The Role of Chemoinformatics in the Design of a Comprehensive Drug Discovery Screening Collection

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Overview

- NIBR compound collection enhancement project
- External compound selection process
- Combinatorial library synthesis – scaffold projects
- Compilation of annotated knowledge-based sets
- Molecular Information System for pharmaceutical ligands
- Knowledge-based ligand design and virtual screening strategies
- Chemoinformatics: Quo Vadis?

Essential Properties of Compounds

Table 2 Essential Properties of Small Molecules at Different Stages of Pre-clinical Drug Discovery from Screening Compound to Investigational Drug Candidate. Adapted from Refs. 94–97 Information regarding the principles of the clinical selection and approval process can be found at the FDA Center for Drug Evaluation and Research (*http://www.fda.gov/cder/*). CYP450 (cytochrome P450), DMPK (drug metabolism and pharmacokinetics), DMSO (dimethylsulfoxid), GMP (good manufacturing practice), IP (intellectual property), PAMPA (partial artificial membrane permeability assay).

Essential Properties	Screening Compound	Hit-to-lead Compound	Lead Compound	Drug Candidate
Chemical properties	— Compounds from synthetic and natural paradigms including targeted and diversity-based design principles — Chemically pure or defined mixtures — Absence of undesirable functionalities impairing stability and chemical cross-reactivity — Fast back supply possible	— Compounds with confirmed chemical structure and purity — Essential SAR established by substructure and similarity searching — Potential for compound IP generation — Amenable for parallel optimization — Assessment of aggregation and chemical cross-reactivity	— Clear SAR — IP protected	— Chemical synthesis or natural products isolation process tractable for large scale industrial manufacturing according to GMP — Chemically stable
Receptor pharmacology		— Dose dependent activity in assays relevant for optimizations — Adequate potency in biochemical and cell-based assay — Adequate selectivity on key anti targets — Assessment of binding kinetics on target	— Nanomolar potency on isolated target — Submicromolar activity in functional assays — Demonstrated activity on paralogue targets in species for animal testing — Desired selectivity profile on key anti targets and safety pharmacology targets	— Knowledge of possible cross targets and possible adverse reactions based on receptor pharmacology

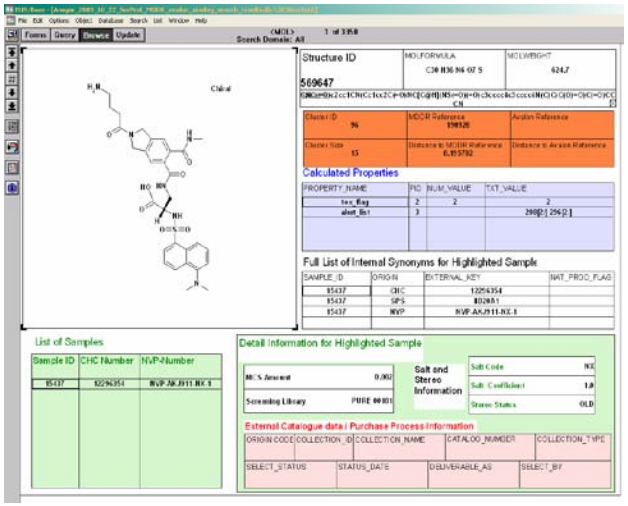
Essential Properties of Compounds - Continued

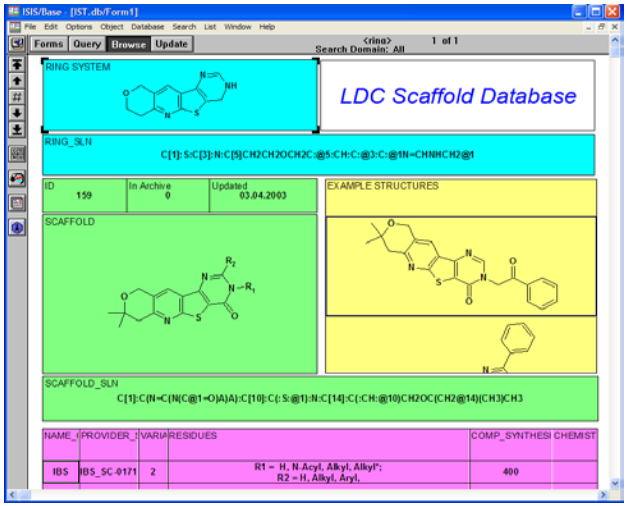
Table 2 (*Continued*)

