Drug Discovery Case Studies

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Basilius Besler
Hortus Eystettensis
Eichstätt, 1613

Squill
(Scilla alba =
Urginea maritima)

Theriak

originally a mixture of 54 materials, as antidote against all kind of poisons (1st century B.C. till 18th century), used also as a remedy against the plague.

Public theriak preparation at a market.

The Stone of Folley

Hieronymus Bosch
(~1450 - 1516)

„Master snyt die keye ras.
Myne name is Lubbert das“

A quack docter, assisted by a priest and a nun, extracts the „stone of folley“ from the brain of a patient.

The Doctrine of Signatures: „Nature helps Mankind“

Mistletoe, *Viscum album*

St. John‘s Wort,
Hypericum perforatum

Truelove, *Paris quadrifolia*

„Diß Beerlein ist von Gestalt wie ein Augapfel oder Äuglein anzusehen ... Zu den kranken und bösen Augen / ein sehr nützlich und heilsamb Kraut ist“ (Johannes Francke, 1618)

Heroic Times: Who Is a Good Surgeon ?

Davy, 1799: Experiments with laughing gas

First Half of 19th Century: Sniffle parties

Long, 1841-1849: Ether acts as anesthetic

Wells, 1844: Laughing gas acts as anesthetic

Heroic Times: Who Is a Good Surgeon ?

Davy, 1799: Experiments with laughing gas

First Half of 19th Century: Sniffle parties

Long, 1841-1849: Ether acts as anesthetic

Wells, 1844: Laughing gas acts as anesthetic

Simpson, 1847: Chloroform

Liebreich, 1868/69: Chloral hydrate as „prodrug“ of chloroform

Schmiedeberg, 1885: Urethane as „prodrug“ of ethanol

Dreser, 1899: i-Amyl carbamate (Hedonal)

von Mering 1903: first barbiturate Barbiton (Barbara / Barbara day)

Queen Victoria (1819-1901)
1853 * Prince Leopold

University of Heidelberg

A. W. Hofmann (1818-1892)

1845: Queen Victoria visits Germany; Prince Albert engages August Wilhelm Hofmann

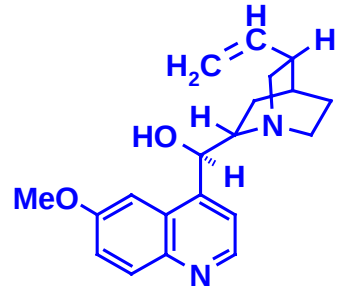
1856: Hofmann asks the 18-years old student William H. Perkin to synthesize quinine by oxidation of allyl-toluidine

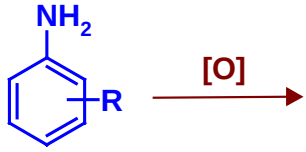
Lack of Success in a Quinine Synthesis (1856)

$C_{10}H_{13}N$ —(3 [O])→ $C_{20}H_{24}N_2O_2$ + H_2O

allyl-toluidine

Quinine





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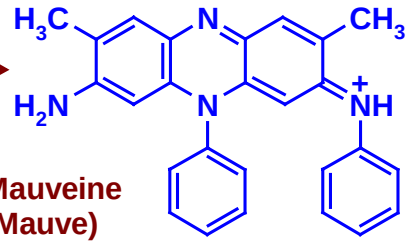


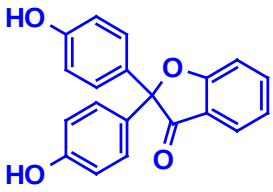
R = H or methyl

Mauveine (Mauve)

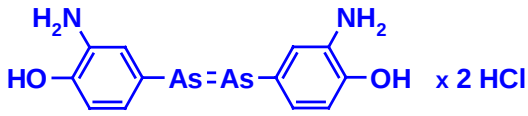
A. W. Hofmann (1818-1892) and W. H. Perkin (1838-1907)

1862: Queen Victoria wears a dress in mauve color

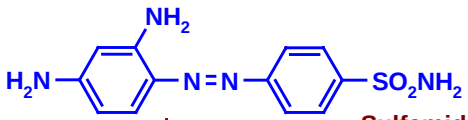
Dyestuffs as Drugs



Phenolphthalein

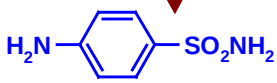


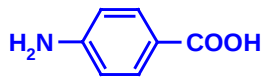
Arsphenamine
(trimer; E 606,
Salvarsan)



Sulfamidochrysoidine
("Prontosil rubrum")

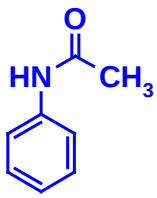
metabolic
degradation



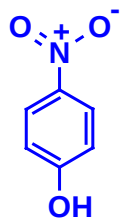


Sulfanilamide, an antimetabolite of p-aminobenzoic acid

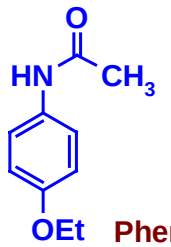
Discovery of Acetanilide and Phenacetin



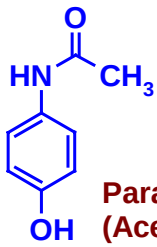
Acetanilide



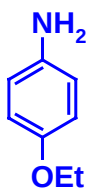
p-Nitrophenol



Phenacetin

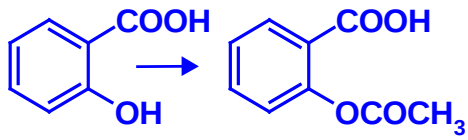


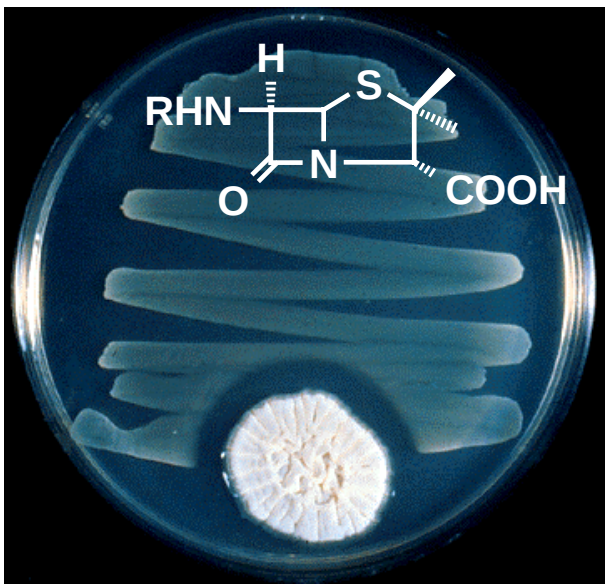
Paracetamol
(Acetaminophen)



Phenetidine

Aspirin®
(Felix Hoffmann, 1897)

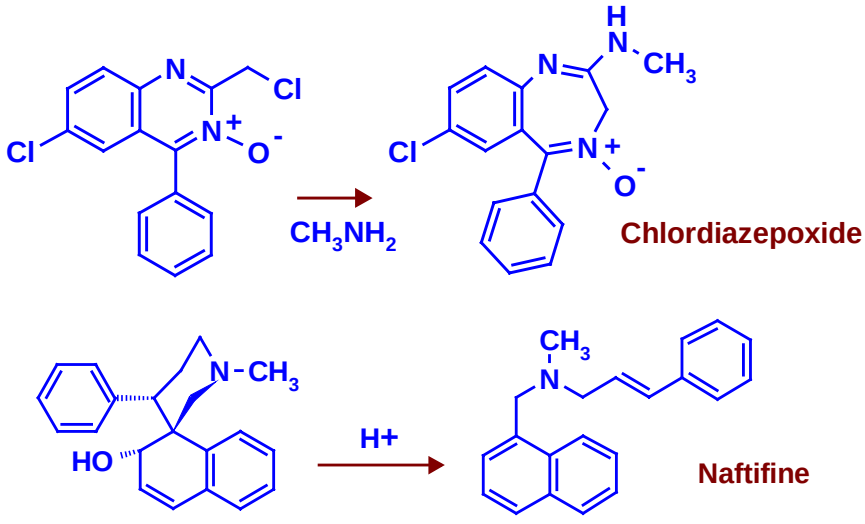




„Penicillin happened, it came out of the blue.“

A. Fleming, 1930

Unexpected Rearrangement Products



Survival of Frogs in a Septic Environment

Michael A. Zasloff (NIH)

Proc. Nat. Acad. Sci. USA 84, 5449-5453 (1987)

Magainine

an antibacterial 23-aa peptide,
GIGKFLHSAKKFGKAFVGEIMNS
(amphipathic helix formation ?),
does not induce resistance.
A potential acne treatment ?

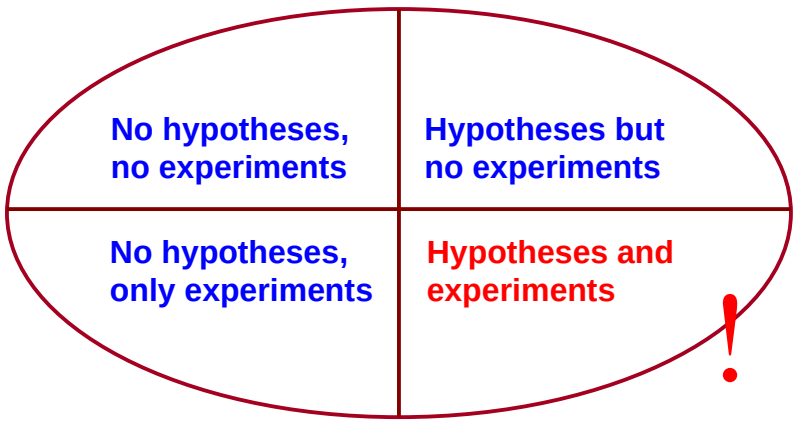
Serendipitous Drug Discoveries

Acetanilide, Acetylsalicylic acid, Aminoglutethimide, Amphetamine, Chloral hydrate, Chlordiazepoxide, Chlorpromazine, Cinnarizine, Cisplatin, Clonidine, Cromoglycate, Cyclosporin, Dichloroisoproterenol, Dicoumarol, Diethylstilbestrol, Diphenhydramine, Diphenoxylate, Disulfiram, Ether, Etomidate, Griseofulvin, Guanethidine, Haloperidol, Heparin, Imipramine, Iproniazid, Isoniazid, Levamisole, Lithium carbonate, Lysergide (LSD), Meprobamate, Merbaphen, Methaqualone, Mifepristone, Naftifine, Nalorphine, Nitrogen mustard, Nitroglycerine, Nitrous oxide, Norethynodrel/Mestranol, Penicillin, Pethidine (Meperidine), Phenylbutazone, Phenolphthalein, Praziquantel, Prednisone, Propafenone, Sulfamidochrysoidine, Sulfonamides, Tamoxifen, Urethane, Valproic acid, Warfarin.

Sweeteners: Saccharin, Cyclamate, Aspartame

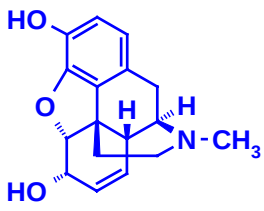
R. M. Roberts, Serendipity - Accidental Discoveries in Science, John Wiley & Sons, New York, 1989.
H. Kubinyi, Chance Favors the Prepared Mind. From Serendipity to Rational Drug Design, J. Receptor & Signal Transduction Research 19, 15-39 (1999).

