From Leads to Drugs

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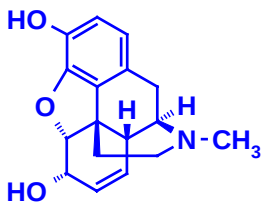
University of Heidelberg

Strategies in Lead Optimization

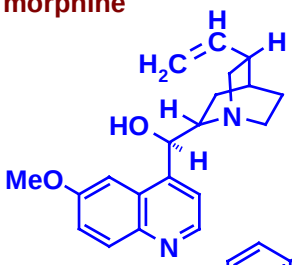
- Bioisosteric replacement of atoms and groups
- Formation of rings - rigidization
- Cleavage of rings
- Modification of side chains and linkers
- „Me too“ and „me better“ approach
- Use of „privileged“ structural elements
- Selective optimization of side activities (SOSA)
- Virtual screening
- Fragment-based ligand design
- Structure-based ligand design
- Computer-aided ligand design
- Modification of ADME properties
- Prodrugs, soft drugs and targeted drugs

Lead Structures: Natural Products from Plants



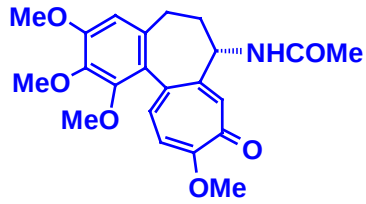
morphine

caffeine



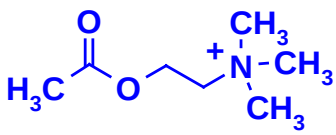
quinine

ephedrine

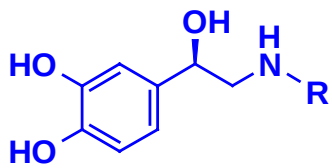


colchicine

Lead Structures: Endogenous Neurotransmitters

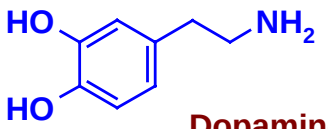


Acetylcholine

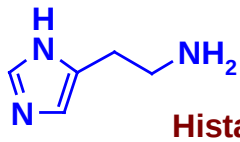


Epinephrine, R = CH_3

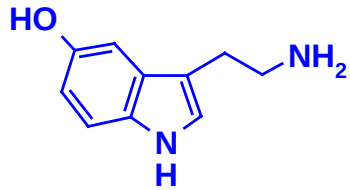
Norepinephrine, R = H



Dopamine



Histamine



Serotonin (5-HT)

Isosteric Replacement of Atoms and Groups

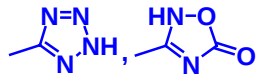
Substituents: F, Cl, Br, I, CF_3 , NO_2
Methyl, Ethyl, Isopropyl, Cyclopropyl, t.-Butyl,
-OH, -SH, $-NH_2$, -OMe, $-N(Me)_2$

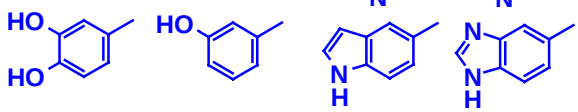
Linkers: $-CH_2-$, -NH-, -O-
$-COCH_2-$, -CONH-, -COO-
>C=O, >C=S, >C=NH, >C=NOH, >C=NOAlkyl

Atoms and Groups in Rings: -CH=, -N=
$-CH_2-$, -NH-, -O-, -S-,
$-CH_2CH_2-$, $-CH_2-O-$, -CH=CH-, -CH=N-

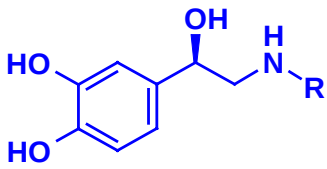
Large Groups: $-NHCOCH_3$, $-SO_2CH_3$

-COOH, -CONHOH, $-SO_2NH_2$,

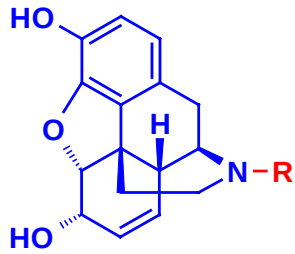




Agonists and Antagonists

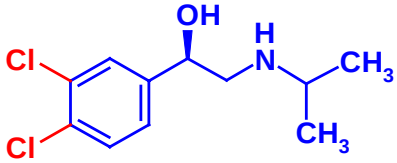


R = H , norepinephrine
R = CH_3, epinephrine
R = $CH(CH_3)_2$, isoproterenol

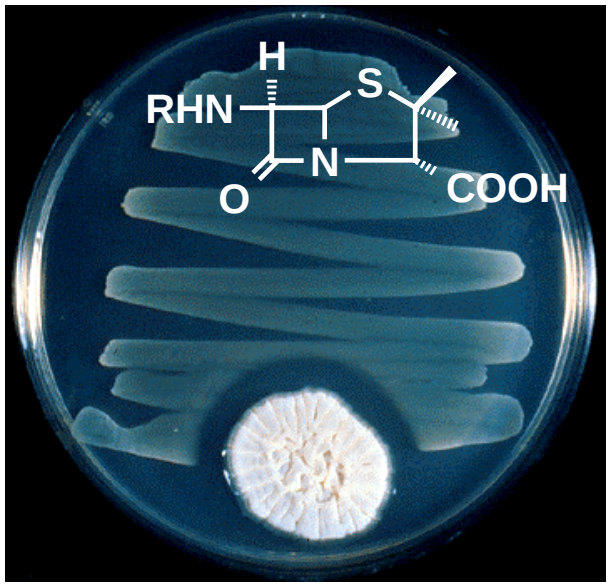


morphine
R = CH_3
(agonist)