Essential Properties	Screening Compound	Hit-to-lead Compound	Lead Compound	Drug Candidate
ADMET/DMPK	— Good water and DMSO solubility — Adequate permeability to reach site of action	— Physicochemical characterization: LogP, LogD, pKa, solubility, aggregation — Assessment of membrane permeability using: CACO-2, PAMPA — Assessment of metabolic characteristics: CYP inhibition in major isoforms to assess drug-drug interaction liabilities and intrinsic clearance in rat and human liver microsomes	— Understanding of key membrane transport mechanisms — Desired metabolic characteristics — Appropriate clearance, volume of distribution and half life in rat — Evaluation of genotox: AMES bacterial mutagenicty — Evaluation of HERG interference	— Identification of appropriate gallenic form for testing in animals — Metabolite profiling for each compound and assessment for reactive metabolite formation — Mammalian cell mutagenicity data — Understanding of *in vivo* ADMET properties, including tissue distribution an elimination properties — Dose escalation experiments and maximum tolerable dose in appropriate species — Decision for safe testing in human without impairing vital functions

Jacoby et al. Chemogenomics 2007, 1-38

Externally Available Chemistry Space





LDCStructuresDB

- Oracle and ISIS databases in place
- 10.000.000+ Unique structures
- 13.000.000+ Catalogue entries
- 130+ Collections
- 50+ Vendors

LDCScaffoldDB

- Oracle and ISIS databases
- 18.000+ Unique scaffolds
- 15 Vendors

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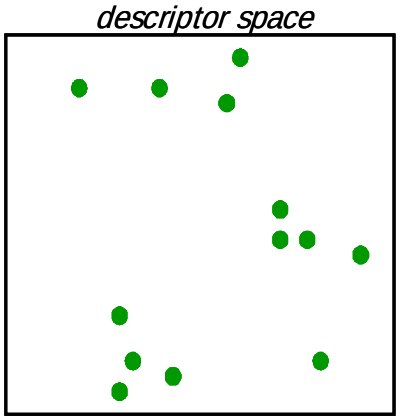
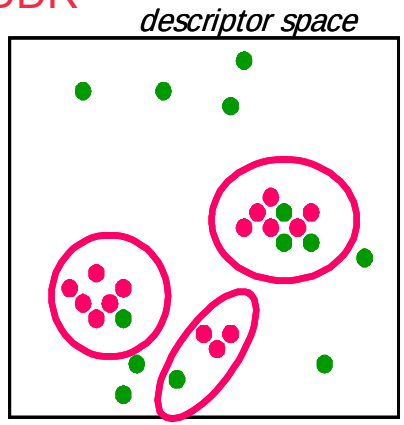
Chemistry, Biology, Informatics Based Compound Selection

0. The existing archive



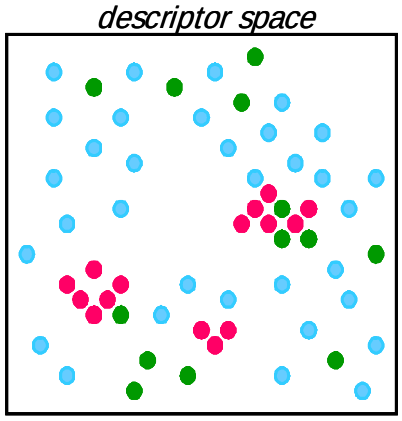
Similar to Know MDDR Actives and Drugs

1. Select from container 1: (target family related affinity) high density, similarity <= 0.95



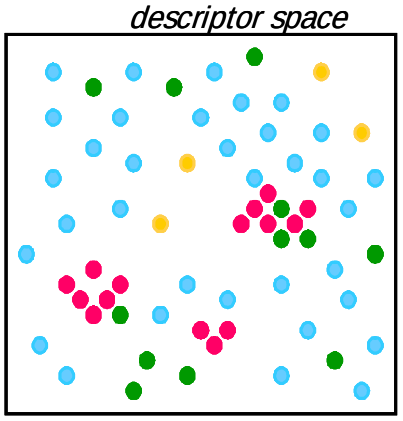
Diverse Drug Like

2. Complete selection by with compounds from container 2: (average structures) average density, similarity <= 0.88



Penalized

3. Fill gaps with compounds from container 3 (penalized structures): lower density, similarity <= 0.80



Jacoby et al. Curr Top Med Chem. 2005, 5, 397-411

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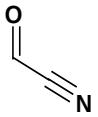
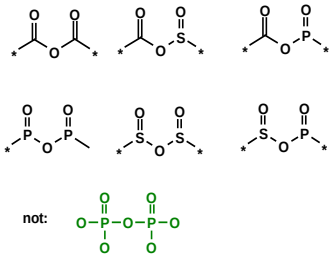
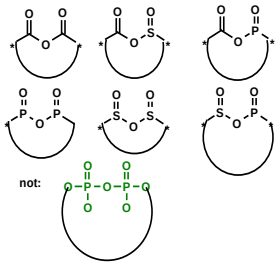
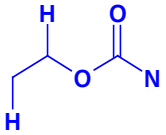
Substructure/Fragment Filters

