Rheinische Friedrich-Wilhelms-Universität

Pharmaceutical Institute

Einführung in die Medizinische Chemie

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Literature (Selection)

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

H.-J. Böhm, G. Schneider, Protein-Ligand Interactions -
from molecular recognition to drug design, Wiley-VCH 2003
(Vol. 19 of Methods and principles in medicinal chemistry)

G. Thomas, Fundamentals of medicinal chemistry, Wiley 2003

R. B. Silverman, The organic chemistry of drug design and drug action, 2nd ed. Elsevier 2004

P. Kroogsgaard-Larsen, T. Liljefors, U. Madsen (eds), Textbook of drug design and discovery, 3rd ed., Taylor and Francis, 2002.

Early Natural Medicinal Chemistry

Drug	Discovery	Use
Opium	Ancient Greece	Pain
Belladonna	ca. 1500	Cosmetic, Poison
Coca	ca. 1688 Peru	Antifatigue
Ma-huang	China, BC	Asthma
Foxglove	ca. 1780, England	Heart failure

Medicaments from ethnobotanical lead structures (Selection)

• Acetylsalicylic acid	analgetic, antiphlogistic
• Codeine	analgetic, antitussive
• Ipecacuanha	emetic
• Pilocarpine	reduces high intraocular tension
• Quinine	antimalarial
• Reserpine	antihypertensive
• Theophylline	bronchospasmolytic
• Taxol	anti-cancer

Impact of Other Disciplines on Medicinal Chemistry

Discipline	gained importance in:
Organic Chemistry	19th Century
Biochem. Pharmacology	20th Century
Microbiology	ca. 1940
Molecular Biology	ca. 1950 (delayed effect)
Informatics	ca. 1980

Vorherrschende Trends in der Arzneistoff-Entwicklung im 20. Jahrhundert

bis in die 70er Jahre	Empirische Wirkstoff-Forschung; Zufalls-Screening, Testung an ganzen Organismen (in vitro)	Empirisch
80er/90er Jahre	Computer-gestütztes Wirkstoff-Design • Quantitative Struktur-Wirkungsbeziehungs-Analyse (QSAR) • Molecular Modelling - Röntgenstruktur - Kernresonanzspektroskopie (NMR) - Testung zunächst in vitro	Rational
90er Jahre	Kombinatorische Chemie; High-throuput screening (HTS)	Empirisch

Technologies and methods of the 21st century in drug development

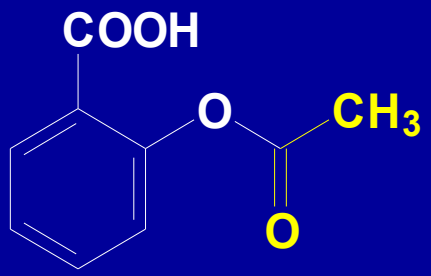
Genomics
Proteomics
Robotics
Bioinformatics
Combinatorial Chemistry
High throughput biology (HTB)
(many different targets)
PET / MRI

Genetics (individualized therapies?)
In silico screening
Disease-based approach (instead of target-based)

Rational & Empiric

Milestones of drug development: Synthetic drugs (selection)

- 1899 Acetylsalicylic acid (Aspirin®)
- 1907 Arsphenamin (Salvarsan®)
- 1963 Diazepam (Valium®)
- 1986 Zidovudine (Retrovir®)



Acetylsalicylsäure (Aspirin)

Azidothymidin (Retrovir)

Diazepam (Valium)

The Drug Market in Germany

Source: „Red list“ 2004

ca. 3.000 different drug substances

ca. 10.000 medicaments

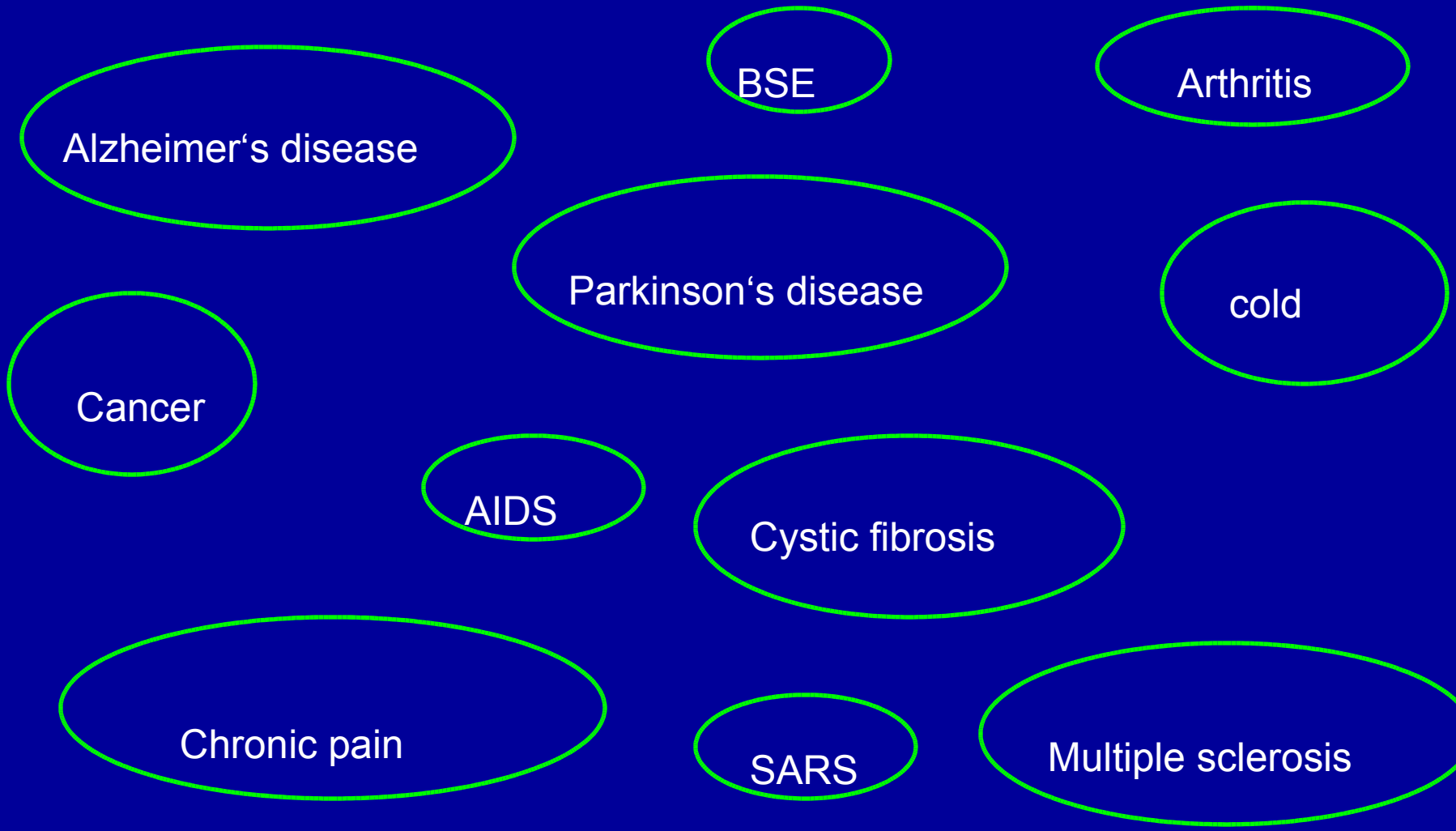
ca. 13.000 different galenic preparations

