The Long Road from QSAR to Virtual Screening .... to Drugs ?

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18th EURO QSAR, Rhodes, Greece
September 19-24, 2010

Ascending and Descending
(M. C. Escher, lithograph, 1960)

QSAR and Modelling: Living in Castalia?

In Castalia, intellectual efforts have no purpose other than the preservation and advancement of intellectual foundations of culture and humanity ... [they] engage in an intellectual exercise, the "Glass Bead Game", which aims at connecting scientific and cultural values within a formal framework of mathematics and music ...

(Hermann Hesse
The Glass Bead Game)

Corwin Hansch (* 1918)

(picture taken at the 5th EuroQSAR, 1984)

S. L. Carney (DDT 9, 158-160 (2004)):
Has there been a single development that, in your opinion, has moved the field of medicinal chemistry ahead more than any other?
Robin Ganellin (Professor of Medicinal Chemistry, University College, London, UK): I would go back to the 1960s to the work of Corwin Hansch on the importance of lipophilicity. ... that changed the way of thinking in medicinal chemistry. .... the application of physical organic chemical approaches to structure–activity analysis [has] been very important.

Hugo Kubinyi, www.kubinyi.de

Beware of q^2!
A.Golbraikh and A. Tropsha, J. Mol. Graphics & Model. 20, 269-276(2002)

3D-QSAR illusions
A. M. Doweyko, J. Comput.-Aided Mol. Design 18, 587-596 (2004)

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

The trouble with QSAR (or how I learned to stop worrying and embrace fallacy)
S. R. Johnson, J. Chem. Inf. Model. 48, 25-26 (2008)

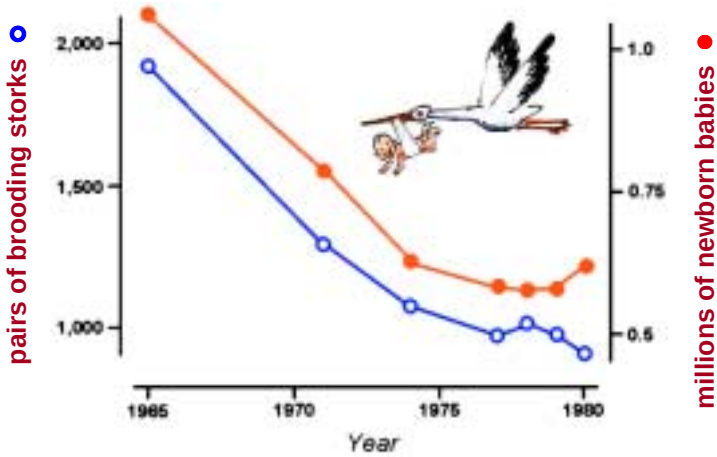
Is QSAR relevant to Drug Discovery?
A. M. Doweyko, Idrugs 11, 894-899 (2008)

QSAR: dead or alive?
A. M. Doweyko, J. Comput.-Aided Mol. Design 22, 81-89 (2008)

How not to develop a QSAR/QSPR relationship
J. C. Dearden et al., SAR and QSAR in Environ. Res. 20, 241-266 (2009)

How to recognize and workaround pitfalls in QSAR studies: a critical review
T. Scior et al., Curr. Med. Chem. 16, 4297-4313 (2009)

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)**

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The Texas Sharpshooter Fallacy

A Texan fires several shots at the door of a barn, then paints a target around the hits and claims to be a sharpshooter.

Information is interpreted or manipulated until it appears to have a meaning: cryptograms in the work of Shakespeare, Nostradamus predictions, more children in town A have leukemia than in town B …

http://en.wikipedia.org/wiki/Texas_sharpshooter_fallacy

A Few Problems in Statistical Analyses

inappropriate biological data
wrong scaling of biological data
data from different labs
different binding modes
mixed data (e.g. oral absorption and bioavailability)
different mechanism of action (e.g. toxicity data)
too few data points
too many single points
lack of chemical variation
clustered data
small variance of y values
systematic error/s in y
too large errors in y values
outliers / wrong values
wrong model selection

Some More Problems in Statistical Analyses

inappropriate x variables
too many x variables (Topliss)
  a) in the model selection
  b) in the final model
x variable scaling in CoMFA fields
interrelated x variables
singular matrix
elimination of variables that are significant only with others
insignificant model (F test)
insignificant x variables (t test)
no qualitative (biophysical) model
no causal relationship (the storks)
extrapolation too far outside of observation space
no validation method applied
wrong validation method, ...

How the Trouble Started: Connectivity Indices $^{i}\chi$

Connectivity indices = electron-weighted subgraph counts

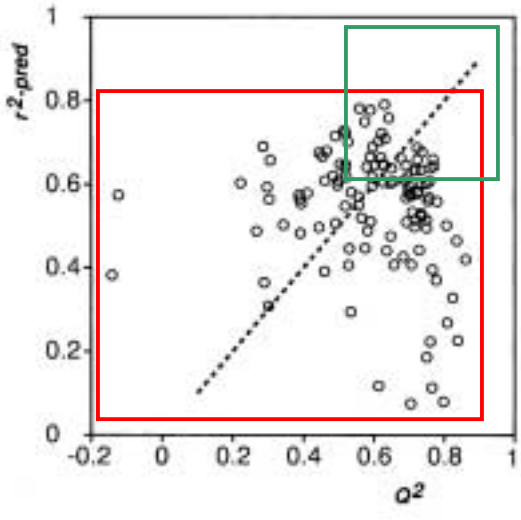
$^{0}\chi = \Sigma$ (# σ-electrons of i)$^{-0.5}$

$^{1}\chi = \Sigma\ (^{0}\chi(i).^{0}\chi(j))^{-0.5}$
(over all bonds ij)

... etc.

$^{0}\chi$ $^{1}\chi$ $^{2}\chi$ $^{3}\chi_{P,}$ $^{3}\chi_{C}$ ...

External vs. Internal Predictivity

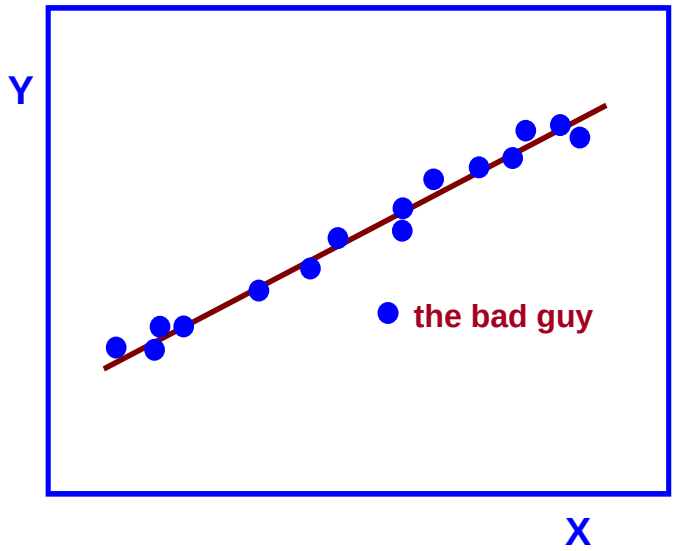


The „Kubinyi Paradox“

J. H. van Drie, Curr. Pharm. Des. 9, 1649-1664 (2003); J. H. van Drie, in: Computational Medicinal Chemistry for Drug Discovery, P. Bultinck et al., Eds., Marcel Dekker, 2004, pp. 437-460.

