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Changing Paradigms in Drug Discovery

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Cutting Edge Approaches to Drug Design, Royal Society of Chemistry Molecular Modelling Group Meeting, Oct. 19, 2005

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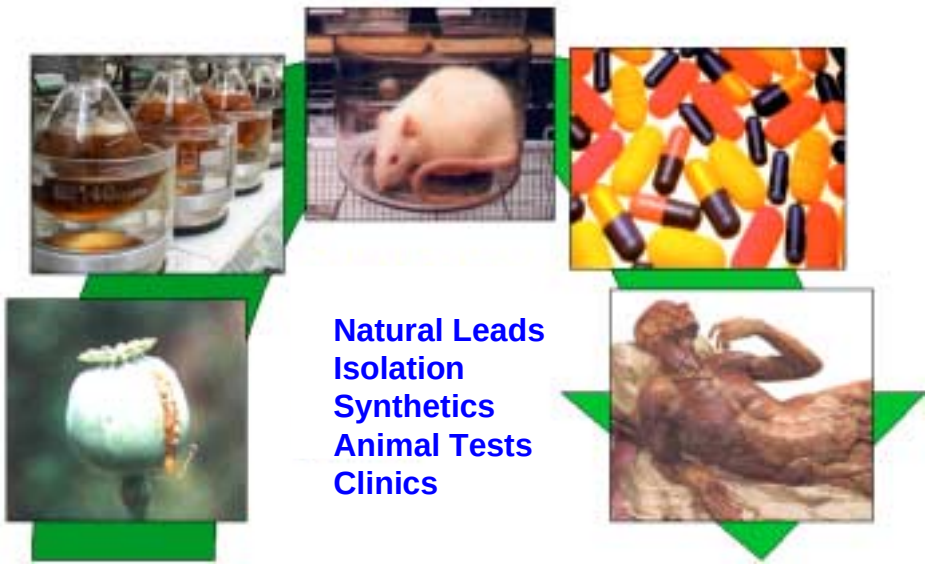
Yesterday's Drug Discovery Process



Natural Leads
Isolation
Synthetics
Animal Tests
Clinics

Technological Changes in Drug Research

Up to the 70s

- Chemistry and hypotheses guide the syntheses
- Bottleneck: Animal experiments, isolated organs

Up to the 90s

- Molecular Modelling
- *In vitro* models (enzyme inhibition, receptor binding)
- Bottleneck: Dedicated syntheses of drugs

Up to the year 2000:

- Gene technology (production of proteins)
- Combinatorial chemistry (mixtures, chemistry-driven)
- Structure-based design of ligands
- High-throughput test models (HTS)
- Bottleneck: ADMET properties

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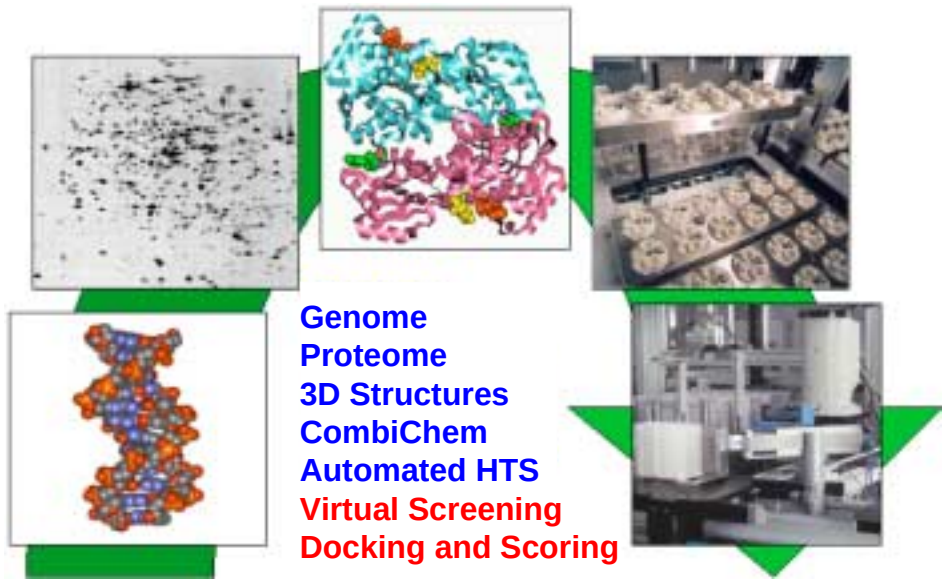
Today's Drug Discovery Process