Altogether ca. 45.000 drugs are registered in Germany

Every year ca. 40 new drug substances are being registered world-wide

Do we need new drugs at all ?

WANTED:
Drugs for the treatment of:



Classification of Drugs

1. Pharmacodynamics
   Interference with (disturbed) metabolic processes
2. Chemotherapeutics
   Treatment of infections by parasites (e.g. bacteria...)
3. Diagnostics
   Detection of diseases; control of therapeutic success
4. Prophylactics
   Prophylaxis of diseases (e.g. immunization)
5. Substitution Therapeutics
   In case of lacking of essential substances (e.g. vitamins)

How to discover a drug?

- By accident
  - Screening of as many compounds as possible in a certain test system
    - Synthetic Compounds
    - Natural Products
  - Single compounds
  - Mixtures of compounds
    - Plant Extracts
    - Combinatorial Chemistry (Combichem)

How to discover a drug?

- By rational drug development
  - Natural, physiological substances serve as basis for drug development
    - e.g. oral contraceptives
  - Viral or bacterial enzymes serve as a basis for drug development
    - e.g. HIV protease: Development of HIV protease inhibitors by means of molecular modeling

Industrielle Arzneistoffentwicklung vor 100 Jahren

„Wenn ich nun verrate, daß wir im Jahre durchschnittlich **500-600** neue chemische Verbindungen hergestellt haben, von denen wir uns eine Wirkung versprachen, daß davon nur **ein halbes Dutzend** im besten Falle zur klinischen Prüfung gelangte, was durchaus noch nicht die Einführung in den Arzneischatz garantierte, so wird man aus der Fülle der Nieten die Schwierigkeiten dieses Forschens erkennen...

Nicht selten ging es so, daß am Vormittage die Chance des Erfinders noch rosenrot leuchtete und daß dann am Nachmittage die bösen Pharmakologen das Stäbchen über dem abgelehnten Produkte brachen. Wir teilten immer wieder das Los von Egmonts Klärchen: Himmelhoch jauchzend - zu Tode betrübt.“

Fritz Hoffmann

Drug development

Identificiation of a biologically active compound („drug“)
(lead structure, prototype)

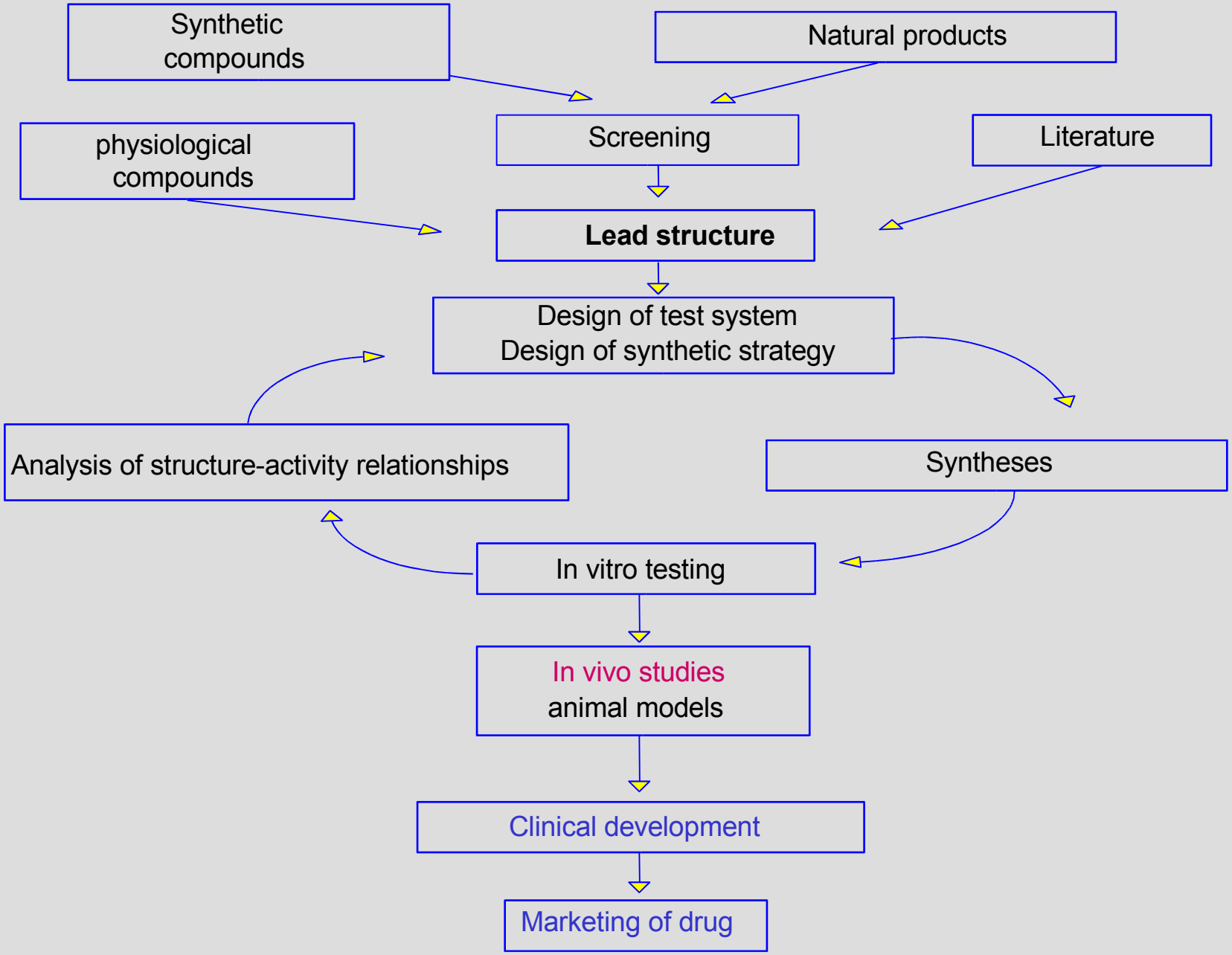
Development
Improvement of desired properties
Elimination or reduction of unwanted properties, side-effects etc.