Data from H. Kubinyi et al., J. Med. Chem. 41, 2553-2564 (1998).

„Good“ and „Bad“ Guys in Regression Analysis



bad guy in the test set:
r^2, Q^2 good
r^2_{pred} poor

bad guy in the training set:
r^2, Q^2 poor
r^2_{pred} good

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)

Proper Validation of QSAR and 3D QSAR Models

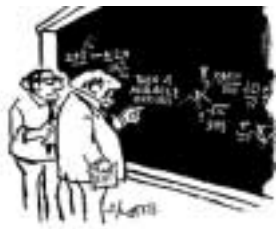
Validation Method	Effect
Crossvalidation, using the original variables (LOO CV, LMO CV)	insufficient for model validation
Y scrambling, using the original variables	misleading
Y scrambling with new variable selection	may be misleading
Leave-one-out crossvalidation with new variable selection in every CV run	misleading in larger data sets
Leave-many-out (up to 30%) cross-validation with new variable selection in every CV run	the only reliable validation procedure

see also T. Scior et al., Curr. Med. Chem. 16, 4297-4313 (2009)

Hugo Kubinyi, www.kubinyi.de

"Good" QSAR

- parameters with biophysical relevance
- few variables to select
- few variables in the model
- leave-many-out crossvalidation



"I think you should be more explicit here in step two."

"Poor" QSAR

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

Sir Karl Popper
★1902 Vienna, ✞ 1998 London

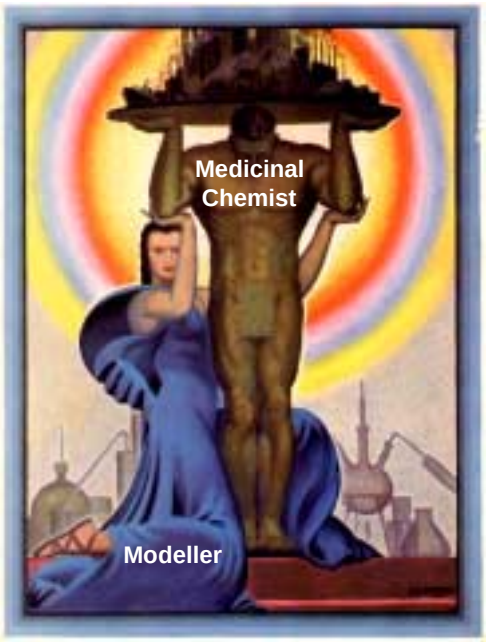
Good and Poor Science

[one has to] „differentiate between science and pseudoscience, knowing very well that science often errs and that pseudoscience may happen to stumble on the truth“

„it is easy to obtain confirmations - if one looks for them“

„a theory which is not refutable ... is non-scientific“

„some theories, when found to be false, are still upheld by their admirers - for example by introducing some auxiliary assumption, or by reinterpreting the theory *ad hoc* in such a way that it escapes refutation“



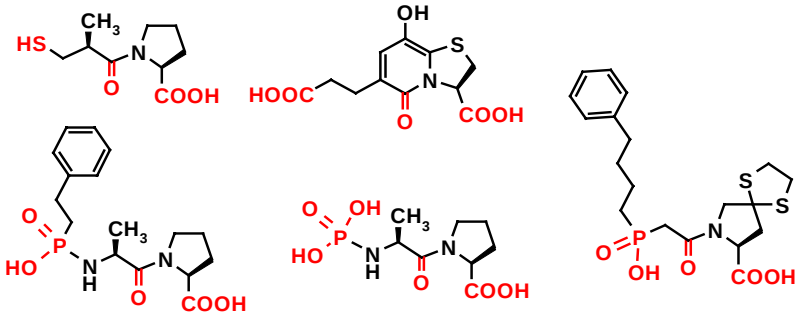
A. Cressy Morrison

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“

Historical Pharmacophore Definition:
ACE Inhibitors

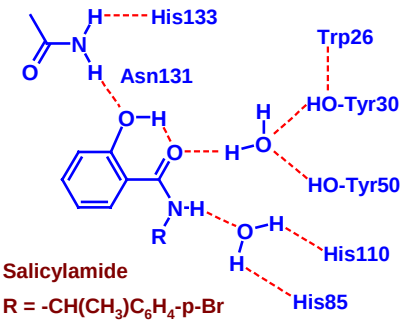


defined by functional groups

-SH, -COOH, $-PO_3H_2$, $>PO_2H$

COOH

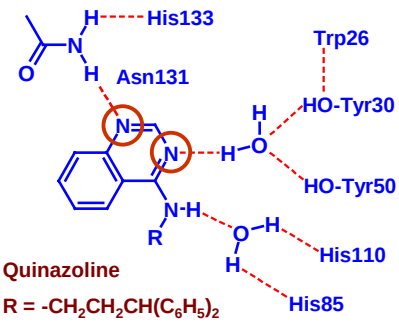
Receptors Just Recognize Properties



Salicylamide

R = $-CH(CH_3)C_6H_4$-p-Br

K_i = 0.14 nM



Quinazoline

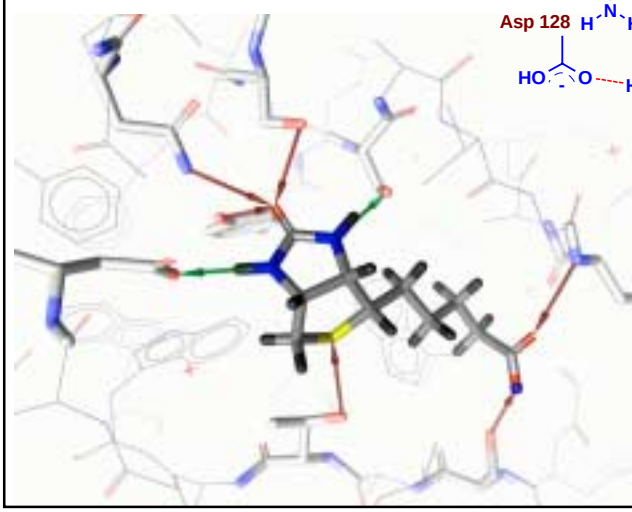
R = $-CH_2CH_2CH(C_6H_5)_2$

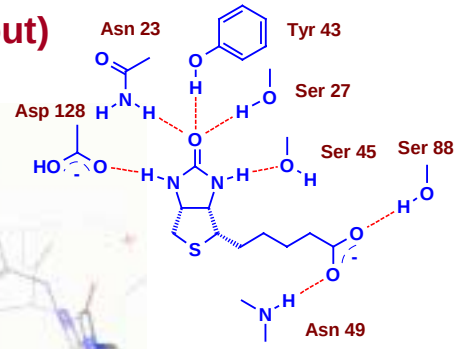
K_i = 0.15 nM

A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger its biological response.

