In Search for New Leads

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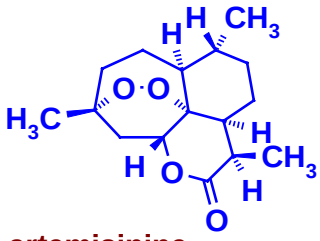
Sources of New Lead Structures

- Plant and microbioal natural products
- Serendipitous discoveries
- Rational approaches (endogeneous transmitters)
- Me too research
- Isosteric replacement
- Optimization of drug side effects
- Chemogenomics
- Chemical biology
- Prodrugs and soft drugs
- Metabolic switch - rescuing poor leads
- Chiral switch
- Combinatorial chemistry / HTS
- Virtual screening
- Structure-based and computer-aided design
- Fragment-based design
- Combinatorial design

H. Kubinyi, EFMC Yearbook 2003, pp. 14-28 (www.kubinyi.de)

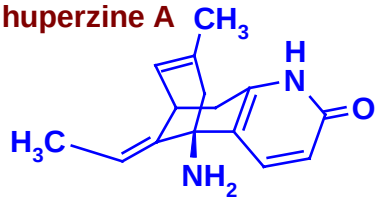
Lead Structures: Natural Products from Plants



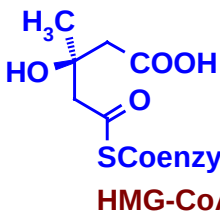
artemisinine

taxol

huperzine A

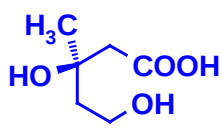


Lead Structures: Microbial Natural Products



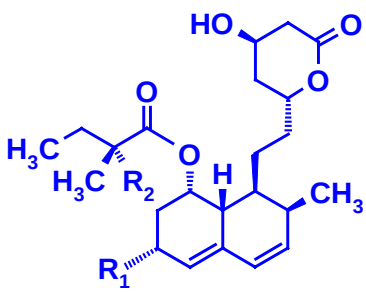
SCoenzym A
HMG-CoA

HMG-CoA reductase



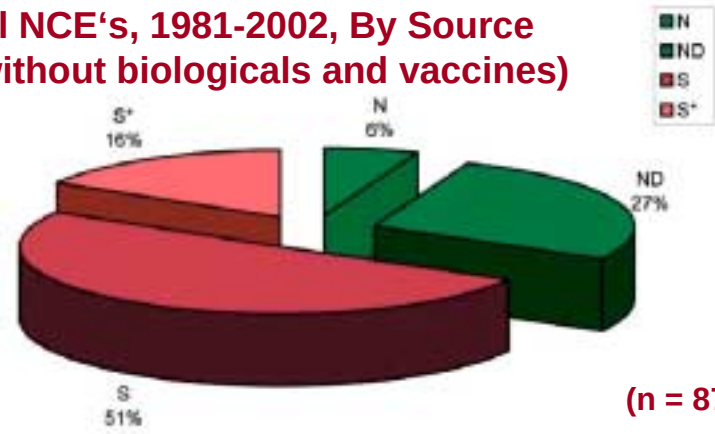
mevalonic acid

cholesterol



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)

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

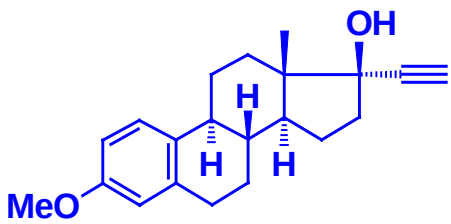


(n = 877)

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

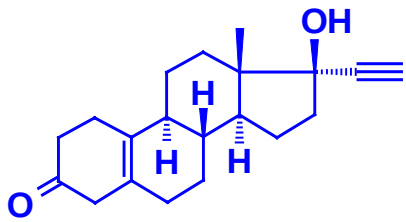
D. J. Newman et al., J. Nat. Prod. 66, 1022-1037 (2003)

The Serendipitous Discovery of the Pill



1. Birch reduction
2. enol ether cleavage

Mestranol



Norethynodrel (Searle)

Serendipitous Drug Discoveries

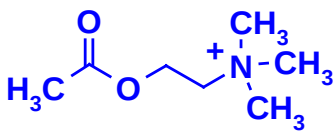
Acetanilide, Acetylsalicylic acid, Aminoglutethimide, Amphetamine, Chloral hydrate, Chlordiazepoxide, Chlorpromazine, Cinnarizine, Cisplatin, Clonidine, Cromoglycate, Cyclosporin, Dichloroisoprotere-nol, Dicoumarol, Diethylstilbestrol, Diphenhydramine, Diphenoxylate, Disulfiram, Ether, Etomidate, Griseofulvin,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

Sweeteners: Saccharin, Cyclamate, Aspartame

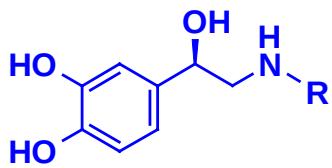
R. M. Roberts, Serendipity - Accidental Discoveries in Science, John Wiley & Sons, New York, 1989.

H. Kubinyi, Chance Favors the Prepared Mind. From Serendipity to Rational Drug Design, J. Receptor & Signal Transduction Research 19, 15-39 (1999).