nalorphine
R = CH_2-CH=CH_2
(antagonist)



dichloroisoproterenol, DCI

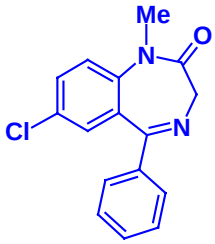


Me too,
me better,
me first,
me only

Several generations of penicillin analogs

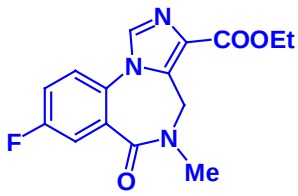
1. active
2. orally available
3. broad spectrum
4. resistant strains

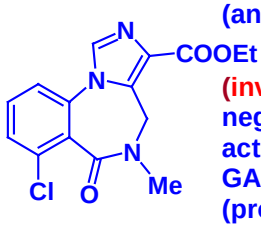
Activities of Benzodiazepines



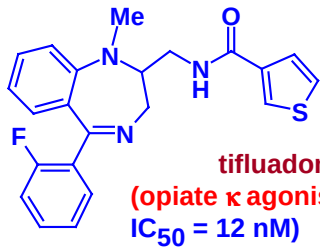
diazepam (agonist)
positive intrinsic activity at the $GABA_A$ receptor (tranquilizer)

flumazenil (antagonist)
no intrinsic activity at the $GABA_A$ receptor (antidot in intoxication)





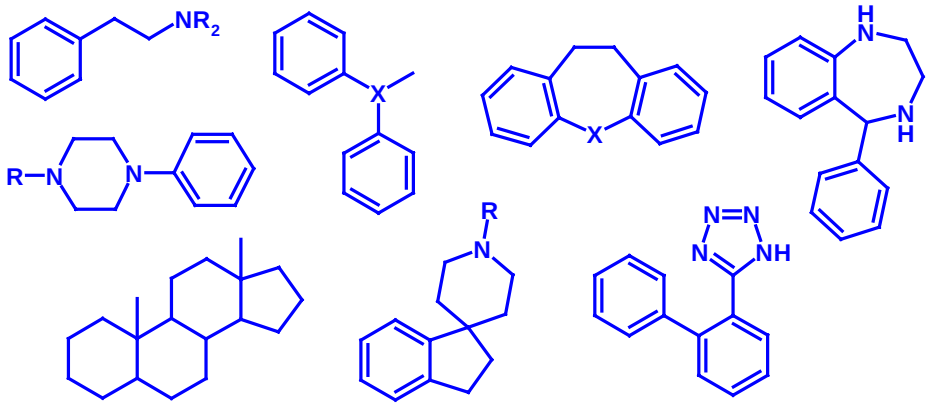
Ro 15-3505
(inverse agonist)
negative intrinsic activity at the $GABA_A$ receptor (proconvulsant)



tifluadom
(opiate κ agonist, IC_{50} = 12 nM)

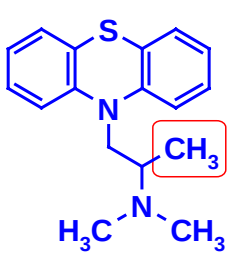
C. Wermuth, The Practice of Medicinal Chemistry, 1996, p. 548;
D. Römer et al., Nature 298, 759-760 (1982)

The Concept of „Privileged Structures“

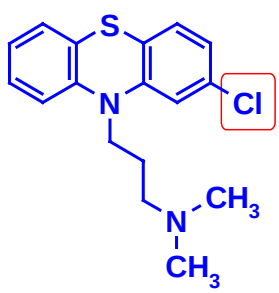


B. E. Evans et al., J. Med. Chem. 31, 2235-2246 (1988); A.A. Patchett, R.P. Nargund, Annu. Rep. Med. Chem. 35, 289-298 (2000); H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004

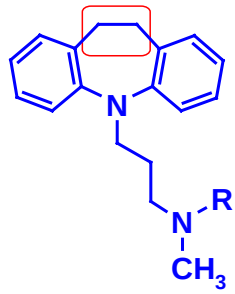
Different Modes of Action of Chemically Similar Molecules



promethazine
(H_1 antagonist)

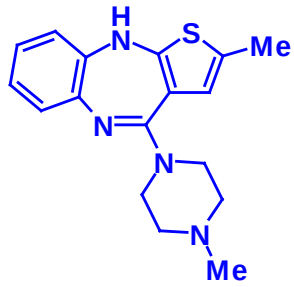


chlorpromazine
(dopamine antagonist)



a, R = CH_3, imipramine
b, R = H, desipramine
(uptake blocker)