Four Possible Strategies in Research



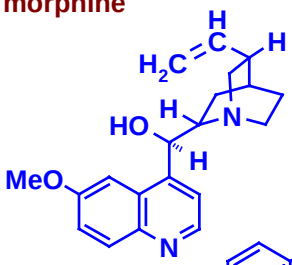
Rolf Zinkernagel (Nobel prize in Medicine 1996)

Lead Structures: Natural Products from Plants



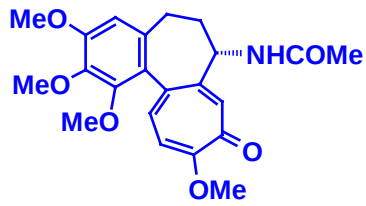
morphine

caffeine



quinine

ephedrine

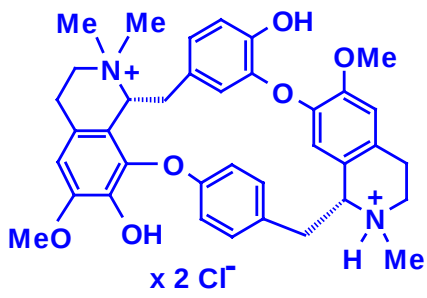


colchicine

Lead Structures: Natural Products from Plants

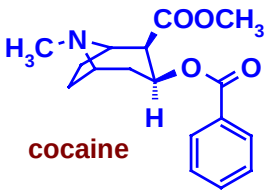
Digitoxin, R = H
Digoxin, R = OH

Tubocurarin

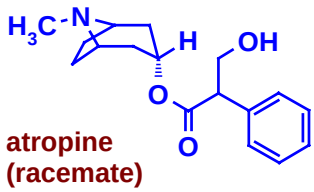


x 2 Cl^-

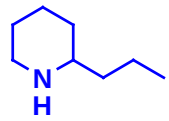
Lead Structures: Natural Products from Plants



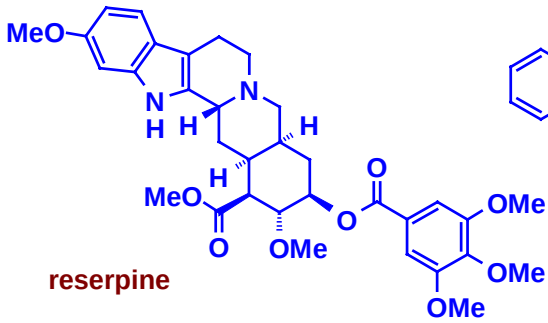
cocaine



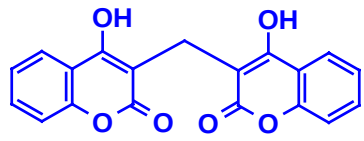
atropine
(racemate)



coniine



reserpine



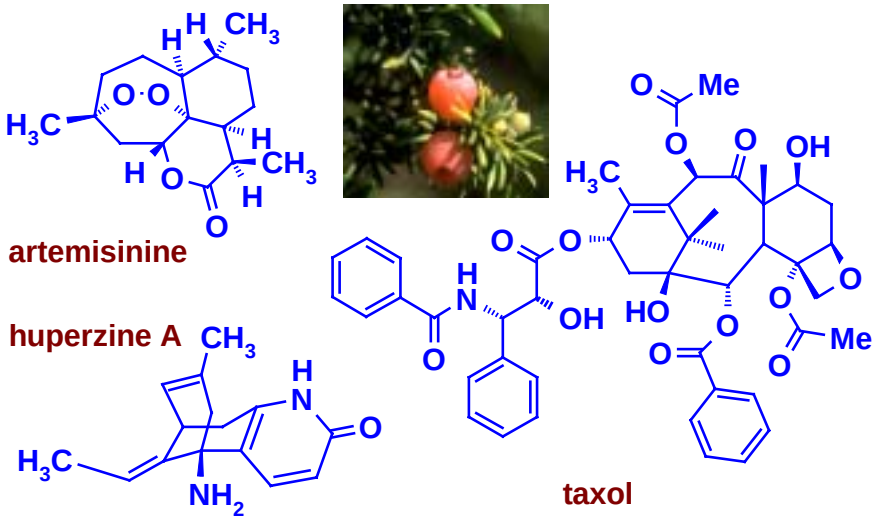
dicoumarol

(microbial degradation product of coumarin)

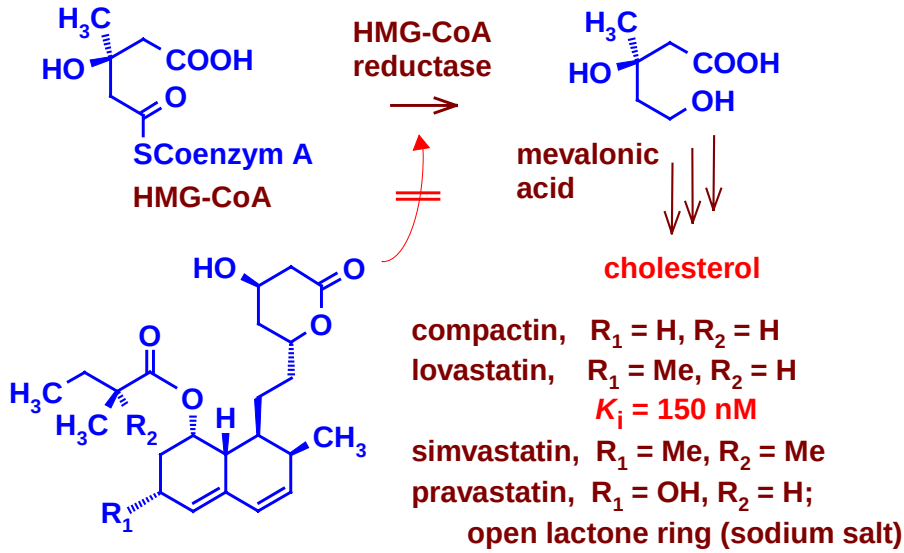
University of Heidelberg

Jaques Louis David, The Last Hours of Socrates, MMA, New York

Lead Structures: Natural Products from Plants

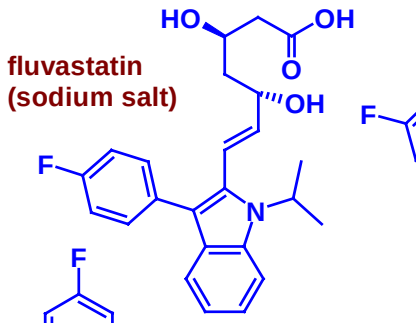


Lead Structures: Microbial Natural Products

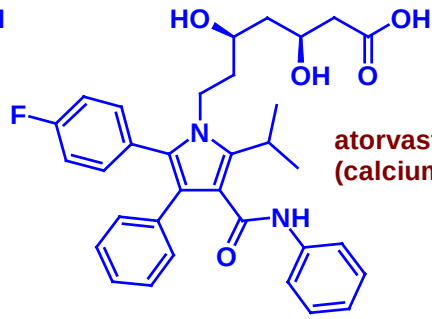


compactin, R_1 = H, R_2 = H
lovastatin, R_1 = Me, R_2 = H
K_i = 150 nM
simvastatin, R_1 = Me, R_2 = Me
pravastatin, R_1 = OH, R_2 = H;
open lactone ring (sodium salt)

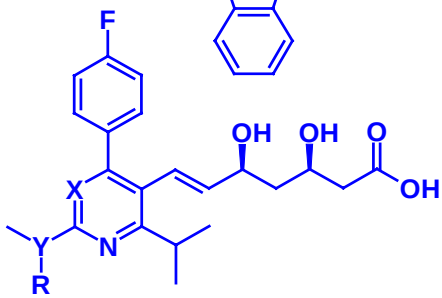
Synthetic Statin Analogs



fluvastatin
(sodium salt)



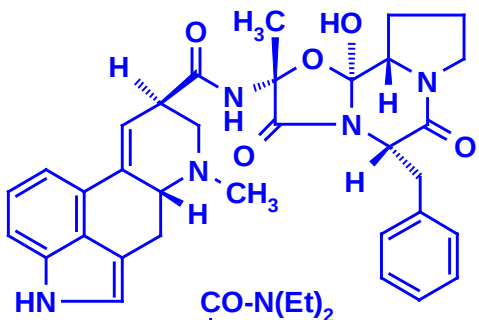
atorvastatin
(calcium salt)



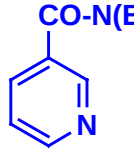
cerivastatin (sodium salt)
X = C-CH_2OMe, Y-R = CH-CH_3
K_i = 1.3 nM

rosuvastatin (calcium salt)
X = N, Y-R = N-SO_2Me
K_i = 11 nM

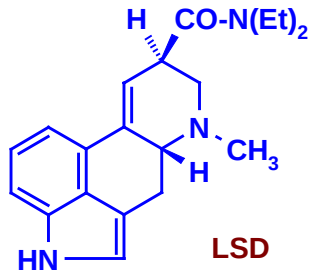
Lead Structures: Other Natural Products
Albert Hofmann and His Problem Child LSD



ergotamine
(*Claviceps purpurea*;
ergot = Secale cornutum)

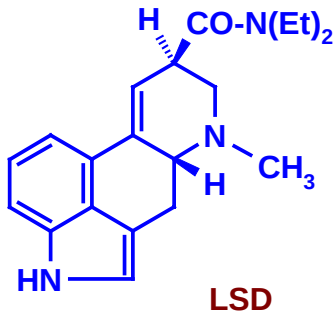


nicotinic acid
diethylamide



LSD

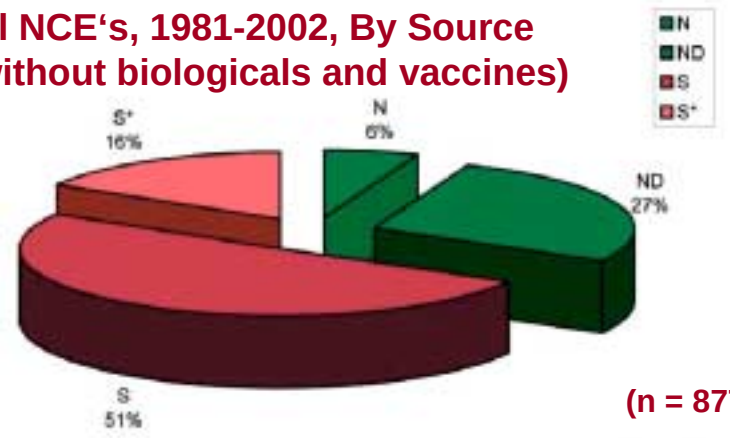
Acute Toxicity of Lysergic Acid Diethylamide in Animals and Maximum Tolerated Dose in Man



LSD

Species	LD_{50} in mg/kg
Mouse	50-60
Rat	16.5
Rabbit	0.3
Elephant	« 0.06
Man	» 0.003

All NCE's, 1981-2002, By Source (without biologicals and vaccines)

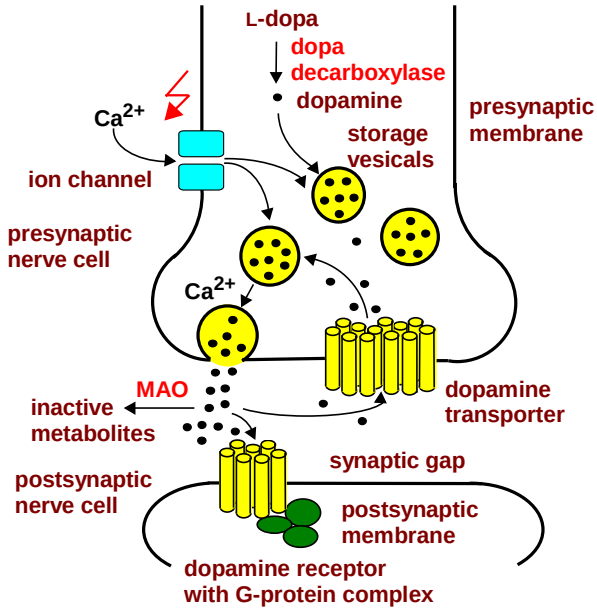


(n = 877)

N = natural products ND = derived from natural products
S = synthetic products
S* = synthetics but pharmacophore derived from natural product

D. J. Newman et al., J. Nat. Prod. 66, 1022-1037 (2003)

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 ↑

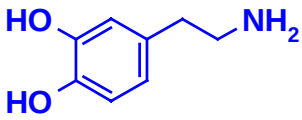
Problems

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

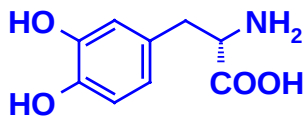
oral L-DOPA, peripheral DOPA decarboxylase blocker, central MAO blocker

Integrated Optimisation of Drug Therapy

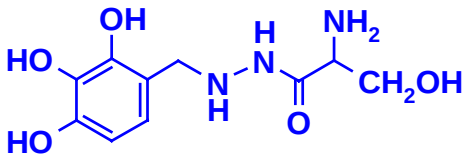
Dopamine Substitution in Parkinson's Disease



dopamine



L-dopa, a dopamine prodrug



benserazide

(R)-(-)-selegiline

University of Heidelberg

The Similarity Principle in Drug Design - Lead Optimization is an Evolutionary Procedure

Medicinal chemists, all the time, used the similarity of chemical compounds to design new analogs of active leads. Whenever they discovered compounds with improved activity, selectivity, pharmacokinetics, etc., they used these compounds to search analogs with even further improved properties. However, ...

