Serendipity and Rational Design

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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

Hugo Kubinyi, www.kubinyi.de

Chance, Good Luck and the Prepared Mind

Serendipity: Sir Horace Walpole, 1754

As Their Highnesses [re: the Princes of Serendip] travelled, they were always making discoveries, by accidents and sagacity, of things which they were not in quest of.

Louis Pasteur, 1854

Dans les champs de l’observation, le hasard ne favorise que les esprits préparés.

Albert Szent-Györgi (1893-1986)

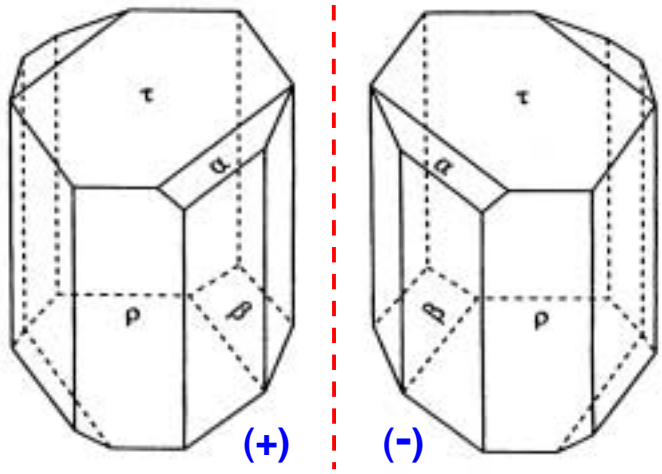
Discovery consists of seeing what everybody else has seen and thinking what nobody else has thought.

Louis Pasteur

(27.12.1822-
28.09.1895)

1848 Prof.
in Dijon,
Strasbourg,
Lille
1857 Paris

Mechanical Separation of Sodium Ammonium Tartrate Crystals (Louis Pasteur, 1848)



Only a few compounds crystallize as separate stereoiso-mers.

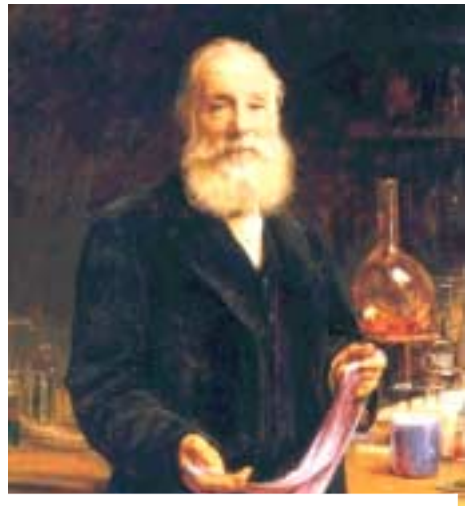
Effect only observed at ambient temperature.

A. W. Hofmann (1818-1892)

1845: Queen Victoria visits Germany; Prince Albert invites August Wilhelm Hofmann to come to London

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

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

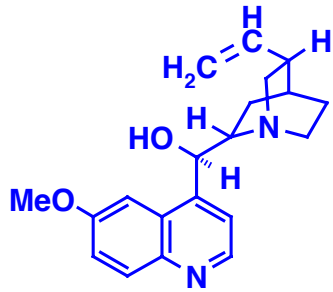


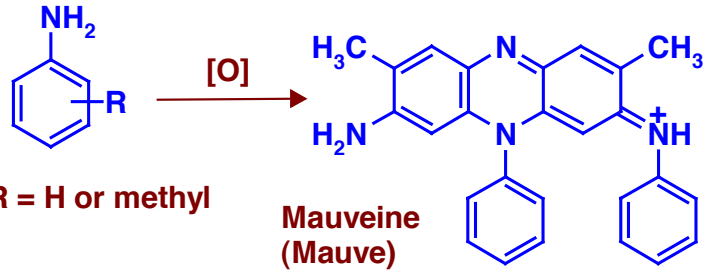
1862: Queen Victoria wears a dress in mauve color

Lack of Success in a Quinine Synthesis (1856)

allyl-toluidine

Quinine

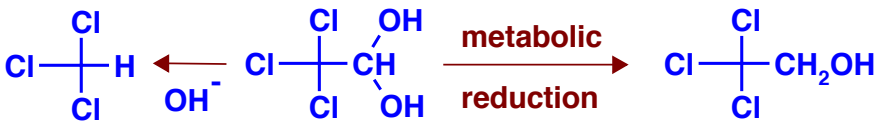




R = H or methyl

Mauveine (Mauve)

Chloral Hydrate, a Prodrug of Chloroform ?