Definition of the Exclusion-Criteria:
A: Don't store in MCS
B: Don't produce as solution or store in SOLAR
C: Don' buy (but take for free)

ID	Archive Exclusion Flag	Structure	Chemical Description	Toxic	Reactive	Uninteresting
33	A		carbonic acid nitriles	Y	Y	N
34	A		acyclic acid anhydrides including phoshonates and phosphinates, but not di- and triphospates	Y	Y	N
35	B		cyclic acid anhydrides including phoshonates and phosphinates, but not di- and triphospates	Y	Y	N
36	C		acyclic alkyl carbamates	Y	N	N

In Silico Substructure Tox Alerts

InSilico ToxCheck [v3.0]

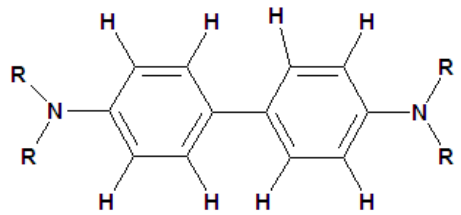
brought to you by the *Cheminformatics* group

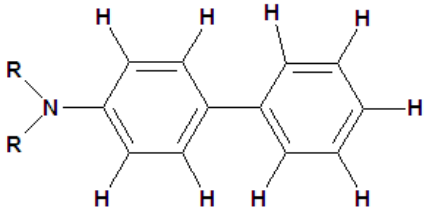
ToxInfo **Edgar Jacoby (09 Aug 2007 14:28:56)**

Alert 209

Alert level: 1

4-Aminodiphenyl, benzidine or precursors (AROMATIC_AMINE)





R: H or non sp3 carbon

Toxicological concerns:

-1- Carcinogenicity
This alert fires for N-derivatives of benzidine or 4-aminodiphenyl. 4-
mutagenic in vitro and in vivo in diverse mammalian and bacterial t
-2- Mutagenicity
see comment for carcinogenicity

InSilico ToxCheck [v3.0]

brought to you by the *Cheminformatics* group

ToxInfo **Edgar Jacoby (09 Aug 2007 14:30:46)**

Alert 209 - Carcinogenicity

This alert fires for N-derivatives of benzidine or 4-aminodiphenyl. 4-Aminobiphenyl and benzidine are carcinogenic to humans (IARC Group 1). Both compounds have been shown to be mutagenic in vitro and in vivo in diverse mammalian and bacterial test systems. Following its oral administration, 4-aminobiphenyl induced bladder papillomas and carcinomas in rabbits and dogs, and neoplasms at various sites in mice, including dose-related increases in the incidences of angiosarcomas, hepatocellular tumours and bladder carcinomas. Following its subcutaneous administration to rats, it induced tumours of the mammary gland and intestine. Following oral administration of benzidine, significant increases in the incidences of benign and malignant liver neoplasms were observed in mice and hamsters and of mammary cancer in rats; benzidine induced bladder carcinomas in dogs. Following subcutaneous administration of benzidine to rats, a high incidence of Zymbal-gland tumours was observed. After intraperitoneal administration of benzidine to rats, a marked increase in the incidence of mammary gland and Zymbal-gland neoplasms was observed.