Isosteric Replacement of Atoms and Groups

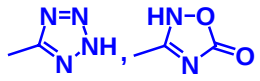
Substituents: F, Cl, Br, I, CF_3 , NO_2
Methyl, Ethyl, Isopropyl, Cyclopropyl, t.-Butyl,
-OH, -SH, $-NH_2$, -OMe, $-N(Me)_2$

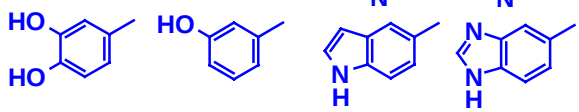
Linkers: $-CH_2-$, -NH-, -O-
$-COCH_2-$, -CONH-, -COO-
>C=O, >C=S, >C=NH, >C=NOH, >C=NOAlkyl

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

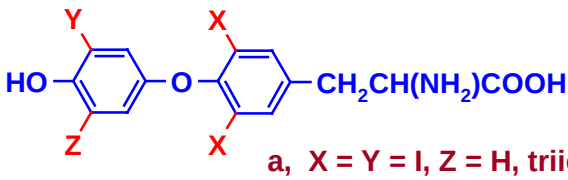
Large Groups: $-NHCOCH_3$, $-SO_2CH_3$

-COOH, -CONHOH, $-SO_2NH_2$,

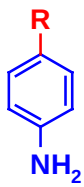




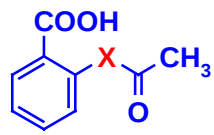
Consequences of Isosteric Replacement



a, X = Y = I, Z = H, triiodothyronine, T3
b, X = Y = Z = I, thyroxine, T4
c, X = I, Y = i-propyl, Z = H
d, X = CH_3, Y = i-propyl, Z = H



p-aminobenzoic acid,
R = COOH
sulfanilamide, R = SO_2NH_2



X = -O-
acetylsalicylic acid

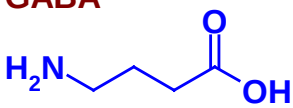
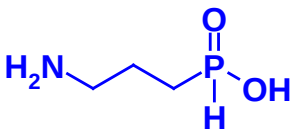
Consequences of Isosteric Replacement

Inhibition of Carbonic Anhydrase by Sulfonamides

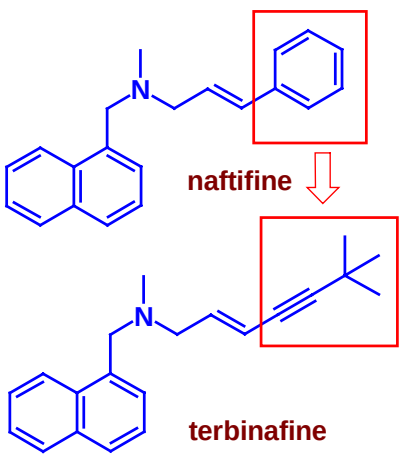
$CH_3SO_2NH_2$, K_i = 100 µM, pK_a = 10.5

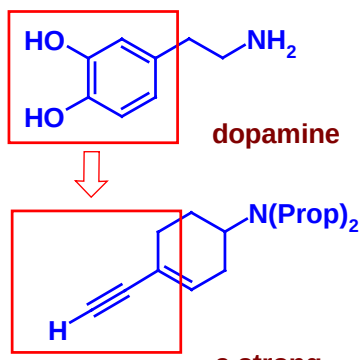
$CF_3SO_2NH_2$, K_i = 2 nM, pK_a = 5.8

Specificity of GABA Receptor Ligands

GABA	$GABA_A$ receptor affinity	$GABA_B$ receptor affinity
	IC_{50} = 20 nM	20 nM
	IC_{50} = 4,500 nM	1 nM

Isosteric Replacement of Aromatic Rings



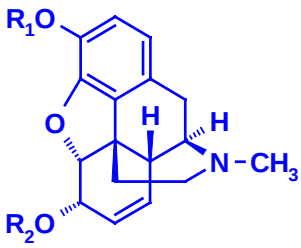


a strong dopamine D3 agonist

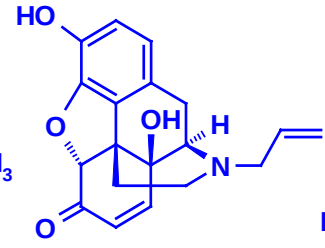
A. Stütz, Angew. Chem. Int. Ed. Engl. 26, 320-328 (1987)

H. Hübner et al., J. Med. Chem. 43, 756-762 (2000)

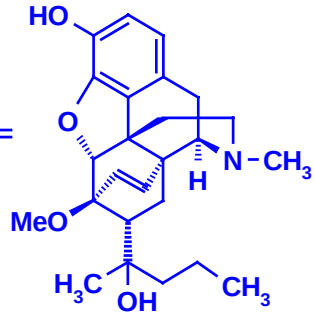
Morphine and its Derivatives



morphine, $R_1 = R_2 = H$
heroin, $R_1 = R_2$ = acetyl (opiates)
codeine, R1 = Me, R2 = H (antitussive)

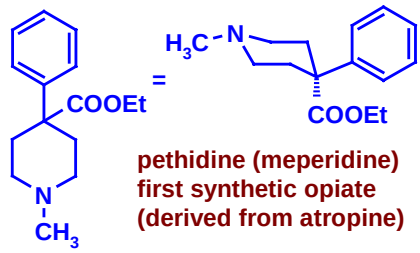


naloxone (morphine antagonist)

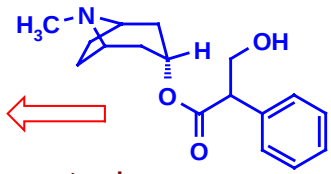


etorphine (2,000-10,000 times more active than morphine)

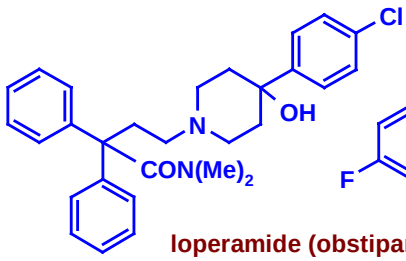
Distant Morphine Analogs



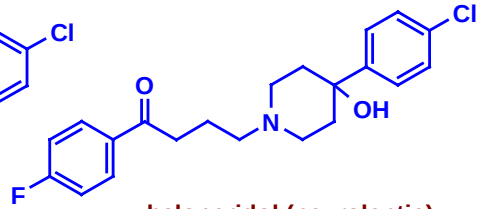
pethidine (meperidine)
first synthetic opiate
(derived from atropine)



atropine (anticonvulsant)

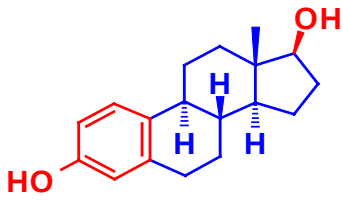


loperamide (obstipant - no CNS activity)

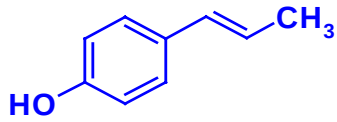


haloperidol (neuroleptic)

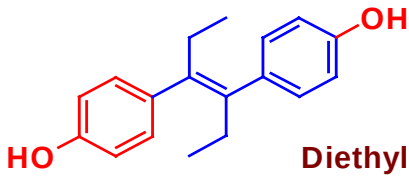
Serendipitous Discovery of Diethylstilbestrol



Estradiol

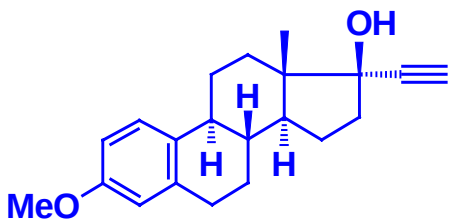


p-Anol



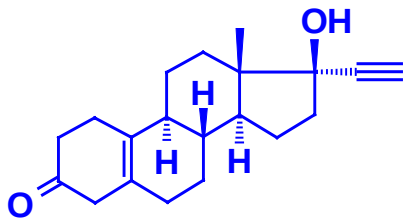
Diethylstilbestrol

The Serendipitous Discovery of the Pill



1. Birch reduction
2. enol ether cleavage

Mestranol

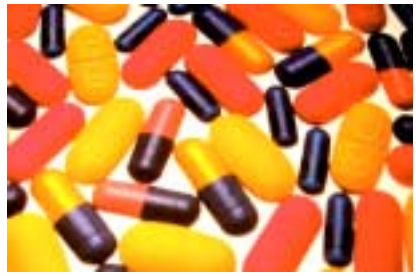


Norethynodrel (Searle)

University of Heidelberg

Pharmacodynamics

the action of the drug on the body

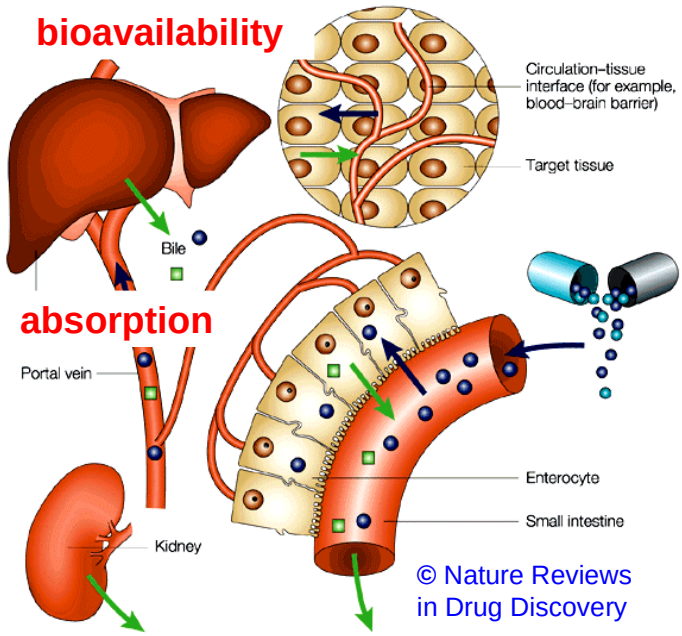


Metabolism

the action of the body on the drug

University of Heidelberg

bioavailability

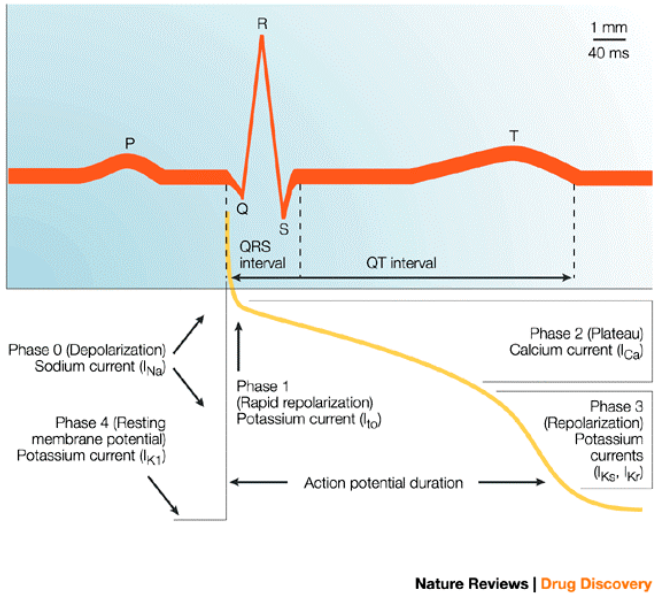


Sites of Drug Metabolism:

(intestinal wall), liver, (organs)

Sites of Drug Elimination:

kidneys (polar compounds), bile, feces (lipophilic analogs), lung



Normal ECG

B. Fermini and A. A. Fossa, Nat. Rev. Drug. Discov. 2, 439-447 (2003)

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The QT Interval Prolongation Problem

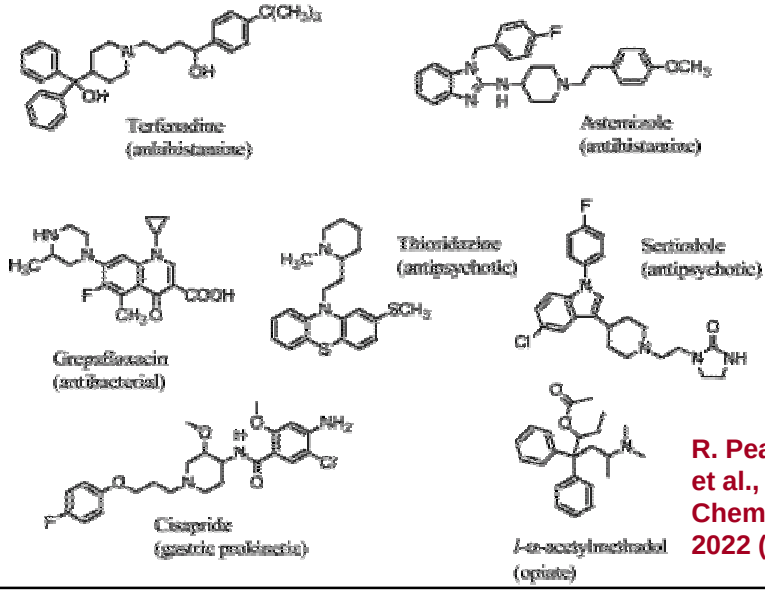
Many different drugs produce prolongation of the QT interval of the ECG (antihistamines, antipsychotics, antimicrobials, Ca antagonists …)

Several drugs have been withdrawn from the market and ~ 10% of drug candidates fail in development due to this problem, e.g. Terfenadine (Seldane™), Sertindole, Astemizole, ...

A typical reason for QT interval prolongation is the blockade of the cardiac hERG K+ channel by interaction of the drug with S6 domain of the protein.

Source: T. Langer, University of Innsbruck, Austria

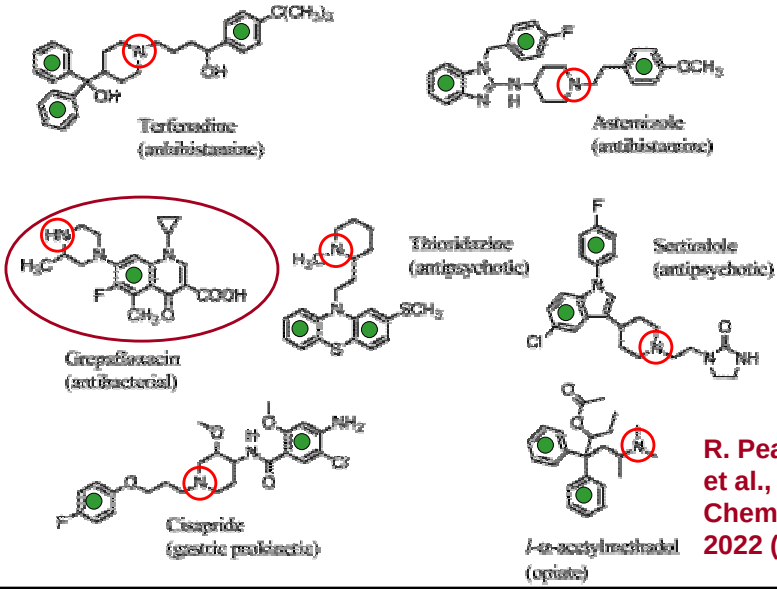
Typical hERG Channel Inhibitors



R. Pearlstein et al., J. Med. Chem. 46, 2017-2022 (2003)

University of Heidelberg

Typical hERG Channel Inhibitors



R. Pearlstein et al., J. Med. Chem. 46, 2017-2022 (2003)

Target and Channel Affinities of hERG Inhibitors

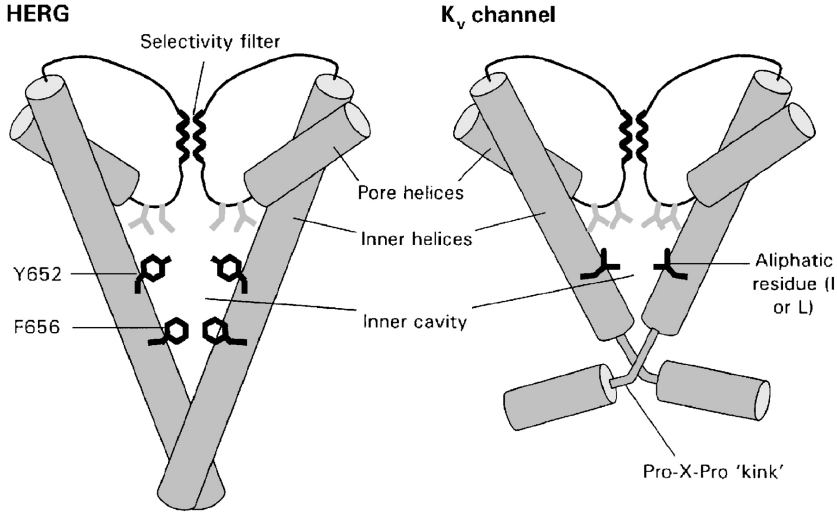
Table 1. Comparison of the HERG Channel Affinity to That of the Intended Pharmacological Target for Several Drugs

drug	target affinity	HERG IC_{50}	comment
terfenadine	58 nM (histamine H1 K_i)	56 nM	withdrawn
astemizole	3 nM (histamine H1 K_i)	0.9 nM	withdrawn
cisapride	29 nM (serotonin 5HT4 K_i)	47 nM	withdrawn
sertindole	0.6 nM (serotonin 5HT2A K_i)	3 nM	withdrawn
thioridazine	27 nM (dopamine D2 K_i)	191 nM	black box[a]
pimozide	12 nM (dopamine D2 K_i)	18 nM	TDP[b]
grepafloxacin	up to 2.4 μM (bacterial MIC[c])	50 μM	withdrawn

[a] Black box label from FDA for proarrhythmia. [b] Torsades de pointes arrhythmia observed clinically. [c] Minimum inhibitory concentration.

R. Pearlstein et al., J. Med. Chem. 46, 2017-2022 (2003)

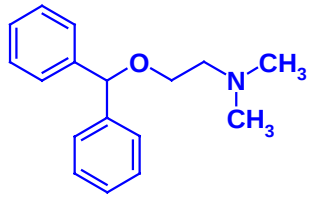
Model of Two hERG Channel Subunits



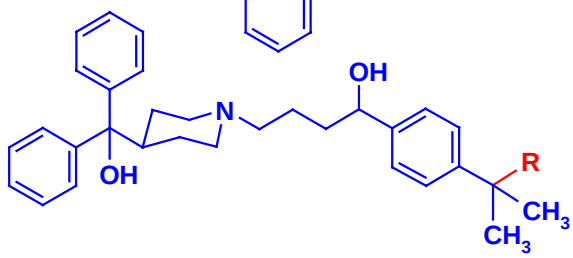
J. S. Mitcheson, Brit. J. Pharmacol. 139, 883-884 (2003)

Oxidative Metabolism and Drug Design

diphenhydramine
lipophilic H_1 antagonist
(sedative side effect)



terfenadine
(Seldane®),
R = CH_3: polar
H_1 antagonist
(originally
designed as an
antipsychotic

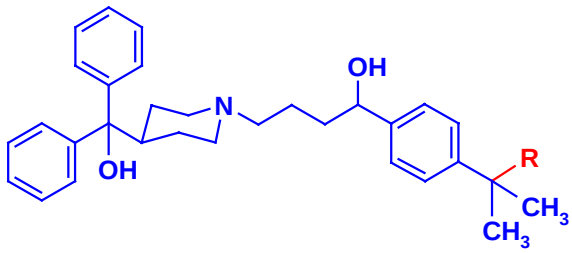


agent; no sedative side effect but cardiotoxic,
especially in combination with CYP 3A4 inhibitors)

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

SAR of hERG Channel Ligands

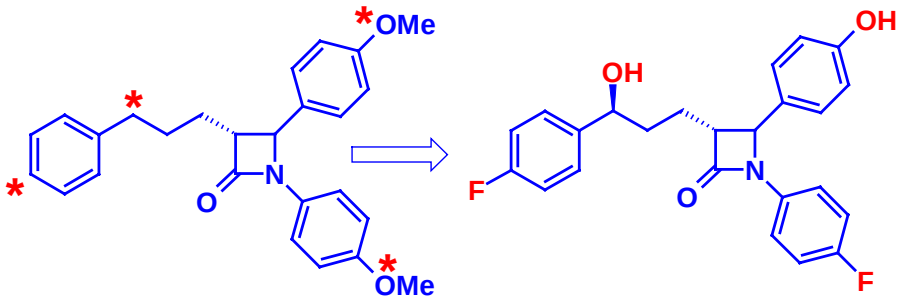
Terfenadine analogs



R = CH_3, Terfenadine	**IC_{50} = 56 nM**
R = OH	**IC_{50} = 460 nM**
R = COOH, Fexofenadine	**IC_{50} = 23,000 nM**

R. A. Pearlstein et al., Bioorg. Med. Chem. Lett. 13, 1829-1835 (2003)

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

Prodrugs, Soft Drugs and Targeted Drugs

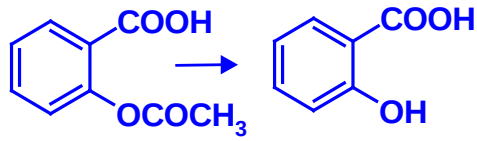
Prodrugs are inactive (less active) drug analogs that have better pharmakokinetic properties (e.g. oral bioavailability, BBB penetration)

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).

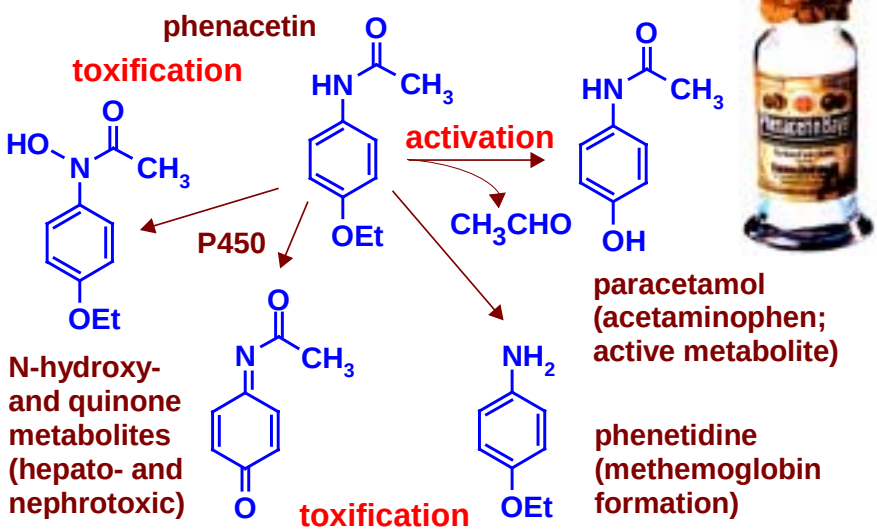
Aspirin®, a prodrug ?

