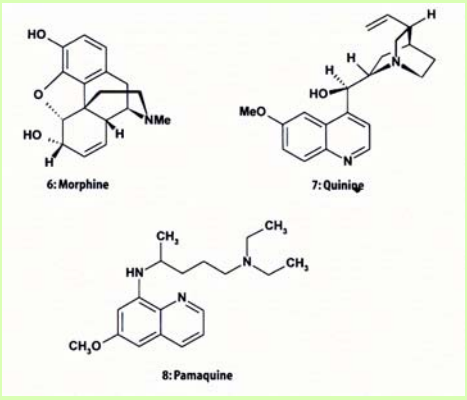
Klassische Naturstoffe



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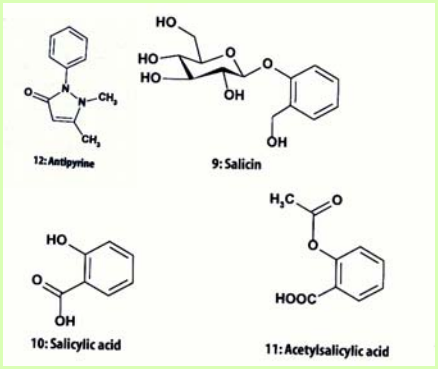
Aspirin



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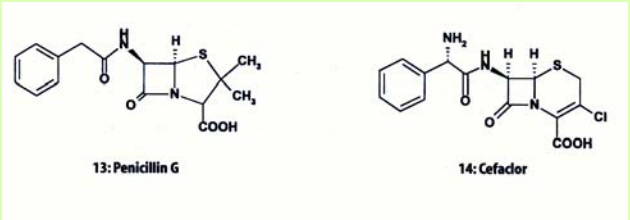
Antibiotika



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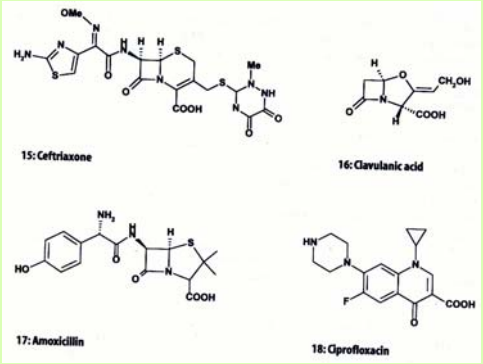
Antibiotika 2



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