Lead Structures: Endogenous Neurotransmitters

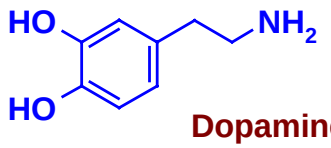


Acetylcholine

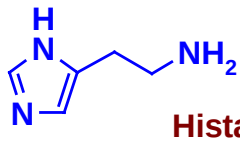


Epinephrine, R = CH_3

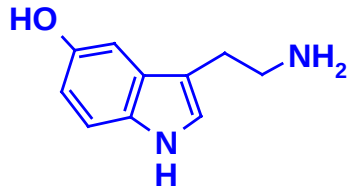
Norepinephrine, R = H



Dopamine



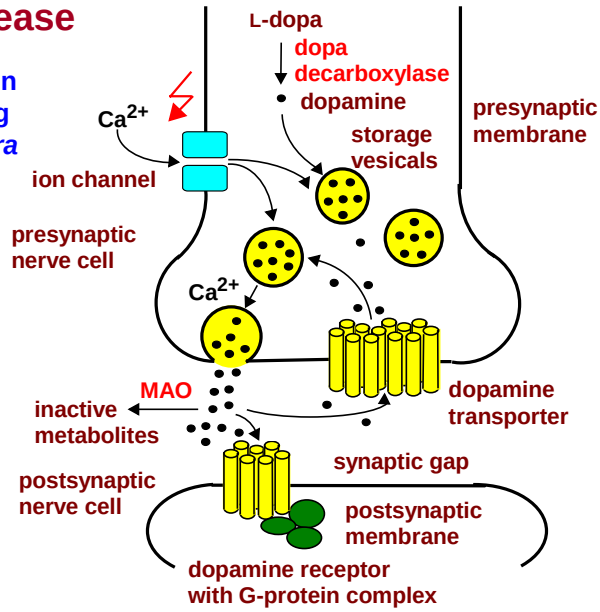
Histamine



Serotonin (5-HT)

Parkinson‘s Disease

caused by degeneration of dopamine-producing cells in *Substantia nigra*



A Rational Therapy of Parkinson‘s Disease

	healthy	sick
ACh	+	+
dopamine	+	-

Therapy

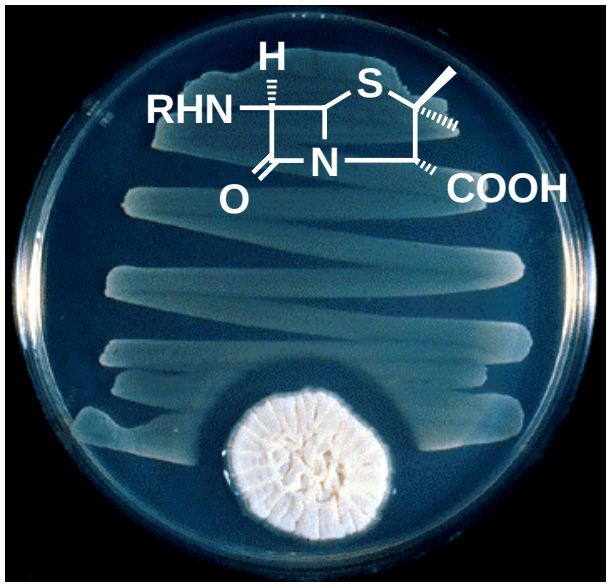
ACh ↓ or

dopamine ↑

Problems

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

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

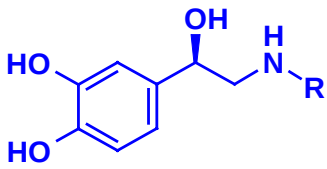


Me too,
me better,
me first,
me only

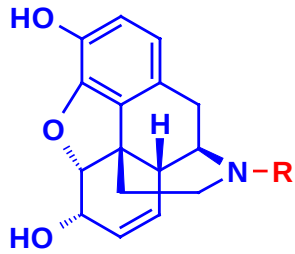
Several generations of penicillin analogs

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

Isosteric Replacement - Agonists and Antagonists

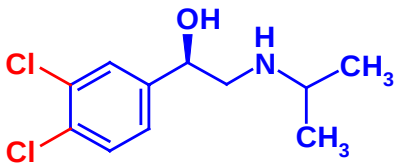


R = H , norepinephrine
R = CH_3, epinephrine
R = $CH(CH_3)_2$, isoproterenol



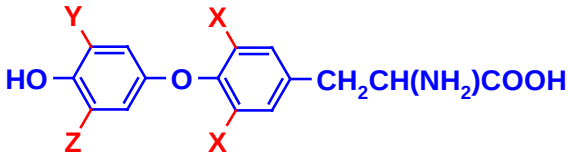
morphine
R = CH_3
(agonist)

nalorphine
R = CH_2-CH=CH_2
(antagonist)

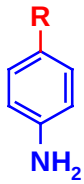


dichloroisoproterenol, DCI

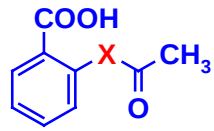
Consequences of Isosteric Replacement



T3 X = Y = iodine, Z = H
Analogs with Y = isopropyl and analogs with X = Y = alkyl are biologically active



p-aminobenzoic acid,
R = COOH, is a metabolite
sulfanilamide, R = SO_2NH_2,
is an antimetabolite



only X = -O- (ASS)
is biologically active

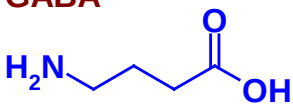
Consequences of Isosteric Replacement

Inhibition of Carbonic Anhydrase by Sulfonamides

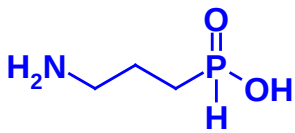
$CH_3SO_2NH_2$, K_i = 100 µM, pK_a = 10.5
$CF_3SO_2NH_2$, K_i = 2 nM, pK_a = 5.8