Pageowner: Joerg Muehlbacher

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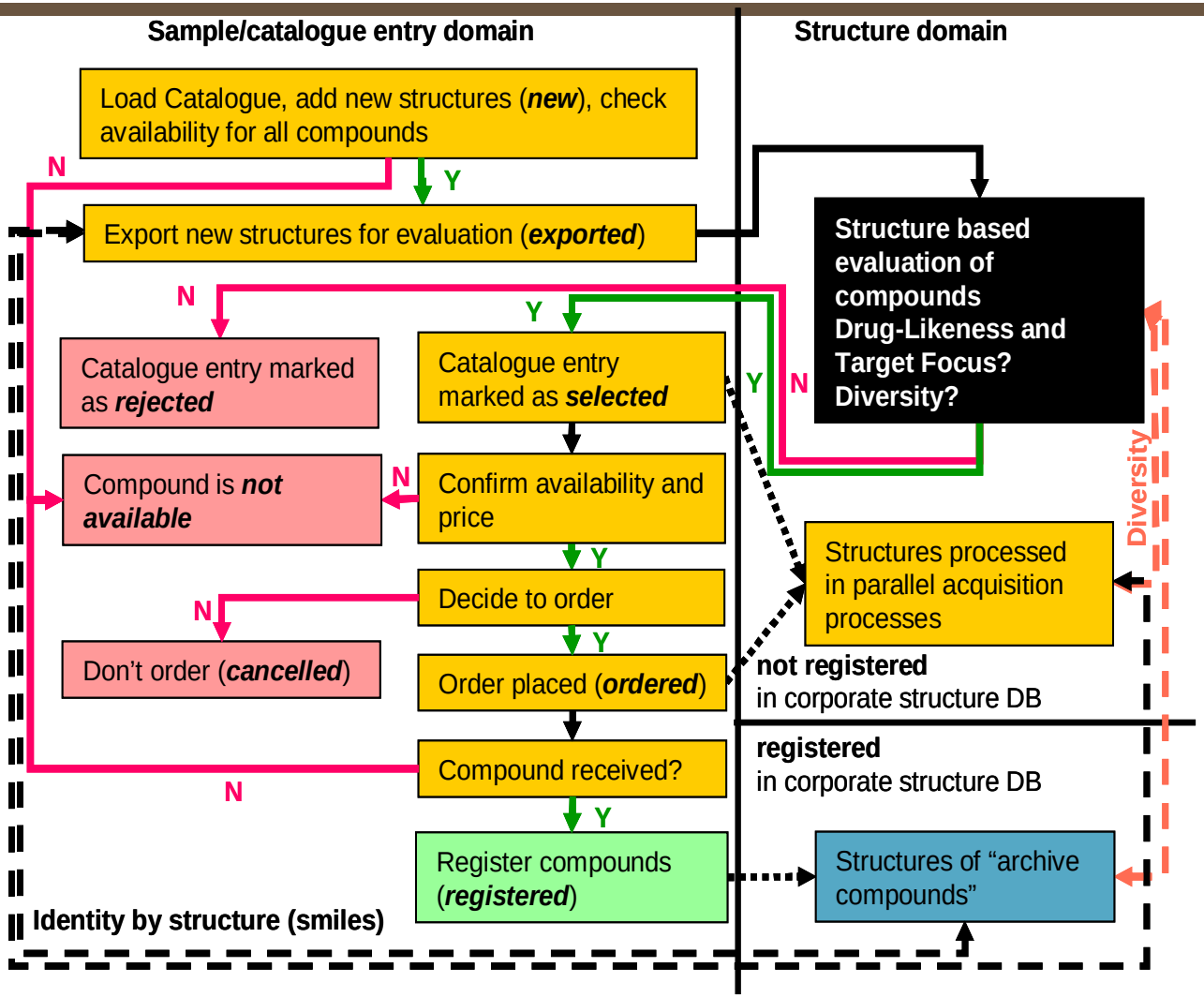
Cheminformatics Platform for Selection and Logistics



Schuffenhauer, A. *et al*. *Comb. Chem. High Throughput Screen. (2004), 7,* 771-782.

