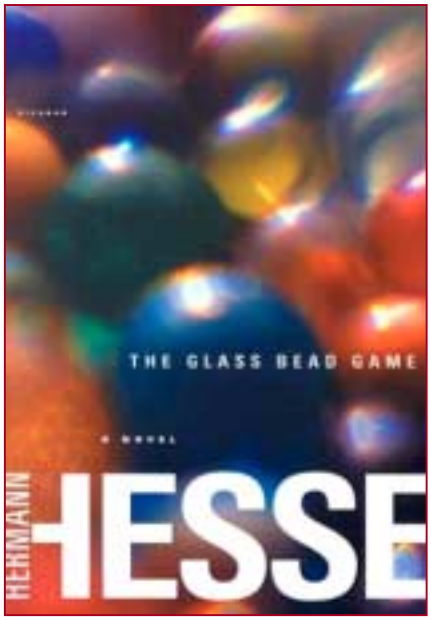

Living in Castalia?

The Pitfalls in "Rational" Design

Hugo Kubinyi
Weisenheim am Sand

E-mail kubinyi@t-online.de
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Castalian Allocution at the EuroCUP II, Strasbourg, 2008

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Castalian Allocution at the EuroCUP II, Strasbourg, 2008

Papal Allocution

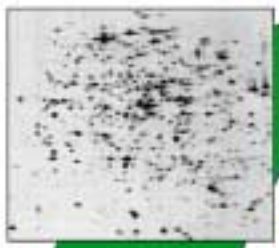
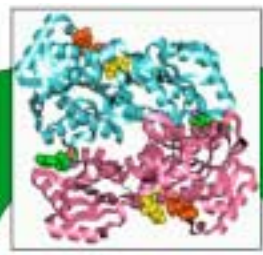
Yesterday's Drug Discovery Process

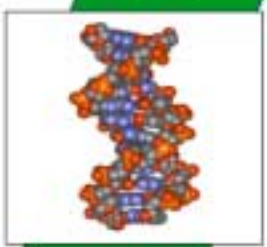




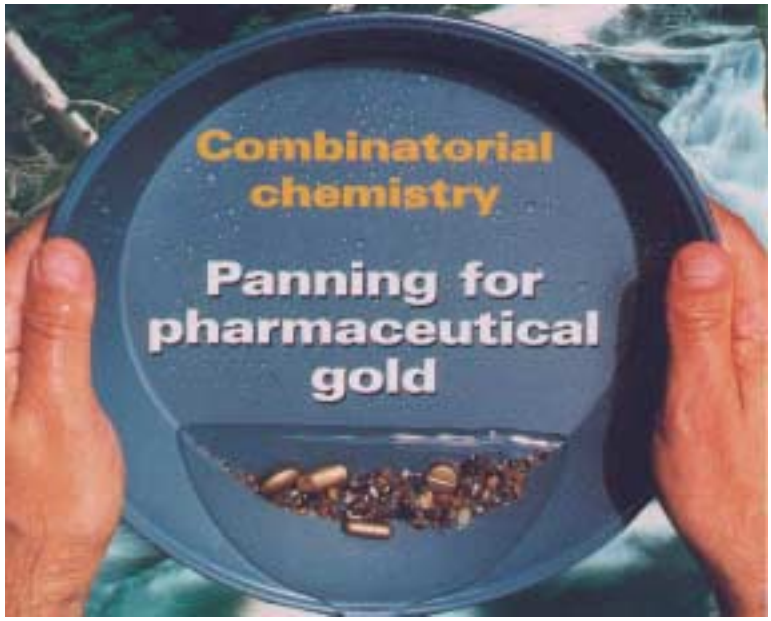
Natural Leads
Isolation
Synthetics
Animal Tests
Clinics

Today's Drug Discovery Process

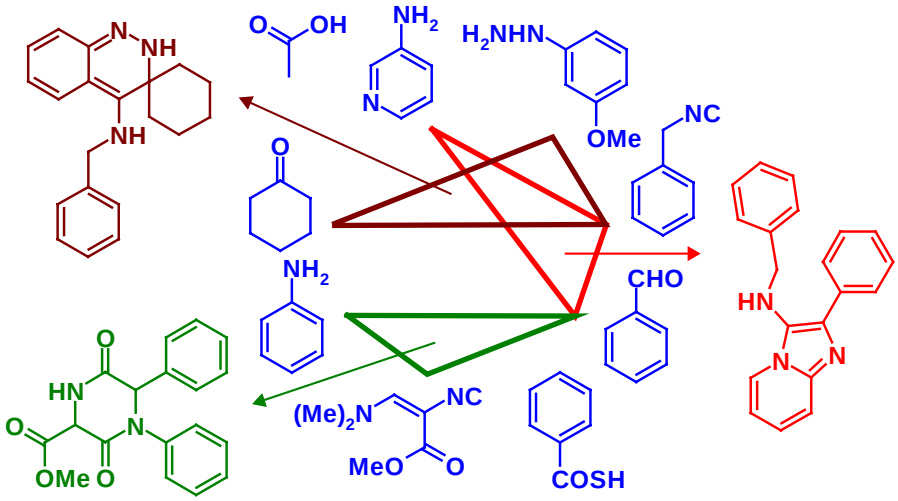






Genome
Proteome
3D Structures
CombiChem
Automated HTS
Virtual Screening
Docking and Scoring