Specificity of GABA Receptor Ligands

GABA

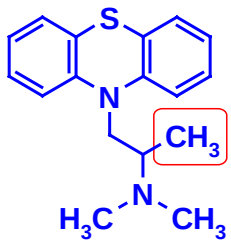


	$GABA_A$ receptor affinity	$GABA_B$
IC_{50} =	20 nM	20 nM

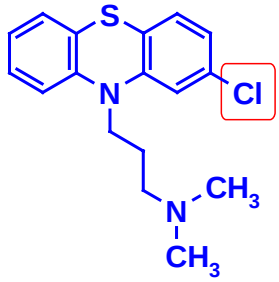


IC_{50} =	4,500 nM	1 nM

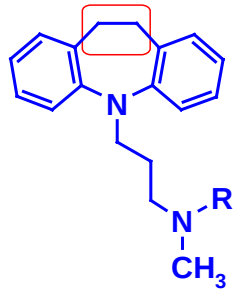
Different Modes of Action of Chemically Similar Molecules



promethazine
(H_1 antagonist)

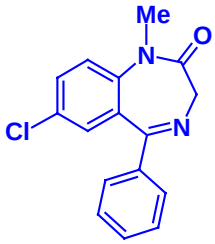


chlorpromazine
(dopamine antagonist)



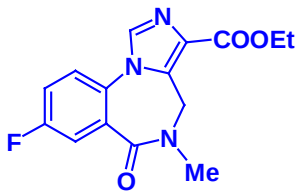
a, R = CH_3, imipramine
b, R = H, desipramine
(uptake blocker)

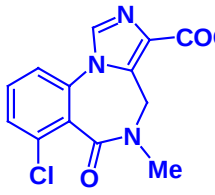
Activities of Benzodiazepines



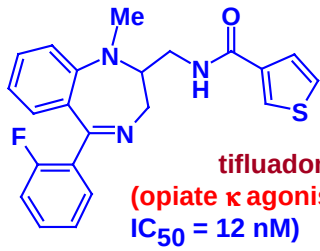
diazepam (agonist)
positive intrinsic activity at the $GABA_A$ receptor (tranquilizer)

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





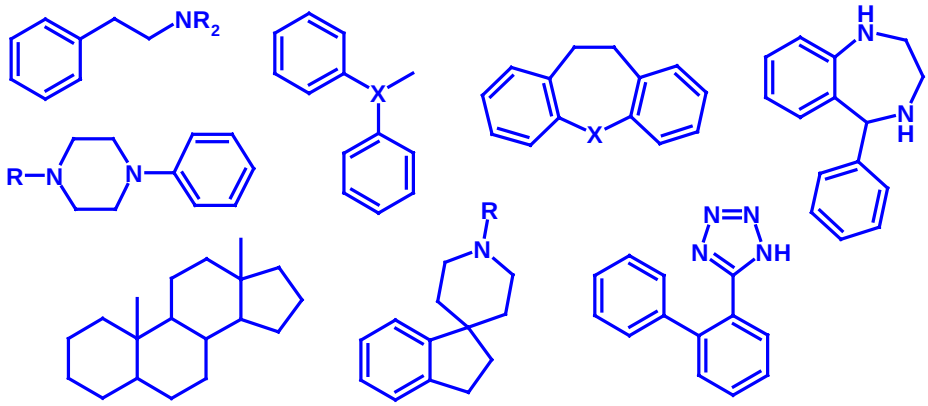
Ro 15-3505
(inverse agonist)
negative intrinsic activity at the $GABA_A$ receptor (proconvulsant)



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“

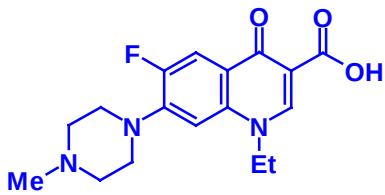


B. E. Evans et al., J. Med. Chem. 31, 2235-2246 (1988); A.A. Patchett, R.P. Nargund, Annu. Rep. Med. Chem. 35, 289-298 (2000); H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004

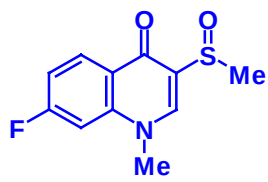
„Selective Optimization of Side Activities“

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

Sir James Black, Nobel Prize 1988



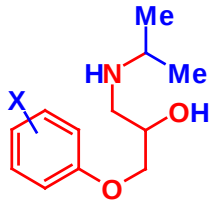
norfloxazin, an antibiotic



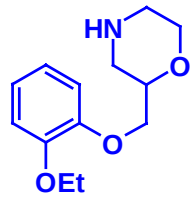
flosequinan, a mixed arterial and venous vasodilator

C. G. Wermuth, Med. Chem. Res. 10, 431-439 (2001); C. G. Wermuth, J. Med. Chem. 47, 1303-1314 (2004); H. Kubinyi, in H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 43-67

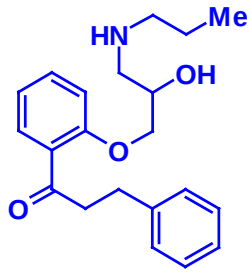
„Selective Optimization of Side Activities“



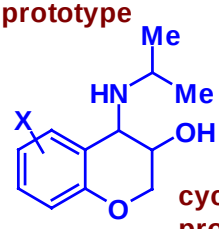
ß-blocker prototype



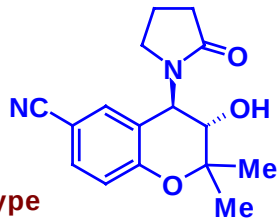
viloxacine antidepressant



propafenone 1c antiarrhythmic



cyclic prototype



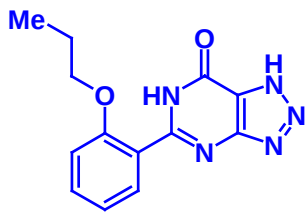
levocromakalim K channel opener

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

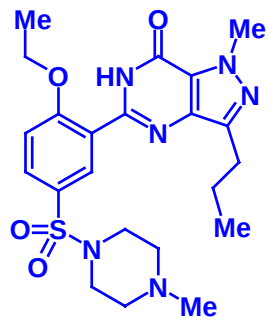
Which Important Drug

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 ....