Many Ligands Bind to Several GPCRs



Olanzapine, a clozapine-like „atypical“ neuroleptic with a promiscuous binding pattern

a) F. P. Bymaster et al., Neuropsychopharmacology 14, 87-96 (1996)
b) F. P. Bymaster et al., Schizophrenia Research 37, 107-122 (1999)

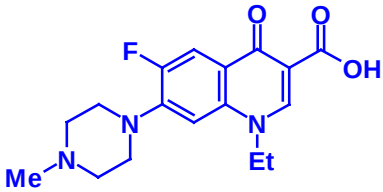
	a)	b)
K_i 5-HT$_{2A}$ =	4 nM	2.5 nM
K_i 5-HT$_{2B}$ =		12 nM
K_i 5-HT$_{2C}$ =	11 nM	2.5 nM
K_i 5-HT$_3$ =	57 nM	
K_i dop D$_1$ =	31 nM	119 nM
K_i dop D$_2$ =	11 nM	
K_i dop D$_4$ =	27 nM	
K_i musc M$_1$ =	1.9 nM	2.5 nM
K_i musc M$_2$ =	18 nM	18 nM
K_i musc M$_3$ =	25 nM	13 nM
K_i musc M$_4$ =	13 nM	10 nM
K_i musc M$_5$ =		6 nM
K_i adr α_1 =	19 nM	19 nM
K_i adr α_2 =	230 nM	
K_i hist H$_1$ =	7 nM	7 nM

"Discouraging data on the antidepressant."

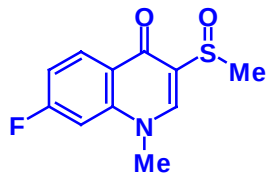
„Selective Optimization of Side Activities“

„The most fruitful basis for the discovery of a new drug is to start with an old drug“

Sir James Black, Nobel Prize 1988



norfloxazin, an antibiotic



flosequinan, a mixed arterial and venous vasodilator

C. G. Wermuth, Med. Chem. Res. 10, 431-439 (2001); C. G. Wermuth, J. Med. Chem. 47, 1303-1314 (2004); T.T. Ashburn and K.B. Thor, Nature Rev. Drug Discov. 3, 673-683 (2004); H. Kubinyi, in H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 43-67

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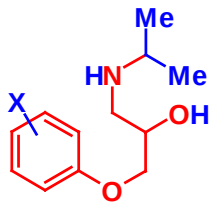
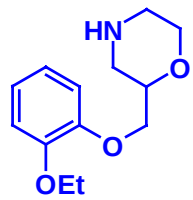
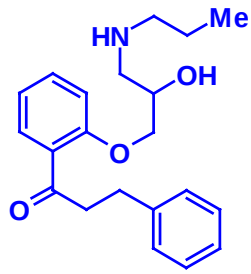
„Selective Optimization of Side Activities“



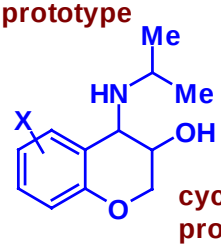
ß-blocker prototype



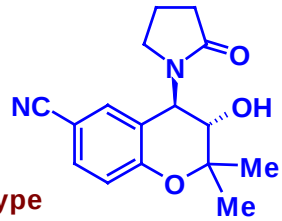
viloxacine antidepressant



propafenone 1c antiarrhythmic



cyclic prototype



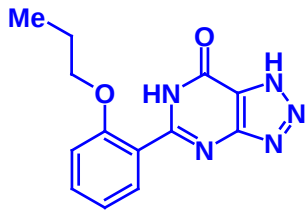
levocromakalim K channel opener

H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004

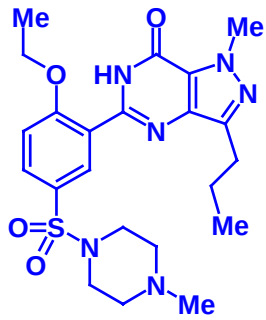
Which Important Drug

started from an anti-allergic lead, which was optimized to an antihypertensive drug but was finally clinically tested as an antianginal drug?

However, in a 10-day toleration study in Wales, an unusual side effect turned up ....

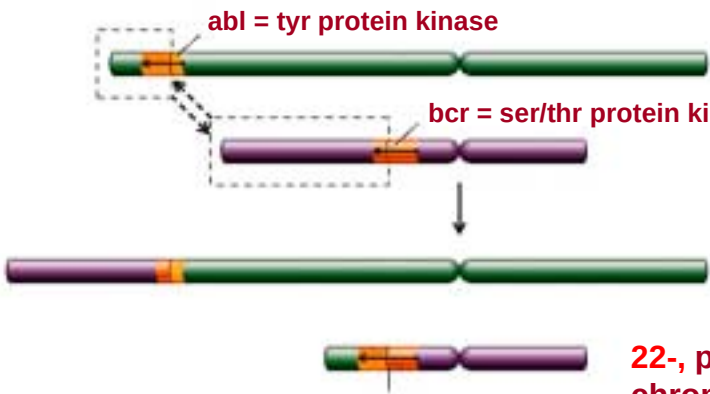


Zaprinast unspecific PDE inhibitor; antiallergic, vasodilator.