C. G. Wermuth et al., Pure Appl. Chem. 70, 1129-1143 (1998)

Automated Pharmacophore Recognition (LigandScout)





Biotin Streptavidin Complex (2rtf, 1.47Å)

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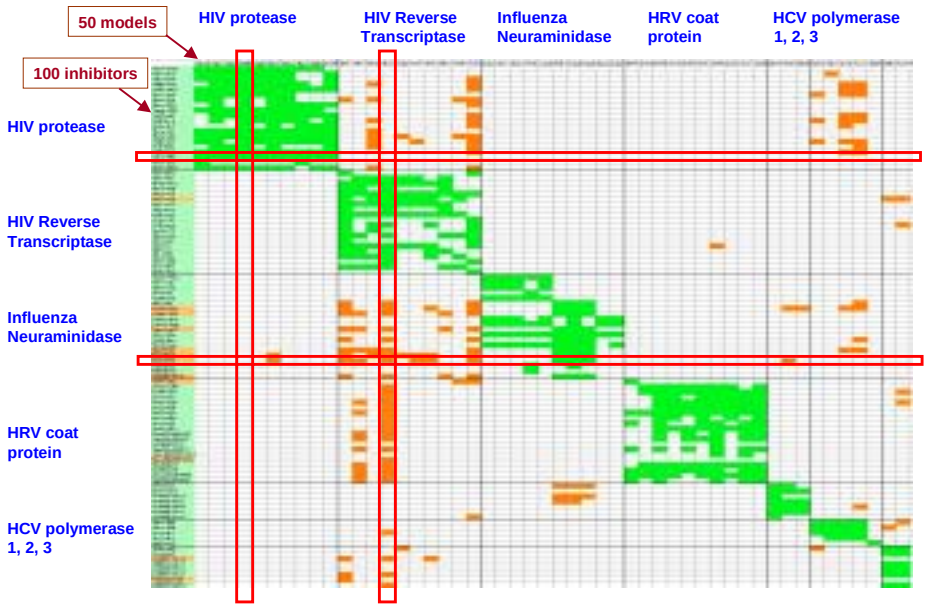
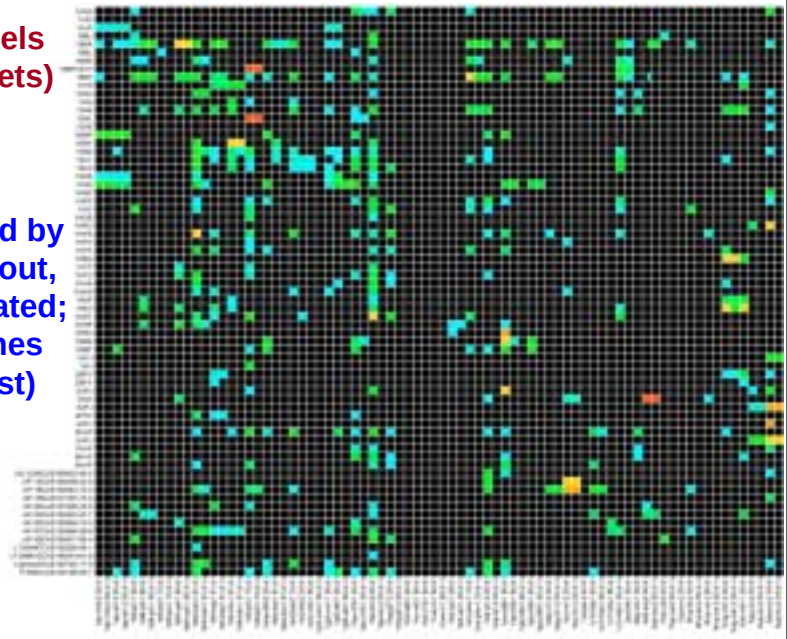


T. Steindl et al., J. Chem. Inf. Model. 46, 2146-2157 (2006)

1846 Models (195 Targets)

Accelrys/ Scitegic (generated by LigandScout, hand-curated; 3D searches by Catalyst)



Problems in Pharmacophore Generation

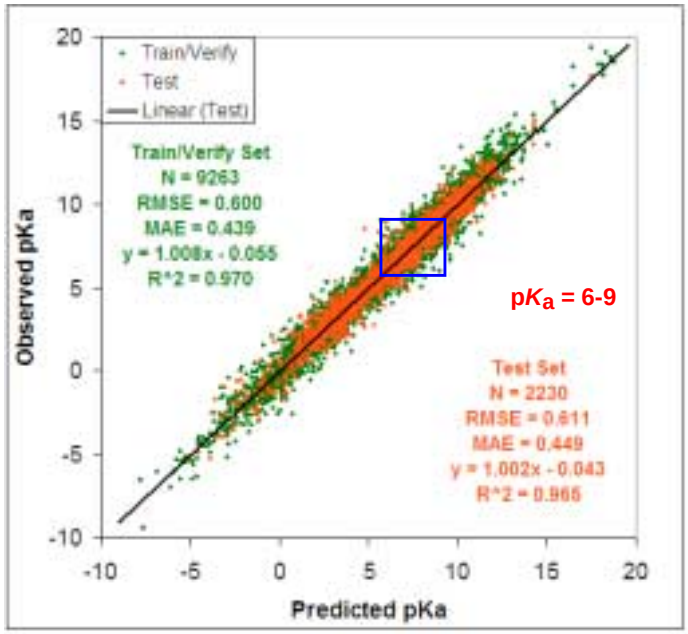
Isomers, enantiomers, diastereomers

Ionisation and Dissociation
(Sadowski rules, ACS Boston, 2002)

Tautomeric and protomeric forms
(program AGENT, ETH Zurich; ChemoSoft, ChemDiv; LigPrep, Schroedinger; and several others)