(Felix Hoffmann, 1897)

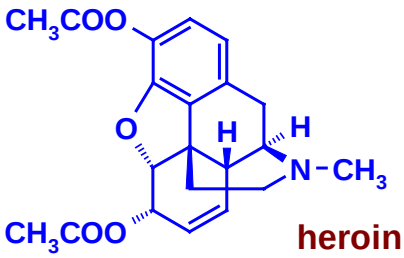


University of Heidelberg

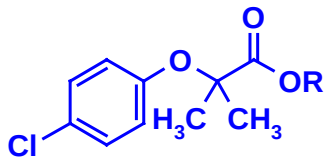
Metabolic Activation and Toxification



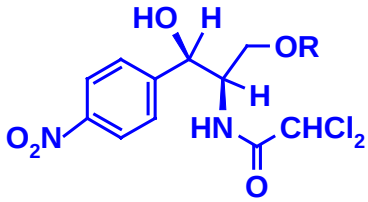
Prodrugs: Esters



heroin



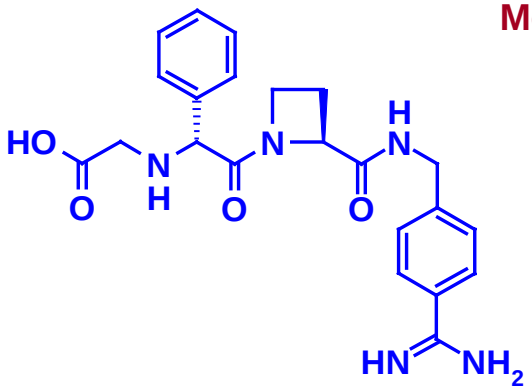
clofibrate, R = Et
clofibric acid, R = H



chloramphenicol
(bitter taste), R = H

tasteless prodrug
R = $CO(CH_2)_{14}CH_3$

Melagatran (Astra)



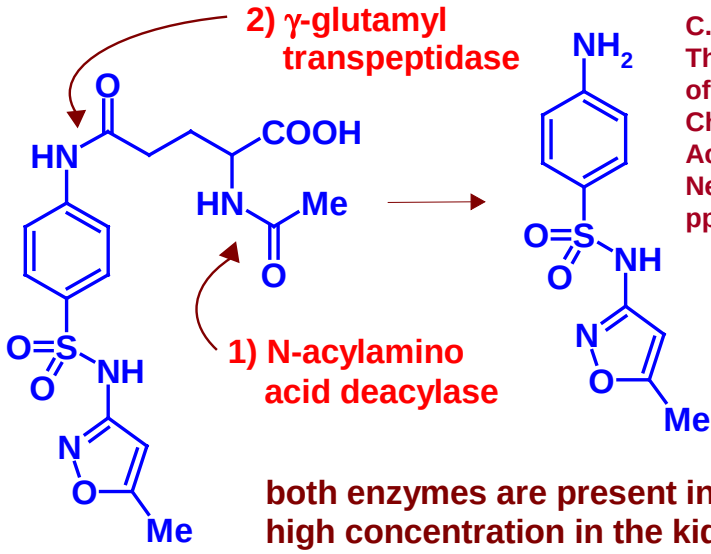
was one of the first thrombin inhibitors with some oral bioavailability

K_i (thrombin) = 2 nM

Ximelagatran (H 376/95) is a double prodrug of melagatran:

- ester group (cleaved by esterases)
- amidoxime (reduced by NADH-cytochrome b5 reductase + CYP 2A6)

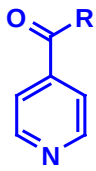
Kidney-Selective Release of Sulfamethoxazole



C. G. Wermuth
The Practice of Medicinal Chemistry, Academic Press, New York 1996, pp. 684-685

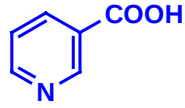
both enzymes are present in high concentration in the kidney

Prodrugs: Hydrazides and Azo Compounds

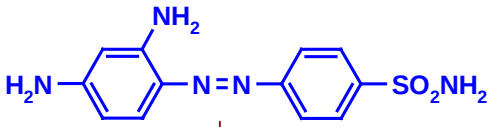


isoniazide, R = -NH-NH$_2$ (tuberculostatic)

the metabolite isonicotinic acid (R = -OH) is an antimetabolite of nicotinic acid

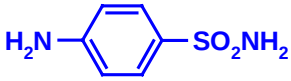


nicotinic acid

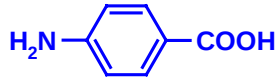


sulfamidochrysoidine ("prontosil rubrum")

metabolic degradation

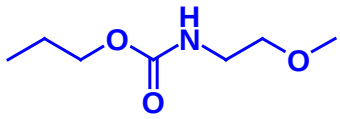


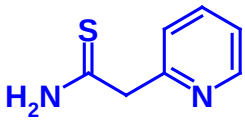
cf.

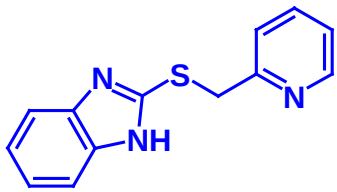


sulfanilamide, an antimetabolite of p-aminobenzoic acid

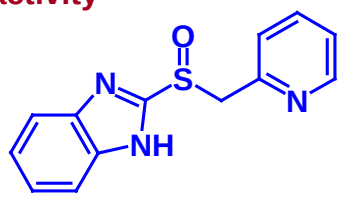
Omeprazole Case Study



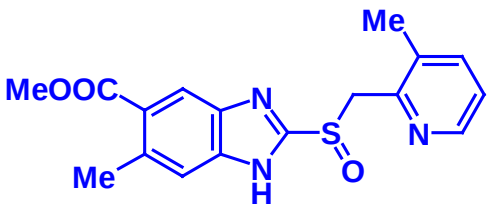




1966: Local anesthetics reduce gastric secretion (Hässle)
1966-1972: First lead
1972-1979: New lead pyridyl-acetamide (from screening of antiviral compounds)
Active analogs; metabolite with higher antisecretory activity



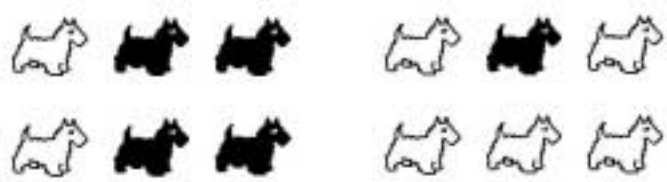
Omeprazole Case Study



Picoprazole, 1976
preclinical candidate

Tox study:

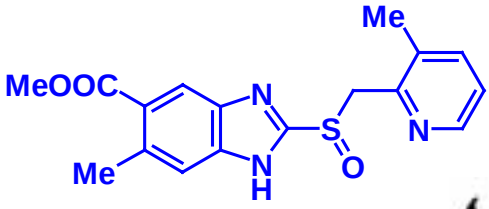
vasculitis



picoprazole group

placebo group

Omeprazole Case Study

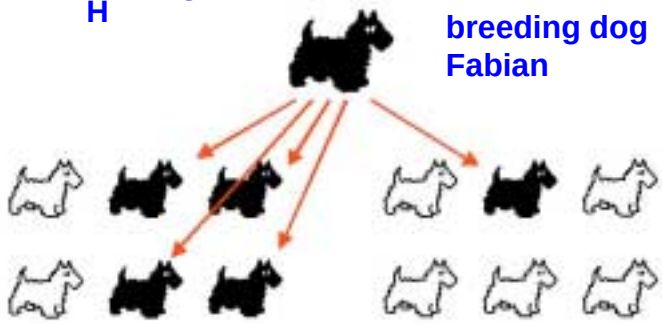


Picoprazole, 1976
preclinical candidate

breeding dog
Fabian

Tox study:

vasculitis

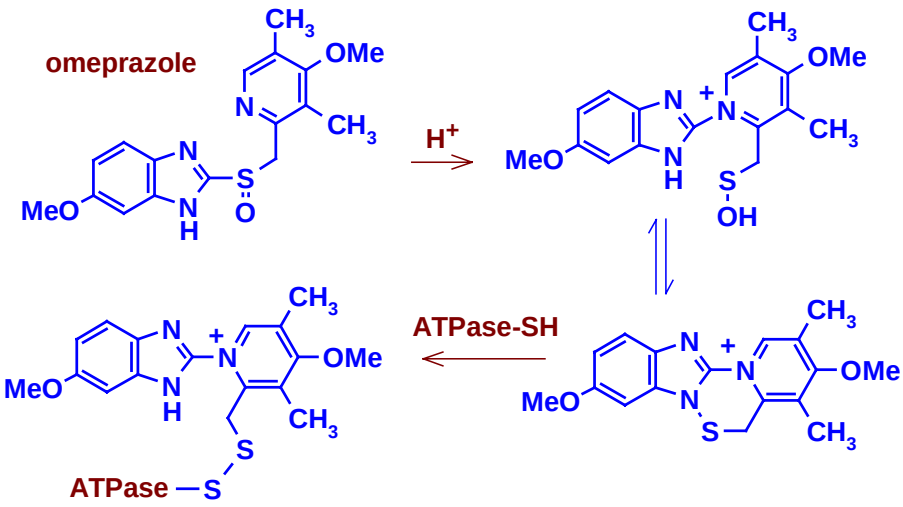


picoprazole group

placebo group

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

omeprazole



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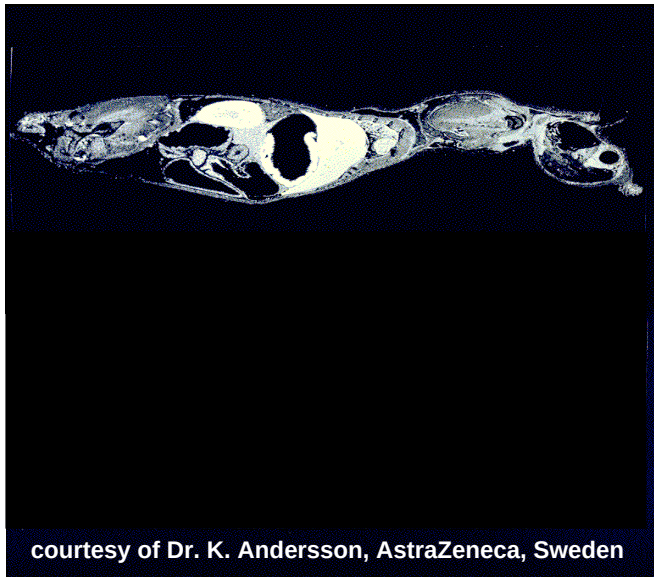
Omeprazole Activation in Acid-Producing Cells

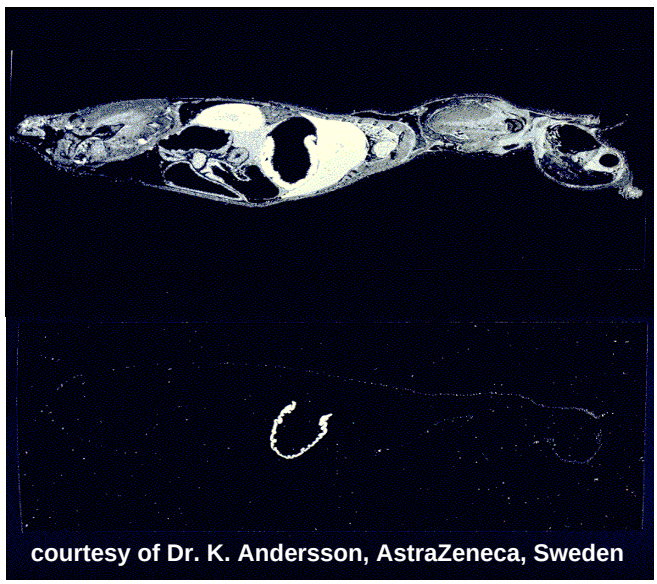


courtesy of Dr. K. Andersson, AstraZeneca, Sweden

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

University of Heidelberg

Omeprazole Activation in Acid-Producing Cells

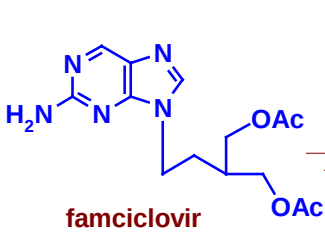


courtesy of Dr. K. Andersson, AstraZeneca, Sweden

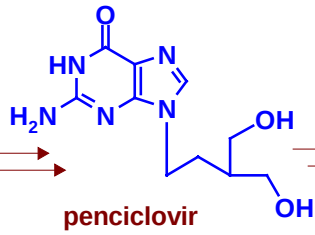
Distribution of radio-labelled omeprazole, one minute after i.v. injection, rat

sixteen hours after i.v. injection, rat

Antiviral Prodrugs are Trojan Horses



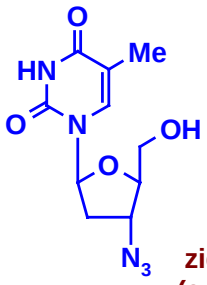
famciclovir



penciclovir

triphosphate

(active form; DNA chain termination)