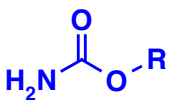


Chloroform

Chloral hydrate

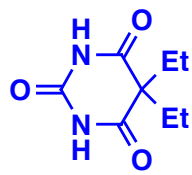
Trichloroethanol

Urethane, a Prodrug of Ethanol ?



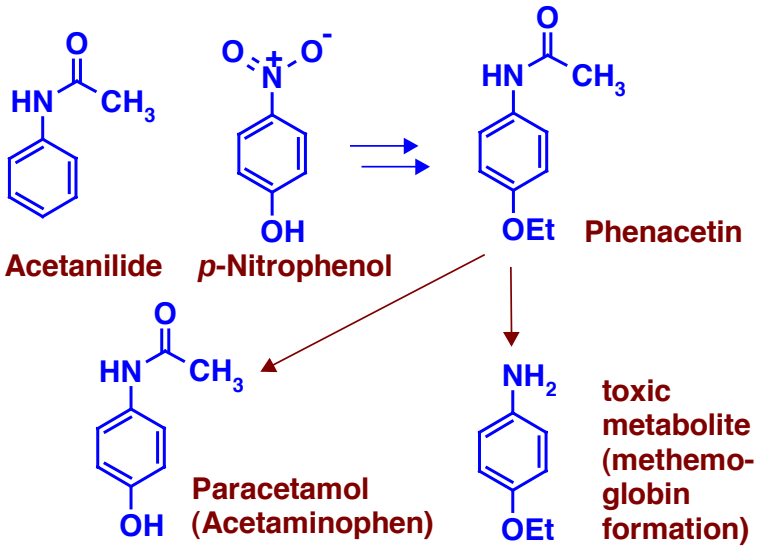
Urethane, R = $-CH_2CH_3$

Isopentylcarbamate, R = $-CH_2CH_2CH(CH_3)_2$

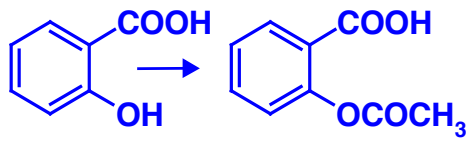


Barbitone

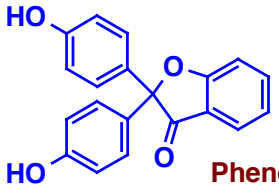
Discovery of Acetanilide and Phenacetin



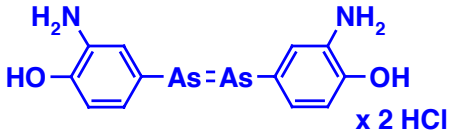
Aspirin®, the Magic Bullett (Felix Hoffmann, 1897)



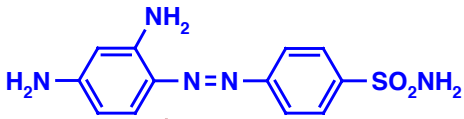
Dyestuffs as Drugs



Phenolphthalein

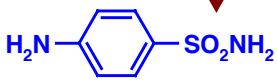


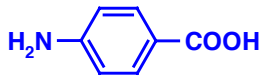
Arsphenamine, E 606
(Salvarsan)