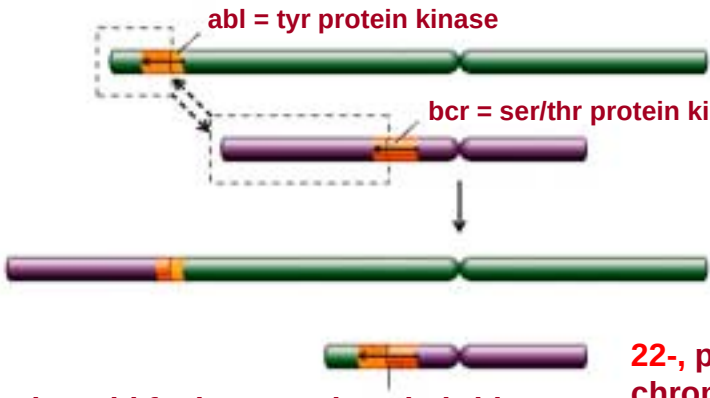


Zaprinast unspecific PDE inhibitor; antiallergic, vasodilator.



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

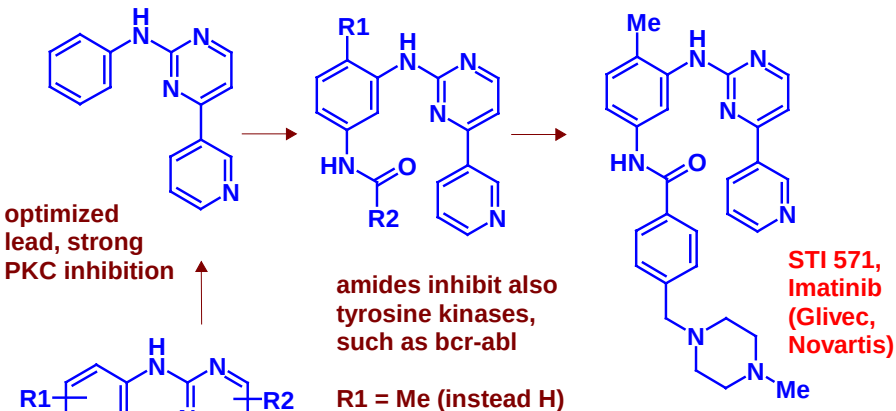
Chromosome Translocation in CML



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

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

Development of STI 571 (Imatinib, Glivec®)



„Chemical Biology“

screening of chemical libraries in biological systems (e.g. whole cells), in order to detect certain new phenotypes

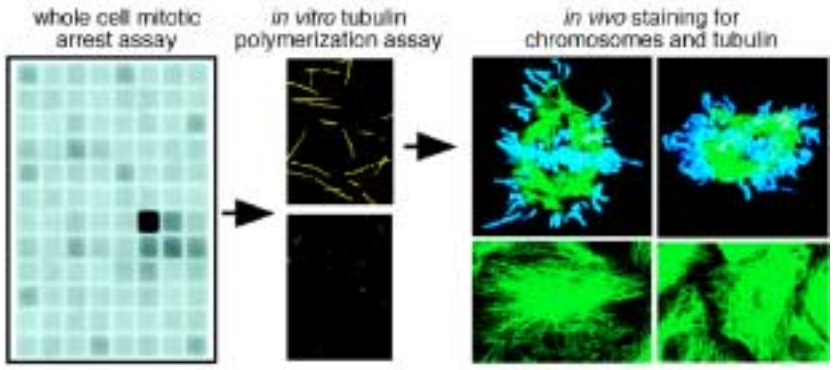
„Chemogenomics“

aims to discover active and/or selective ligands for biologically related targets in a systematic manner

Principle: screening of the chemical universe against the target universe

Real world: library screening vs. target families (GPCRs, integrins, steroid receptors, tyrosine and serine/threonine protein kinases, metalloproteases, serine proteases, aspartyl proteases, etc.)

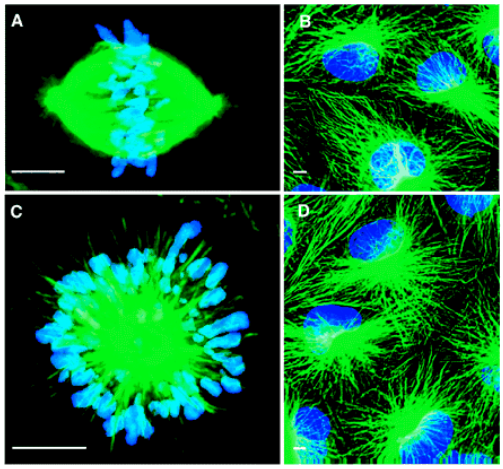
Discovery of Monastrol, a Small Molecule Inhibitor of Mitotic Spindle Bipolarity



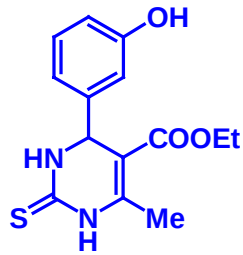
microtubules (green), chromatin (blue)

T. U. Mayer et al., Science 286, 971-974 (1999)

Discovery of Monastrol, a Small Molecule Inhibitor of Mitotic Spindle Bipolarity



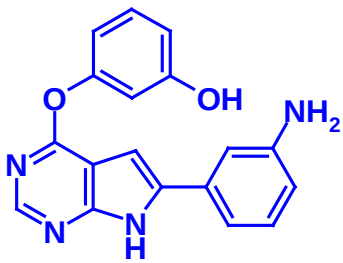
Control cells (A, B) and Monastrol-treated cells (C, D).



