Drug Discovery Technologies - A Closer Look

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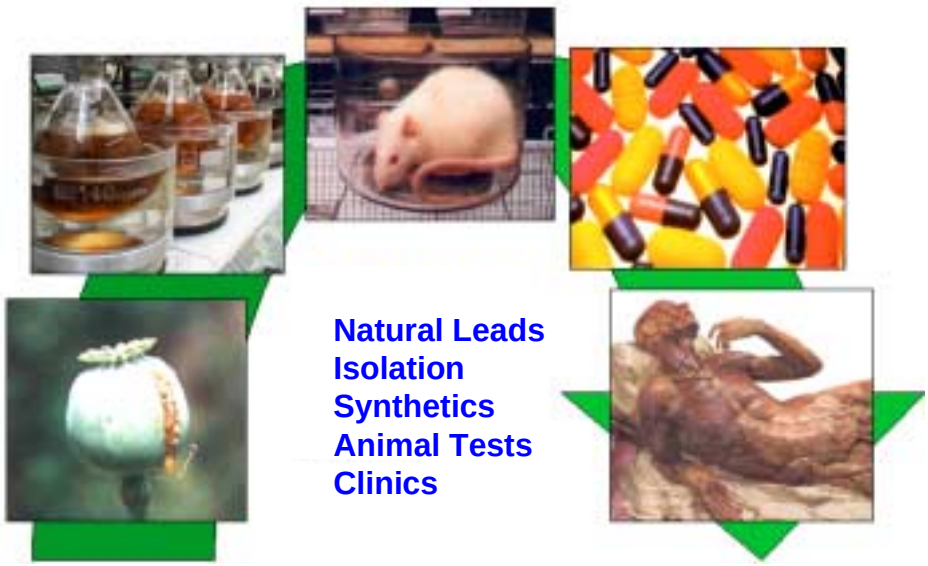
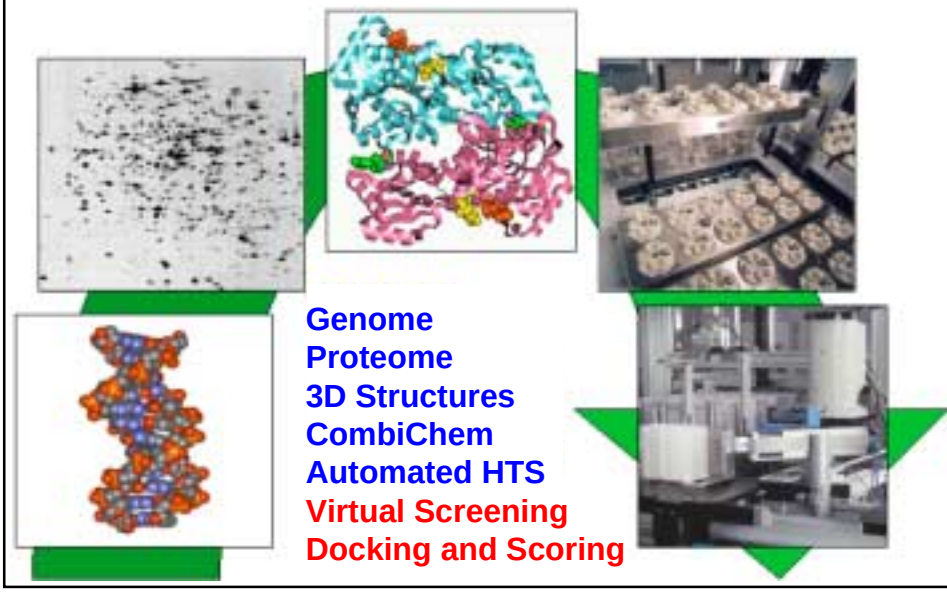
Mastering Medicinal Chemistry
RSC, Cambridge, April 27, 2009