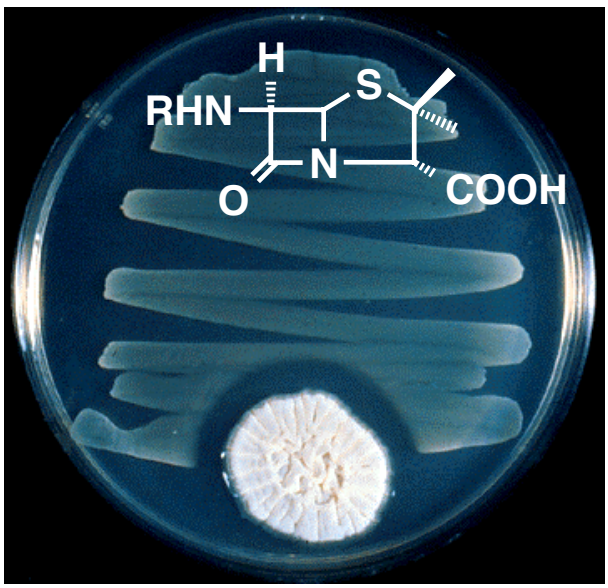
Sulfamidochrysoidine
("Prontosil rubrum")

metabolic degradation





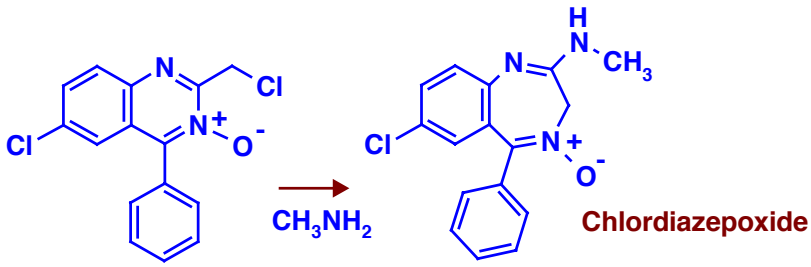
Sulfanilamide, an antimetabolite of p-aminobenzoic acid

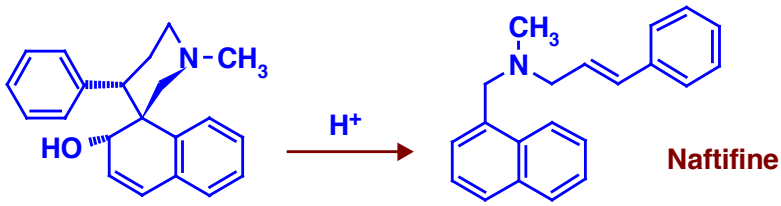


„Penicillin
happened,
it came out
of the blue.“

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, 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.

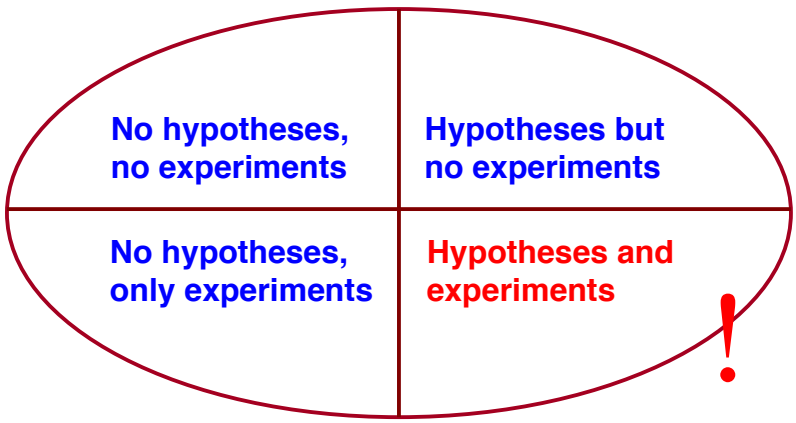
Sweeteners: Saccharin, Cyclamate, Aspartame

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).