drug

formulation

medicament

Drug design cycle

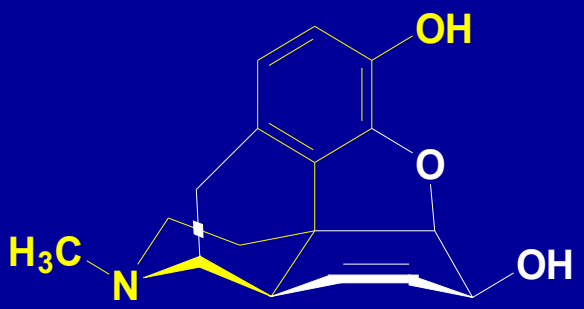


Drug development

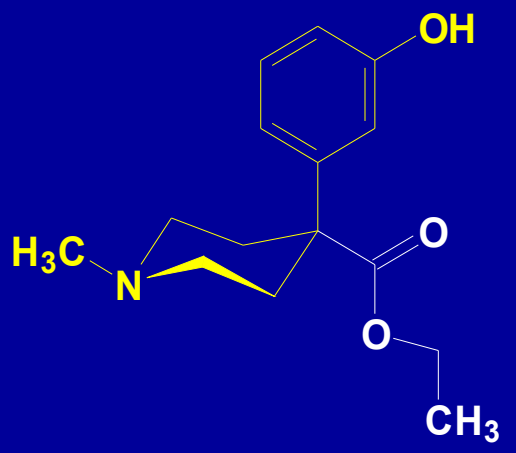
- Identification of the Pharmakophor
  - the minimal partial structure of a molecule that is responsible for the pharmacological effect

e.g. Morphine

Der Pharmakophor



Morphin
(Naturstoff)



Pethidin
(synthetisches Analogon)

Drug - Receptor Binding

- ionic binding
- ion - dipole interaction
- dipole - dipole interaction
- hydrogen bonding
- charge - transfer complexes
- hydrophobic interactions

Drug Development

- Search for bioactive conformation

- Rigid molecules with fixed active conformation show increased activity

Property-Based Drug Design

- Compounds may be very active in vitro, but inactive in vivo due to e.g.
  - high lipophilicity
  - low water solubility
  - high MW
- Absorption of a compound is generally bad if the molecule contains
  - > 5 H-bond donors or
  - > 10 H-bond acceptors or
  - has a MW > 500 or
  - a log P value > 5

Lipinski's „rule of five"

C.A. Lipinski, J. Pharmacol. Toxicol. Methods **44**, 235 (2000)

Drug Development

- Analysis of Structure-Activity Relationships (SAR)
  - QSAR (Quantitative SAR)
    - Electronic, lipophilic and sterical facters are correlated with biological activity (quantitative correlation)
  - Molecular Modeling
    - active analog approach
    - receptor modeling (protein modeling)