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

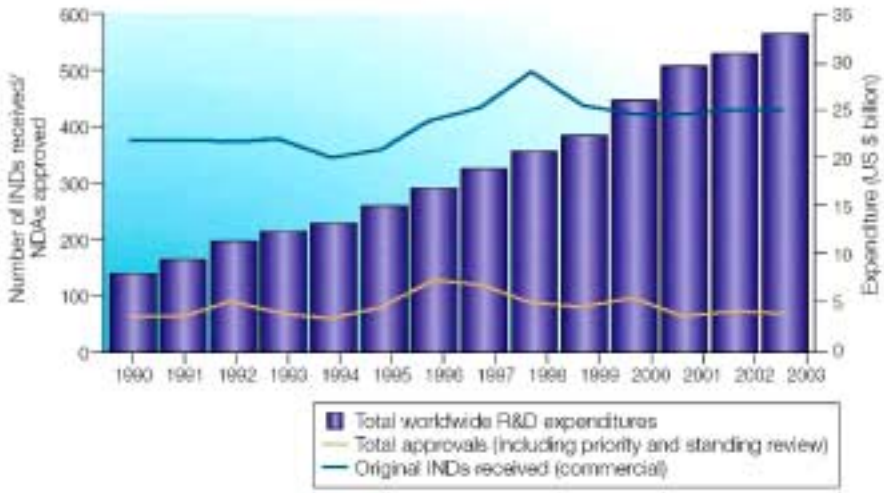
Technological Changes in Drug Research

Today:

- Genomics, proteomics and bioinformatics
- Transgenic animals for proof of concept
- Combinatorial chemistry
  (single compounds, design-driven)
- Structure-based and computer-aided design
  of ligands
- Ultra-high-throughput test models (u-HTS)
- Data mining
- Virtual screening
- ADMET profiles (HTS and *in silico*)

Bottleneck: Target validation, "drugable" targets

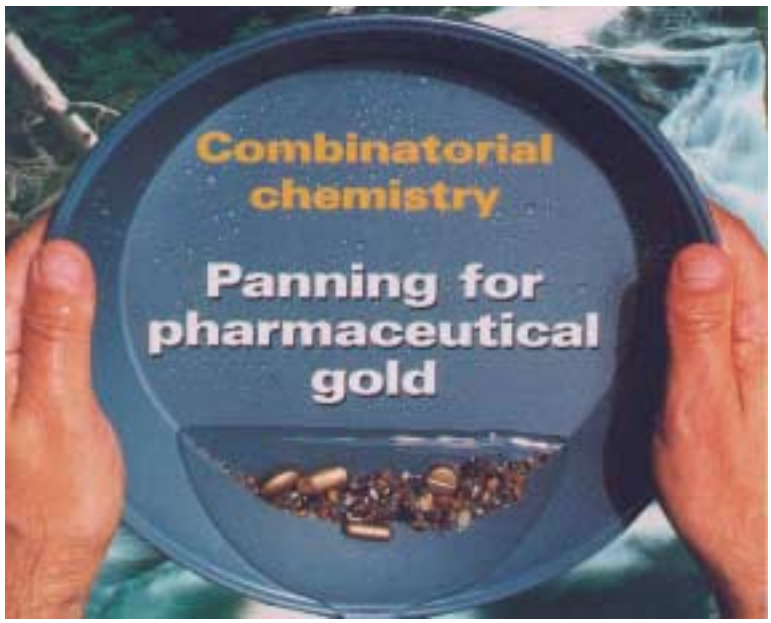
The Productivity Gap in Pharmaceutical Industry



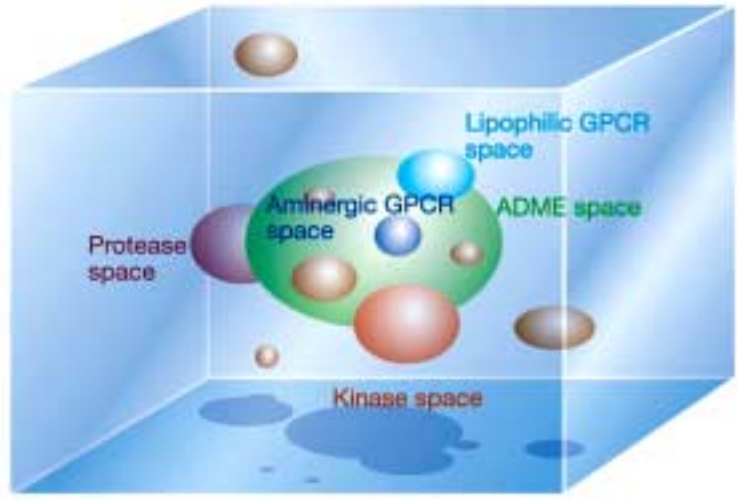
T.T. Ashburn and K.B. Thor, Nature Rev. Drug Discov. 3, 673-683 (2004)

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)