Yesterday's Drug Discovery Process



Today‘s Drug Discovery Process

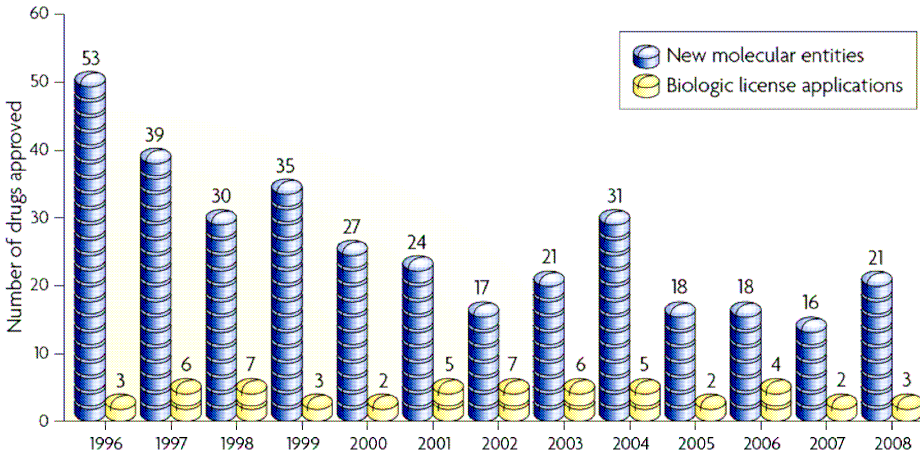


Genome
Proteome
3D Structures
CombiChem
Automated HTS
Virtual Screening
Docking and Scoring

Bottlenecks of the Past

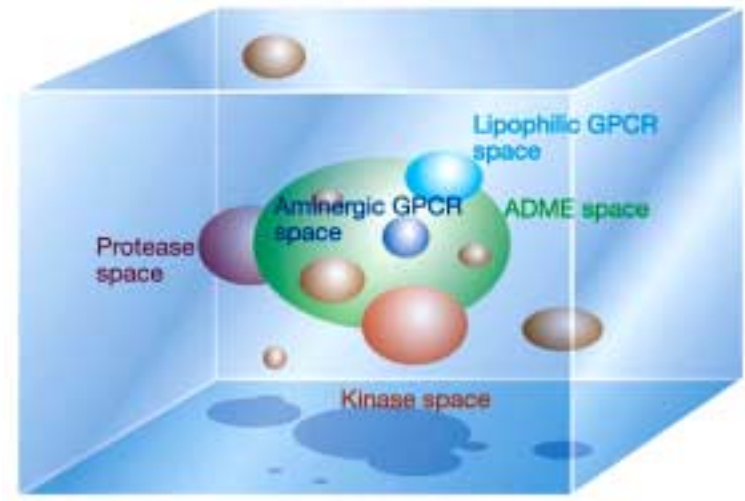
Problem	Solution
Target search	genome information
Target validation	knock-outs, RNA silencing
Lead search	in vitro test models, HTS
Lead optimization	parallel syntheses, chemogenomics
Absorption, permeability	Lipinski rules, Caco cells, prodrugs
Metabolism	liver microsomes
Toxicity	Ames test, hERG models
Drug drug interactions	CYP inhibition/induction

FDA-Approved NCEs Over the Last Years



B. Hughes, Nature Rev. Drug Discov. 8, 93-96 (2009)

The Medicinal Chemistry Space



C. Lipinski and A. Hopkins, Nature 432, 855-861 (2004)

Drug Research is ....

the Search for a Needle in a Haystack

New Technologies: Open Questions

Is there a „druggable genome“ ?

Is a target focus always best ?

Is QSAR predictive ?

Is poor ADME the main problem ?

Are we using the right virtual screening techniques?

What are the problems in virtual screening ?

What‘s wrong and could we do better?

H. Kubinyi, Drug Research: Myths, Hype and Reality, Nature Rev. Drug Discov. 2 (8), 665-668 (2003)

Is there really a „druggable genome“ ?

Alternative splicing and posttranslational modification generate a multitude of proteins

→ **the „druggable proteome“ ?**

Protein complexes (nAChR, GABA-R, integrins, hetero-dimeric GPCRs, cross-talking)