Monastrol inhibits kinesin Eg5

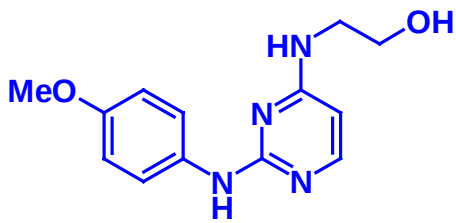
T. U. Mayer et al., Science 286, 971-974 (1999)

In vitro Differentiation of Embryonic Stem Cells



TWS 119 induces neuron formation from embryonic stem cells by modulation of glycogen synthase kinase 3ß (GSK 3ß)

S. Ding et al, Proc. Natl. Acad. Sci. USA 100, 7632-7637 (2003)



Cardiogenol C, from a 100,000-member hetero-cycles library, induces cardiac muscle cell formation from embryonic stem cells

X. Wu et al., J.Am. Chem. Soc. 126, 1590-1591 (2004)

University of Heidelberg

Dedifferentiation and Redifferentiation in Amphibia

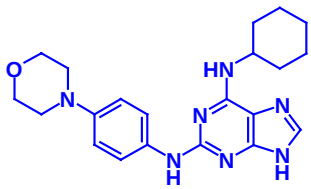
Newt

can regenerate limbs, tail and eye lense

P. A. Tsonis, Molecular Interventions 4, 81-83 (2004)

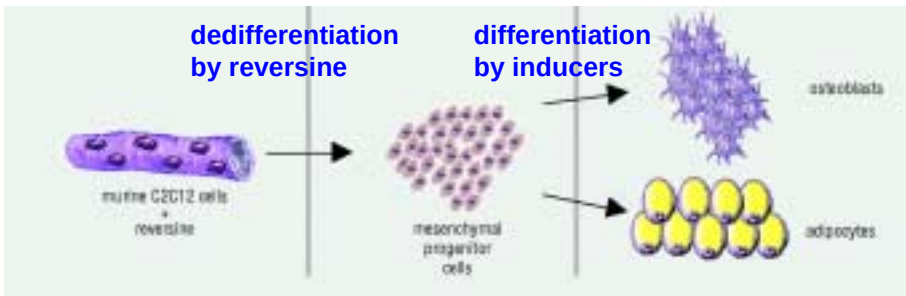
University of Heidelberg

Reversine Dedifferentiates Adult Murine Cells



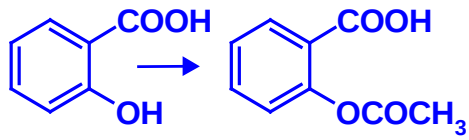
Reversine

discovered in kinase inhibitor libraries, dedifferentiates adult murine myotube cells to mesenchymal progenitor cells



S. Ding and P.G. Schultz, Nat. Biotechnol. 22, 833-840 (2004);
S. Chen et al., J. Am. Chem. Soc. 126, 410-411 (2004)

Is Aspirin® a Prodrug ? (Felix Hoffmann, 1897)



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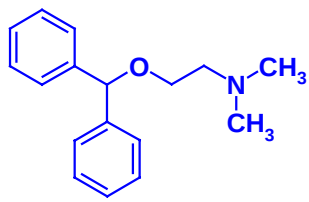
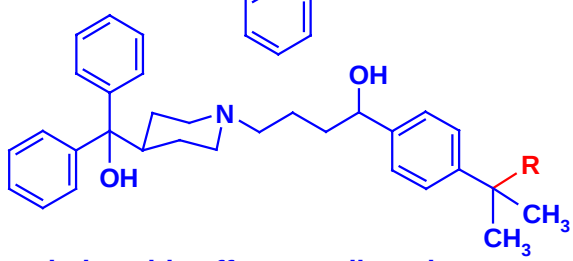
Metabolic Switch - Rescuing a Poor Lead

diphenhydramine
lipophilic H_1 antagonist
(sedative side effect)

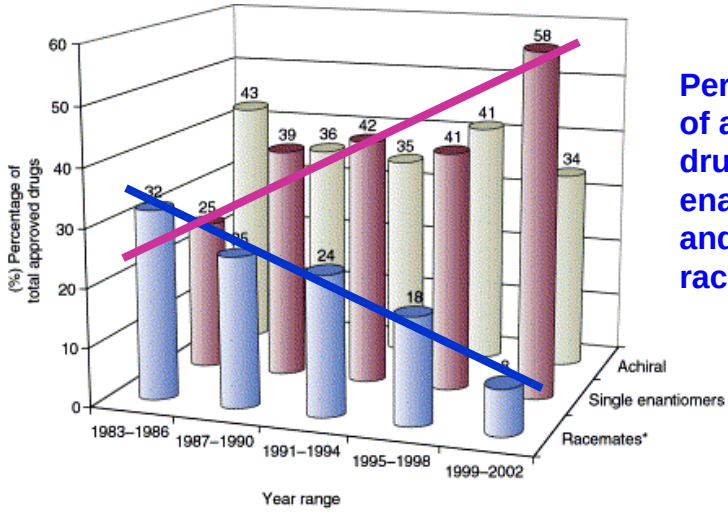




terfenadine (Seldane®), R = CH_3: polar H_1 antagonist (no sedative side effect; cardiotoxic, especially in combination with CYP 3A4 inhibitors)