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

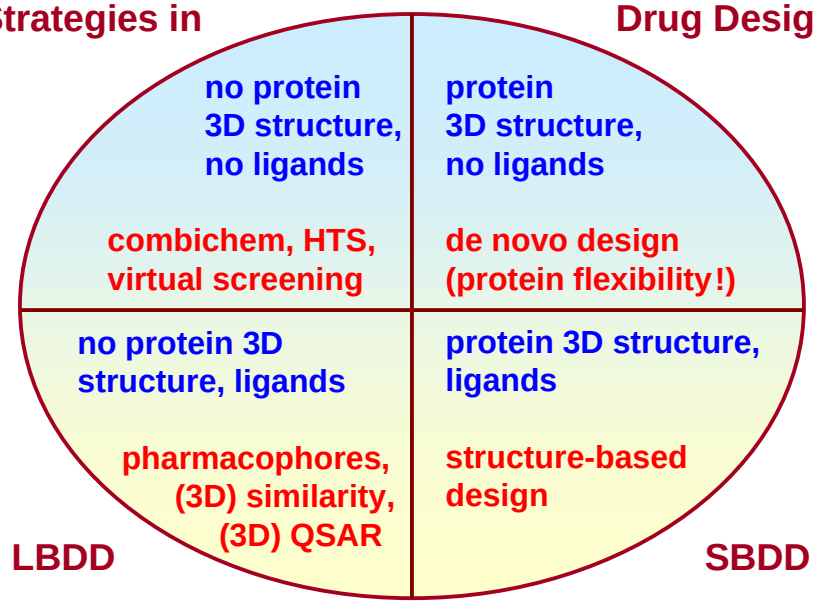
Types and Features of Combinatorial Libraries

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

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

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

Strategies in Drug Design



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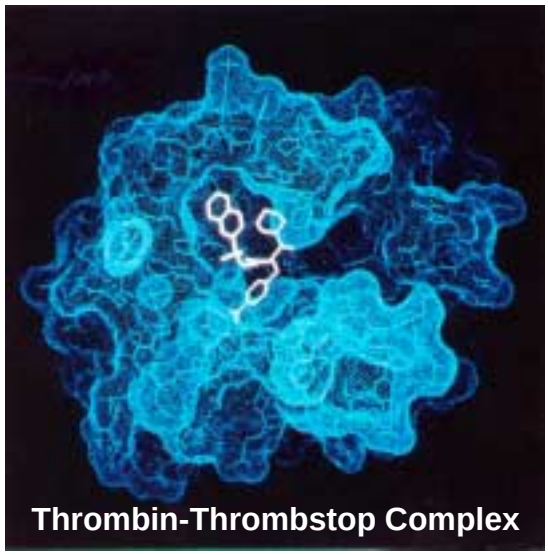
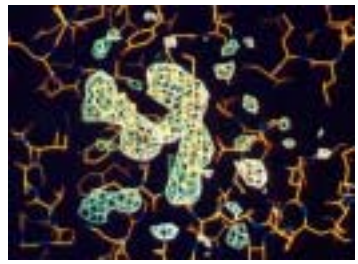
Protein Crystallography of Inhibitor Complexes



Thrombin-Thrombstop Complex



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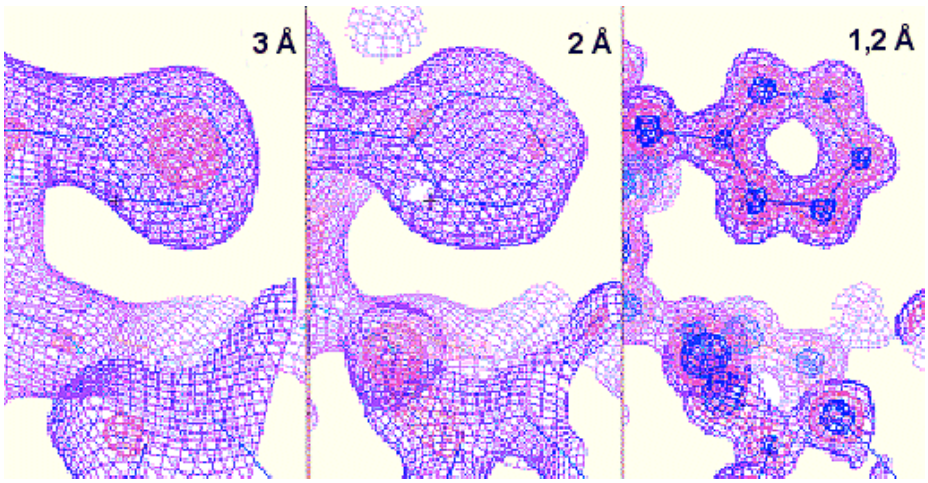
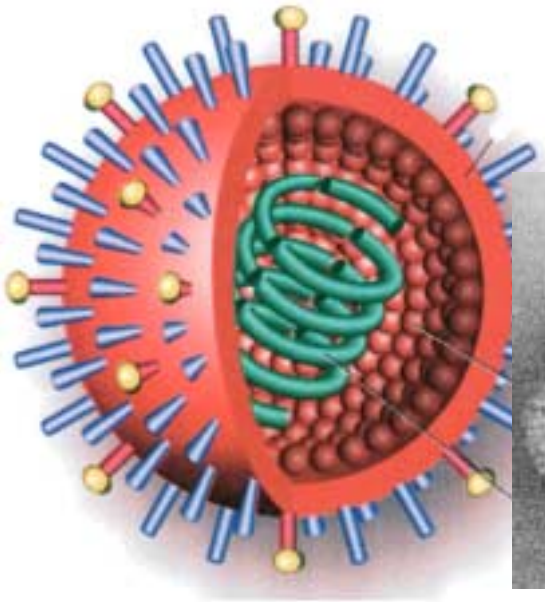
Problems of Resolution of Protein 3D Structures