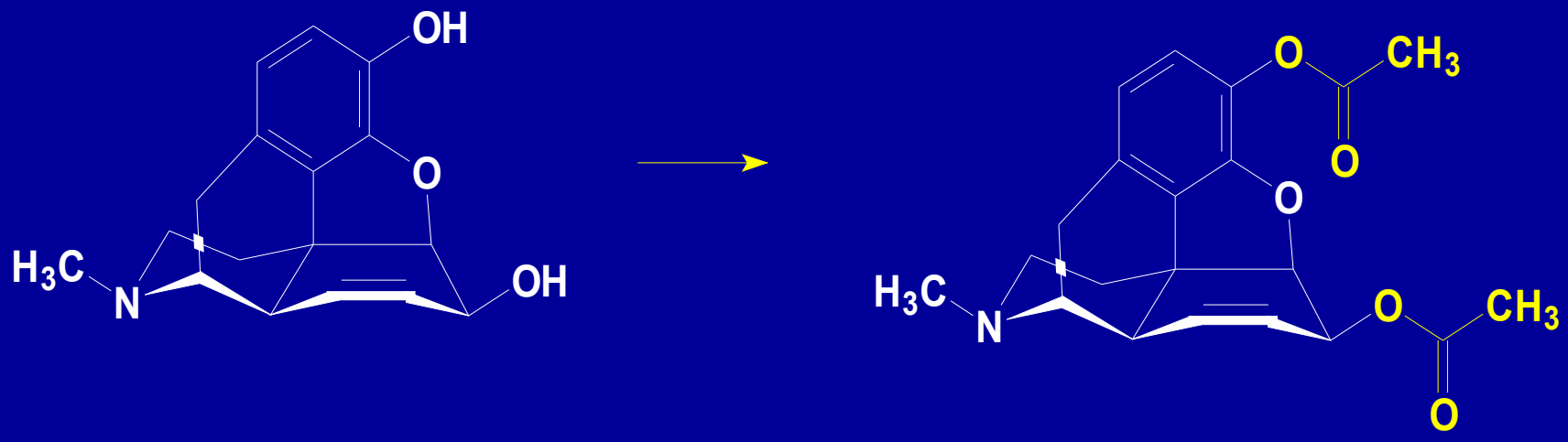
Drug Development

- Modification of functional groups
  - bioisosteric modification

- Modulation of bioavailability
  - prodrugs
  - drug targeting (e.g. antibodies attached)

Heroin

Lipophilic „prodrug“ of morphine with very high brain (central nervous system = CNS) bioavailability



Morphin

Diacetylmorphin = Heroin

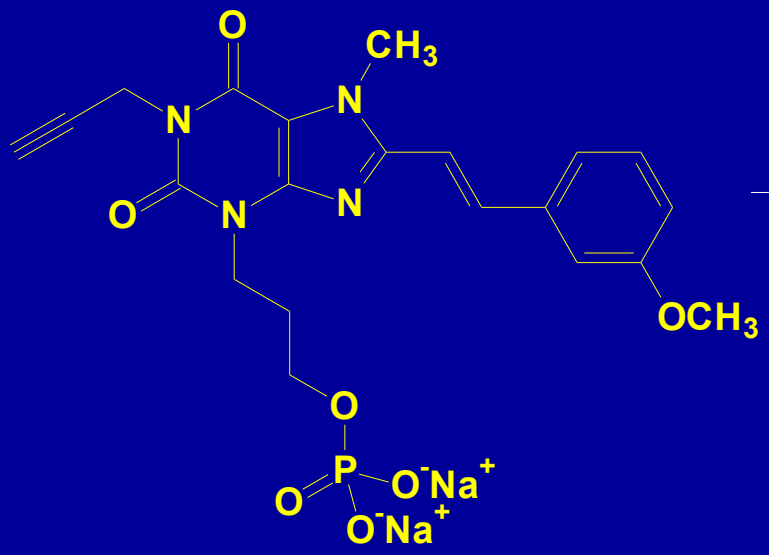
Highly polar compounds cannot or only poorly penetrate cell membranes

- poor peroral absorption
- poor penetration into the CNS
- poor penetration into cells (important in case of intracellular targets)

Lipophilic compounds with low water-solubility cannot be applied as injection

Water-soluble prodrugs for injection

- for preclinical animal studies
- for some indications

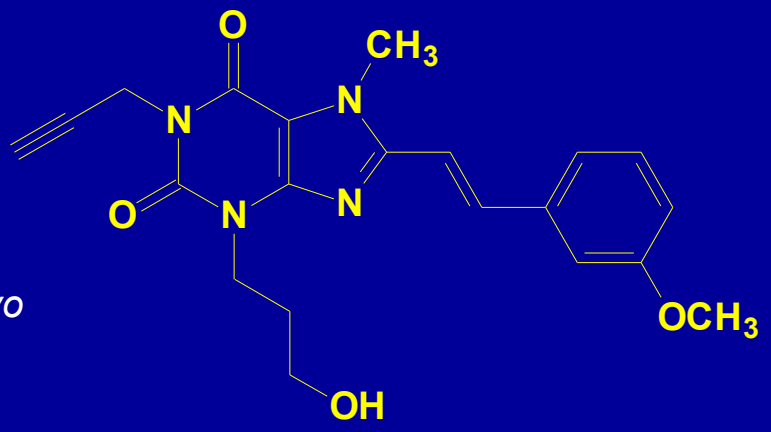


MSX-3

Prodrug

Phosphatases

in vitro and presumably *in vivo*



MSX-2

A_{2A} antagonist

- Solubility: 9 mg/ mL (17 mM/L)
- pH value of aqueous solution = 7
- stable in aqueous solution at room temperature

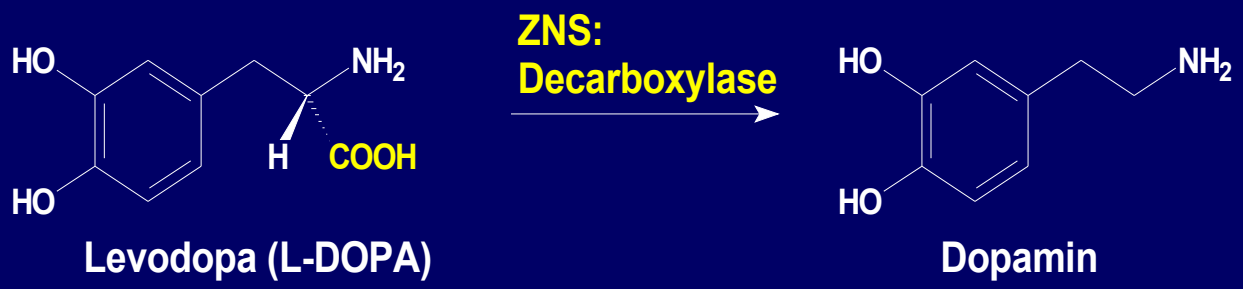
- high selectivity versus A_1 AR
- inactive at human A_{2B} and A_3 AR

in vivo studies using MSX-3:

Hauber et al., *NeuroReport* 9, **1998**, 1803.
Strömberg et al., *Eur. J. Neuroscience* 12, **2000**, 4033.
Ferré et. al., *Parkinsonism and Related Disorders* 7, **2001**, 235.
Diaz-Cabiale et al., *Neurosci. Lett.* **2002**, 324, 154.
Blum et al., *J. Neuroscience* **2003**, 23, 5361.