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

Superposition of flexible molecules



Software for pK_a Prediction

pKa model in ADMET Predictor 4.0

www.simulations-plus.com/Definitions.aspx?IID=55

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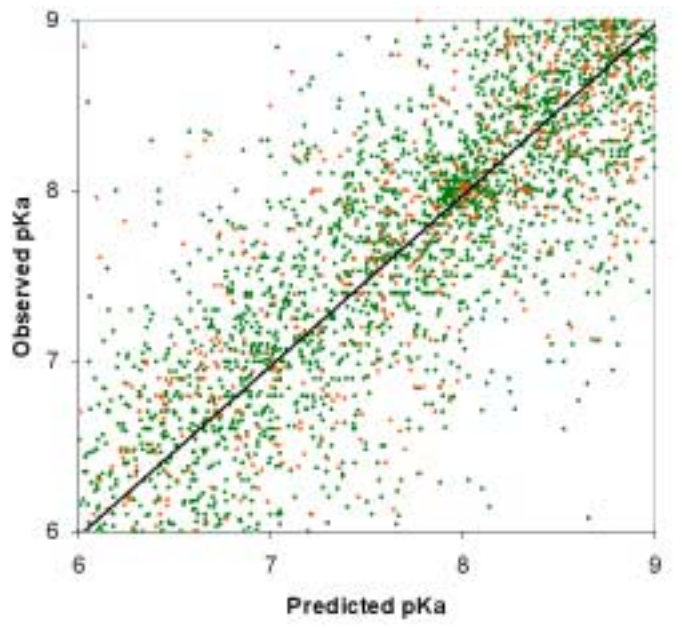
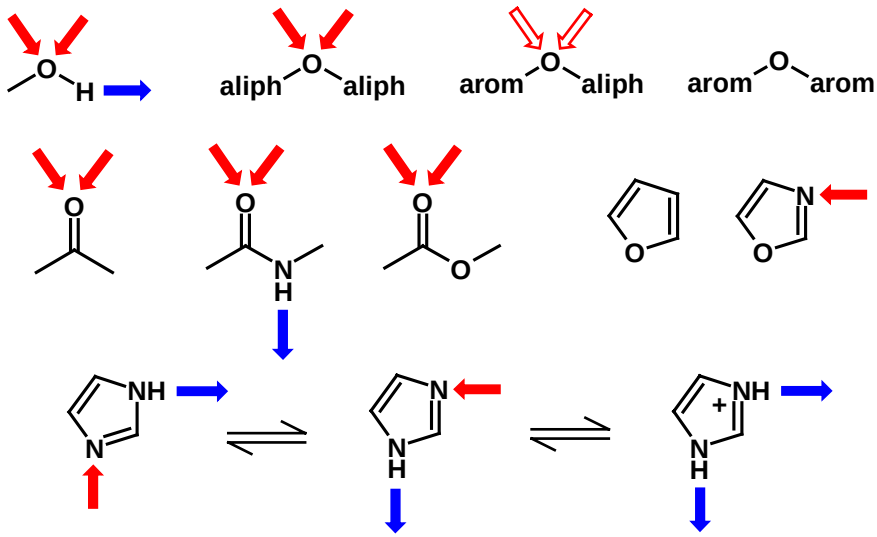


Software for pK_a Prediction

pKa model in ADMET Predictor 4.0

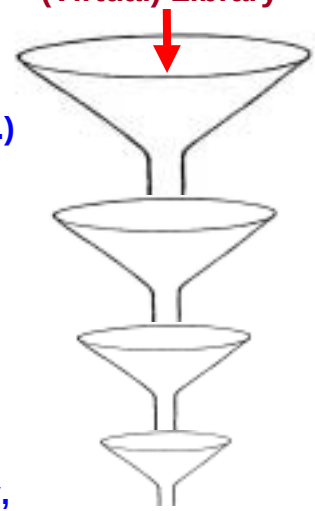
courtesy of Robert Fraczkiewicz, Simulations Plus, Inc.

Donor and Acceptor Properties of O and N



Stepwise Virtual Screening

(Virtual) Library



Property Filters
(MW, rule of 5, nRot, drug-like, ...)

1D Pharmacophore and
3D Pharmacophore Searches

Docking and Scoring

Selection by Diversity, Similarity,
and Visual Inspection

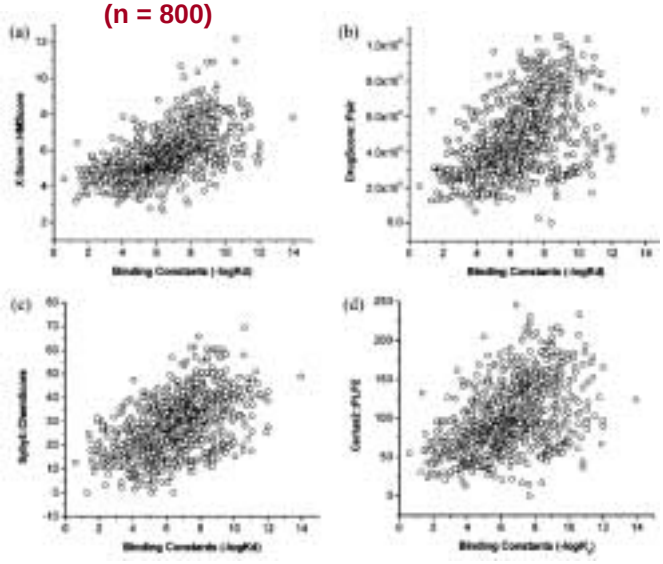
Leads / Candidates

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% ?

Performance of Different Scoring Functions

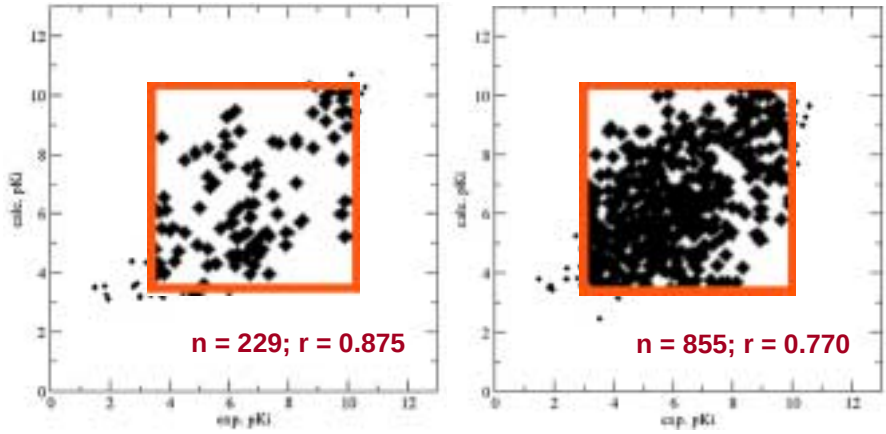
(n = 800)