Hugo Kubinyi, www.kubinyi.de

Four Possible Strategies in Research



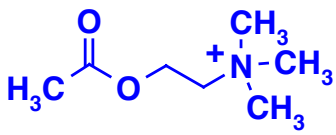
Rolf Zinkernagel (Nobel prize in Medicine 1996)

Sources of New Lead Structures

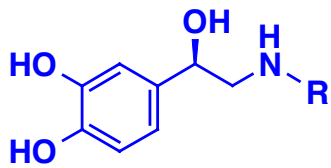
Plant and microbioal natural products
Serendipitous discoveries
Rational approaches (endogeneous transmitters)
Me too research
Isosteric replacement
Optimization of drug side effects
Chemogenomics
Chemical biology
Prodrugs and soft drugs
Metabolic switch - rescuing poor leads
Chiral switch
Combinatorial 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)

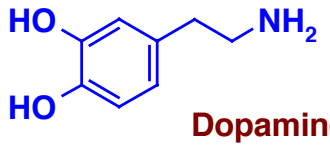
Lead Structures: Endogenous Neurotransmitters



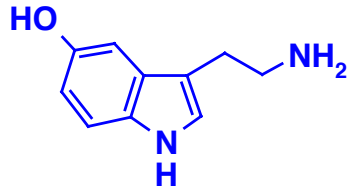
Acetylcholine



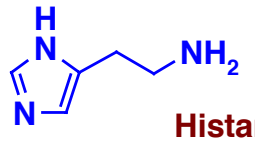
Epinephrine, R = CH_3
Norepinephrine, R = H



Dopamine

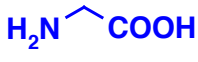


Serotonin (5-HT)

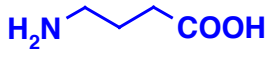


Histamine

Lead Structures: AAs, Peptides, Hormones



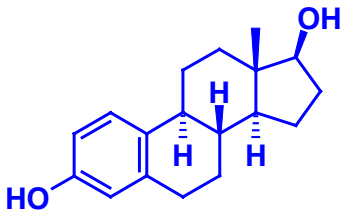
Glycin



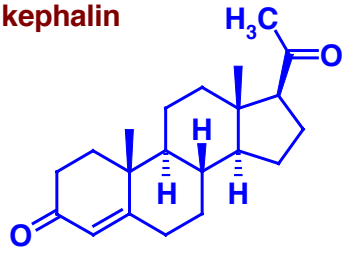
γ-Aminobutyric acid (GABA)

Tyr-Gly-Gly-Phe-Met Met-Enkephalin

Tyr-Gly-Gly-Phe-Leu Leu-Enkephalin

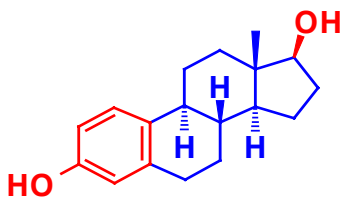


Estradiol

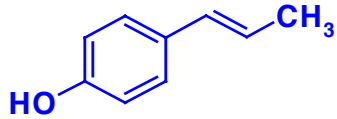


Progesterone

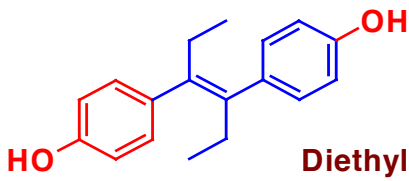
Serendipitous Discovery of Diethylstilbestrol



Estradiol

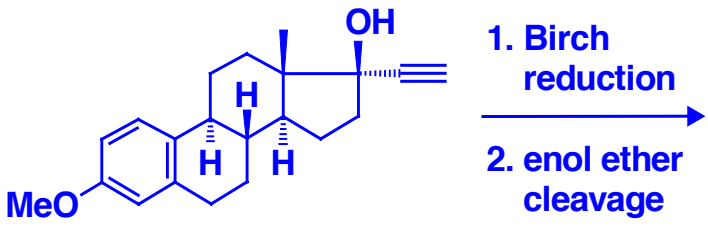


p-Anol



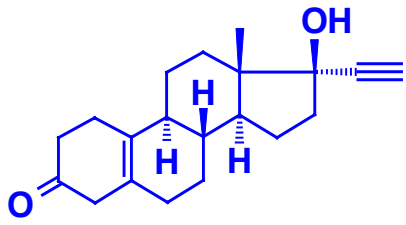
Diethylstilbestrol

The Serendipitous Discovery of the Pill

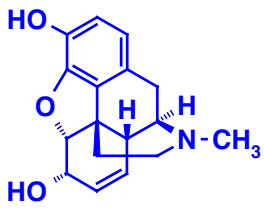


Mestranol

Norethynodrel (Searle)