.....and many more

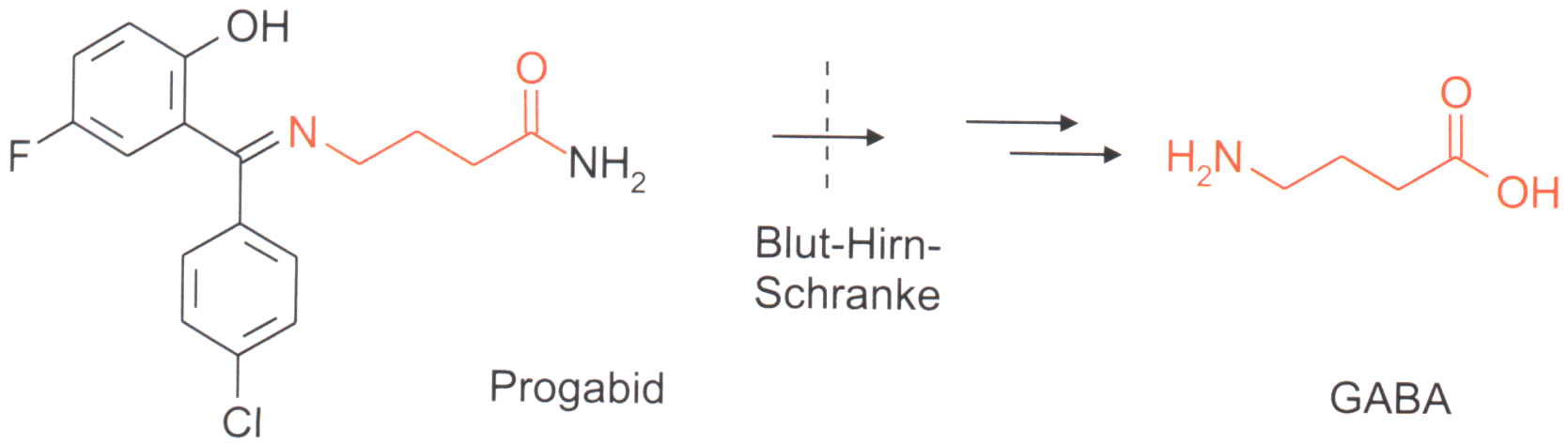
L-DOPA (Levodopa)



Levodopa (L-DOPA) **Dopamin**

- 1967 eingeführt; damals als "Wundermedikament" betrachtet
- heute immer noch der "Goldstandard"
- langanhaltende Wirkung trotz kurzer Halbwertszeit durch Speicherung
- **Kombination mit peripheren DOPA-Decarboxylase-Hemmstoffen (Carbidopa, Benserazid)**
- Die Wirkung nimmt im Laufe der jahrelangen Therapie ab bzw. schwankt sehr stark

Levodopa *(Dopaflex®)*
Levodopa + Carbidopa *(isicom®, NACOM®, Striation®)*
Levodopa + Benserazid *(Madopar®)*