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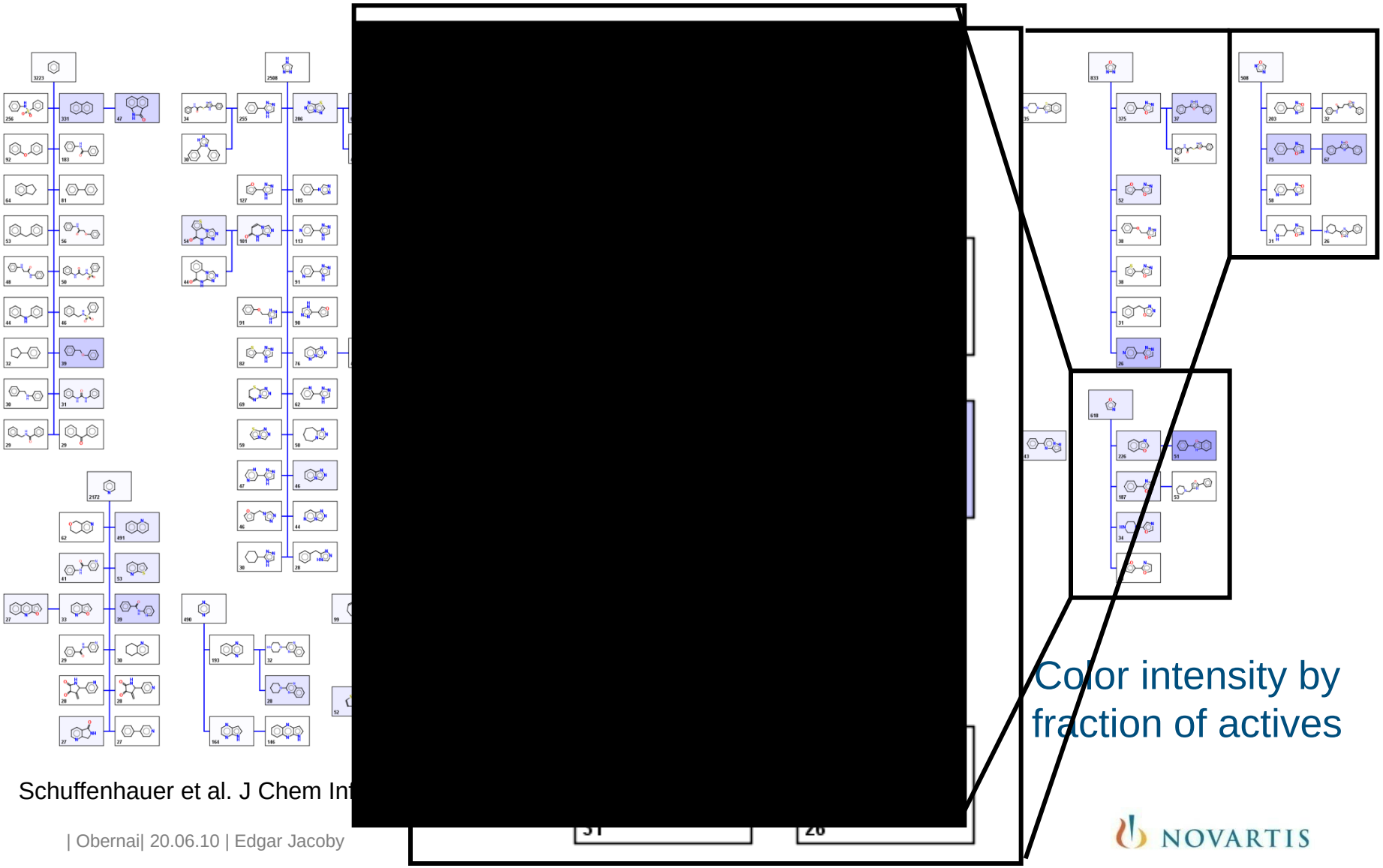
Scaffold Tree Example for HTS Results

PubChem Pyruvate Kinase Data Set



Color intensity by fraction of actives

Schuffenhauer et al. J Chem Inf

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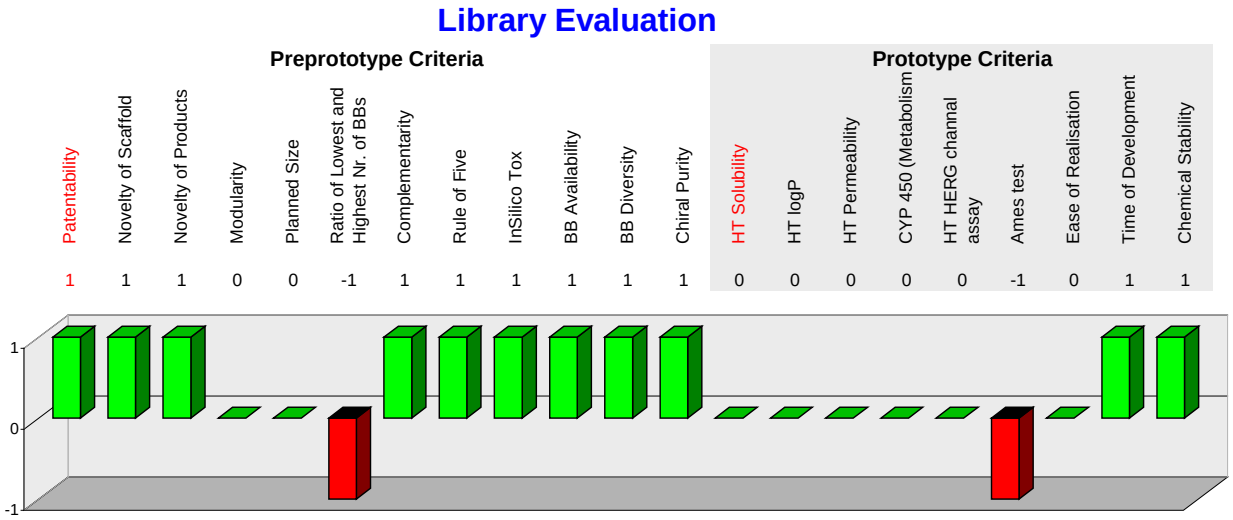
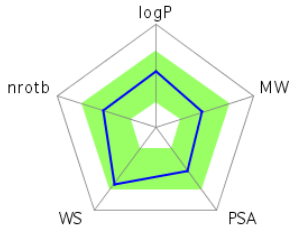
Evaluation Scheme for Combinatorial Hit Discovery Libraries