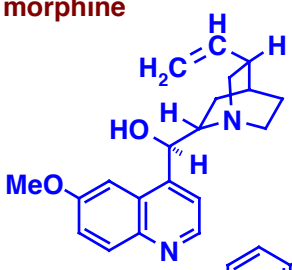


Lead Structures: Natural Products from Plants



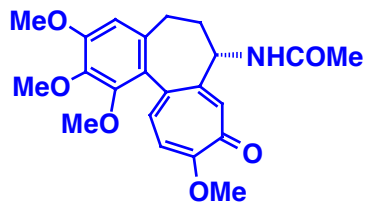
morphine

caffeine



quinine

ephedrine

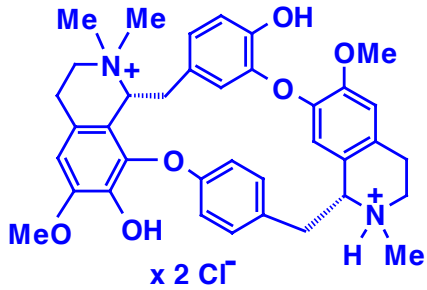


colchicine

Lead Structures: Natural Products from Plants

Digitoxin, R = H
Digoxin, R = OH

Tubocurarin



x 2 Cl⁻

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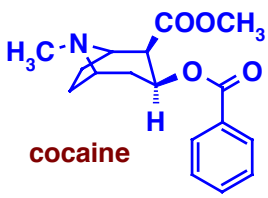
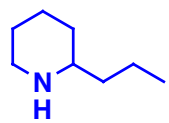
Lead Structures: Natural Products from Plants

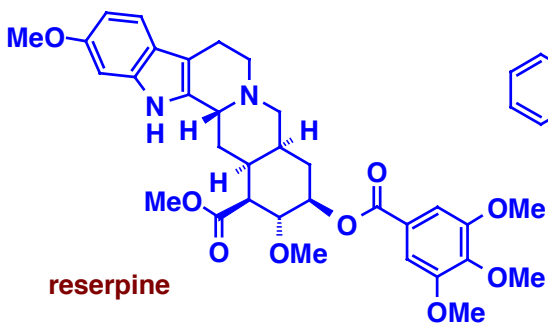


cocaine

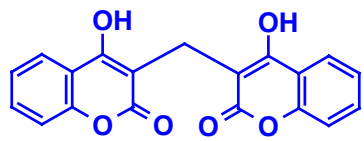
atropine
(racemate)



coniine



reserpine

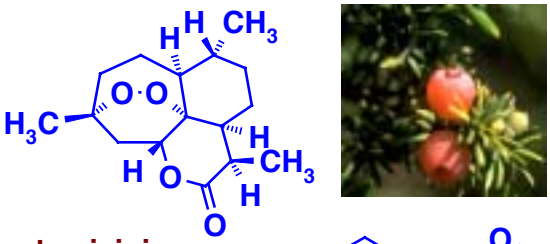


dicoumarol

(microbial degradation product of coumarin)

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

Lead Structures: Natural Products from Plants

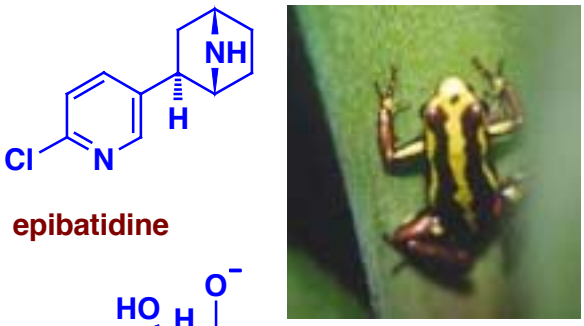


artemisinine

huperzine A

taxol

Lead Structures: Natural Products from Animals



epibatidine

compare: nicotine

tetrodotoxin

batracho-toxin

Lead Structures: Microbial Natural Products

tetracyclin

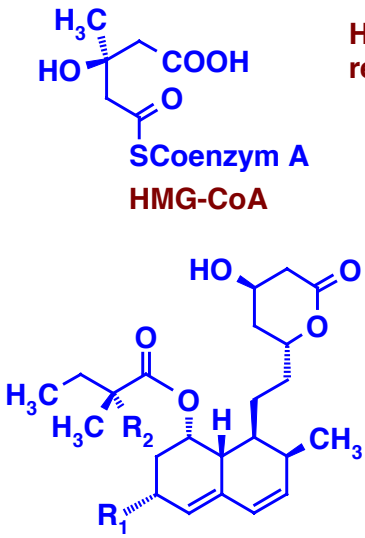
asperlicin (CCK antagonist)