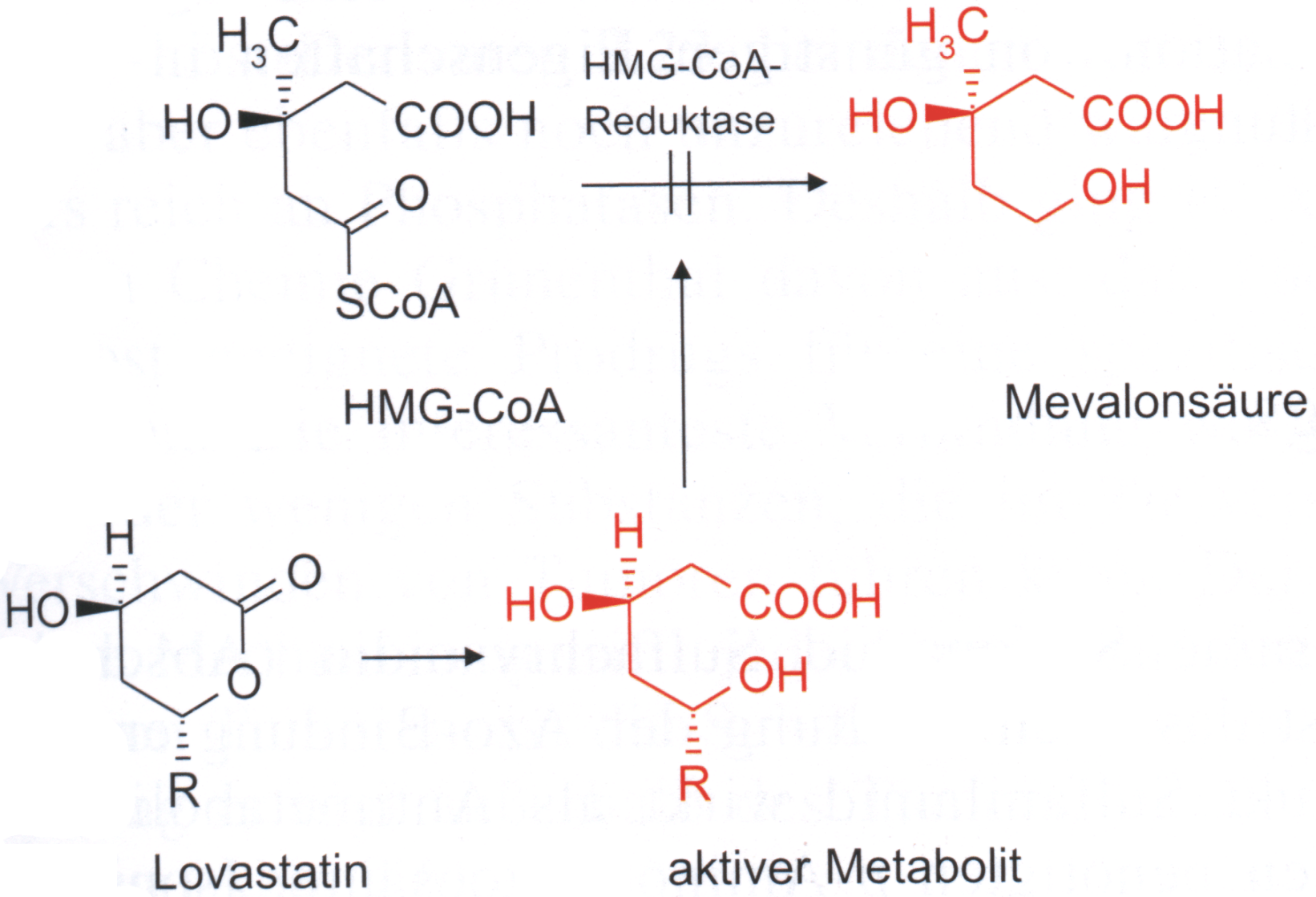

OH
O
F
N
NH2
Cl
Progabid
Blut-Hirn-
Schranke
O
H2N
OH
GABA

Example of „bioactivation“ of a drug by enzymes:

Cyclophosphamide (Endoxan®)

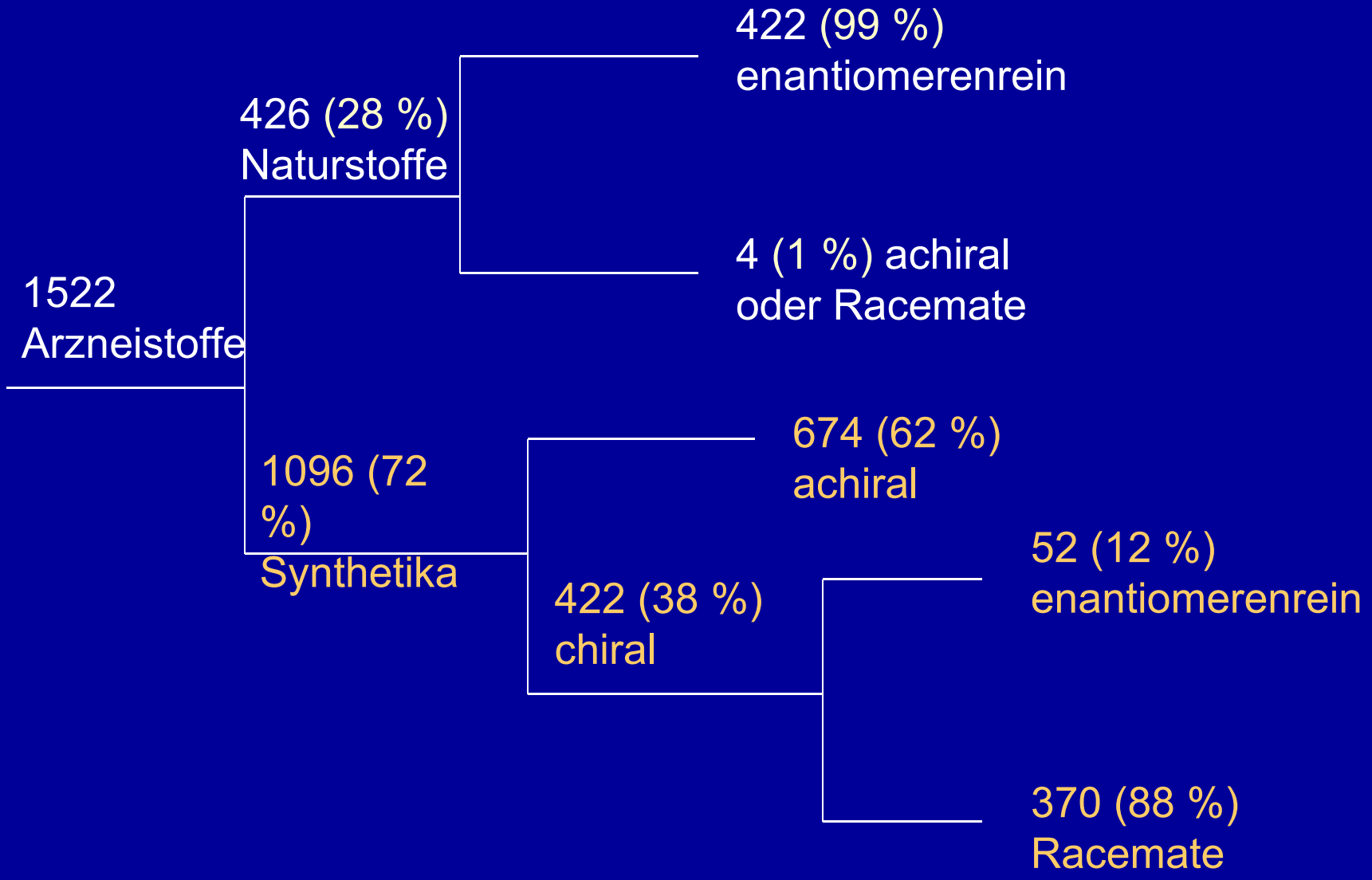
Examples of Common and Less Common Carrier Groups Used in Prodrug Design