a) X-Score
b) DrugScore
c) ChemScore
d) PLP2

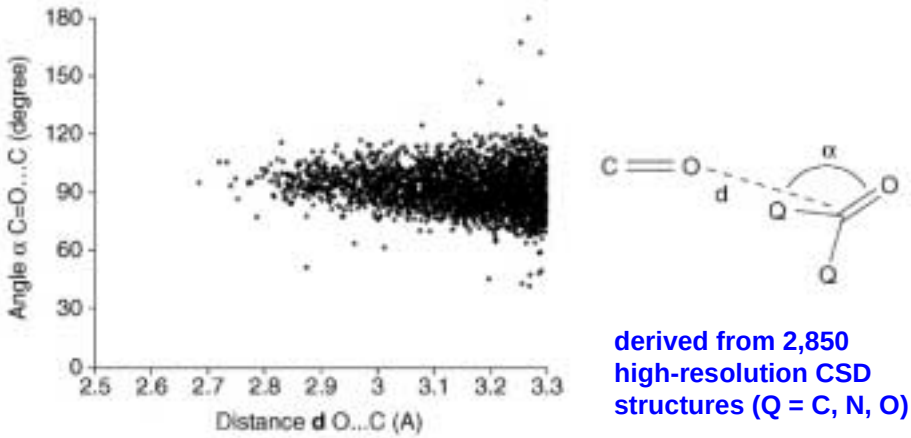
R. Wang et al., J. Chem. Inf. Model. 44, 2114-2125 (2004)

SFCscore (Scoring Function Consortium): Affinity Prediction of Protein-Ligand Complexes



C. A. Sotriffer et al., Proteins 73, 395-419 (2008); cf. A. M. Davis et al., Angew. Chem. Int. Ed. Engl. 42, 2718-36 (2003)

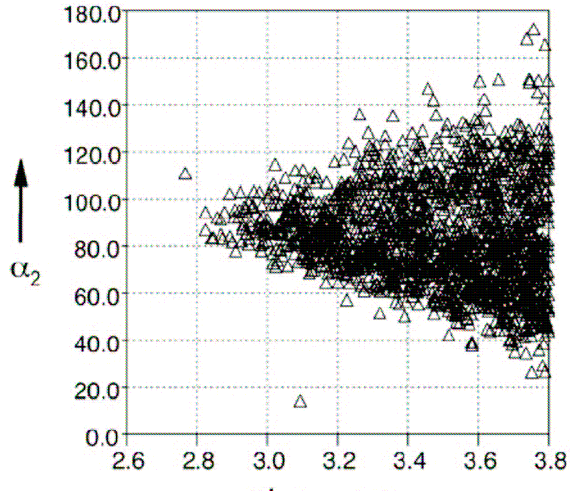
Unrecognized Favorable Interactions

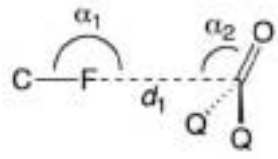


derived from 2,850 high-resolution CSD structures (Q = C, N, O)

T. Schulz-Gasch and M. Stahl, Drug Discov. Today: Technologies 1, 231-239 (2004)

Unrecognized Favorable Interactions





derived from 1,087 high-resolution CSD structures (Q = C, N, O)

M. Zürcher and F. Diederich, J.Org. Chem. 73, 4345-4361 (2008)

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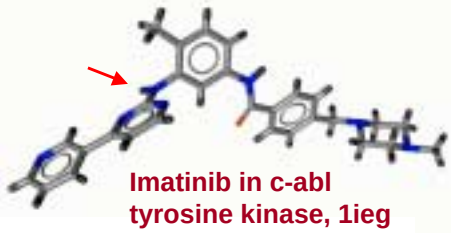
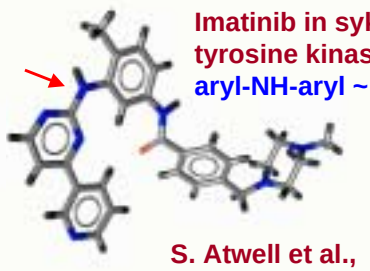
Energies of Different Ligand Conformations?

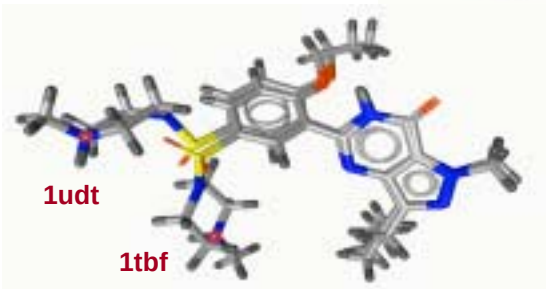


Imatinib in c-abl tyrosine kinase, 1ieg aryl-NH-aryl ~ 0°, 80°



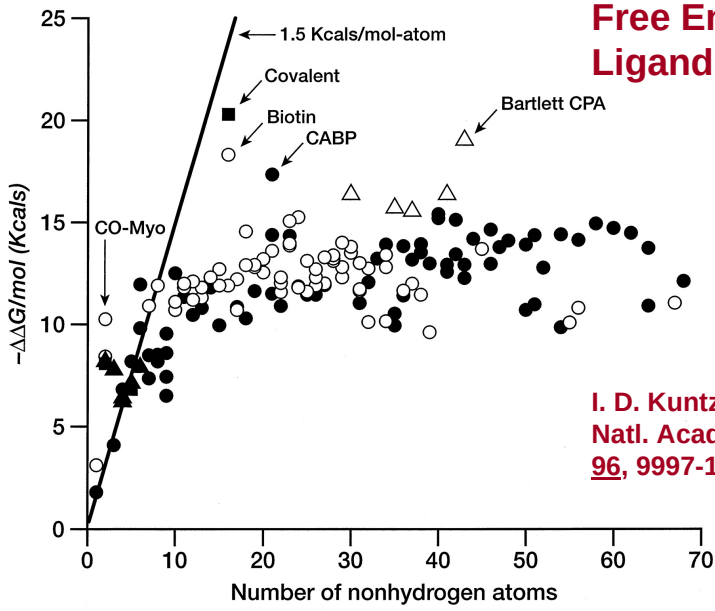
Imatinib in syk tyrosine kinase, 1xbb aryl-NH-aryl ~ 0°, 0°

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



Sildenafil in hPDE 5 (LigandScout super-position by binding site Cα atoms)