streptomycin

R_1 = -CH_2OH

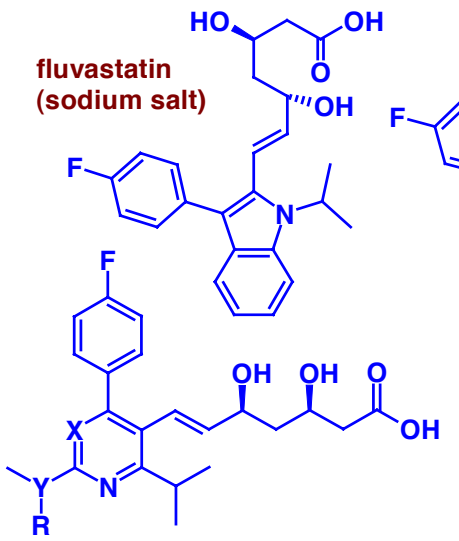
R_2 = -$NHCH_3$

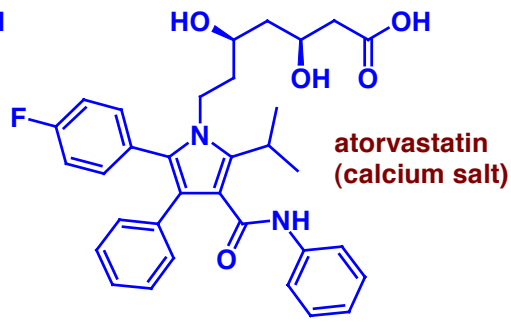
Lead Structures: Microbial Natural Products



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

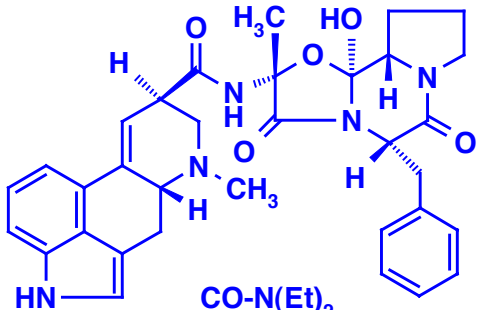




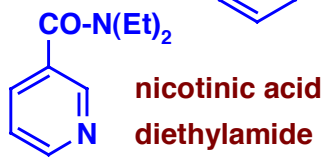
cerivastatin (sodium salt)
X = C-CH_2OMe, Y-R = CH-CH_3
K_i = 1.3 nM

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

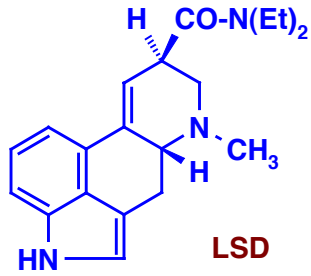
Lead Structures: Other Natural Products
Albert Hofmann and His Problem Child LSD



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



nicotinic acid
diethylamide

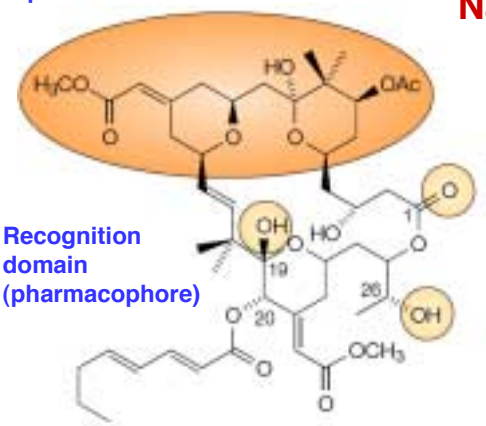


LSD

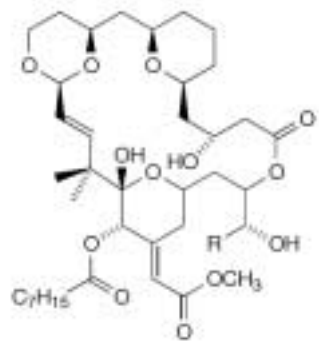
Simplification of a Natural Product

Spacer domain

Recognition domain (pharmacophore)