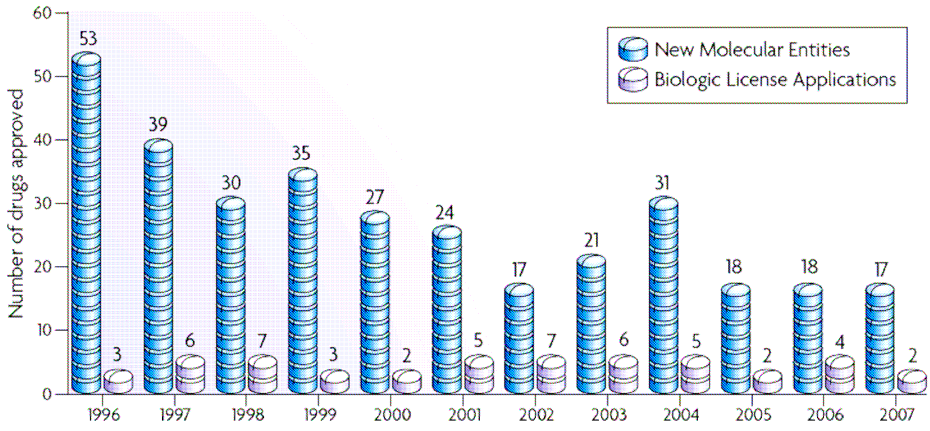


The Generation of Scaffold Diversity



L. Weber, Drug Discov. today 7, 143-147 (2002)

FDA-Approved NCEs Over the Last Years



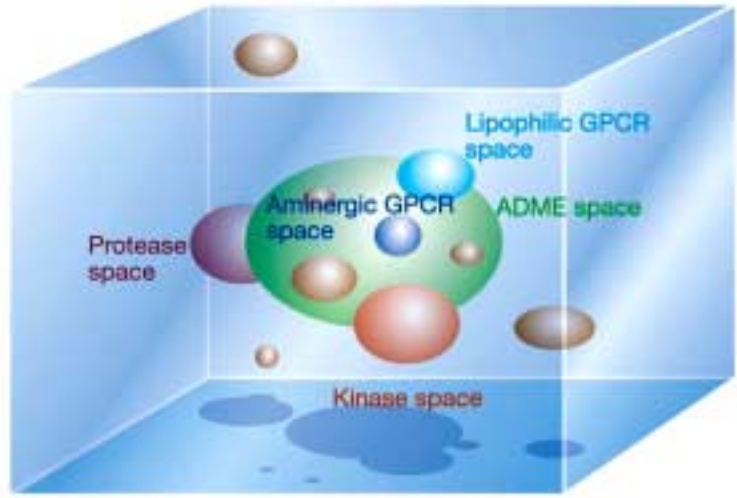
B. Hughes, Nature Rev. Drug Discov. 7, 107–108 (February 2008)

Hugo Kubinyi, www.kubinyi.de

Drug Research is ....

the Search for a Needle in a Haystack

The Medicinal Chemistry Space



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

Success in Drug Research

➔ A compound — hundred thousands

is no hit — thousands

➔ is no lead — dozens

optimization: — thousands

is no candidate — some

is no drug — 1

by courtesy of Dr. Simona Ceccarelli, Hoffmann-La Roche

The New Technologies

Do we already live in Castalia, the land of Hermann Hesse's novel „The Glass Bead Game", where the Magister Ludi (sic!) organizes and plays the most wonderful, brilliant, exciting and elaborate game ... without any practical relevance?

D. F. Horrobin, Modern biomedical research: an internally self-consistent universe with little contact with medical reality, Nature Rev. Drug Discov. 2, 151-154 (2003).

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)

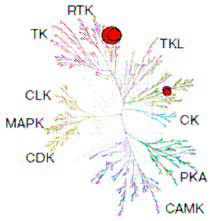
→ the „druggable targetome“ ?