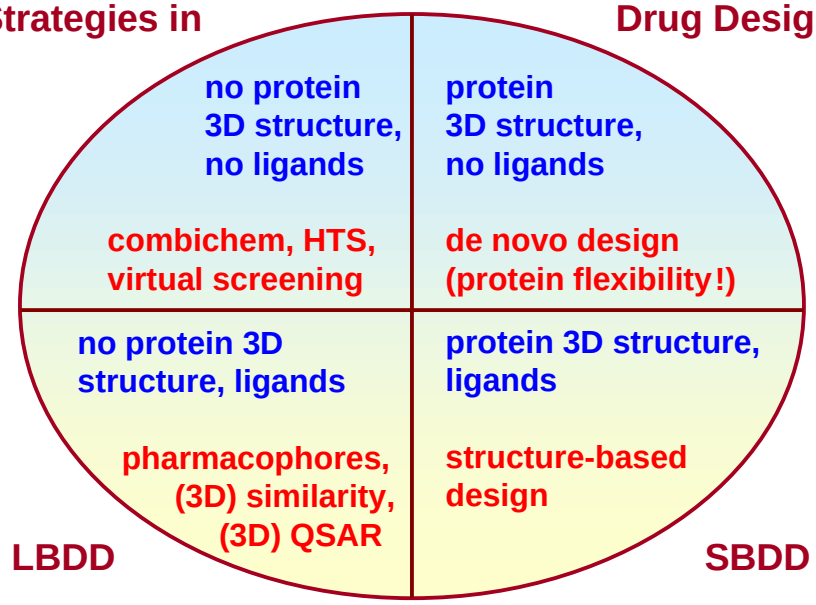
zidovudine (azidothymidine, AZT)

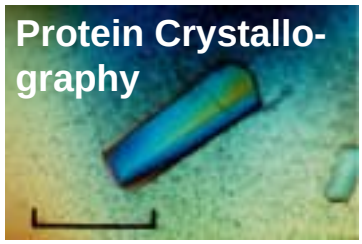
intracellular phosphorylation

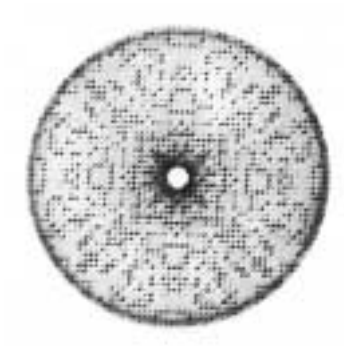
triphosphate

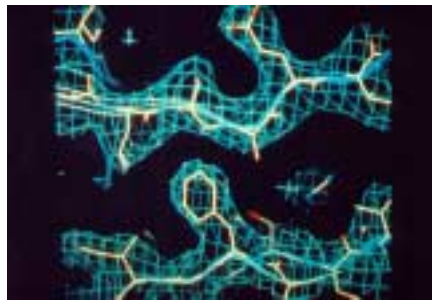
(inhibits reverse transcriptase; inactive against incorporated viruses)

Strategies in Drug Design

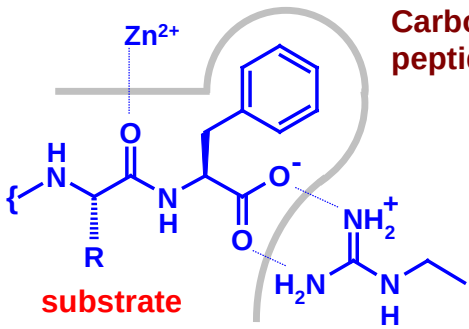






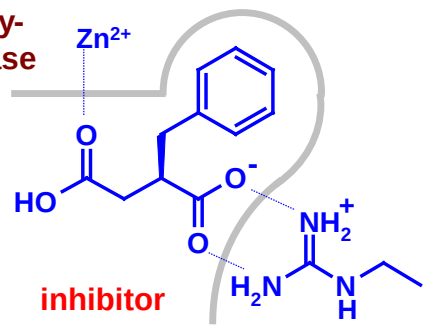


Structure-Based Design of Captopril

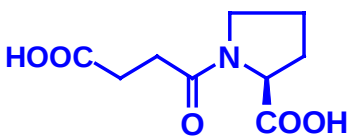


substrate

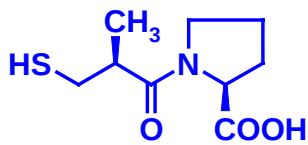
Carboxy-
peptidase



inhibitor

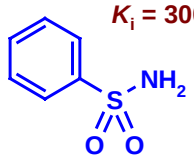


IC_{50} = 330 µM

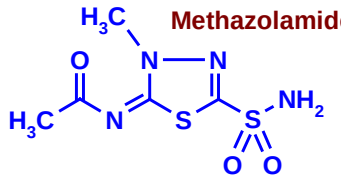


Captopril IC_{50} = 23 nM

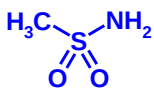
Structure-Based Design of Dorzolamide



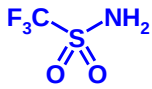
K_i = 300 nM



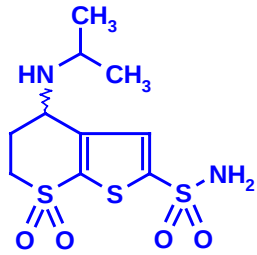
Methazolamide



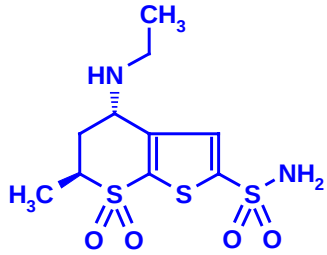
K_i = 100 µM



K_i = 2.0 nM

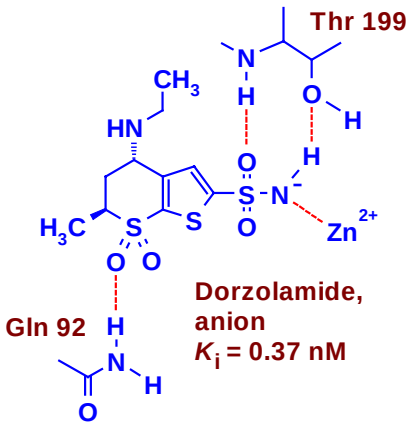


MK 927
K_i = 0.7 nM

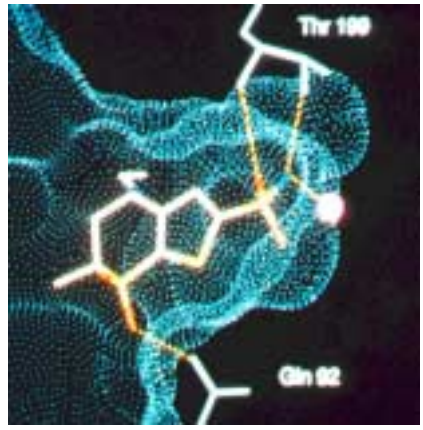


Dorzolamide
K_i = 0.37 nM

Binding Mode of Carbonic Anhydrase Inhibitors



Dorzolamide, anion
K_i = 0.37 nM

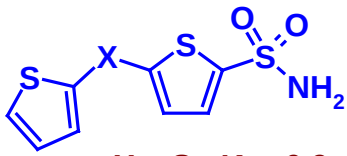


$CH_3SO_2NH_2$, K_i = 100 µM, pK_a = 10.5

$CF_3SO_2NH_2$, K_i = 2 nM, pK_a = 5.8

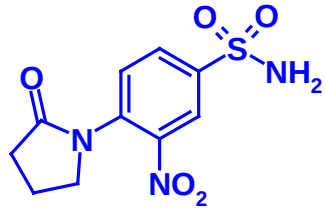
Virtual Screening, Carbonic Anhydrase Inhibitors

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

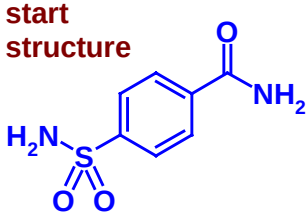


K_i = 0.6 nM

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

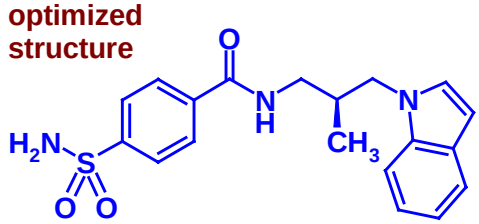
Combinatorial Design of Carbonic Anhydrase Inhibitors

start structure



K_d = 120 nM

optimized structure



R enantiomer, K_d = 30 pM

(*S* enantiomer: K_d = 230 pM)

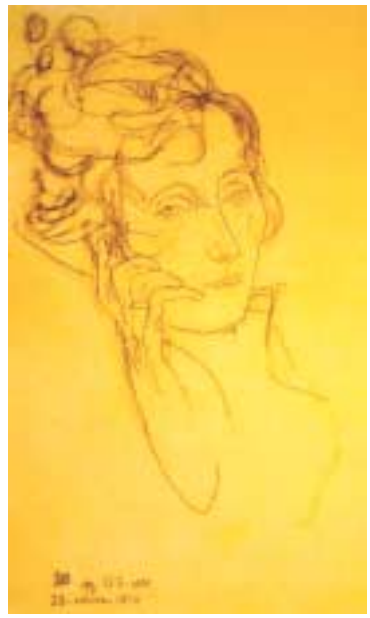
Program CombiSMoG, „best“ N-substituents from 100,000 candidates (20 scored by knowledge-based potentials)

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)

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.



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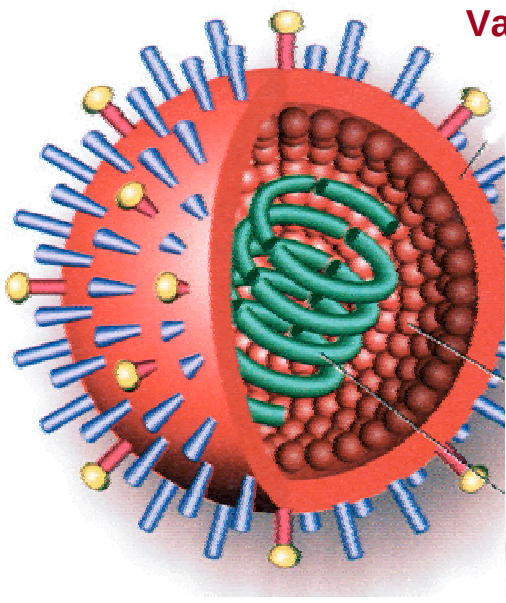
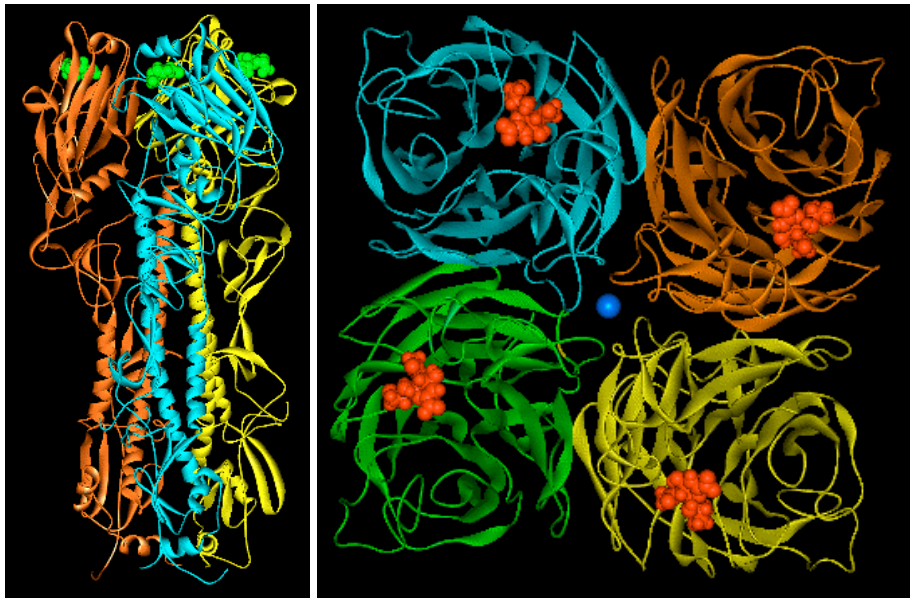
Vaccination ?