Free Energy of Ligand Binding



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

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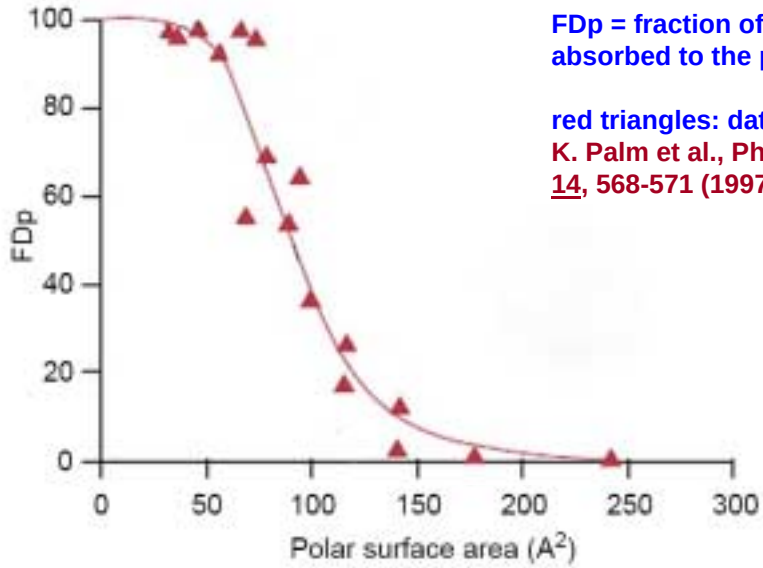
Drug Discovery Bottlenecks of the Past

Problem	Solution
Target search	genome information
Target validation	knock-outs, RNA silencing
Lead search	in vitro test models, HTS
Lead optimization	parallel syntheses, chemogenomics
Permeability, absorption	Lipinski rules, Caco cells, prodrugs
Metabolism	MetaSite, MetaPrint2D, liver microsomes, hepatocytes
Toxicity	Ames test, hERG models
Drug-drug interactions	CYP inhibition/induction

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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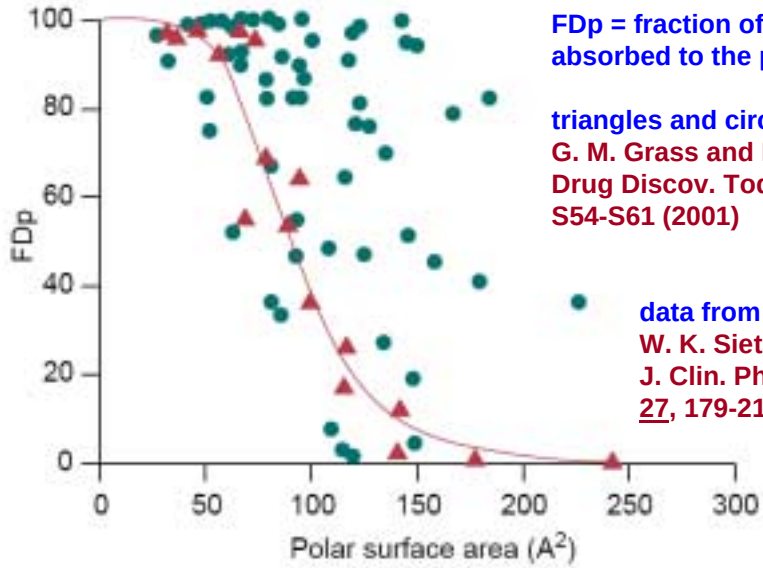
Human Absorption and Polar Surface Area

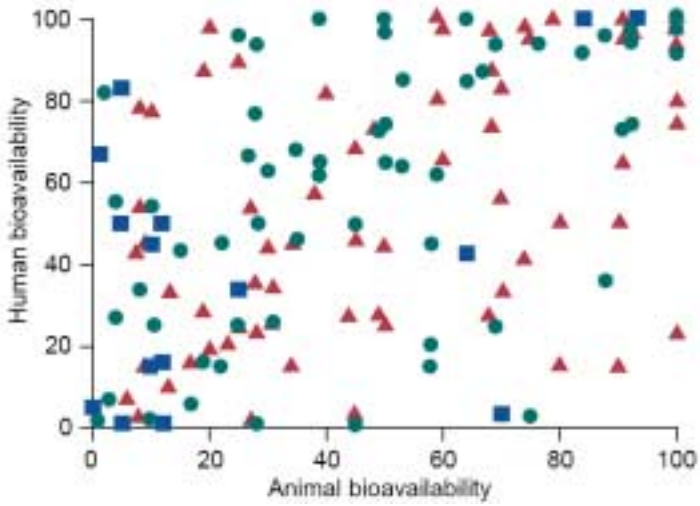


FDp = fraction of dose absorbed to the portal vein

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

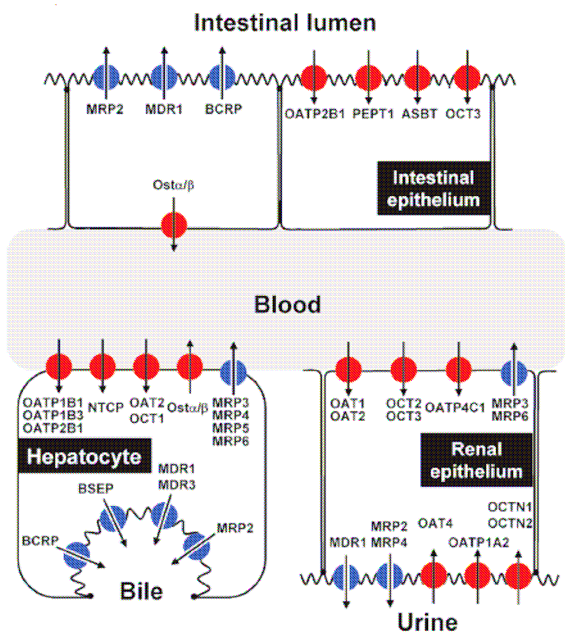
Dog
red triangles

Primates
blue squares

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

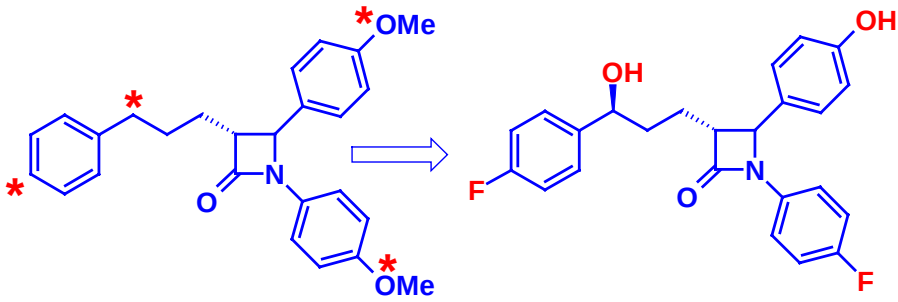
G. M. Grass and P. J. Sinko, Drug Discov. Today 6, S54-S61 (2001)

The Role of Transporters in Drug Absorption and Elimination



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

Oxidative Metabolism and Drug Design



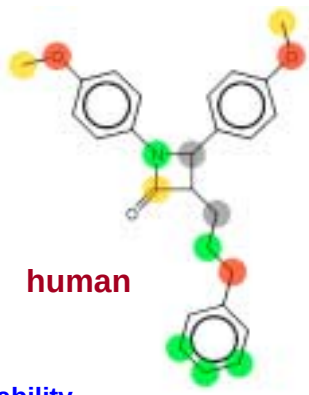
SCH 48461
ED_{50} (hamster) = 2.2 mg/kg

Ezetimib (SCH 58235, oral cholesterol absorption inhibitor)
ED_{50} (hamster) = 0.04 mg/kg