Balanced activity against a series of targets

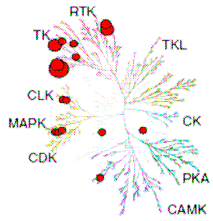
→ the „druggable physiome“

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

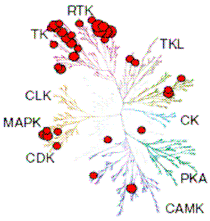
Kinase Inhibitor Specificity



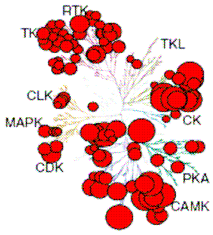
Tykerb



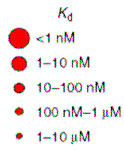
Gleevec



Nexavar



Staurosporine

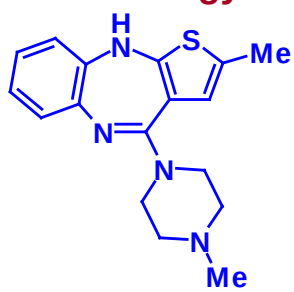


Sunitinib, Sutent®
approved by FDA
in January 2006

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	

“Discouraging Data on the New Antidepressant”

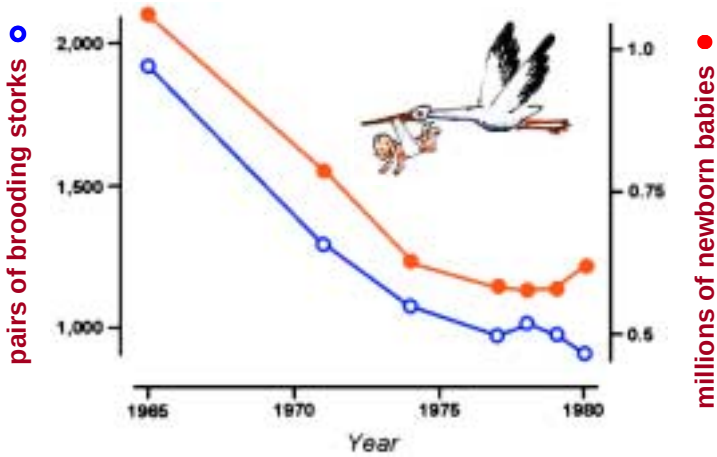
The Problem of Prediction

inside: trivial

outside: wrong

at the edge: 50/50

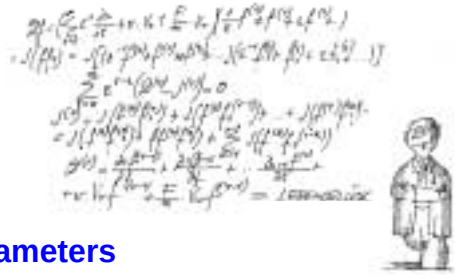
The Storks and the Babies



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

"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")**

A Common Situation in QSAR (and 3D QSAR)

A chemist synthesizes about 30 compounds.

The biologists determines the activity values.

Both ask the chemoinformatician to derive a QSAR model.

The chemoinformatician loads 1500 variables (e.g. from the program DRAGON, Roberto Todeschini) and derives a QSAR model, containing only a few variables, which meets all statistical criteria.

Chemist, biologist and chemoinformatician publish the results. Everybody is happy.

The Real Situation (e.g. the Selwood data set)

A chemist prepares some 20 compounds.

The biologist determines the activity values.

Both ask the chemoinformatician to derive a QSAR model.

The resulting model does not contain more than four variables, is selected from about fifty variables and is validated by all statistical criteria, including LOO/LMO cross-validation and y scrambling.

How good is the predictivity of the model for a test set of 10 compounds?

The Real Situation (e.g. the Selwood data set)

A chemist prepares some 20 compounds.

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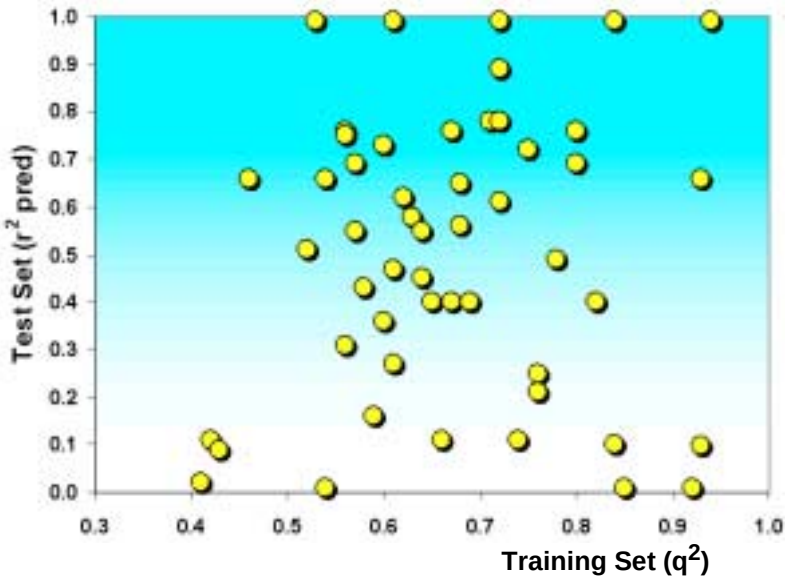
The resulting model does not contain more than four variables, is selected from about fifty variables and is validated by all statistical criteria, including LOO/LMO cross-validation and y scrambling.