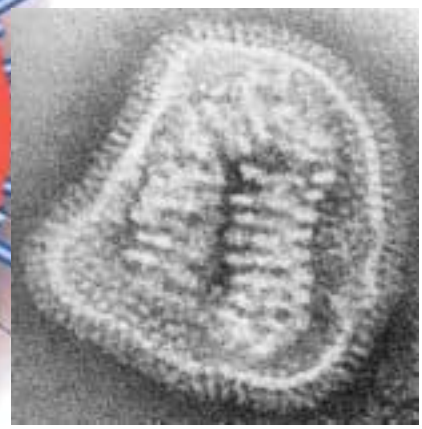


lacking hydrogens, no differentiation between C, O and N (thr, asp, asn, glu, gln, orientation of amide groups, imidazole, etc.)

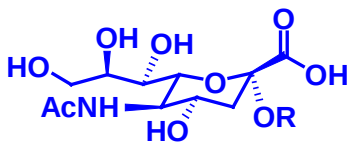


Influenza Virus

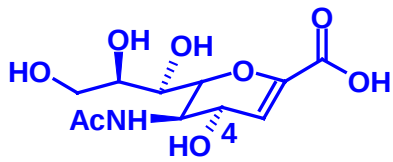
schematic view
and electron micro-
scopic picture



Design of Neuraminidase Inhibitors

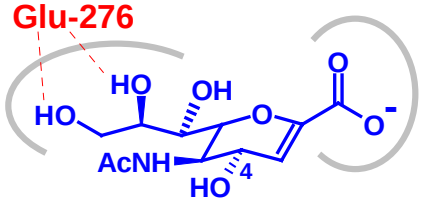


sialic acid, R = H



Neu5Ac2en
K_i = 1 000 nM

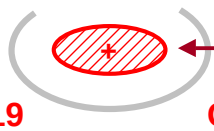
Glu-276



Arg-371

Arg-292

Arg-118

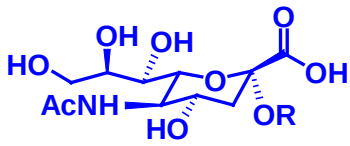


result of a GRID search with
a positively charged probe

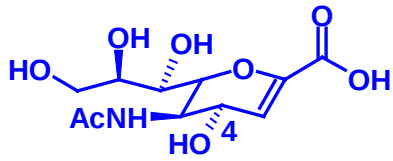
Glu-119

Glu-227

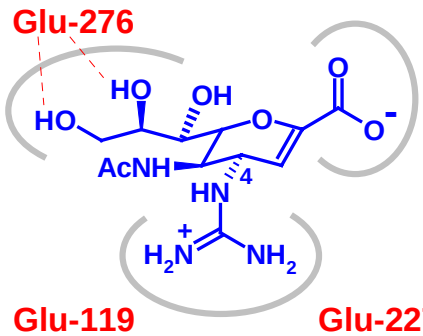
Design of Neuraminidase Inhibitors



sialic acid, R = H



Neu5Ac2en
K_i = 1 000 nM



Arg-371
Arg-292
Arg-118

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

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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 poor ADME the main problem ?