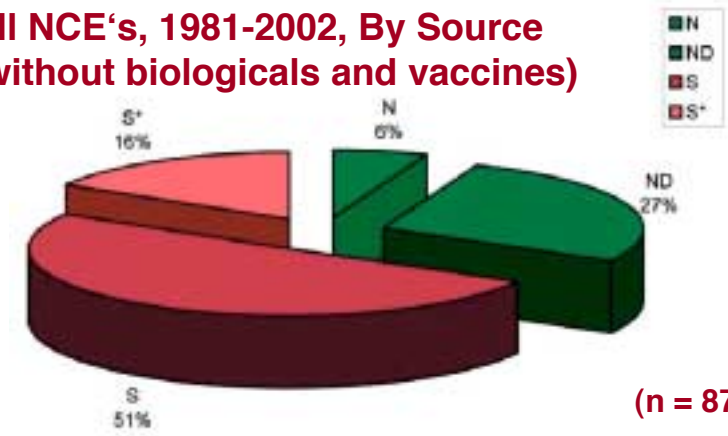
K_i = 1.35 nM Bryostatin 1



K_i = 3 nM Analogue X R = CH_3
K_i = 0.25 nM Analogue Y R = H

J. L. Baryza, P. A. Wender et al., Chem. Biol. 11, 1261-1267 (2004);
F. E. Koehn and G. T. Carter, Nature Rev. Drug Discov. 4, 206-220 (2005)

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

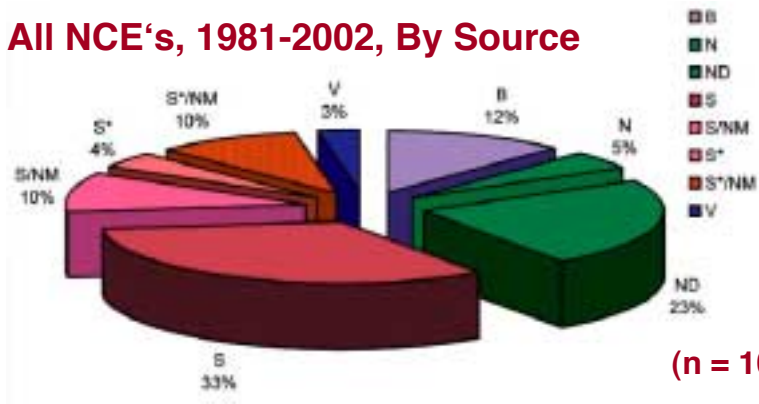


(n = 877)

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)