How good is the predictivity of the model for a test set of 10 compounds? Lousy !!

Test vs. Training Set Predictivity (A. Doweyko, ACS 2004)



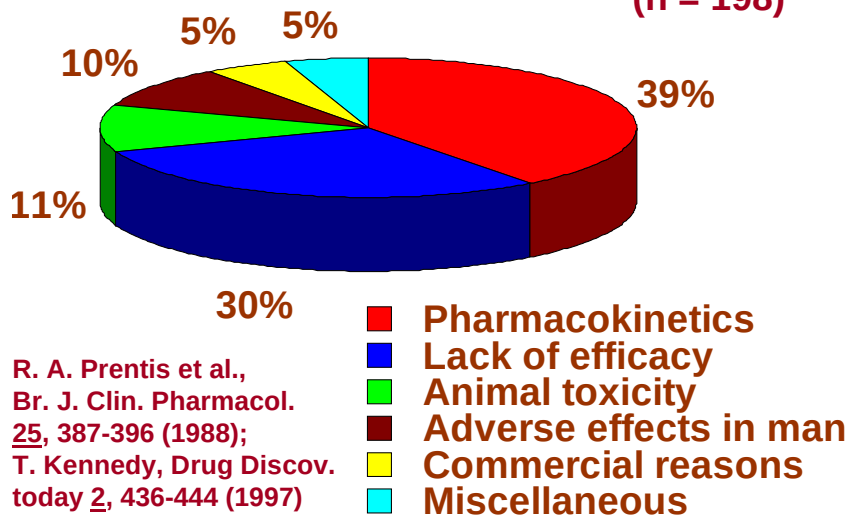
Chemical vs. Biological Landscapes

"Activity landscapes are not continuous, they contain cliffs, like the Bryce Canyon"

rem: applies also to scoring functions !

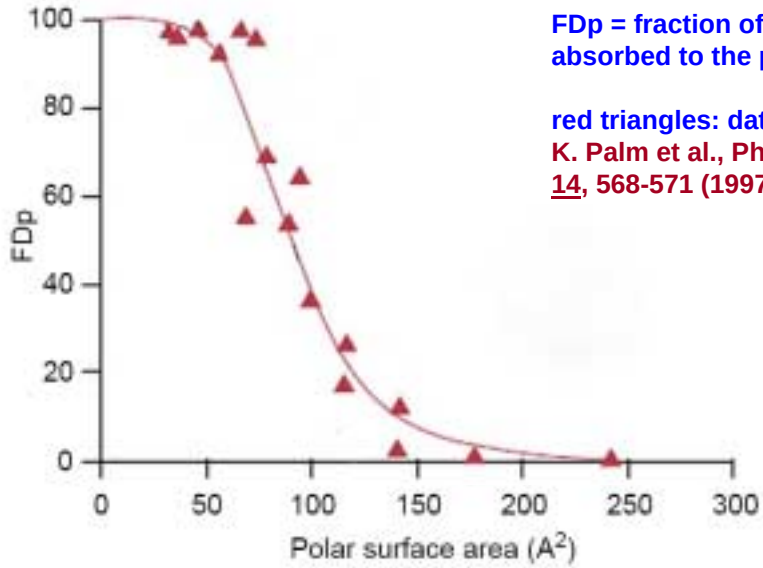
G. M. Maggiora, On outliers and activity cliffs - why QSAR often disappoints, J. Chem. Inf. Model. 46, 1535 (2006)