- Carrier groups linked to a hydroxy group (R-OH)
  - Esters of simple or functionalized aliphatic carboxylic acids, e.g., R-O-CO-R′
  - Esters of carbamic acids, e.g., R-O-CO-NR′R″
  - Esters of amino acids (e.g., lysine), e.g., R-O-CO-CH(NH_2)R′
  - Esters of ring-substituted aromatic acids, e.g., R-O-CO-aryl
  - Esters of derivatized phosphoric acids, e.g., R-O-PO(OR′)(OR″)
  - (Acyloxy)methyl or (acyloxy)ethyl ethers, e.g., R-O-CH_2-O-CO-R′ or R-O-CH(CH_3)-O-CO-R′
  - (Alkoxycarbonyloxy)methyl or (alkoxycarbonyloxy)ethyl ethers, e.g., R-O-CH_2-O-CO-O-R′ or R-O-CH(CH_3)-O-CO-O-R′
  - O-glycosides
- Carrier groups linked to a carboxylic group (R-COOH)
  - Esters of simple alcohols or phenols, e.g., R-CO-O-R′
  - Esters of alcohols containing an amino or amido function, e.g., R-CO-O-$(CH_2)_n$-NR′R″ or R-CO-O-$(CH_2)_n$-CO-NR′R″ or R-CO-O-$(CH_2)_n$-NH-COR′
  - (Acyloxy)methyl or (acyloxy)ethyl esters of the type R-CO-O-CH_2-O-CO-R′ or R-CO-O-CH(CH_3)-O-CO-R′
  - Hybrid glycerides formed from diacylglycerols, e.g., R-CO-O-CH(CH_2-O-CO-R′)$_2$
  - Esters of diacylaminopropan-2-ols, e.g., R-CO-O-CH(CH_2-NH-COR′)$_2$
  - *N*,*N*-dialkyl hydroxylamine derivatives, e.g., R-CO-O-NR′R″
  - Amides of amino acids (e.g., glycine), e.g., R-CO-NH-CH(R′)-COOH
- Carrier groups linked to an amino or amido group (RR′-NH)
  - Amides formed from simple or functionalized acyl groups, e.g., RR′N-CO-R″
  - Amides cleaved by intramolecular catalysis (with accompanying cyclization of the carrier moiety)
  - Alkyl carbamates, e.g., RR′N-CO-O-R″
  - (Acyloxy)alkyl carbamates, e.g., RR′N-CO-O-CH(R″)-O-CO-R‴
  - (Phosphoryloxy)methyl carbamates, e.g., RR′N-CO-O-CH_2-O-PO_3H_2
  - *N*-(acyloxy)methyl or *N*-(acyloxy)ethyl derivatives, e.g., RR′N-CH_2-O-CO-R″ or RR′N-CH(CH_3)-O-CO-R″
  - *N*-Mannich bases, e.g., RR′N-CH_2-NR″R‴
  - *N*-(*N*,*N*-dialkylamino)methylene derivatives of primary amines, e.g., RN=CH-NR′R″
  - *N*-α-hydroxyalkyl derivatives of peptides
  - Imidazolidinone derivatives of peptides
  - Oxazolidines of ephedrines and other 1-hydroxy-2-aminoethane congeners

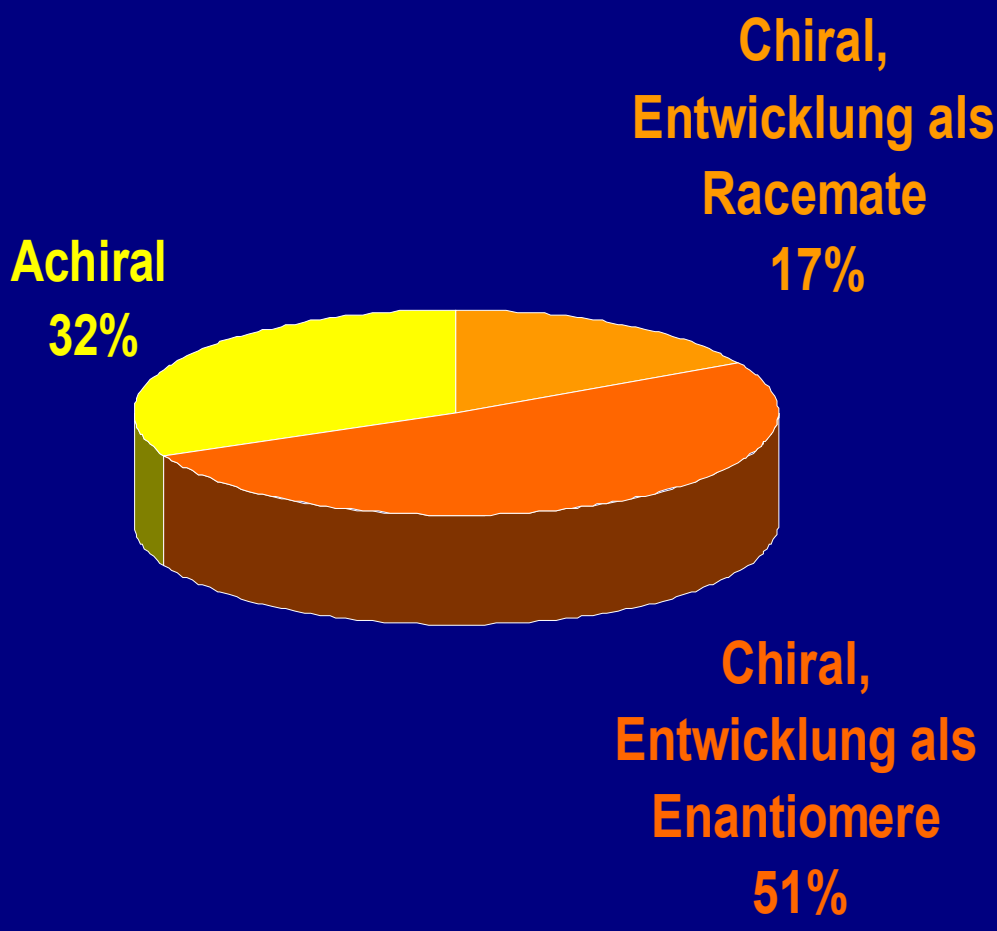

H3C
HO
COOH
O
SCoA
HMG-CoA-
Reduktase
H3C
HO
COOH
OH
HMG-CoA
Mevalonsäure
H
HO
O
O
R
H
HO
COOH
OH
R
Lovastatin
aktiver Metabolit

Chirale Arzneistoffe: Racemate oder reine Enantiomere?