→ **the „druggable targetome“ ?**

Balanced activity against a series of targets

→ **the „druggable physiome“**

H. Kubinyi, Drug Research: Myths, Hype and Reality, Nature Rev. Drug Discov. 2 (8), 665-668 (2003)

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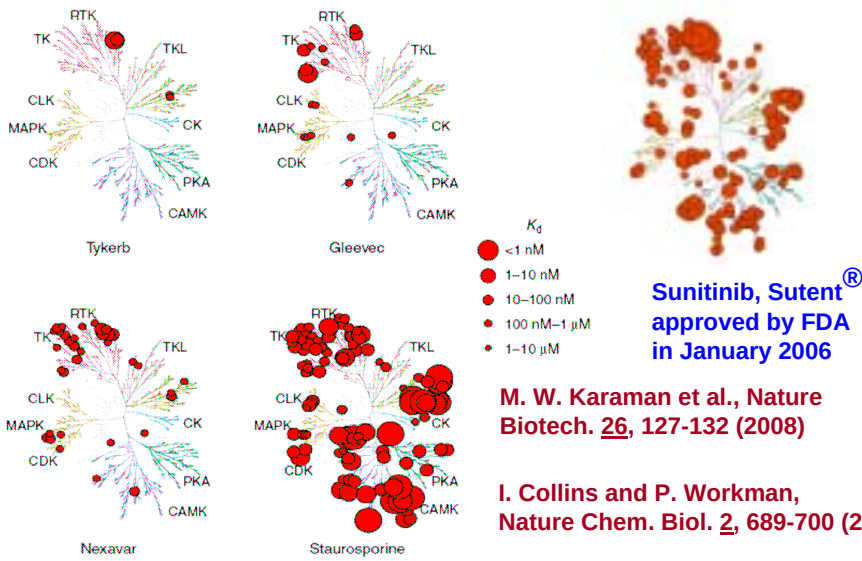
Kinase Inhibitor Specificity

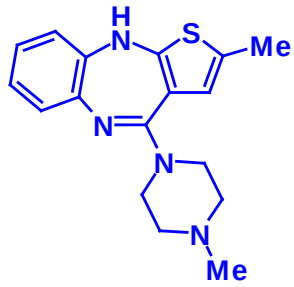


Sunitinib, Sutent® approved by FDA in January 2006

M. W. Karaman et al., Nature Biotech. 26, 127-132 (2008)

I. Collins and P. Workman, Nature Chem. Biol. 2, 689-700 (2006)

Is Target Focus the Best Strategy?



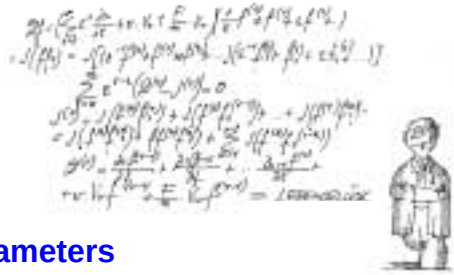
Olanzapine, a clozapine-like „atypical“ neuroleptic with a promiscuous binding pattern

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

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

“Good” QSAR

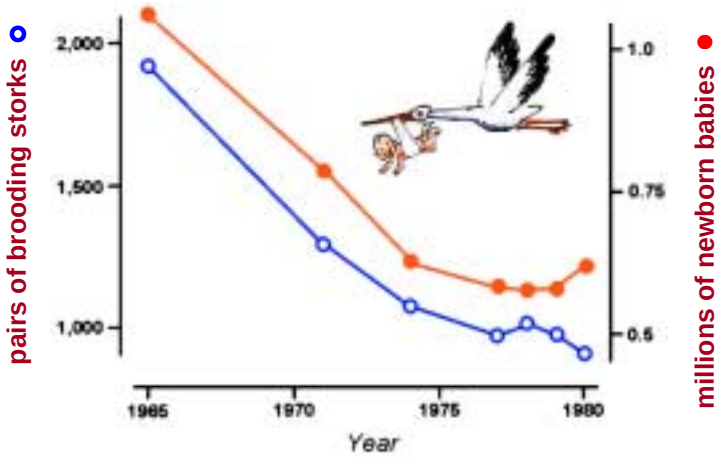
- parameters with biophysical relevance
- few variables to select
- few variables in the model
- validation by LOO, LMO, y scrambling



“Poor” QSAR

- artificial parameters
- too many variables to select
- too many variables in the model
- no test set predictivity (“Kubinyi paradox”)