Sildenafil (Viagra®), specific cGMP PDE5 inhibitor; male sexual dysfunction.

Chromosome Translocation in CML



bcr-abl fusion protein, a hybrid with constitutionally enhanced tyrosine protein kinase activity

22-, philadelphia chromosome, present in 90+% of all cases of chronic mye-logenous leukemia

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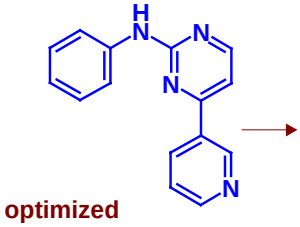
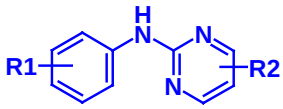
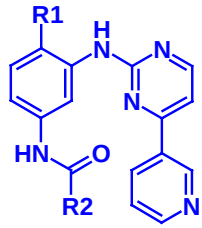
Development of STI 571 (Imatinib, Glivec®)



optimized lead, strong PKC inhibition

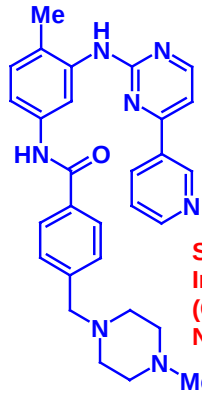


lead structure, active against PKC



amides inhibit also tyrosine kinases, such as bcr-abl

R1 = Me (instead H) abolishes undesired PKC affinity



STI 571, Imatinib (Glivec, Novartis)

N-Me-piperazine increases solubility

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Drug Research is ....

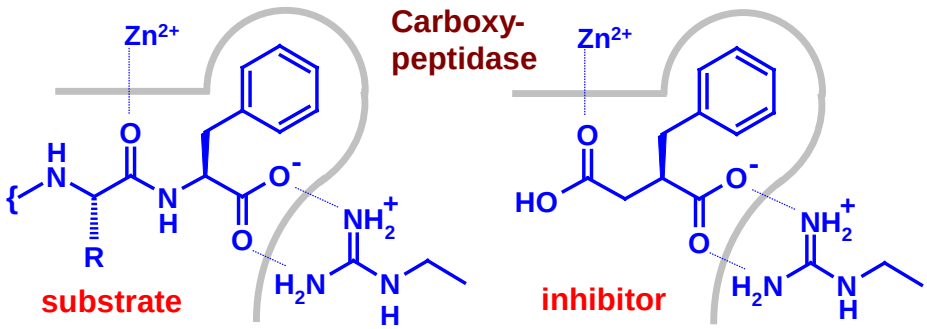
the Search for a Needle in a Haystack

Virtual Screening Reduces the Size of the Haystack by Selecting:

Compounds or libraries that are either
- lead-like, or
- drug-like, or have the potential of oral bioavailability,
- or are similar to a lead,

by
- rules (e.g. Lipinski bioavailability rules),
- neural nets (e.g. drug-like character),
- pharmacophore analyses,
- similarity analyses,
- scaffold hopping, or
- docking and scoring

Structure-Based Design of Captopril



IC_{50} = 330 µM

Captopril IC_{50} = 23 nM

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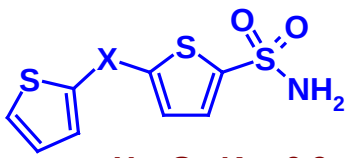
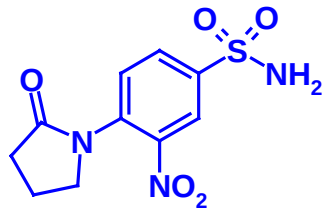
Virtual Screening, Carbonic Anhydrase Inhibitors

A 3D search in a database of ≈ 90,000 compounds yielded 3,314 molecules; these were rank-ordered by their pharmacophores, 100 were finally docked and 13 docking hits were biologically tested.



X = S K_i = 0.9 nM

X = SO_2 K_i = 0.8 nM



K_i = 0.6 nM

S. Grüneberg et al., Angew. Chem., Int. Ed. Engl. 40, 389-393 (2001); J. Med. Chem. 45, 3588-3602 (2002).

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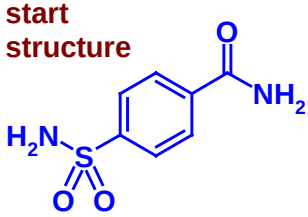
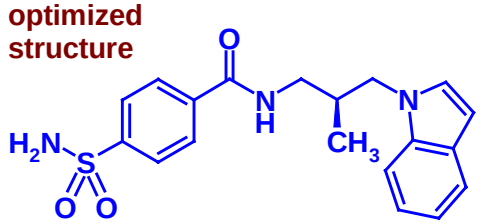
Fragment-based Design of Carbonic Anhydrase Inhibitors

start structure



K_d = 120 nM

optimized structure



R enantiomer, K_d = 30 pM

(*S* enantiomer: K_d = 230 pM)