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

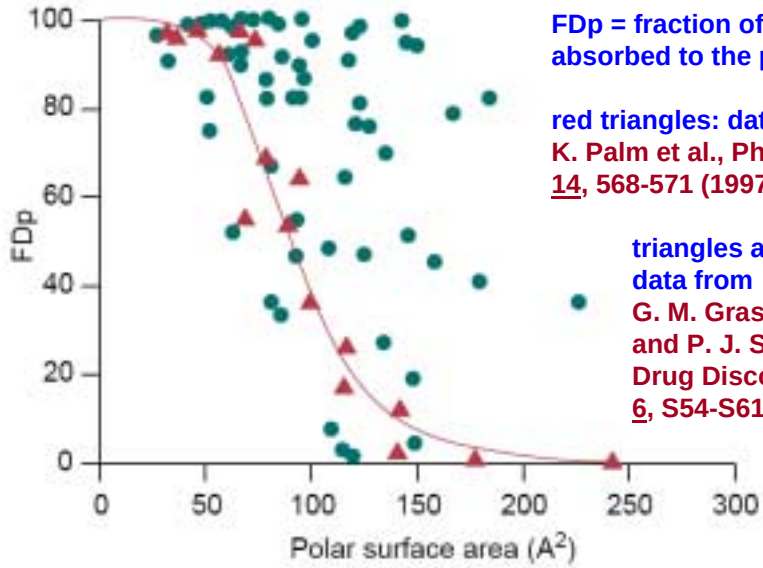


FDp = fraction of dose absorbed to the portal vein

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

Hugo Kubinyi, www.kubinyi.de

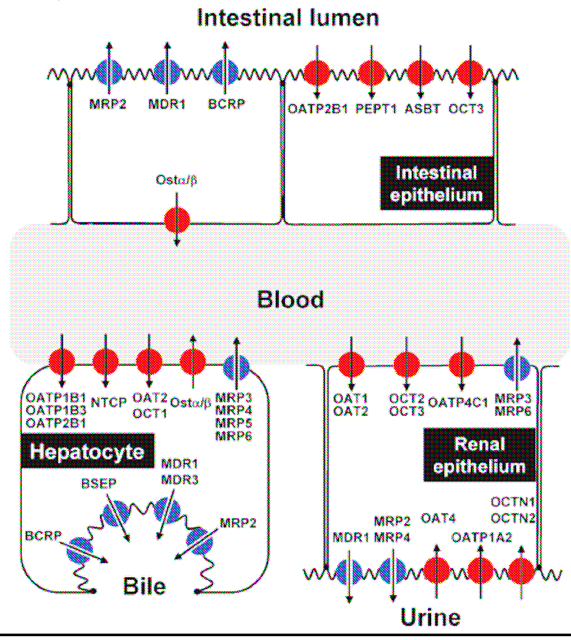
Human Absorption and Polar Surface Area



FDp = fraction of dose absorbed to the portal vein

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

triangles and circles: data from 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

Hugo Kubinyi, www.kubinyi.de

OPINION

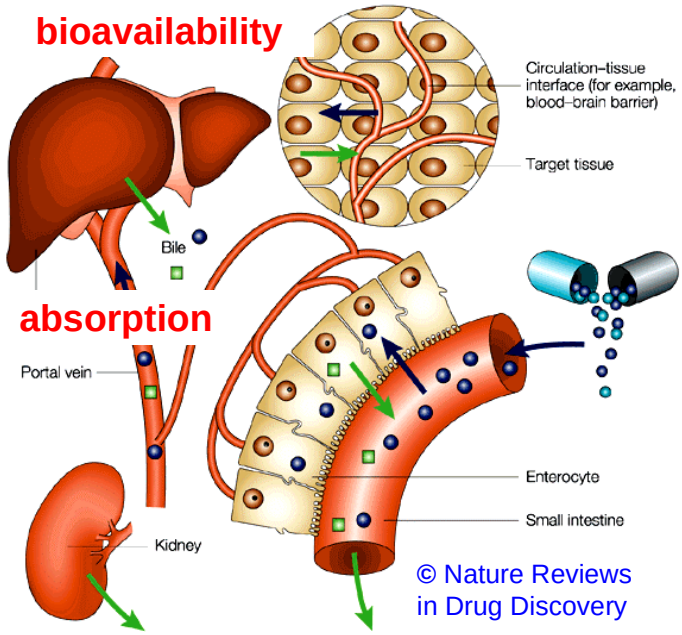
Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule?

Paul D. Dobson and Douglas B. Kell

Abstract | It is generally thought that many drug molecules are transported across biological membranes via passive diffusion at a rate related to their lipophilicity. However, the types of biophysical forces involved in the interaction of drugs with lipid membranes are no different from those involved in their interaction with proteins, and so arguments based on lipophilicity could also be applied to drug uptake by membrane transporters or carriers. In this article, we discuss the evidence supporting the idea that rather than being an exception, carrier-mediated and active uptake of drugs may be more common than is usually assumed — including a summary of specific cases in which drugs are known to be taken up into cells via defined carriers — and consider the implications for drug discovery and development.

P. D. Dobson and D. B. Kell, Nature Rev. Drug Discov. 7, 205-220 (2008)

bioavailability



© Nature Reviews in Drug Discovery

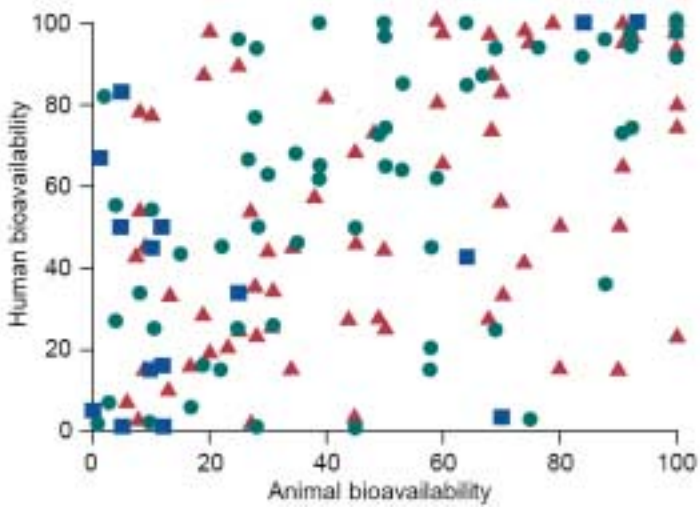
Sites of Drug Metabolism:

(intestinal wall), liver, (organs)

Sites of Drug Elimination:

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

Rodent, Dog, Primate and Human Bioavailability



Rodents
green circles

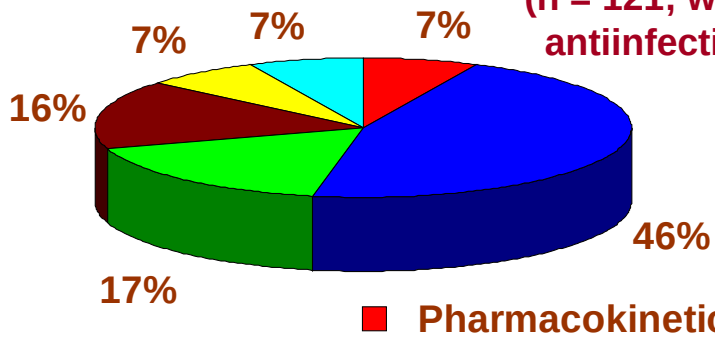
Dog
red triangles

Primates
blue squares

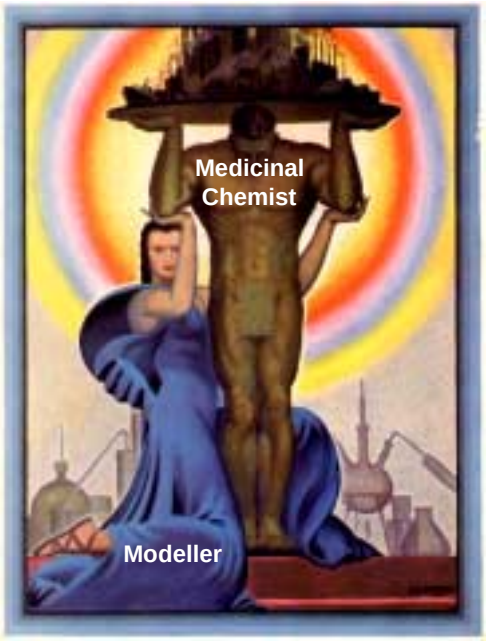
data from:
W. K. Sietsema, Int. J. Clin. Pharmacol. 27, 179-211 (1989)

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

Reasons for Failure in Drug Development (n = 121; without antiinfectives)



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



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"

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)

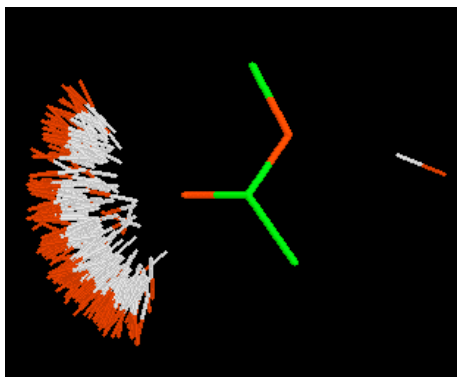
Acceptor properties of oxygen and sulfur atoms
(esters, aromatic ethers, oxazoles, isoxazoles, thiazoles, etc.)

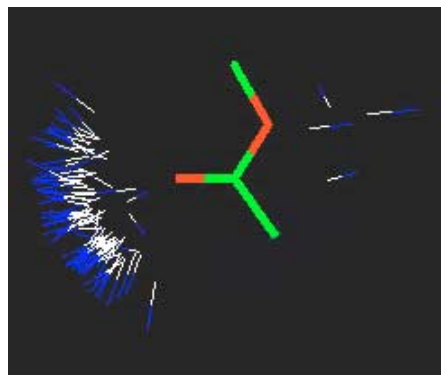
Hugo Kubinyi, www.kubinyi.de

Pharmacophore Analyses Must Consider Correct Donor and Acceptor Properties of Ligands