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

Chiral and Achiral Drugs, 1983-2002

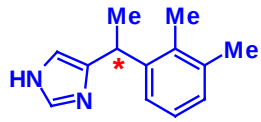


Percentage of achiral drugs, single enantiomers and racemates

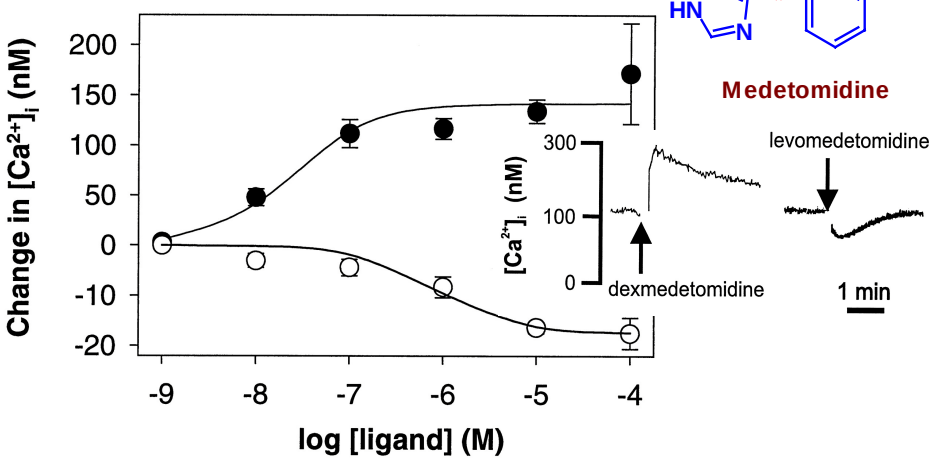
H. Caner et al., Drug Discov. today 9, 105-110 (2004)

Enantiomers as α_{2A} Agonists and Inverse Agonists

(influence on intracellular Ca^{2+} concentration)

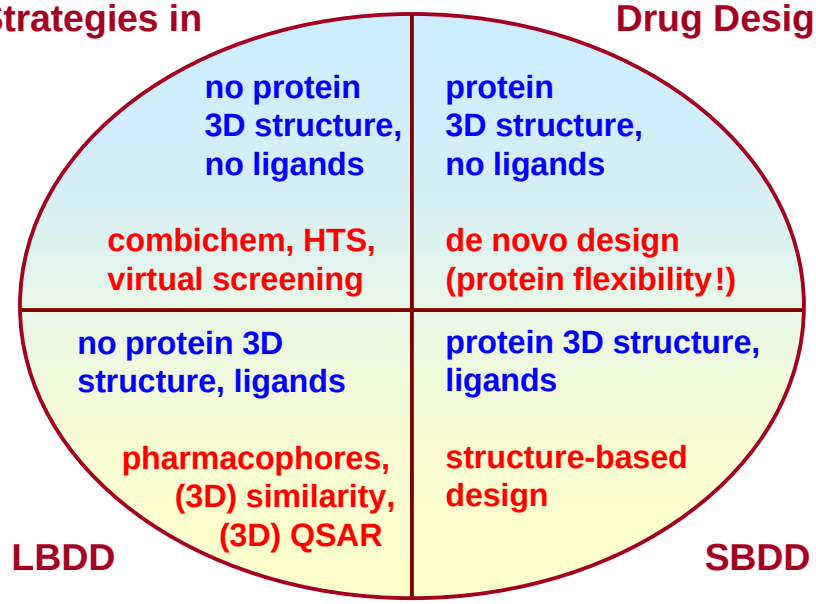


Medetomidine

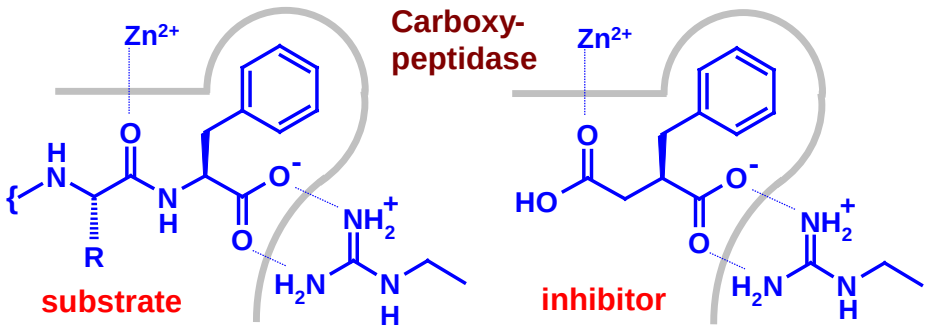


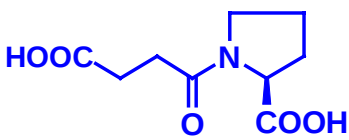
C.C. Jansson et al., Mol. Pharmacol. 53, 963-968 (1998)

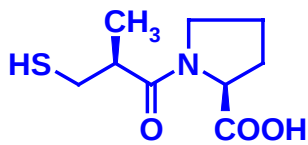
Strategies in Drug Design



Structure-Based Design of Captopril



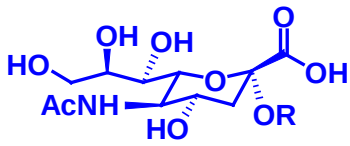




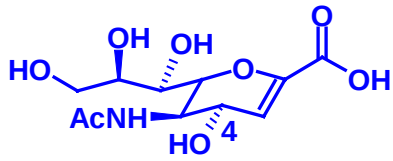
IC_{50} = 330 µM

Captopril IC_{50} = 23 nM

Design of Neuraminidase Inhibitors

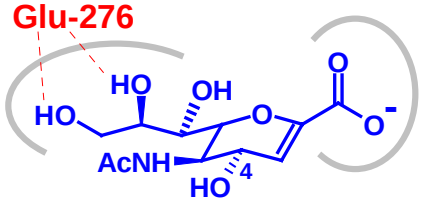


sialic acid, R = H



Neu5Ac2en
K_i = 1 000 nM

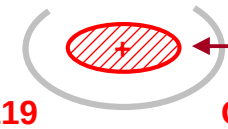
Glu-276



Arg-371

Arg-292

Arg-118



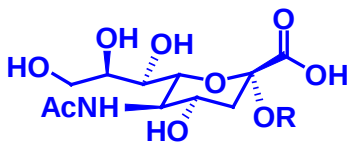
result of a GRID search with a positively charged probe