Program CombiSMoG, „best“ N-substituents from 100,000 candidates (20 scored by knowledge-based potentials)

B. A. Grzybowski et al., Acc. Chem. Res. 35, 261-269 (2002);
B. A. Grzybowski et al., Proc. Natl. Acad. Sci. USA 99, 1270-1273 (2002)

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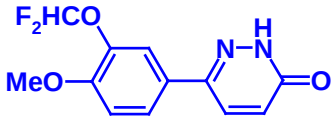
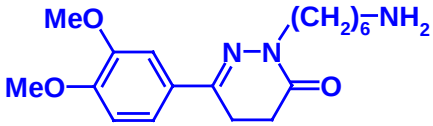
Scaffold-Linker-Functional Group Approach



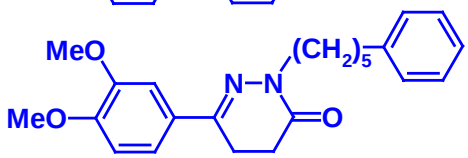
Zardaverine
IC_{50} PDE4 = 800 nM

Design of a structure-based 320-member virtual library with four different scaffolds or ring connections, five linkers and 16 different functional groups; best docking results with FlexX



N-substituted dihydro-pyridazinone analogs

IC_{50} PDE4 = 20 nM



IC_{50} PDE4 = 0.9 nM

M. Krier et al., J. Med. Chem. 48, 3816-3822 (2005)

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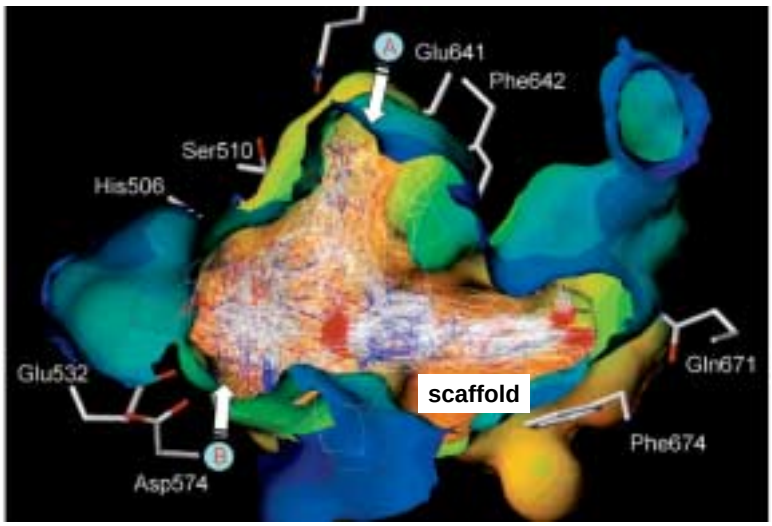
Scaffold-Linker-Functional Group Approach



Docking of a 320-member library into PDE4 pocket

subsite A favors a phenyl ring

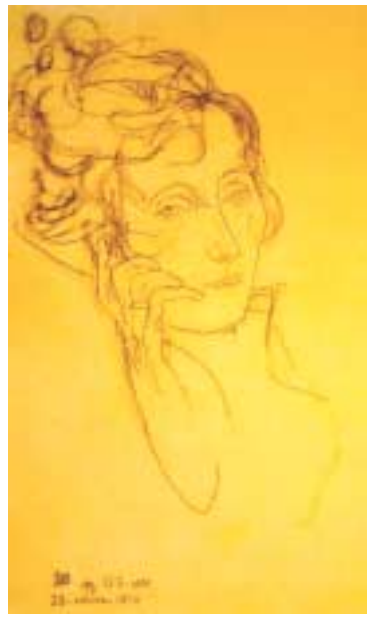
subsite B favors a basic group (amine)

M. Krier et al., J. Med. Chem. 48, 3816-3822 (2005)

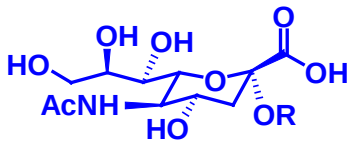
Influenza

In 1918/19, the „Spanish Flu“ killed about 20-40 mio people. Especially young and very old people died from influenza. The heavy death toll of this pandemic disease has to be compared to the number of 11 mio victims of World War I.

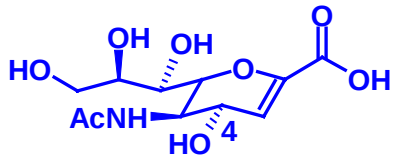
Egon Schiele prepared this drawing of his wife, one day before her death and four days before he died himself, only 28 years old.