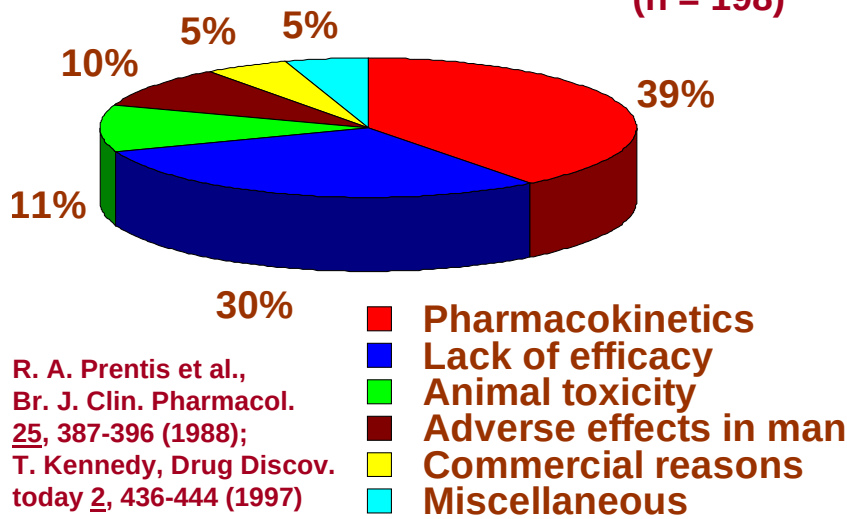
The Storks and the Babies



Sir – There is concern in West Germany over the falling birth rate. The accompanying graph might suggest a solution that every child knows makes sense. H. Sies, Nature 332, 495 (1988)

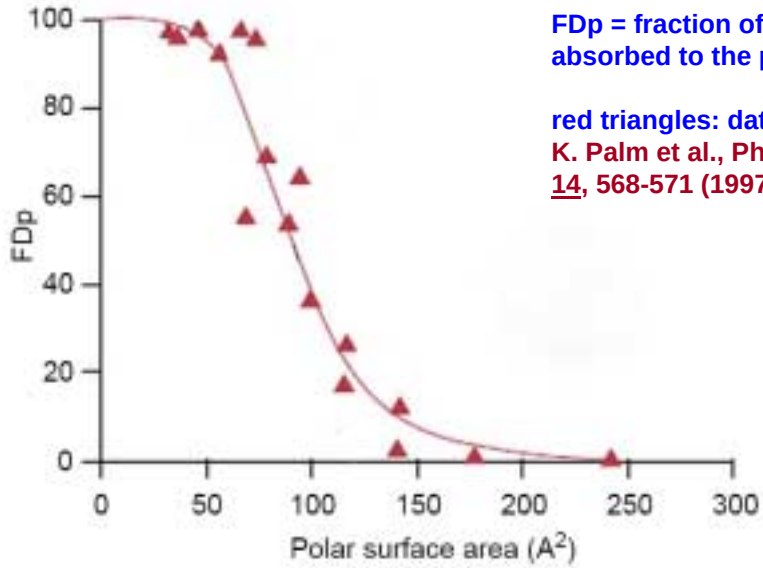
Hugo Kubinyi, www.kubinyi.de

Reasons for Failure in Drug Development (n = 198)



R. A. Prentis et al., Br. J. Clin. Pharmacol. 25, 387-396 (1988); T. Kennedy, Drug Discov. today 2, 436-444 (1997)

Human Absorption and Polar Surface Area



FDp = fraction of dose absorbed to the portal vein

red triangles: data from K. Palm et al., Pharm. Res. 14, 568-571 (1997)

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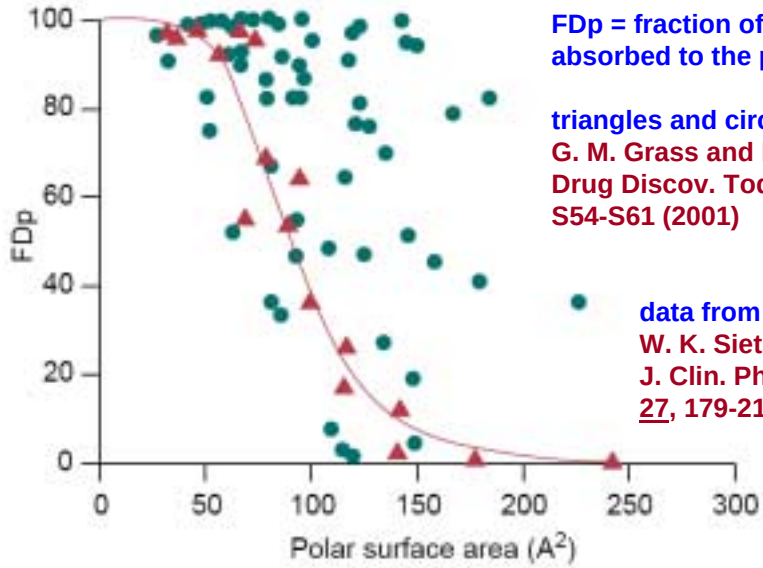
Human Absorption and Polar Surface Area