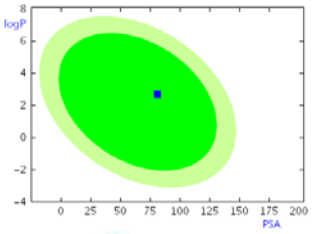
2004



2007

novelty	**target focus**	**synthetic complexity**	**potential for HLO**	**computed properties**





Jacoby et al. Curr Top Med Chem. 2005, 5, 397-411

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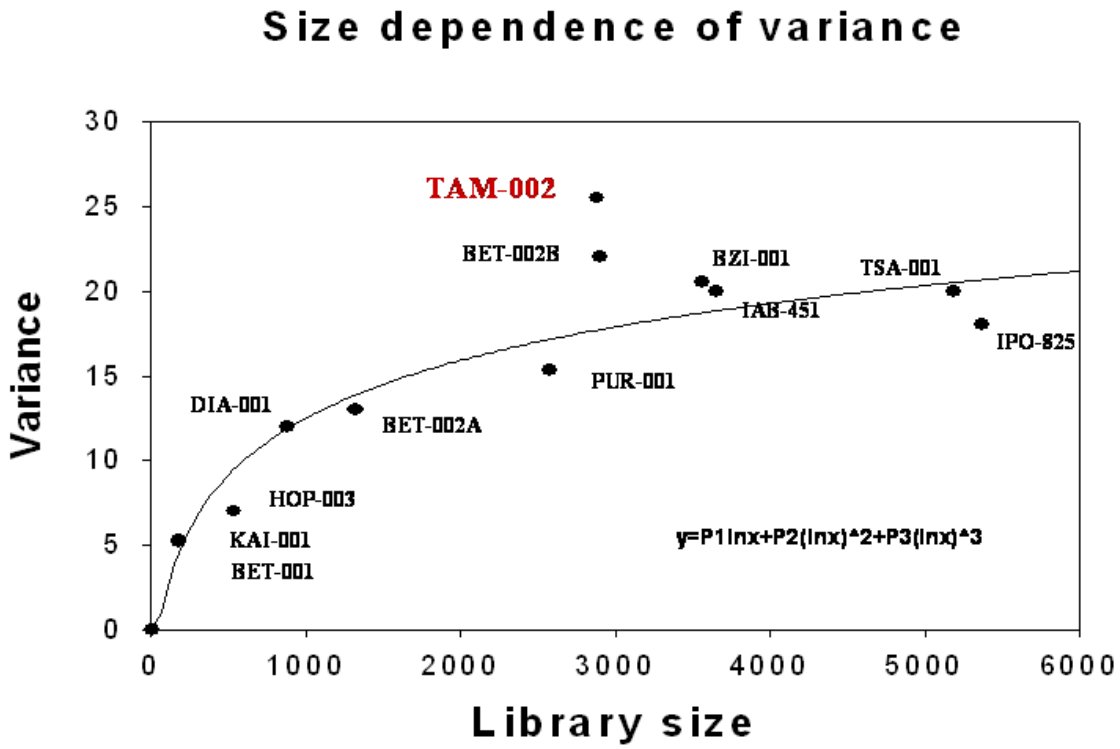
The Ideal Size of Combinatorial Libraries