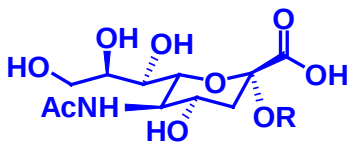
University of Heidelberg



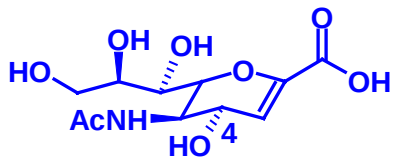
hemagglutinine + sialic acid (green) neuraminidase + DANA (red)

University of Heidelberg

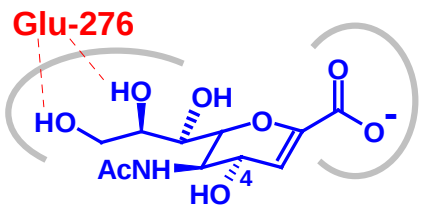
Design of Neuraminidase Inhibitors



sialic acid, R = H



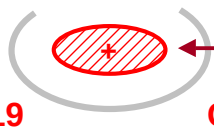
Neu5Ac2en
K_i = 1 000 nM



Arg-371

Arg-292

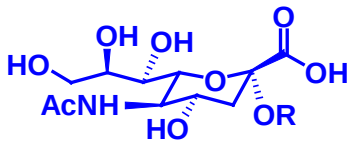
Arg-118



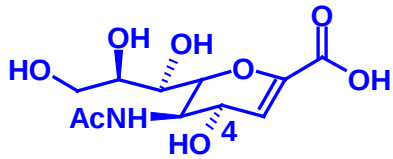
result of a GRID search with a positively charged probe

Glu-119 Glu-227

Design of Neuraminidase Inhibitors



sialic acid, R = H



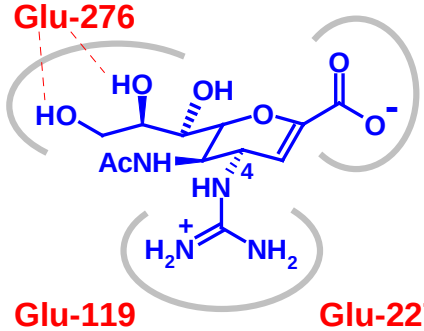
Neu5Ac2en
K_i = 1 000 nM

Glu-276

Arg-371

Arg-292

Arg-118

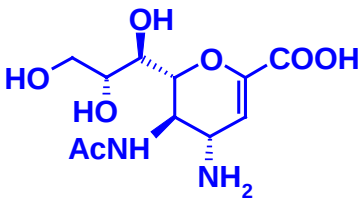


4-Guanidino-Neu5Ac2en
K_i = 0.1-0.2 nM
Zanamivir (Relenza, Glaxo-Wellcome)

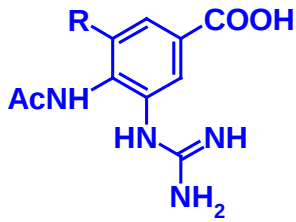
Glu-119

Glu-227

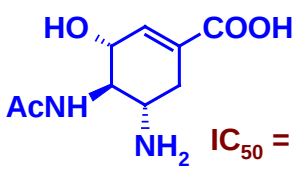
Design of Bioavailable Neuraminidase Inhibitors



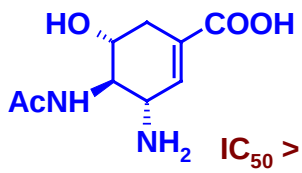
4-NH_2-Neu5Ac2en
K_i = 50 nM



a) R = H K_i = 8 µM
b) R = CH(OH)CH(OH)CH_2OH
K_i > 100 µM



IC_{50} = 6.3 µM



IC_{50} > 200 µM

Design of Bioavailable Neuraminidase Inhibitors

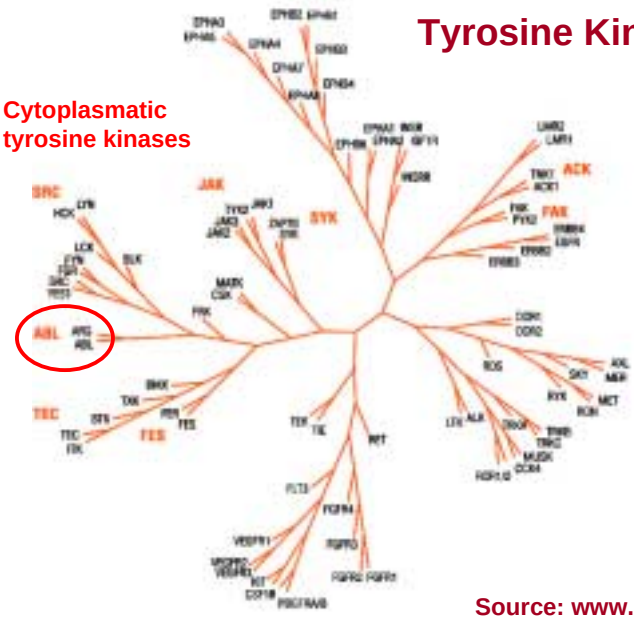
GS 4071, R = $CH(Et)_2$
IC_{50} = 1 nM

GS 4104 (ester prodrug of GS 4071)
Oseltamivir (Tamiflu, Roche)

R =	IC_{50} (nM)
H	6 300
CH_3	3 700
CH_2CH_3	2 000
$CH_2CH_2CH_3$	180
$CH_2CH_2CF_3$	225
CH_2OCH_3	2 000
$CH_2CH{=}CH_2$	2 200
$CH_2CH_2CH_2CH_3$	300
$CH_2CH(CH_3)_2$	200
$CH(CH_3)CH_2CH_3$	10
$CH(CH_2CH_3)_2$	**1**
$CH(CH_2CH_2CH_3)_2$	16
Cyclopentyl	22
Cyclohexyl	60
Phenyl	530

Tyrosine Kinases

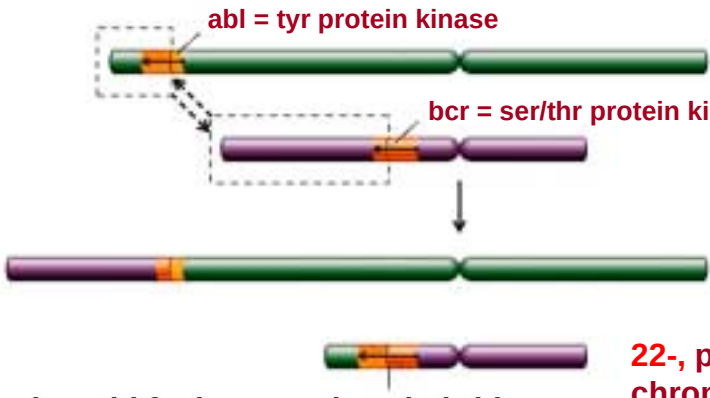
Cytoplasmatic tyrosine kinases



Receptor tyrosine kinases

Source: www.cellsignal.com

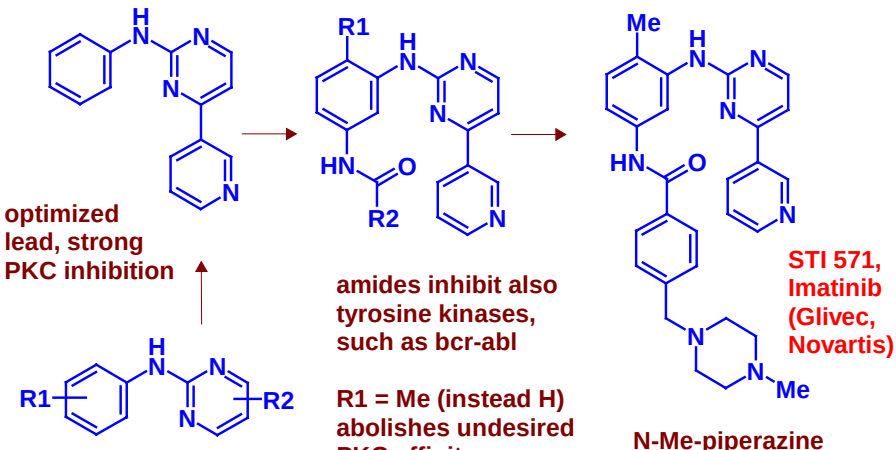
Chromosome Translocation in CML



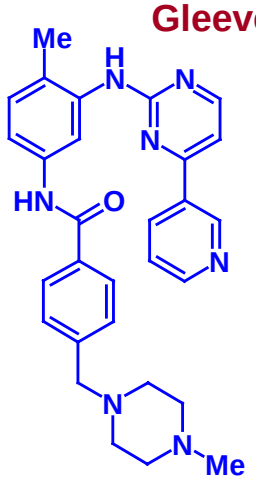
bcr-abl fusion protein, a hybrid with constitutionally enhanced tyrosine protein kinase activity

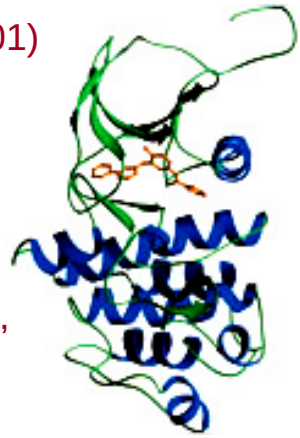
22-, philadelphia chromosome, present in 90+% of all cases of chronic myelogenous leukemia

Development of STI 571 (Imatinib, Glivec®)



Gleevec® (May 2001)



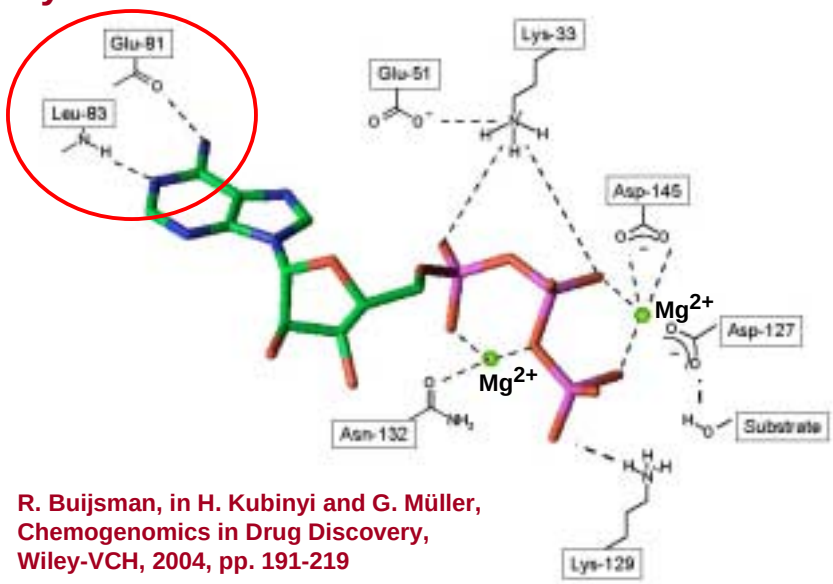


1fpu,
1iep

Glivec®, Imatinib (Novartis), for the treatment of chronic myelogenous leukemia

K_i ABL = 38 nM; K_i PGDFR = 50 nM (PDGFR = platelet-derived growth factor receptor); > 1000-fold selective vs. EGFR, c-src, PKA, PKCα
(R. Capdeville et al., Nature Rev. Drug Discov. 1, 493-502 (2002))