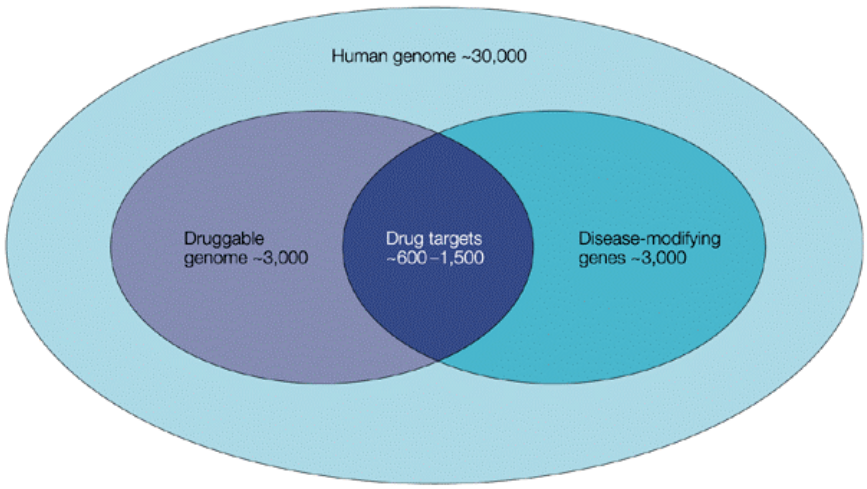
Are we using the right virtual screening techniques?

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)

Genome, Druggable Genome and Drug Targets



A. L. Hopkins and C. R. Groom, Nature Rev. Drug Discov. 1, 727-730 (2002); © Nature Reviews Drug Discovery

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)

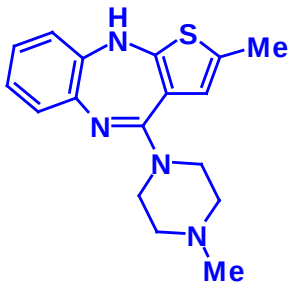
→ **the „druggable targetome“ ?**

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)

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 antidepressant."

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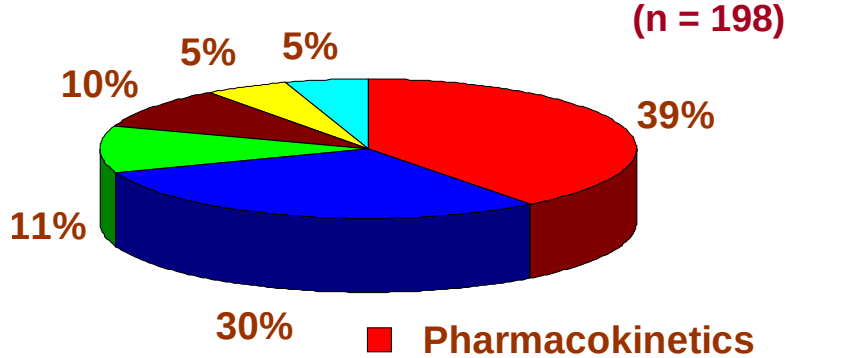
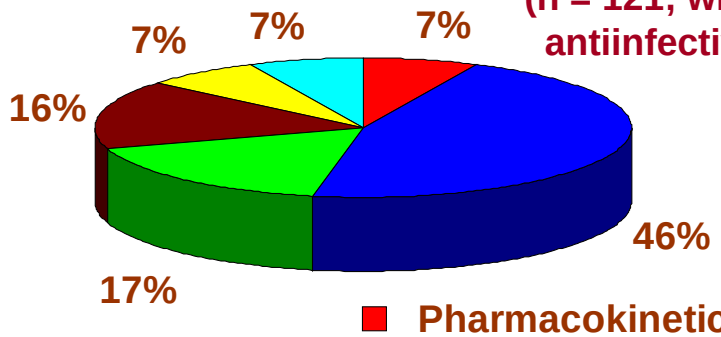
Reasons for Failure in Drug Development (n = 198)



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

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)

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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

Problems in Virtual Screening

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

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.)

Too many filters?

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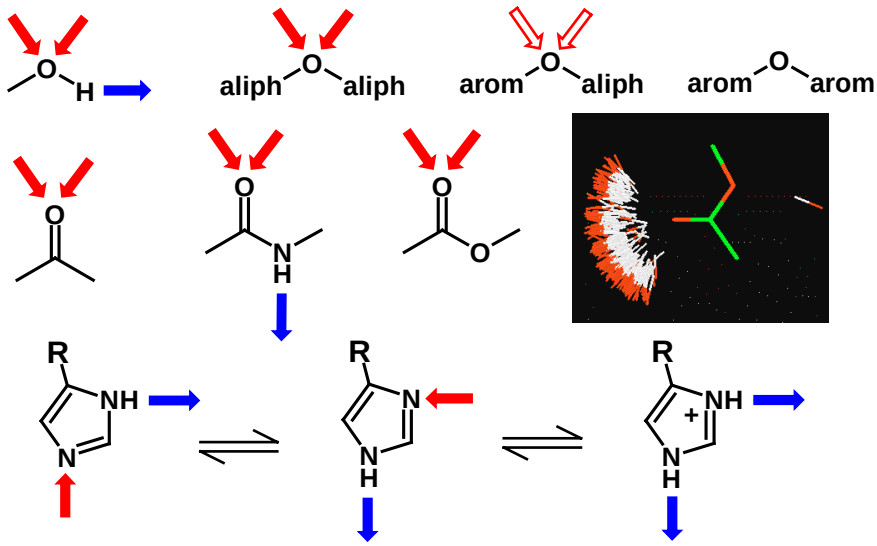
Donor and Acceptor Properties of O and N