Glu-119

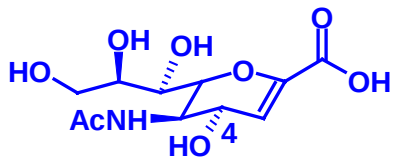
Glu-227

University of Heidelberg

Design of Neuraminidase Inhibitors

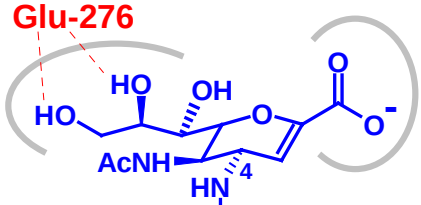


sialic acid, R = H



Neu5Ac2en
K_i = 1 000 nM

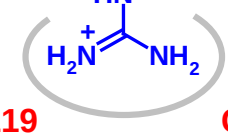
Glu-276



Arg-371

Arg-292

Arg-118



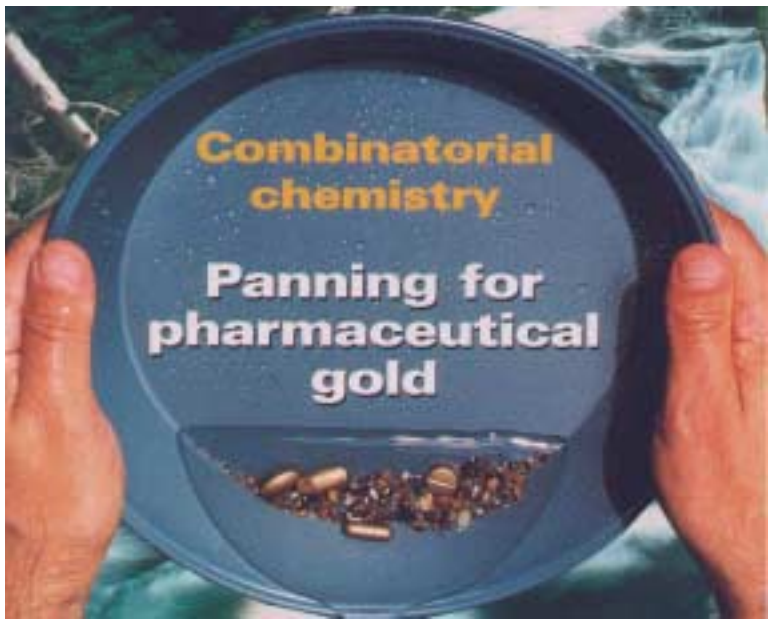
4-Guanidino-Neu5Ac2en
K_i = 0.1-0.2 nM
Zanamivir (Relenza, Glaxo-Wellcome)

Glu-119

Glu-227

Disadvantages of Traditional Medicinal Chemistry

- Complex and time-consuming syntheses
- Low diversity (insufficient for new lead discovery)
- Synthetic output too small
- Slow development of structure-activity profiles within a class of compounds
- Slow optimization in evolutionary cycles
- Insufficient patent coverage
- High costs (about 5,000 – 10,000 US-$ per compound)



Types and Features of Combinatorial Libraries

Random libraries → **druglike**, **diverse scaffolds**

Chemogenomics
Targeted libraries → **target-directed**, **diverse substitution**
(target families)

Focused libraries → **similar to lead**, **complete**

Drug Research is ....

the Search for a Needle in a Haystack

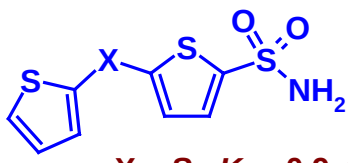
Virtual Screening Reduces the Size of the Haystack by Selecting:

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

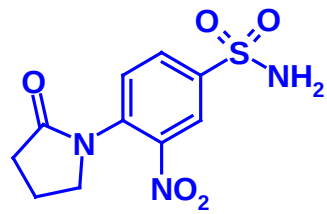
Virtual Screening, Carbonic Anhydrase Inhibitors

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

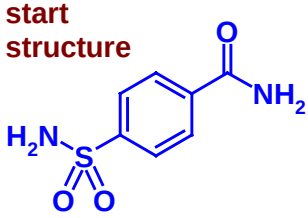


K_i = 0.6 nM

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

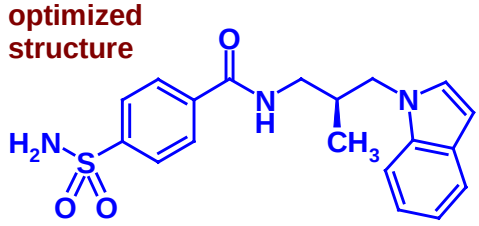
Combinatorial Design of Carbonic Anhydrase Inhibitors

start structure



K_d = 120 nM

optimized structure



R enantiomer, K_d = 30 pM

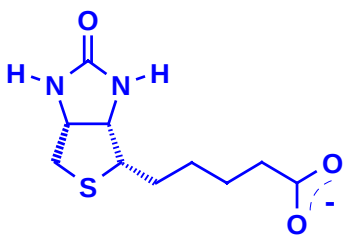
(*S* enantiomer: K_d = 230 pM)