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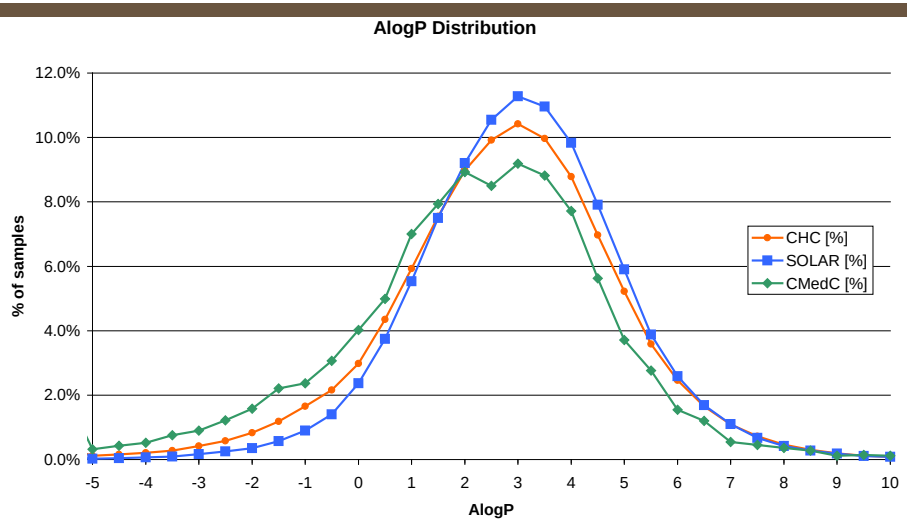
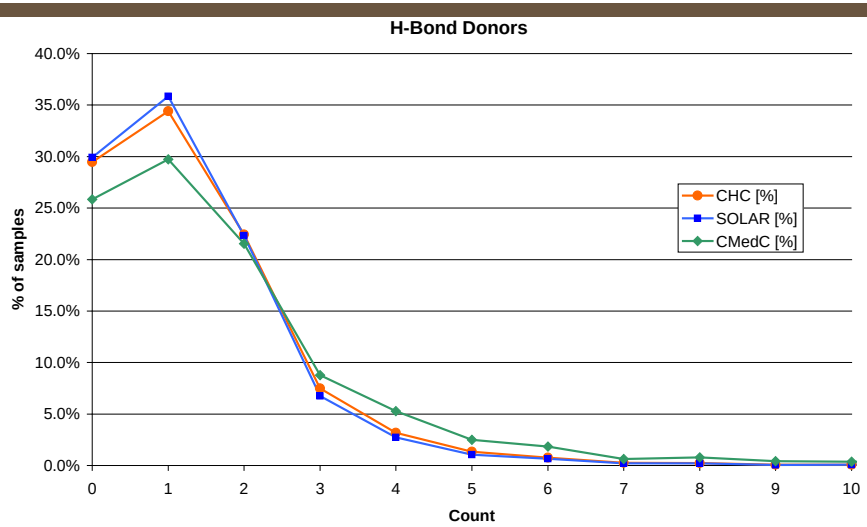
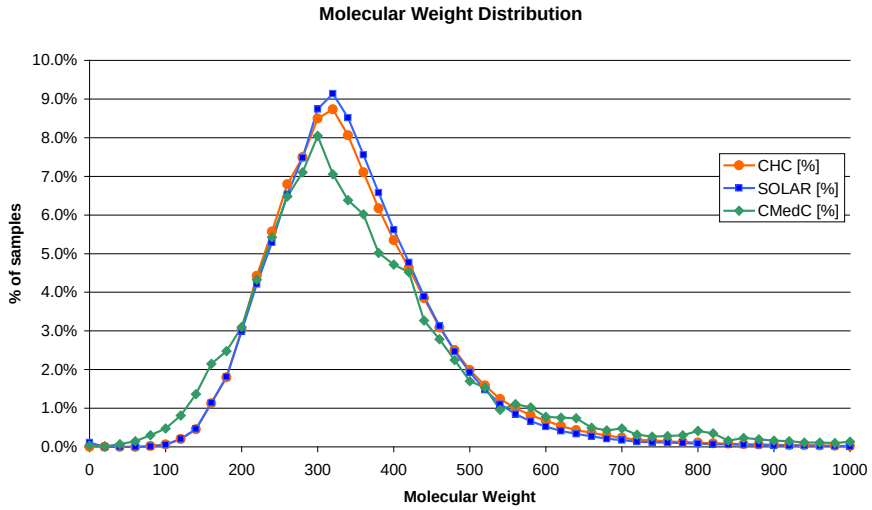
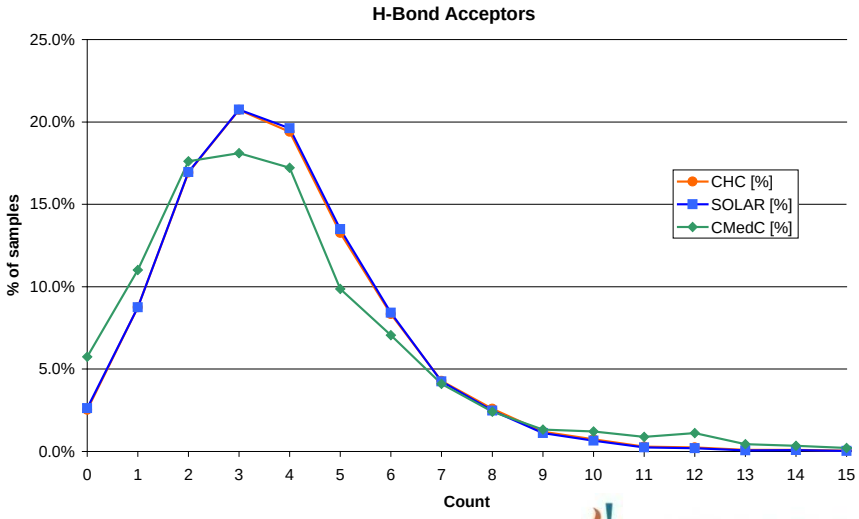
Monitoring of Compound Collections - Lipinski Profiles