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Filters for Virtual Screening	remaining
Garbage filter	100%
Druglike / Non-druglike	80%
Bioavailability	:
Cytotoxicity	:
hERG channel inhibiton	:
Antitargets	:
α1a (orthostatic hypotension)	:
D2 (extrapyramidal syndrome)	:
5-HT2c (obesity)	:
musc. M1 (hallucinations, memory)	:
CYP inhibition (3A4, 2C9, 2D6)	0% ?

A Virtual Screening / Docking Success Story

Comparison of the performance of high-throughput screening and virtual screening of potential leads of protein tyrosine phosphatase 1B (PTP1B):

a) High throughput screening of 400,000 compounds from a corporate collection → 300 hits < 300 µM, 85 validated hits with IC_{50} <100 µM
= 0.021 % hit rate (many violate Lipinski rules)

b) Virtual screening of 235,000 commercially available compounds, using DOCK, version 3.5
→ 365 high-scoring molecules, 127 with IC_{50} <100 µM
= 34,8% hit rate (hits are more drug-like)

T. N. Doman et al., J. Med. Chem. 45, 2213-2221 (2002)

Stepwise Virtual Screening

Aventis in-house compound repository

↓ MW, rot-bond filter, 3D pharmacophore search

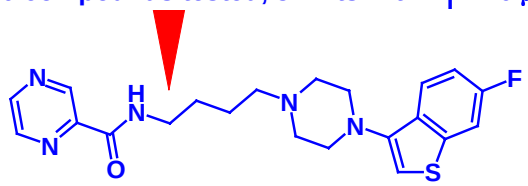
22,950 compounds

↓ docking into an α_{1A} receptor model (GOLD, PMF)

300 top-scoring compounds

↓ clustering, diversity selection

80 compounds tested, 37 hits with K_i < 10 µM



α_{1A} adrenergic receptor antagonist, K_i = 1.4 nM

A. Evers and T. Klabunde, J. Med. Chem. 48, 1088-1097 (2005)

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Virtual Screening of Carbonic Anhydrase Inhibitors

98,850 compounds (LeadQuest and Maybridge libraries)

↓ filter for Zn^{2+}-binding anchor groups

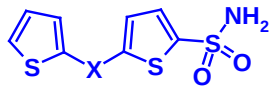
5,904 hits

↓ 2D and 3D pharmacophore searches (derived from binding site analysis)

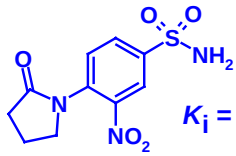
3,314 hits

↓ FlexS superposition with dorzolamide, followed by FlexX docking of 100 hits into carbonic anhydrase binding site

13 hits



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);
S. Grüneberg et al., J. Med. Chem. 45, 3588-3602 (2002).

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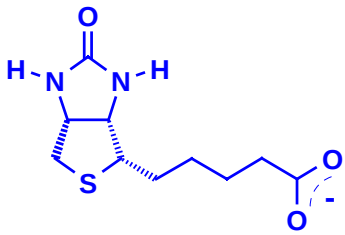
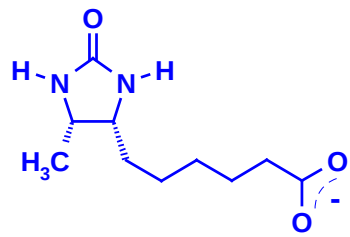
Binding Constants of Biotin and Analogs

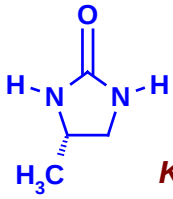
(N. M. Green, Adv. Protein Chem. 29, 85-133 (1975))