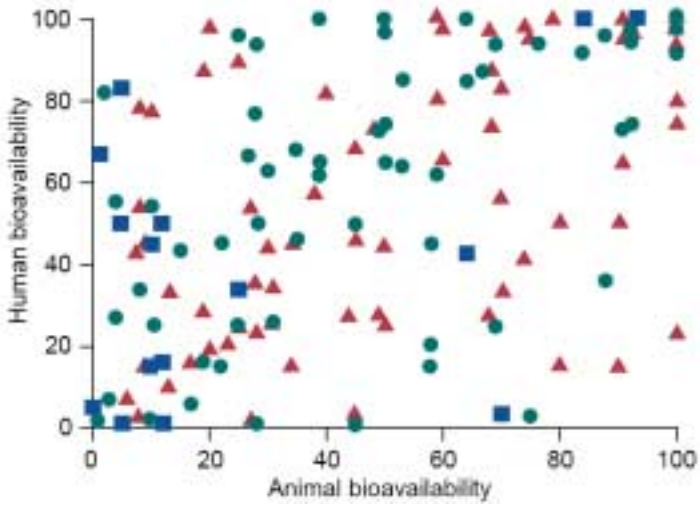


FDp = fraction of dose absorbed to the portal vein

triangles and circles: G. M. Grass and P. J. Sinko, Drug Discov. Today 6, S54-S61 (2001)

data from W. K. Sietsema, Int. J. Clin. Pharmacol. 27, 179-211 (1989)

Rodent, Dog, Primate and Human Bioavailability



Rodents
green circles

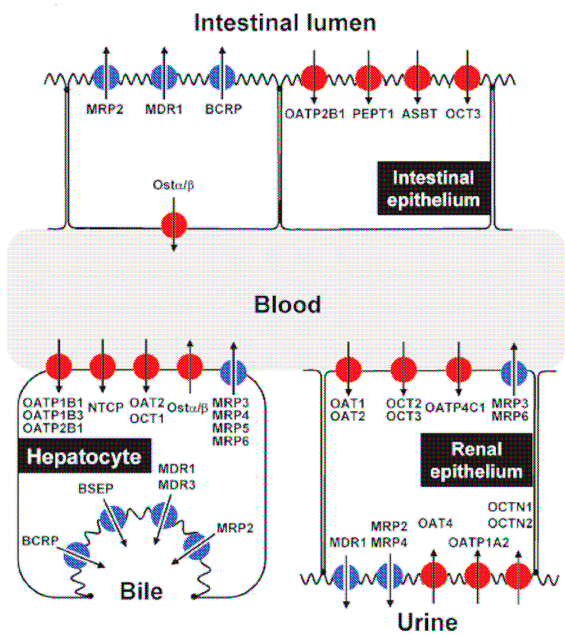
Dog
red triangles

Primates
blue squares

data from:
W. K. Sietsema, Int. J. Clin. Pharmacol. 27, 179-211 (1989)

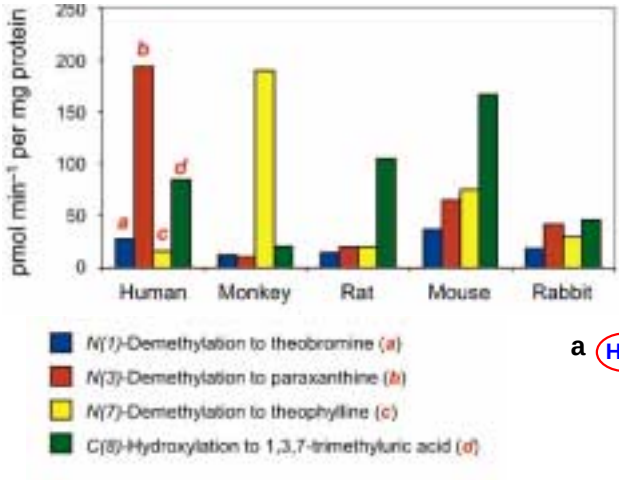
G. M. Grass and P. J. Sinko, Drug Discov. Today 6, S54-S61 (2001)