All NCE's, 1981-2002, By Source

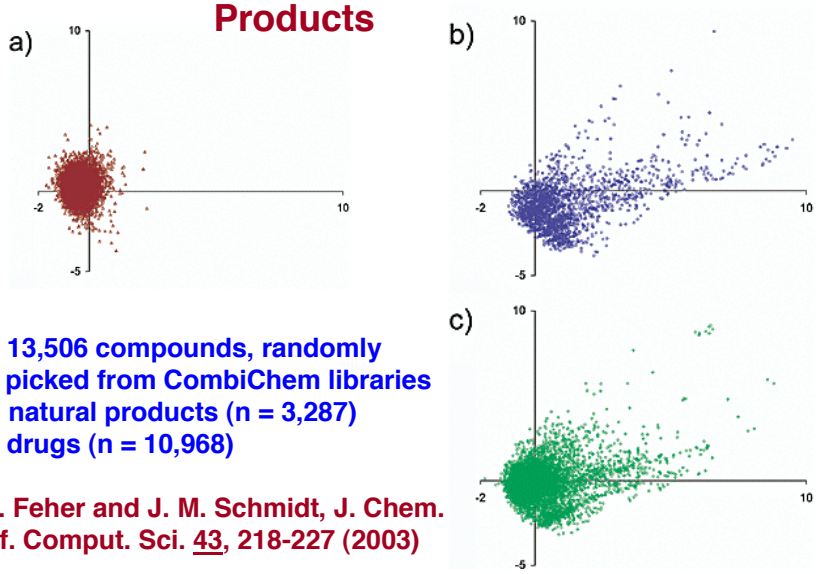


(n = 1031)

B = biologicals (usually peptides >45 aa) N = natural products
ND = derived from natural products S = synthetic products
S/NM and S*/NM = synthetics but natural product mimics
S* = synthetics but pharmacophore derived from natural product
V = vaccine

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

Diversity of Synthetics, Drugs and Natural Products



a) 13,506 compounds, randomly picked from CombiChem libraries
b) natural products (n = 3,287)
c) drugs (n = 10,968)

M. Feher and J. M. Schmidt, J. Chem. Inf. Comput. Sci. 43, 218-227 (2003)

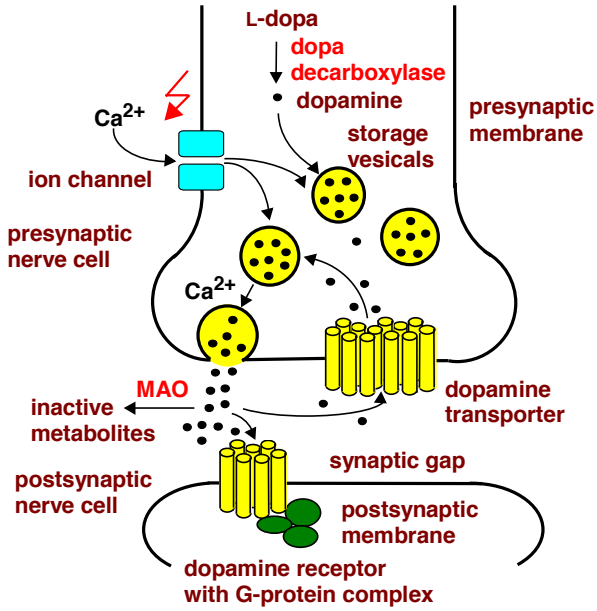
Treatment of Parkinson's Disease

Parkinson's disease is caused by a degeneration of dopamine-producing cells in certain brain areas

Approaches for drug treatment
a) anticholinergics:
- no causative therapy,
- side effects

b) dopamine substitution:
- dopamine is not bioavailable
- dopamine does not cross the blood-brain barrier
- systemic application of dopamine results in peripheral side effects
- dopamine action only very short

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 ↑

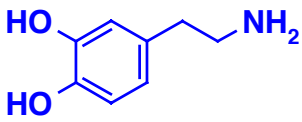
Problems

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

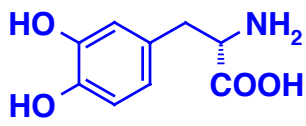
oral L-DOPA, peripheral DOPA decarboxylase blocker, central MAO blocker

Integrated Optimisation of Drug Therapy

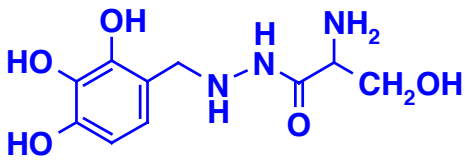
Dopamine Substitution in Parkinson's Disease



dopamine



L-dopa, a dopamine prodrug



benserazide

(R)-(-)-selegiline

Hugo Kubinyi, www.kubinyi.de

New Strategies in Drug Design

Design of inhibitors from the structure of the substrate

Pharmacophore hypotheses and peptidomimetics

Structure-based design of ligands
affinity, selectivity and drug resistance

Computer-aided design of ligands
de novo design: LUDI, FlexX

Virtual screening for favourable drug properties
drug character, bioavailability (rule of five)

Combinatorial design of ligands