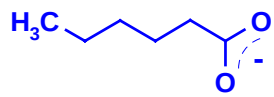
Biotin, $K_i = 1{,}3 \times 10^{-15}$ M



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



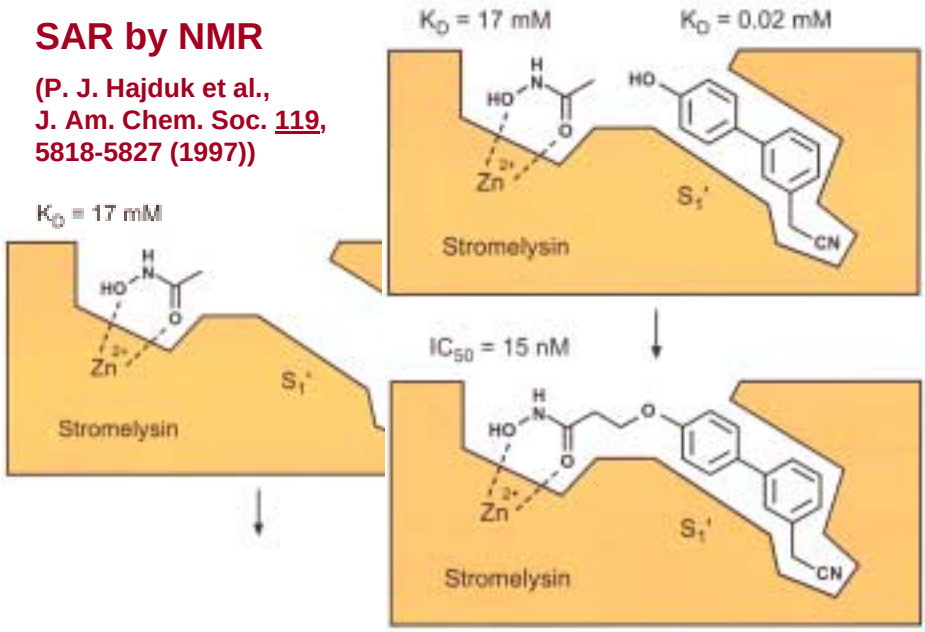
$K_i = 3{,}4 \times 10^{-5}$ M



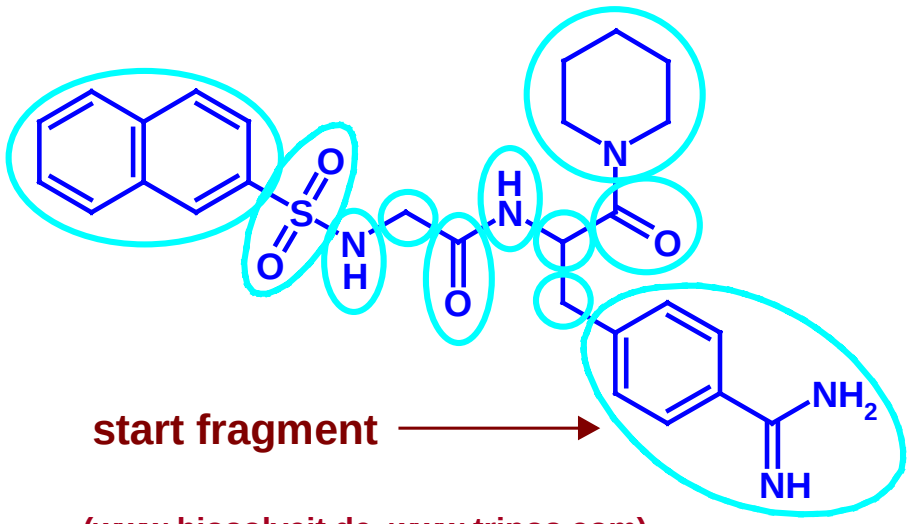
$K_i = 3 \times 10^{-3}$ M

SAR by NMR

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



FlexX (GMD, BASF): Dissection of a Ligand



(www.biosolveit.de, www.tripos.com)

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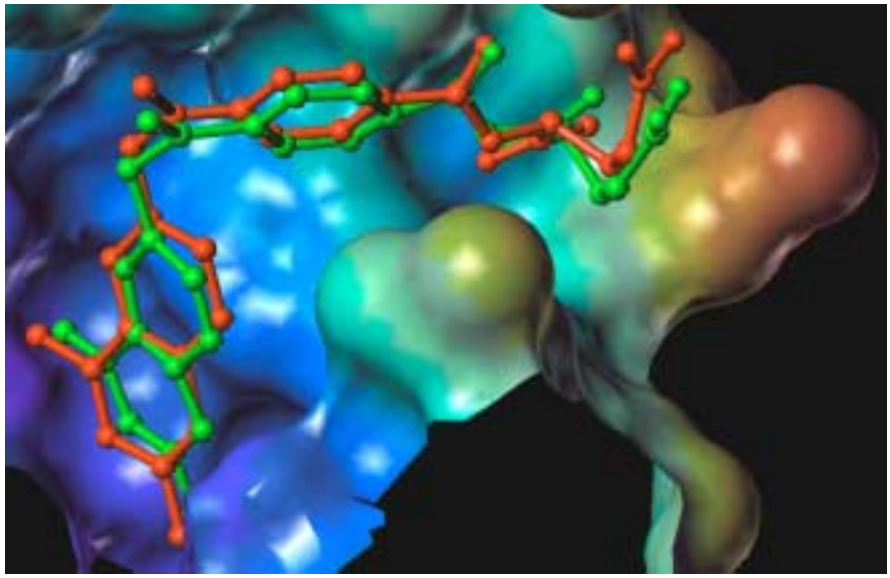
Binding of Methotrexate to DHFR