Key Interactions of ATP in the CDK2 Active Site



R. Buijsman, in H. Kubinyi and G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 191-219

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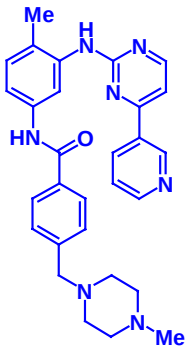
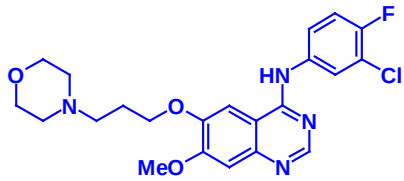
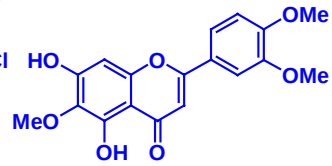
Kinase Inhibitors in Human Therapy



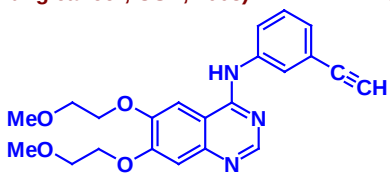
Imatinib (bcr-abl, KIT and PDFRB; CML and GIST; USA, 2001)



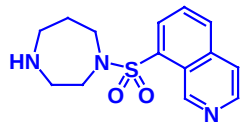
Gefitinib (EGFR; non-small-cell lung cancer; USA, 2003)



Eupatilin (ERK1, ERK2 and CDKs;gastritis; Korea, 2003)



Erlotinib (EGFR; non-small-cell lung cancer; USA, 2004)

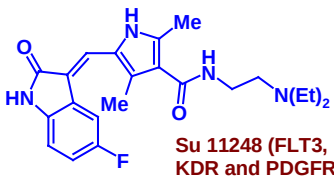


Fasudil (ROCK1; i.v., brain hemorrhage; Japan, 1995)

M. Vieth et al., Drug Discov. today 10, 839-846

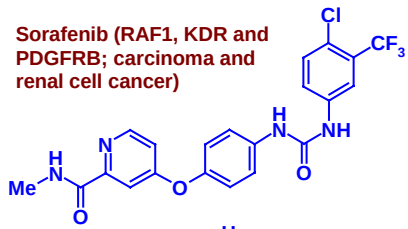
University of Heidelberg

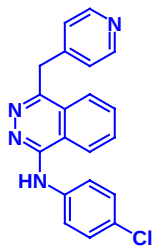
Kinase Inhibitors in Phase III Studies



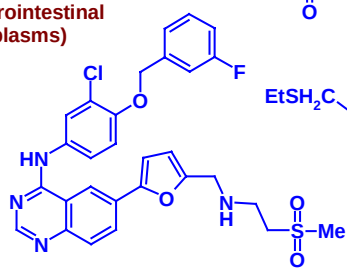
Su 11248 (FLT3, KIT, KDR and PDGFRB; renal cell cancer and gastrointestinal neoplasms)

Sorafenib (RAF1, KDR and PDGFRB; carcinoma and renal cell cancer)

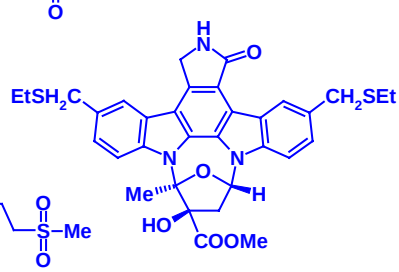




Vatalanib (KDR; colorectal, colonic and rectal neoplasms)

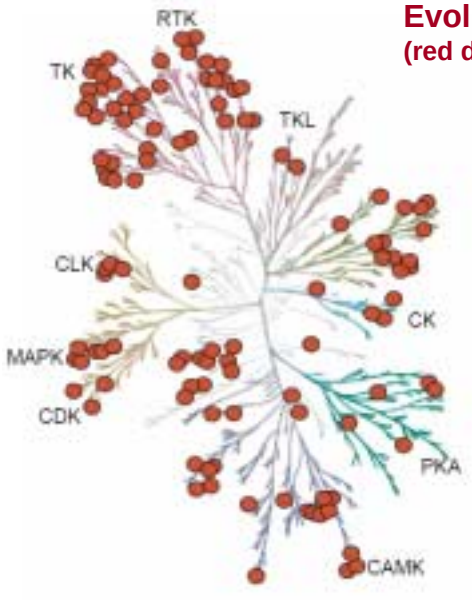


Lapatinib (EGFR and ERBB2; metastatic breast cancer)



CEP 1347 (MAPK8 and MAPK9; Parkinson's disease)

M. Vieth et al., Drug Discov. today 10, 839-846



Evolutionary Tree of Kinases
(red dots indicate 113 tested kinases)

TK	**= non-receptor tyrosine kinases**
RTK	**= receptor tyrosine kinases**
TKL	**= tyrosine kinase-like kinases**
CK	**= casein kinase family**
PKA	**= protein kinase A family**
CAMK	**= calcium/calmodulin-dependent kinases**
CDK	**= cyclin-dependent kinases**
MAPK	**= mitogen-activated kinases**
CLK	**= Cdk-like kinases**

M. A. Fabian et al., Nature Biotech. 23, 329-336 (2005)

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Selectivity of Kinases

(20 inhibitors tested vs. 113 kinases)

M. A. Fabian et al., Nature Biotech. 23, 329-336 (2005)

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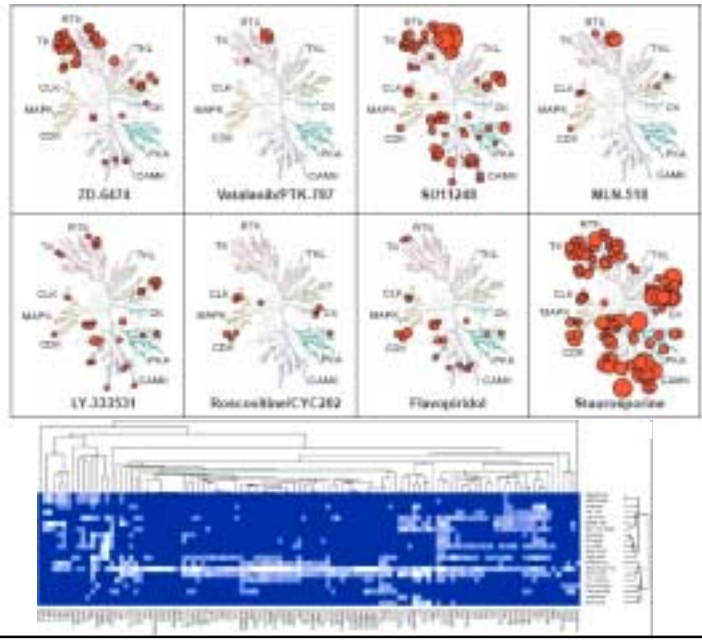
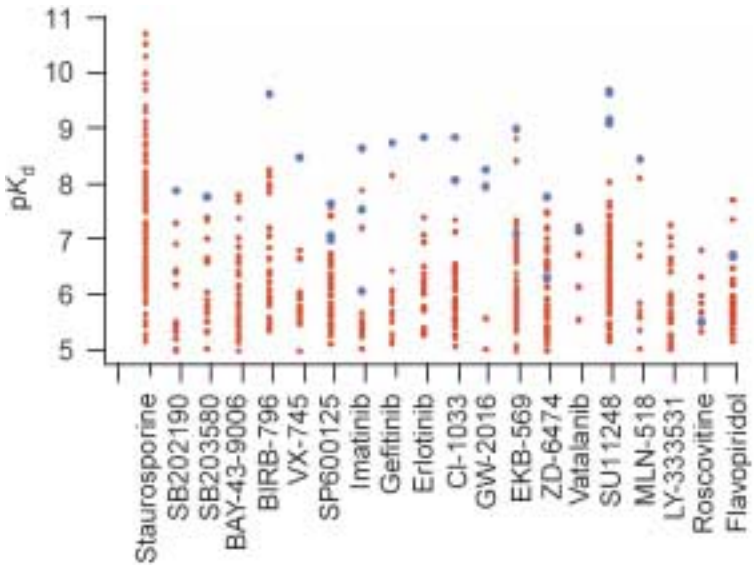


Selectivity of Kinases

(20 inhibitors tested vs. 113 kinases)

M. A. Fabian et al., Nature Biotech. 23, 329-336 (2005)

University of Heidelberg



Selectivity of Kinases

blue dots = targets
red dots = off-targets

M. A. Fabian et al., Nature Biotech. 23, 329-336 (2005)

Voltaire, by J. A. Houdon

The Past

Voltaire (1694-1778):

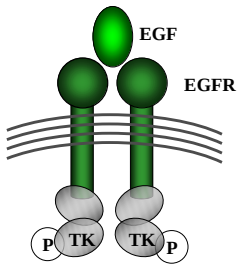
**Doctors
pour drugs of which
they know little,
to cure diseases of which
they know less,
into human beings
of whom
they know nothing.**

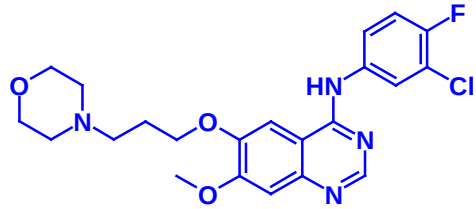
The Future: Pharmacogenomics - New Opportunities from Personalized Medicine

Genotyping of drug targets and metabolic enzymes enables

- **cost savings in drug development through better design of clinical trials**
- **selection of the „best drug“ for a certain patient**
- **individual dose ranges (variance in target sensitivity, reduced or increased metabolism)**
- **fewer toxic side effects**
- **fewer unexpected drug-drug interactions**

Gefitinib®, Iressa, ZD1839 (EGFR TK inhibitor)





cell proliferation ⇧
apoptosis ⇩
angiogenesis ⇧
metastasis ⇧

third-line therapy for non-small-cell lung cancer (75% of lung cancer cases)

clinical response to Iressa ~ 10%

J. G. Paez et al.
EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy
Science 304 (5676), 1497-1500 (2004)

T. J. Lynch et al.
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer and Gefitinib
New Engl. J. Med. 350, 2129-2139 (2004)

8 out of 9 Iressa-responsive patients showed mutations in the kinase domain
0 out of 7 non-responsive patients showed mutations
2 out of 25 non-treated patients showed mutations (8%)

Recommended Literature

F. J. Clarke, How Modern Medicines are Discovered, Futura Publishing Company, Mount Kisco, 1973.

●● A. Burger, A Guide to the Chemical Basis of Drug Design, John Wiley & Sons, New York, 1983.

● W. Sneader, Drug Discovery: The Evolution of Modern Medicines, John Wiley & Sons, Chichester, 1985

● E. Bäumler, Die großen Medikamente. Forscher und ihre Entdeckungen schenken uns Leben, Gustav Lübbe Verlag, Bergisch Gladbach, 1992.

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● H.-J. Böhm, G. Klebe and H. Kubinyi, Wirkstoffdesign, Spektrum Akademischer Verlag, Heidelberg, 1996.

●● J. Ryan, A. Newman, and M. Jacobs, Editors, The Pharmaceutical Century. Ten Decades of Drug Discovery, Supplement to ACS Publications, American Chemical Society, Washington, 2000.

R. Silverman, The Organic Chemistry of Drug Design and Drug Action, 2nd Edition, Elsevier Academic Press, Burlington, 2004.