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

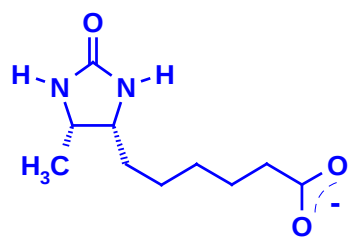
B. A. Grzybowski et al., Acc. Chem. Res. 35, 261-269 (2002);
B. A. Grzybowski et al., Proc. Natl. Acad. Sci. USA 99, 1270-1273 (2002)

Binding Constants of Biotin and Analogs

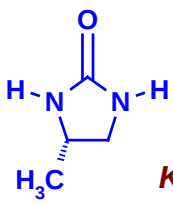
(N. M. Green, Adv. Protein Chem. 29, 85-133 (1975))



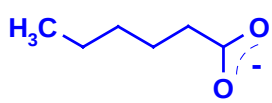
Biotin, $K_i = 1{,}3 \times 10^{-15}$ M



Desthiobiotin, $K_i = 5 \times 10^{-13}$ M



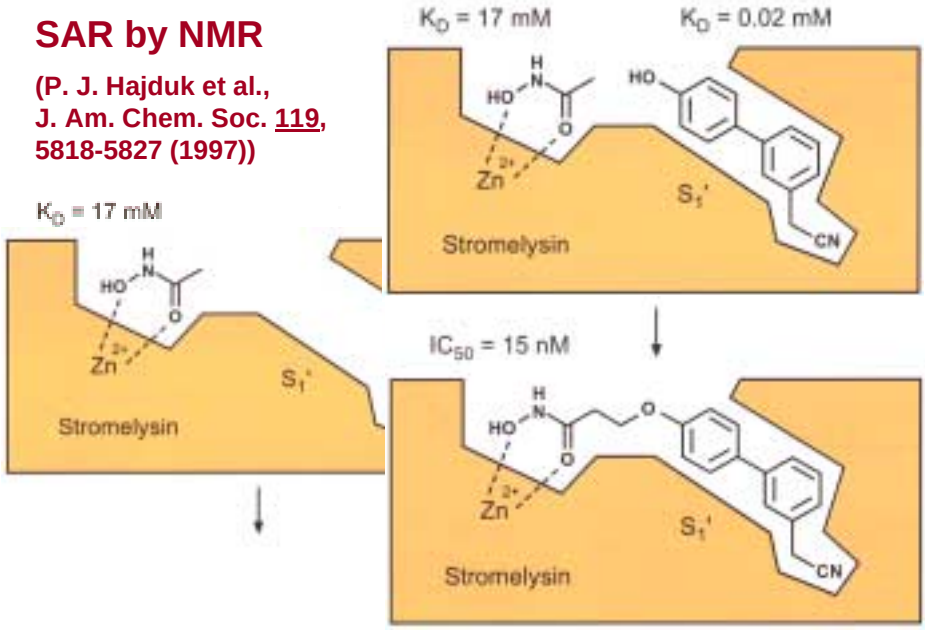
$K_i = 3{,}4 \times 10^{-5}$ M



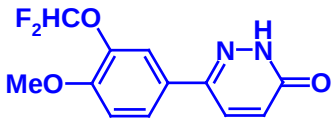
$K_i = 3 \times 10^{-3}$ M

SAR by NMR

(P. J. Hajduk et al., J. Am. Chem. Soc. 119, 5818-5827 (1997))

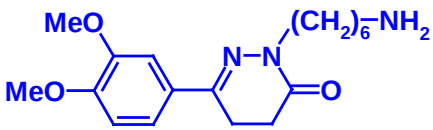


Scaffold-Linker-Functional Group Approach



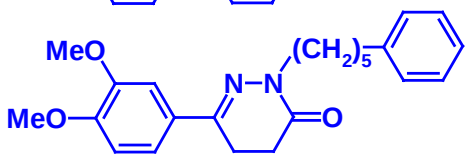
Zardaverine
IC_{50} PDE4 = 800 nM

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

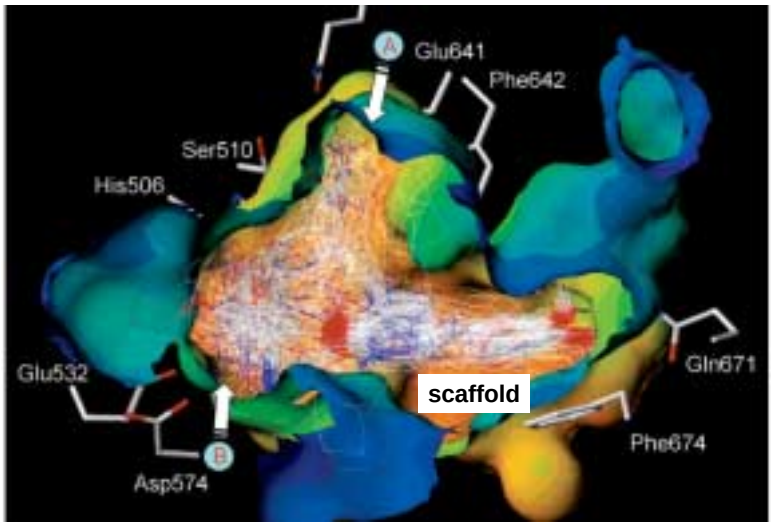
IC_{50} PDE4 = 20 nM



IC_{50} PDE4 = 0.9 nM

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

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)

The Future: Combinatorial Drug Design