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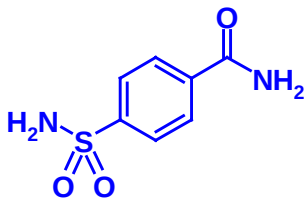
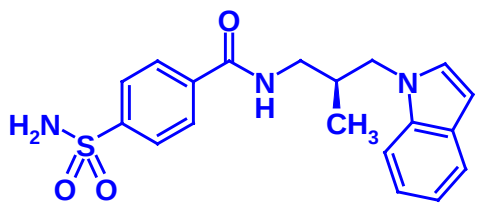
Combinatorial Design of Carbonic Anhydrase Inhibitors

start structure



K_d = 120 nM

optimized structure



R enantiomer, K_d = 30 pM

(*S* enantiomer: K_d = 230 pM)

Program CombiSMoG, selection of „best“ N-substituents from 100,000 candidate structures (20 of them 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)

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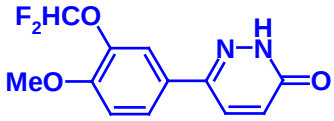
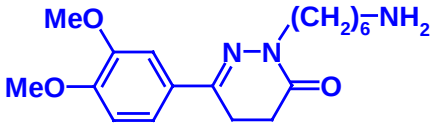
Scaffold-Linker-Functional Group Approach



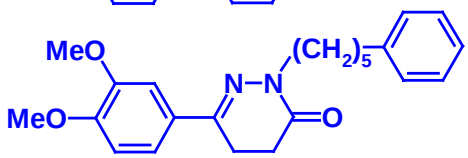
Zardaverine
IC_{50} PDE4 = 800 nM

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

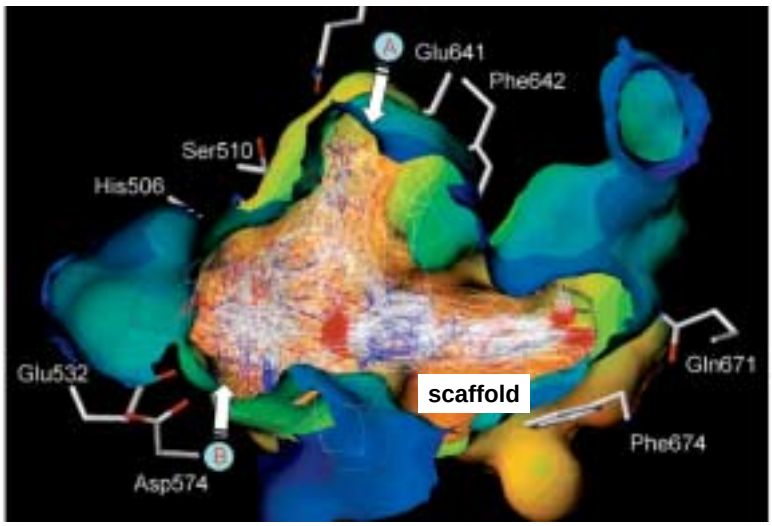


IC_{50} PDE4 = 0.9 nM

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

University of Heidelberg

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)

Voltaire, by J. A. Houdon

The Past

Voltaire (1694-1778):

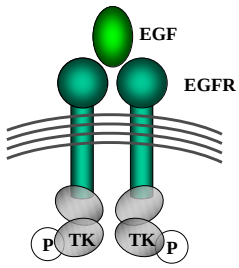
**Doctors
pour drugs of which
they know little,
to cure diseases of which
they know less,
into human beings
of whom
they know nothing.**

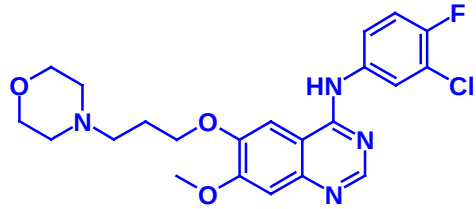
The Future: Pharmacogenomics - New Opportunities from Personalized Medicine

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**

Gefitinib®, Iressa, ZD1839 (EGFR TK inhibitor)





cell proliferation ⇧
apoptosis ⇩
angiogenesis ⇧
metastasis ⇧

third-line therapy for non-small-cell lung cancer (75% of lung cancer cases)

clinical response to Iressa ~ 10%

J. G. Paez et al.
EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy
Science 304 (5676), 1497-1500 (2004)

T. J. Lynch et al.
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer and Gefitinib
New Engl. J. Med. 350, 2129-2139 (2004)

8 out of 9 Iressa-responsive patients showed mutations in the kinase domain
0 out of 7 non-responsive patients showed mutations
2 out of 25 non-treated patients showed mutations (8%)