The Role of Transporters in Drug Uptake and Elimination

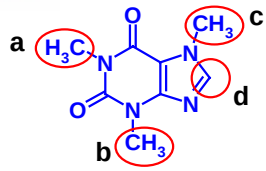


H. Gleaser et al., in R. J. Vaz and T. Klabunde, Antitargets, Wiley-VCH, 2008, pp. 341-366

Species Differences of Caffeine Oxidation

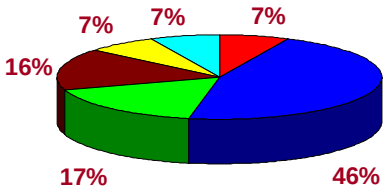


production of caffeine metabolites by liver microsomes of different species



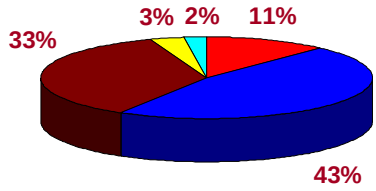
F. Berthou et al., Xenobiotica 22, 671-680 (1992); figure from from S. D. Krämer and B. Testa, Chemistry & Biodiversity 5, 2465-2578 (2008)

The Ultimate (Unavoidable) Bottlenecks?



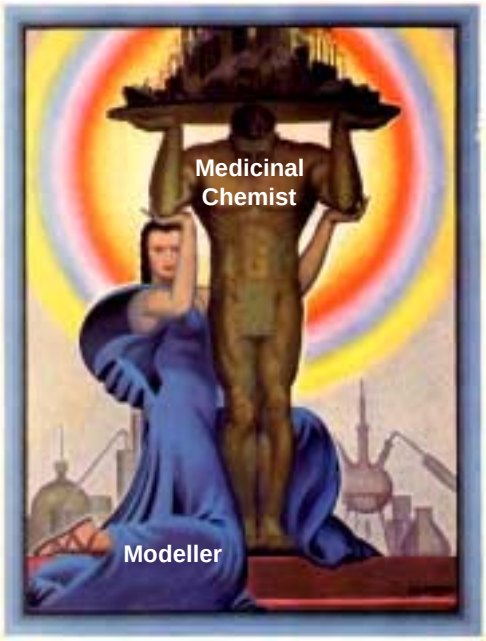
- ADME
- Lack of efficacy
- Animal toxicity
- Adverse effects in man
- Commercial reasons
- Miscellaneous

Reasons for failure in clinical development, 1964-1985 (n = 121; without antiinfectives) T. Kennedy, Drug Discov. today 2, 436-444 (1997)



- Liberation + ADME
- Lack of efficacy
- Toxicity
- Economic
- Other

Reasons for failure in clinical development, 1992-2002 (n = 73) (reasons for market withdrawal, n = 17: toxicity 93%, efficacy 7%) D. Schuster et al., Curr. Pharm. Design 11, 3545-3559 (2005)



A. Cressy Morrison

Man in a Chemical World
The Service of Chemical Industry

Ch. Scribner's Sons, NY, 1937

„Chemical Industry, Upheld by Pure Science, Sustains the Production of Man's Necessities"

Tools for Virtual Screening

	remaining
Garbage filter	90%
Druglike / Non-druglike	75%
Bioavailability	60%
Cytotoxicity	:
hERG channel inhibiton	:
Antitargets	:
α_{1a} (orthostatic hypotension)	:
D2 (extrapyramidal syndrome)	:
5-HT_{2c} (obesity)	:
musc. M1 (hallucinations, memory)	:
CYP inhibition (3A4, 2C9, 2D6)	:
Pharmacophore searches	:
Docking and scoring	0% ?

Problems in Pharmacophore Generation

Isomers, enantiomers, diastereomers

Superposition of flexible molecules

Ionization and dissociation
(Sadowski rules)

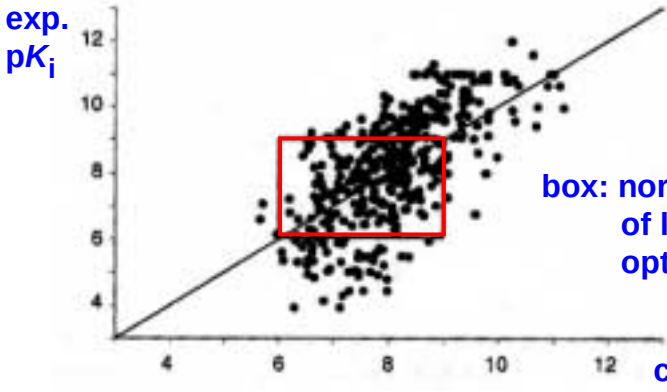
Tautomeric and protomeric forms
(program AGENT, ETH Zurich; ChemoSoft tautomer recognition, ChemDiv)

Acceptor properties of oxygen and sulfur atoms
(esters, aromatic ethers, oxazoles, isoxazoles, thiazoles, etc.)