Statistik von 1982

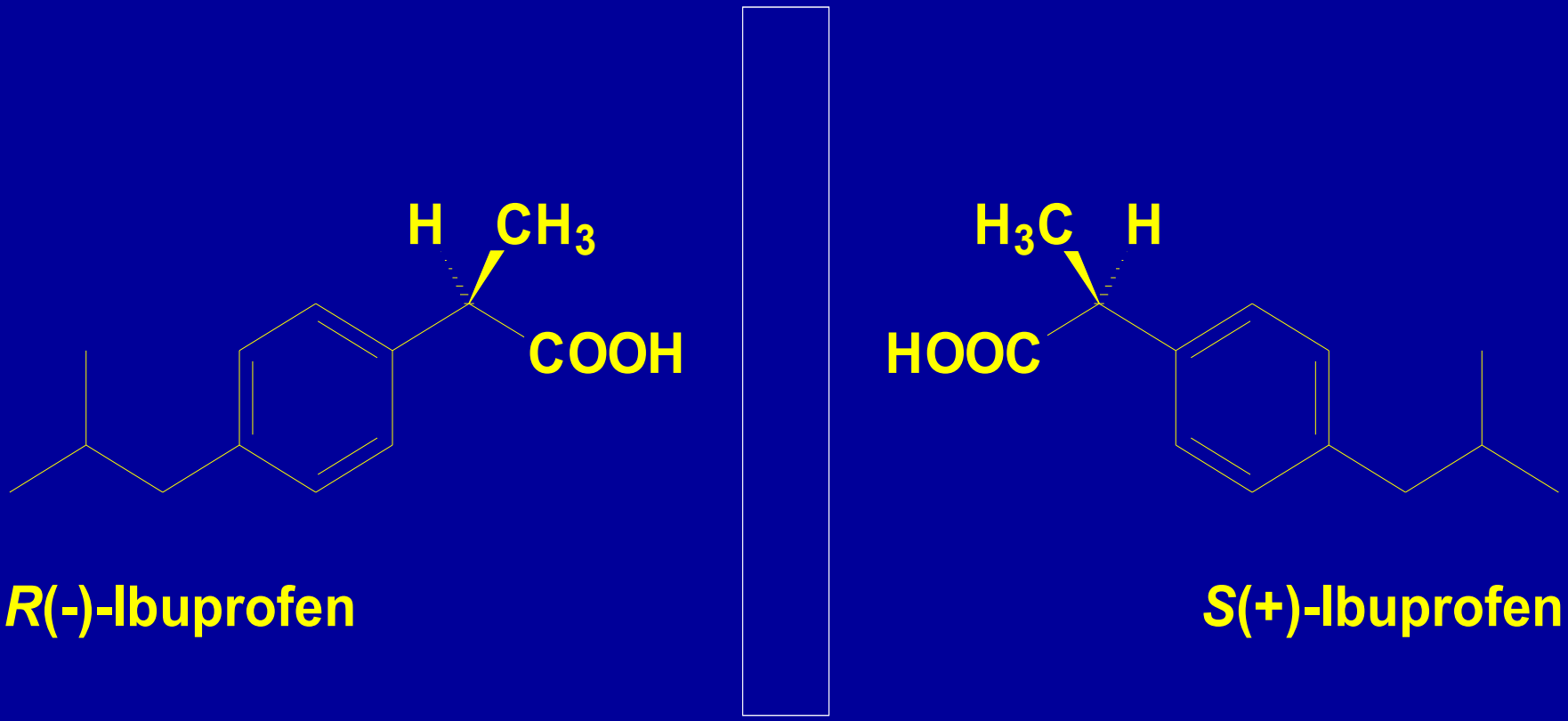


Zwei Drittel der Arzneistoffe in der Entwicklung sind chiral



Chiralität am Beispiel des Arzneistoffs Ibuprofen: Bild und Spiegelbild lassen sich nicht zur Deckung bringen

Die Enantiomere zeigen unterschiedliche pharmakologische Eigenschaften



***R*(-)-Ibuprofen**

***S*(+)-Ibuprofen**

Peptidomimetics

- Many biologically active compounds are peptides.

- Peptides are unstable due to cleavage by peptidases
- Absorption of peptides from the gut is generally low

- Solution: Development of non-peptide compounds, that mimic the structures of peptides, but are stable and exhibit increased absorption.

Phasen der klinischen Prüfung

Phase I	Erstanwendung am Gesunden ("Probanden") Suche nach dosisabhängigen Wirkungen Verträglichkeit unterschiedlicher Dosierungen Untersuchungen zur Aufnahme, Verteilung, Verstoffwechselung und Ausscheidung des Wirkstoffs
Phase II	Erstanwendung am Patienten Erwünschte und unerwünschte Wirkungen beim Patienten Dosisfindung
Phase III	Nachweis der therapeutischen Wirksamkeit und der Unbedenklichkeit an größeren Patientengruppen Vergleichende Nutzen-Risiko-Untersuchungen zu bereits bekannten Arzneimitteln
Zulassung	
Phase IV	Anwendungsüberwachung nach der Zulassung Nutzen-Risiko-Überwachung des Arzneimittels unter therapeutischen Routinebedingungen

The development of a new drug

takes ca. 14 Jahre

Preclinical phase:	ca. 6 a
Clinical phases I-III:	ca. 8 a

and costs ca. 150-400 Mio. € or even more...