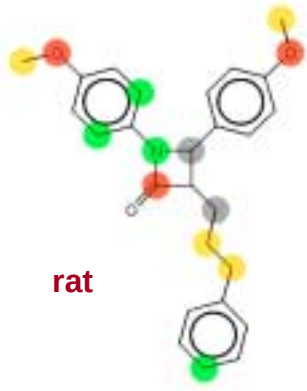
M. van Heek et al., J. Pharmacol. Exp. Ther. 283, 157-163 (1997);
D. A. Smith, H. van de Waterbeemd and D. K. Walker, Pharmacokinetics and Metabolism in Drug Design, Wiley-VCH, 2001, p. 85

Prediction of Drug Metabolism: MetaPrint2D

predictions for human, dog, rat, all



human



rat

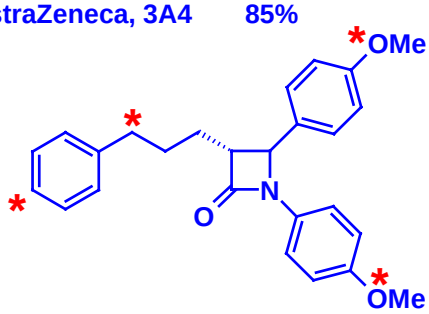
red = high probability
orange = medium proability
green = low probability
white = no probability

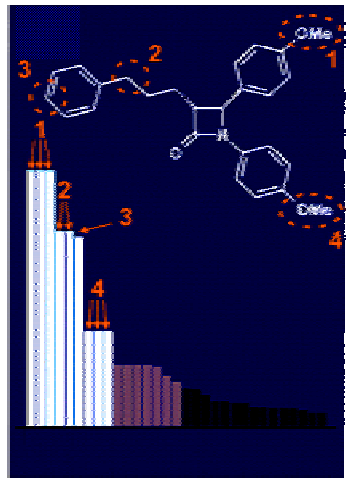
S. Boyer et al.,
www-metaprint2d.ch.cam.ac.uk/

Prediction of Drug Metabolism: MetaSite

correct predictions:

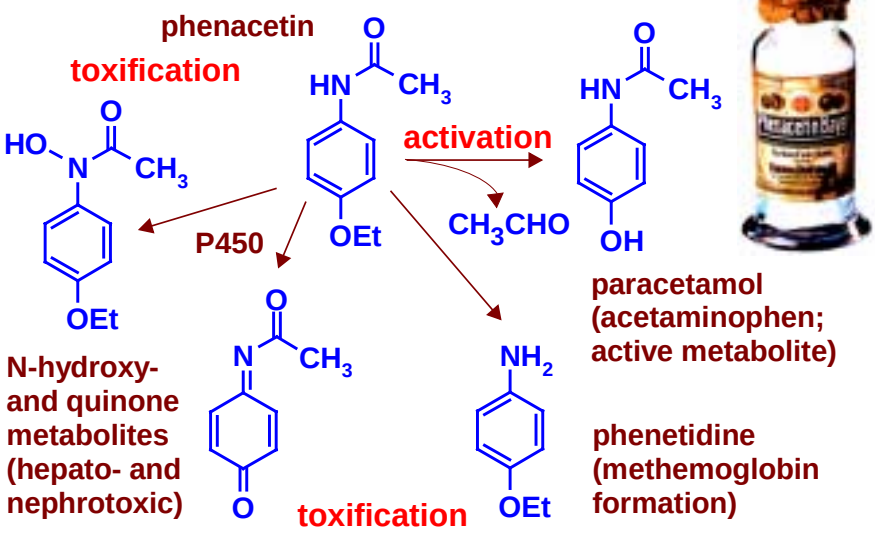
Sanofi-Aventis, 2C9	84%
Pfizer, 2D6	85%
3A4	86%
J&J, 2C9, 2D6, 3A3	85%
AstraZeneca, 3A4	85%





G. Cruciani et al., J. Med. Chem. 48, 6970-6979 (2005)

Metabolic Activation and Toxification

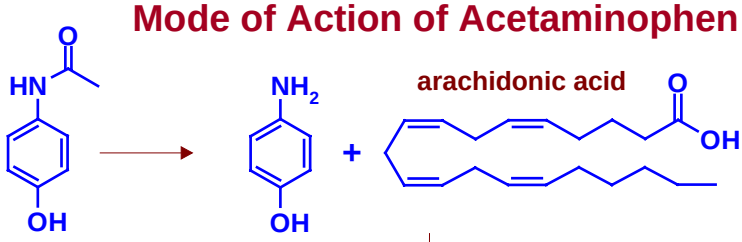


paracetamol (acetaminophen; active metabolite)

N-hydroxy- and quinone metabolites (hepato- and nephrotoxic)

phenetidine (methemoglobin formation)

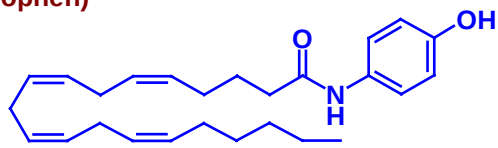
Mode of Action of Acetaminophen



paracetamol (acetaminophen)

p-amino-phenol

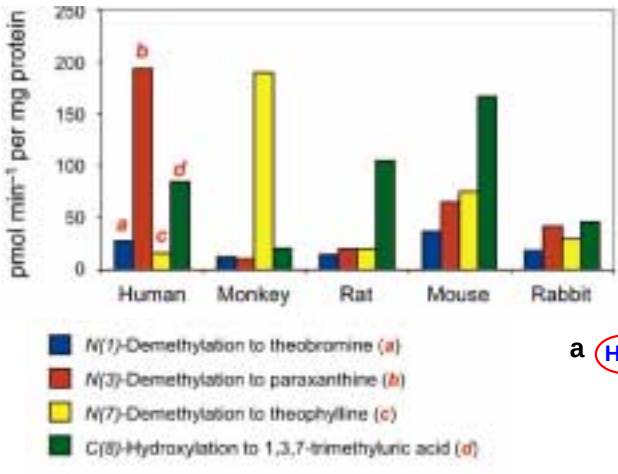
fatty acid amido hydrolase (FAAH)



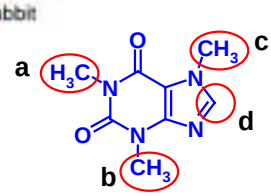
E. D. Högestätt et al., J. Biol. Chem. 280, 31405-31412 (2005)

N-arachidonoyl phenolamine, a potent TRPV1 (transient receptor potential vanilloid 1, vanilloid receptor) agonist, pEC_{50} = 7.80 (about 16 nM), binds also to the cannabinoid CB_1 receptor and inhibits cellular anandamide uptake.