Factors to be Considered in Scoring Functions

Desolvation enthalpy and entropy (ligand and protein)
Protonation state of the ligand and the binding site
Distortion energy of the ligand and its binding site
Loss of translational and rotational degrees of freedom of the ligand
MEP + dielectric constant at the binding site
Dipole moment of the ligand and local dipole moment at the binding site
Binding enthalpy of the ligand-protein complex
Repulsive effects (e.g. -O···O-)
Inserted water molecules
Solvation enthalpy and entropy of the complex

pK_i values of HIV Protease Inhibitors: VALIDATE II Predictions



A. M. Davis et al., Angew. Chem. Int. Ed. Engl. 42, 2718-36 (2003); Angew, Chem. 115, 2822-2841 (2003)

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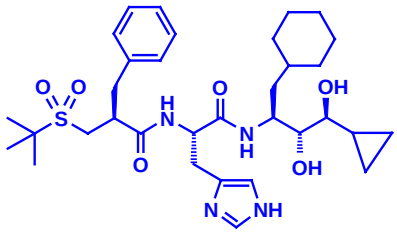
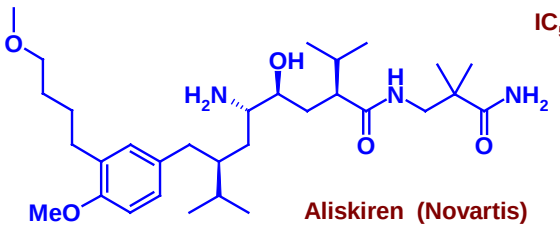
Species Specificity of Renin Inhibitors



Remikiren (Roche)

IC_{50} =	0.8 nM	(human)
	1.0-1.7 nM	(monkeys)
	107 nM	(dog)
	3 600 nM	(rat)



Aliskiren (Novartis)

IC_{50} =	0.6 nM	(human)
	2 nM	(marmoset)
	7 nM	(dog)
	11 nM	(rabbit)
	63 nM	(guinea pig)
	80 nM	(rat)
	150 nM	(pig)
	8 500 nM	(cat)

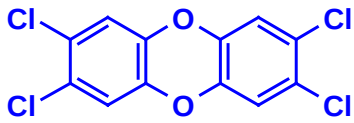
J. M. Wood et al., Biochem. Biophys. Res. Comm. 308, 698-705 (2003)

Alle Dinge ſind Gift
und nichts ohn Gift;
allein die Doſis macht,
daß ein Ding kein Gift iſt.

„All things are poison and nothing without poison; only the dose determines, whether a thing be no poison“

Salt, Fat, Alcohol ...
Aspirin, Corticoids ...
Phenacetin, Phenphen, Cerivastatin ...

Acute Toxicity of Tetrachlorodibenzodioxin



2,3,7,8-Tetrachloro-dibenzodioxin

Species	LD_{50} in µg/kg
Mouse	114-280
Rat	22-320
Hamster	1,150-5,000
Guinea Pig	0.5-2.5
Mink	4
Rabbit	115-275
Dog	> 100 < 3,000
Monkey	< 70
Man	??

An Early Clinical Study - Coffee or Tea ?

In late 18th century Gustav III, King of Sweden, performed a "clinical study" to confirm the negative effects of coffee drinking on health.
One convicted murder had to drink only coffee, another one tea, instead.
Two physicians supervised the study.

First, one physician died.
Then the other physician died.
Then the king was murdered.
The tea drinker died in the age of 83.
The coffee drinker survived all others.

Nevertheless, in 1794 coffee drinking was forbidden in Sweden and later again, in 1822.

An early clinical trial, Ann. Int. Med. 117, 1, 30 (1992)

Clinical Studies - the Typical Volunteer

Phase I

healthy volunteers, age 18-55 years, males and females (however, no females who could be or could become pregnant), normal weight, no smokers, no alcohol (ab)use, standard food, drug taken with 150 ml water, no other therapy, no intake of fruit juices or illegal drugs.

Patients

plus other disease(s)

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.**

Hugo Kubinyi, www.kubinyi.de

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**