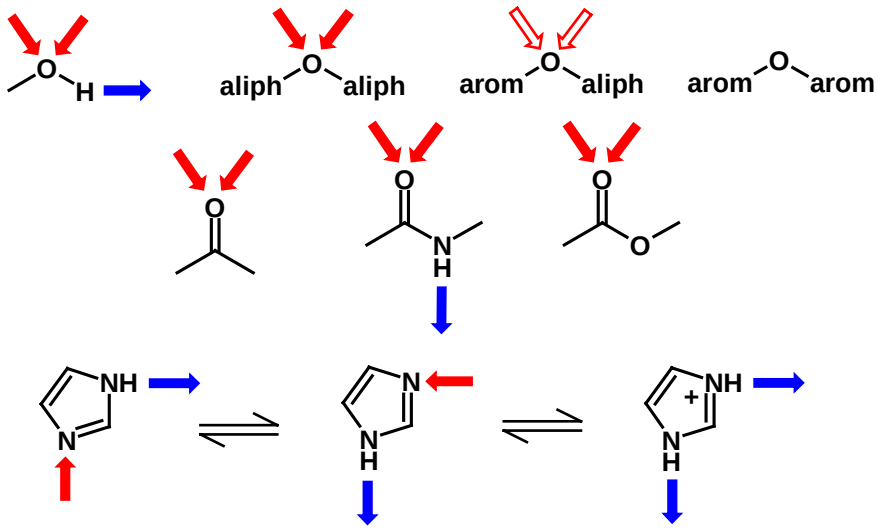
The billion dollar question:
how many acceptor positions has an ester group ?

Correct answer: Two ...., but why?

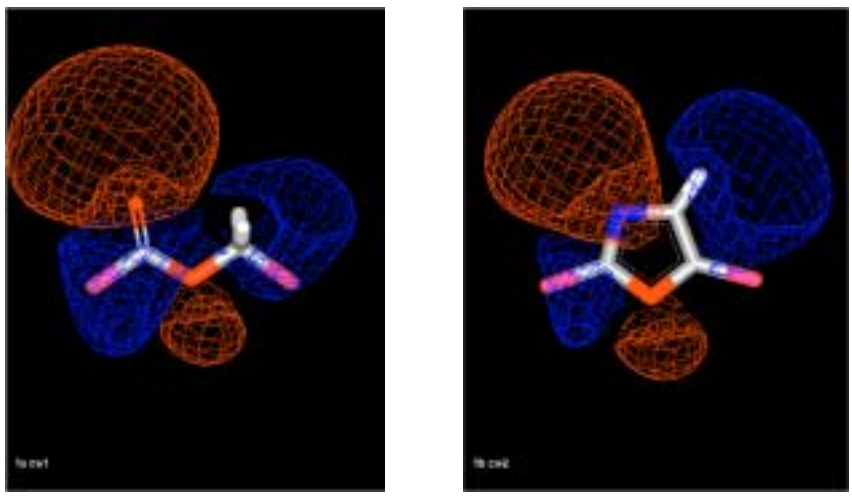




Donor and Acceptor Properties of O and N



Brood (OpenEye) for Isostere Prediction

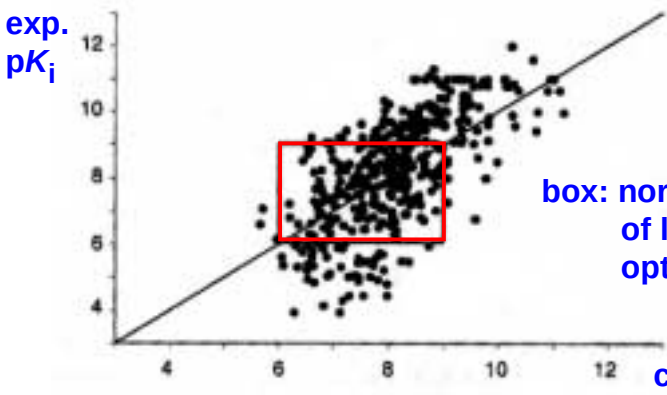


electrostatic isopotential contour surfaces of ester and oxazole fragments (www.eyesopen.com/products/applications/brood.html)

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

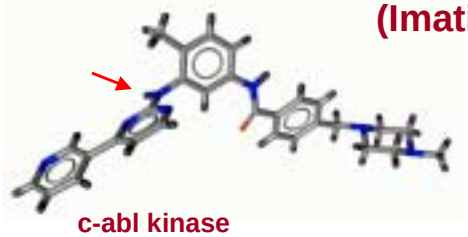
pK_i values of HIV Protease Inhibitors: VALIDATE II Predictions



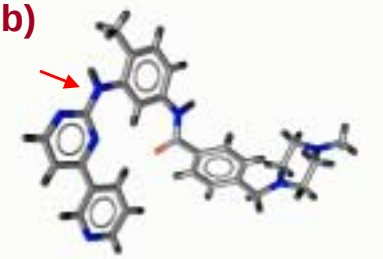
box: normal range of lead-to-drug optimization

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

Energies of Different Ligand Conformations? (Imatinib)