Species Differences of Caffeine Metabolism

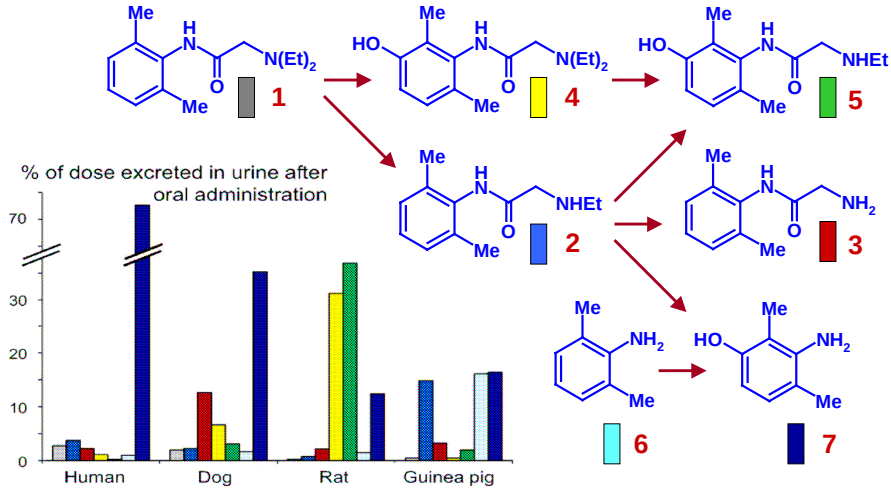


production of caffeine metabolites by liver microsomes of different species



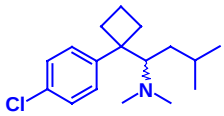
F. Berthou et al., Xenobiotica 22, 671-680 (1992)
figure: S. D. Krämer and B. Testa, Chemistry & Biodiversity 5, 2465-2578 (2008)

Species Differences of Lidocaine Metabolism



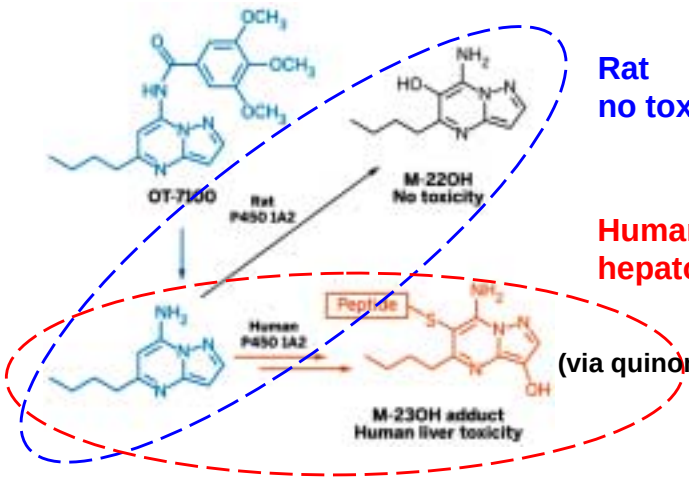
J. B. Keenaghan and R. N. Boyes, J. Pharmacol. Exp. Ther. 180, 459-463 (1972)
figure: S. D. Krämer and B. Testa, Chemistry & Biodiversity 5, 2465-2578 (2008)

Biological Activities of Metabolites

Compound	monoamine uptake inhibition rat synaptosomes, IC_{50} in nM		
Sibutramine (racemate)	**DAT**	**NET**	**SERT**
	1200	350	2800
(R) NHMe	12	4	44
(S) NHMe	180	870	9200
(R) NH_2	9	13	140
(S) NH_2	12	62	4300

D. L. Nelson and D. R. Gehlert, Endocrine 29, 49-60 (2006);
data from S. D. Glick et al., Eur. J. Pharmacol. 397, 93-102 (2000)

Biological Activities of Metabolites



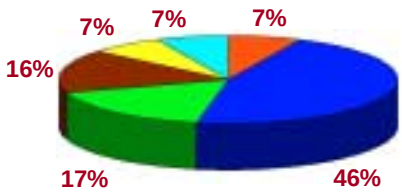
Rat
no toxicity

Human
hepatotoxicity

(via quinone imine)

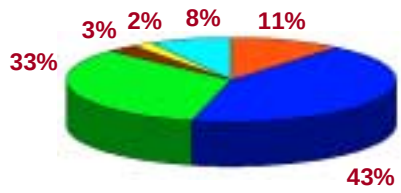
S. Kuribayashi et al., Chem Res. Toxicol. 22, 323-331 (2009);
cf. Chem. &Eng. News, August 31, 2009, p. 27

Reasons for Failure in Drug Development



- 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
- Not published

Reasons for failure in clinical development, 1992-2002 (n = 73)
(reasons for market withdrawal, n = 16: toxicity 93%, efficacy 7%)
D. Schuster et al., Curr. Pharm. Design 11, 3545-3559 (2005)

Biological Activity Profiling by PASS

Compound	PASS - most probable biological activities	Score
Glycerol trimyristate	Antiinflammatory, pancreatic	0.745
	Multiple sclerosis treatment	0.727
Glycerol	Bone formation stimulant	0.793
	Metabolic	0.762
Saccharose	Corneal wound healing stimulator	0.893
	Antineoplastic	0.748
	Antiinfective (HIV)	0.714
Saccharine	Anticonvulsant	0.766
	Psychosexual dysfunction treatment	0.744
Cyclamate	Anticoagulant	0.919
	TNF alpha release inhibitor	0.851
	Analgesic, non-opioid	0.837
Phenylalanine	Factor VIIa inhibitor	0.731
Citric acid	Adrenergic transmitter uptake inhibitor	0.919
	Arrhythmogenic	0.890

www.ibmc.msk.ru/PASS; source of scores: http://129.43.27.140/ncidb2/

Yes, We Can? No, We Can't

What we can

- Estimation of lipophilicity
- Prediction of 3D structure/s
- 3D pharmacophore generation
- 3D pharmacophore searches
- Prediction of plausible metabolites

What we can't

- Prediction of crystal lattices
- Prediction of melting points
- Prediction of (difficult) pK_a values

Where we fail

- Prediction of solubility (pK_a, mp)
- ADME prediction (log S, transporters)
- Affinity prediction (scoring functions)
- Prediction of biological activities
- Prediction of selectivity and toxicity

The Basis of Calculations in Natural Sciences

Pieter van Musschenbroek (1692-1761)
professor in Duisburg, Leiden and St. Petersburg
author of the books *Elementa Physicæ* and *Tentamina Experimentorum Naturalium*
inventor of the Leiden jar (first condenser)

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