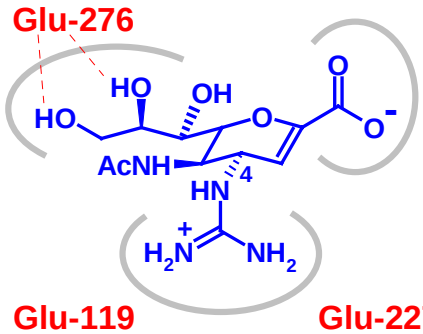
Design of Neuraminidase Inhibitors



sialic acid, R = H



Neu5Ac2en
K_i = 1 000 nM



Arg-371

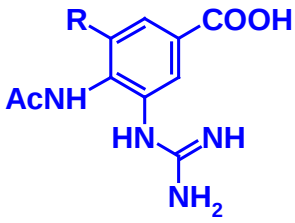
Arg-292

Arg-118

4-Guanidino-Neu5Ac2en
K_i = 0.1-0.2 nM
Zanamivir (Relenza, Glaxo-Wellcome)

University of Heidelberg

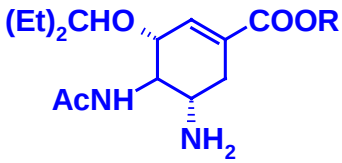
Design of Bioavailable Neuraminidase Inhibitors



IC_{50} = 6.3 µM

a) R = $CH(OH)CH(OH)CH_2OH$
K_i > 100 µM

b) R = H K_i = 8 µM



GS 4071, R = H
IC_{50} = 1 nM
GS 4104 (R = Et, prodrug of GS 4071)
Oseltamivir (Tamiflu, Roche)

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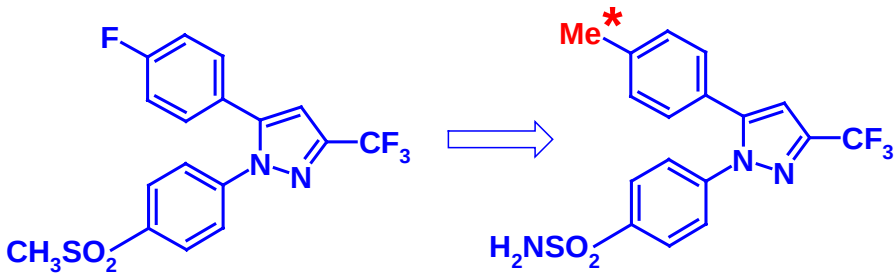
Oxidative Metabolism and Drug Design

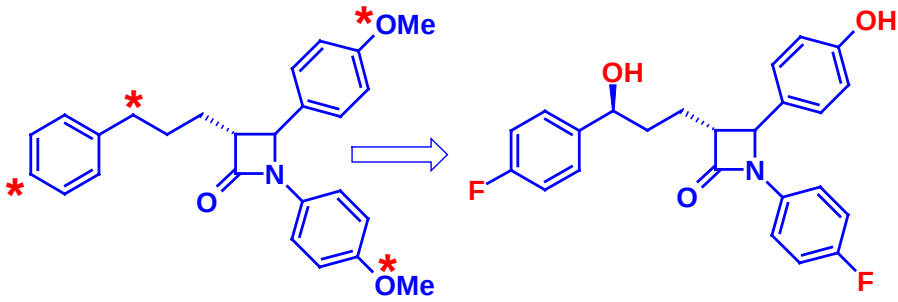


early COX2 inhibitor
$t_{1/2}$ (rat) up to 220 h

celecoxib
$t_{1/2}$ (rat) = 3.5 h

T. D. Penning et al., J. Med. Chem. 40, 1347-1365 (1997);
D. A. Smith, H. van de Waterbeemd and D. K. Walker, Pharmacokinetics and Metabolism in Drug Design, Wiley-VCH, 2001, p. 83

Oxidative Metabolism and Drug Design



SCH 48461
ED_{50} (hamster) = 2.2 mg/kg

Ezetimib (SCH 58235, oral cholesterol absorption inhibitor)
ED_{50} (hamster) = 0.04 mg/kg

M. van Heek et al., J. Pharmacol. Exp. Ther. 283, 157-163 (1997); D. A. Smith, H. van de Waterbeemd and D. K. Walker, Pharmacokinetics and Metabolism in Drug Design, Wiley-VCH, 2001, p. 85

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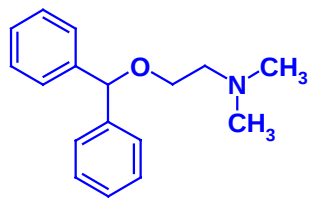
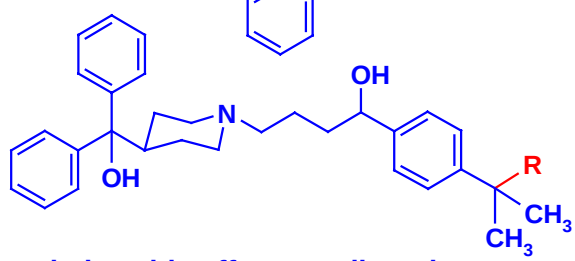
Oxidative Metabolism and Drug Design

diphenhydramine
lipophilic H_1 antagonist
(sedative side effect)





terfenadine
(Seldane®),
R = CH_3: polar
H_1 antagonist (no sedative side effect; cardiotoxic, especially in combination with CYP 3A4 inhibitors)

fexofenadine (Allegra®), R = COOH: active terfenadine metabolite (no sedative side effect, no cardiotoxicity)

Prodrugs, Soft Drugs and Targeted Drugs

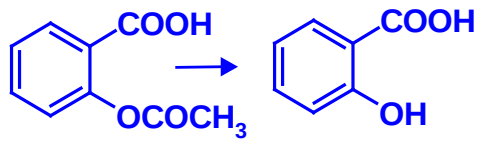
Prodrugs are inactive (less active) drug analogs that have better pharmakokinetic properties (e.g. oral bioavailability, BBB penetration)

Soft drugs are biologically active derivatives of inactive drug analogs; they are degraded to inactive analogs, e.g. esters of corticosteroid carboxylic acids, which are (topically) active.