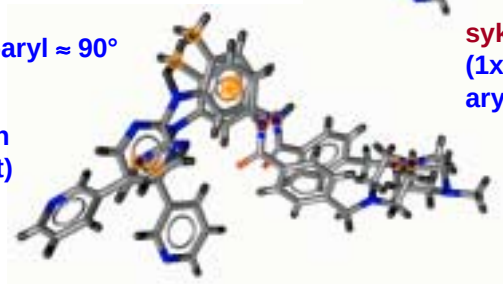


c-abl kinase
(1iep)
aryl-NH-aryl ≈ 90°



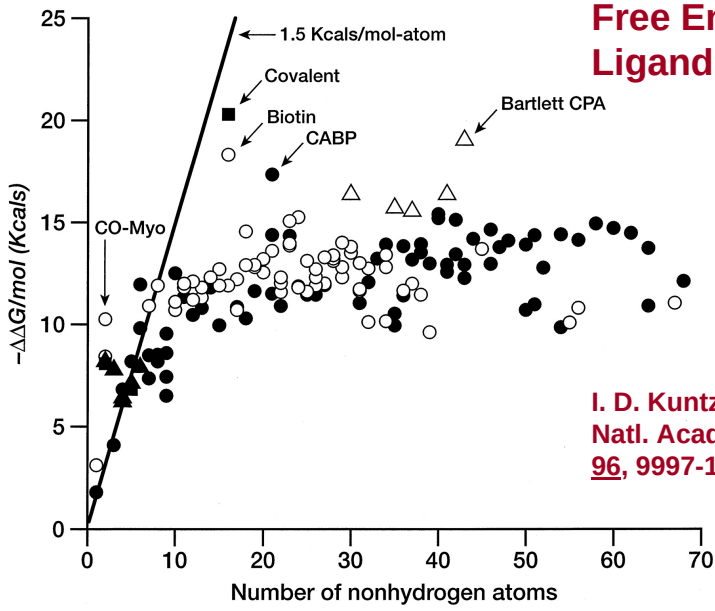
syk tyrosine kinase
(1xbb)
aryl-NH-aryl ≈ 0°

superposition
(LigandScout)



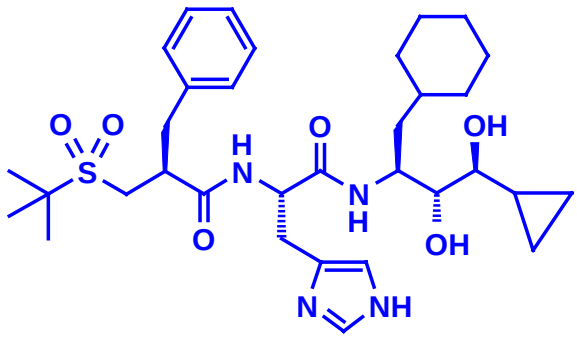
S. Atwell et al., J. Biol. Chem. 279, 55827-55832 (2004)

Free Energy of Ligand Binding



I. D. Kuntz et al., Proc. Natl. Acad. Sci. USA 96, 9997-10002 (1999)

Species Specificity of a Renin Inhibitor



Remikiren

IC_{50} =

0.8 nM (human)

1.0-1.7 nM (monkeys)

107 nM (dog)

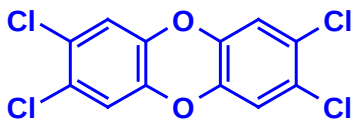
3 600 nM (rat)

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

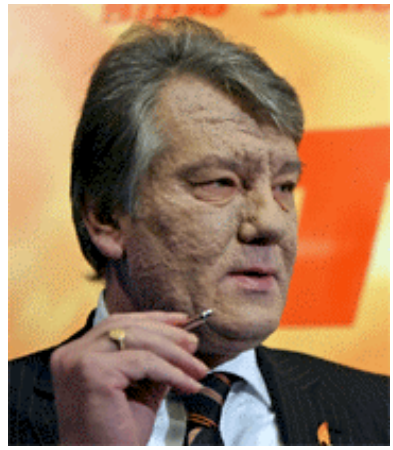


2,3,7,8-Tetrachloro-dibenzodioxin

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	??

Dioxine Poisoning of Victor Yushchenko

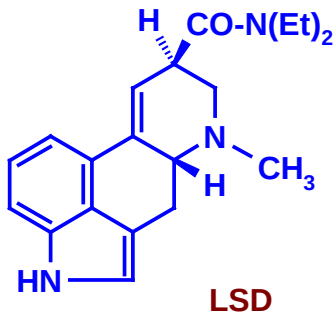
Victor Yushchenko, Ukraine's opposition leader, looks fit and healthy on August 02, 2004, before his mystery illness.



Yushchenko in Kiev on November 19, 2004. A British toxicologist says his skin condition is characterisitic of dioxin poisoning (Nature online, Nov. 23, 2004).

Hugo Kubinyi, www.kubinyi.de

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

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)

Hugo Kubinyi, www.kubinyi.de

Clinical Studies - the Typical Volunteer

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.**

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**