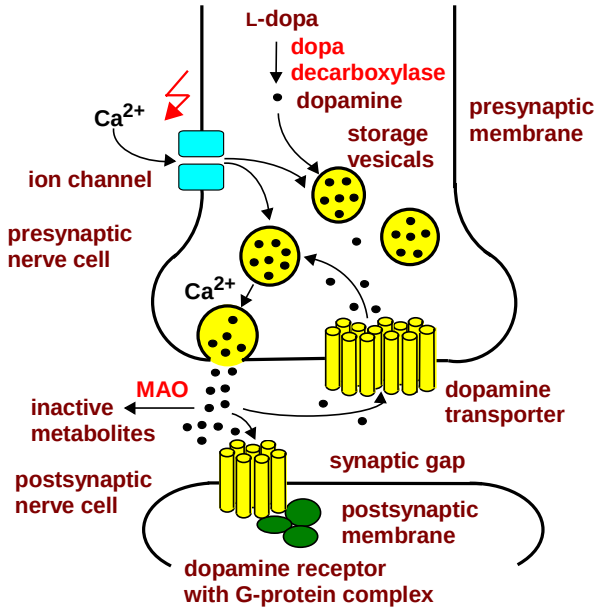
Targeted drugs are drugs or prodrugs that exert their biological action only in certain cells or organs (e.g. Omeprazole, Aciclovir).

Aspirin®, a prodrug ?

(Felix Hoffmann, 1897)



Interaction of Enzymes, Receptors, Ion Channels and Transporters in the Trans-mission of the Electric Signal of a Nerve Cell



A Rational Therapy of Parkinson's Disease

	healthy	sick
ACh	+	+
dopamine	+	-

Therapy

ACh ↓ or

dopamine ↑

Problems

dopamine is not bio-available, peripheral side effects, MAO

oral L-DOPA, peripheral DOPA decarboxylase blocker, central MAO blocker

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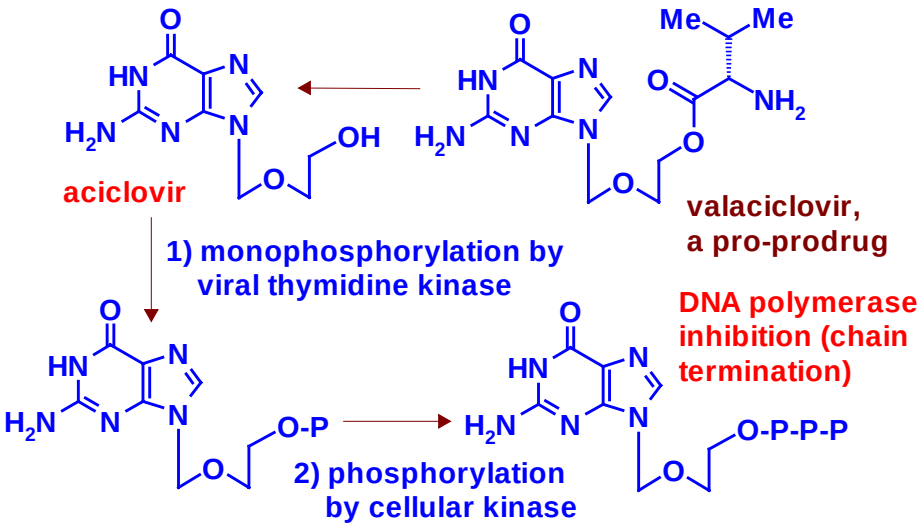
Antiviral Prodrugs are Trojan Horses



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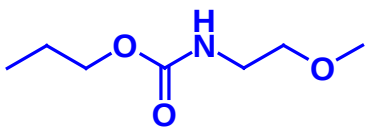
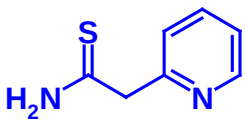
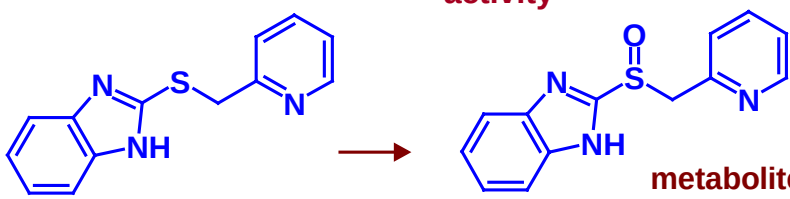
Omeprazole Case Study







- 1966: Local anesthetics reduce gastric secretion (Hässle)
- 1966-1972: First lead
- 1972-1979: New lead pyridyl-acetamide (from screening of antiviral compounds)
- Active analogs; metabolite with higher antisecretory activity

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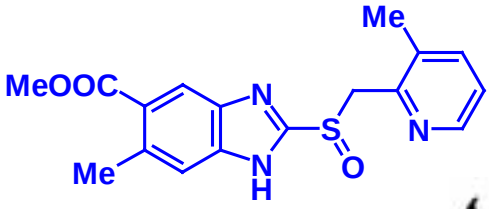
Omeprazole Case Study

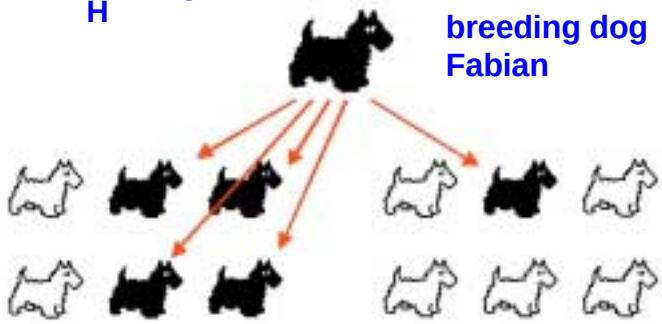


Picoprazole, 1976
preclinical candidate

breeding dog
Fabian

Tox study:

vasculitis



picoprazole group

placebo group

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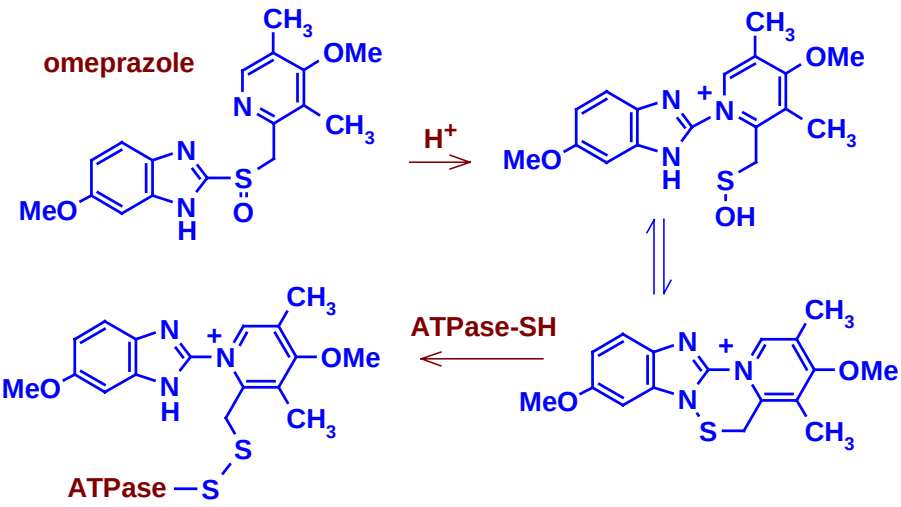
Drug Activation in Acid-Producing Cells - A Serendipitous Discovery of a Targeted Drug

omeprazole



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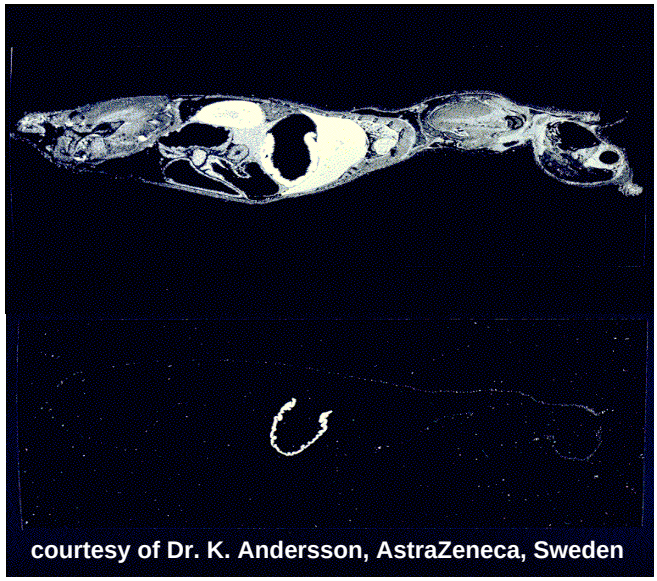
Omeprazole Activation in Acid-Producing Cells



courtesy of Dr. K. Andersson, AstraZeneca, Sweden

Distribution of radio-labelled omeprazole, one minute after i.v. injection, rat

sixteen hours after i.v. injection, rat

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Success in Lead Optimization Results From

„Real“ lead structures

small, polar (Ro3 compliant), selective

Systematic bioisosteric replacement

Wermuth strategy (N, S, W, E, center modifications)

SOSA approach

„Complete“ coverage of the chemistry around the lead

Valid screening and test models

Simultaneous optimization of

affinity - selectivity - bioavailability - hERG - metabolism - CYP inhibition - lack of side effects and toxicity

Creative individuals in cooperative teams (an oxymoron)

Engaged and experienced management (an oxymoron?)