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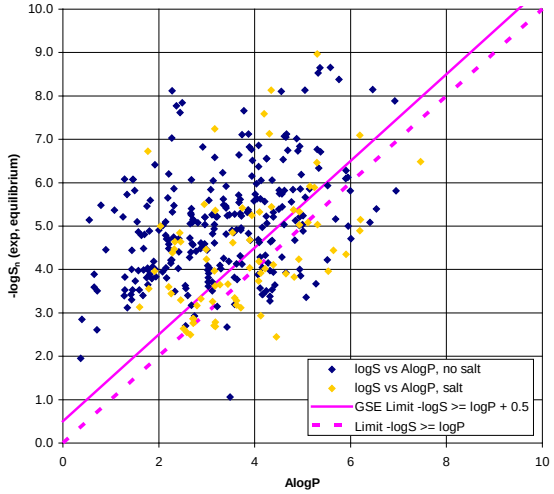
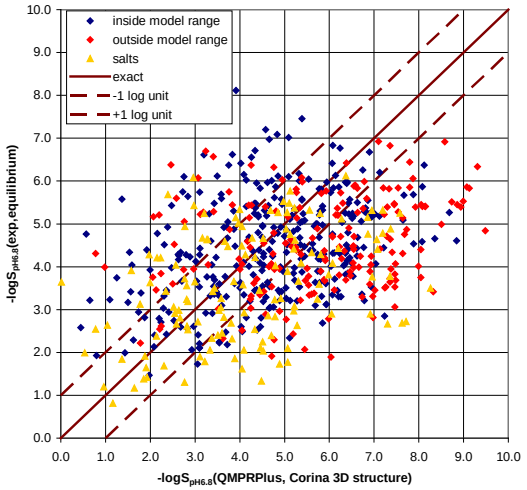
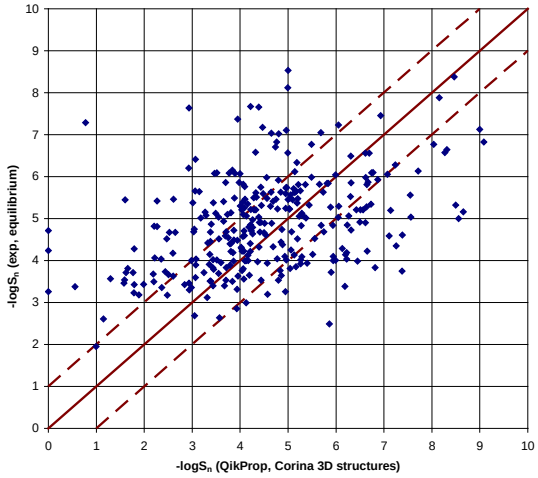
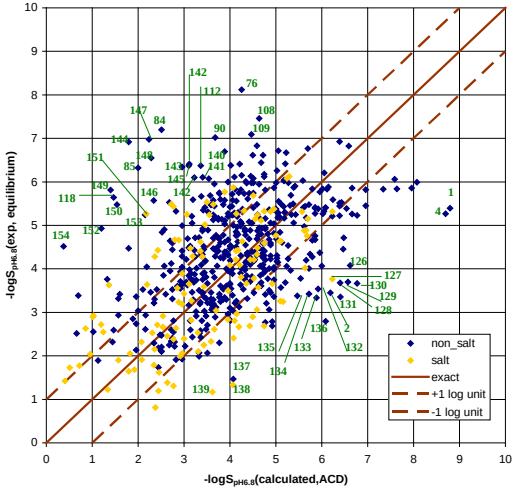
Prediction of Water Solubility









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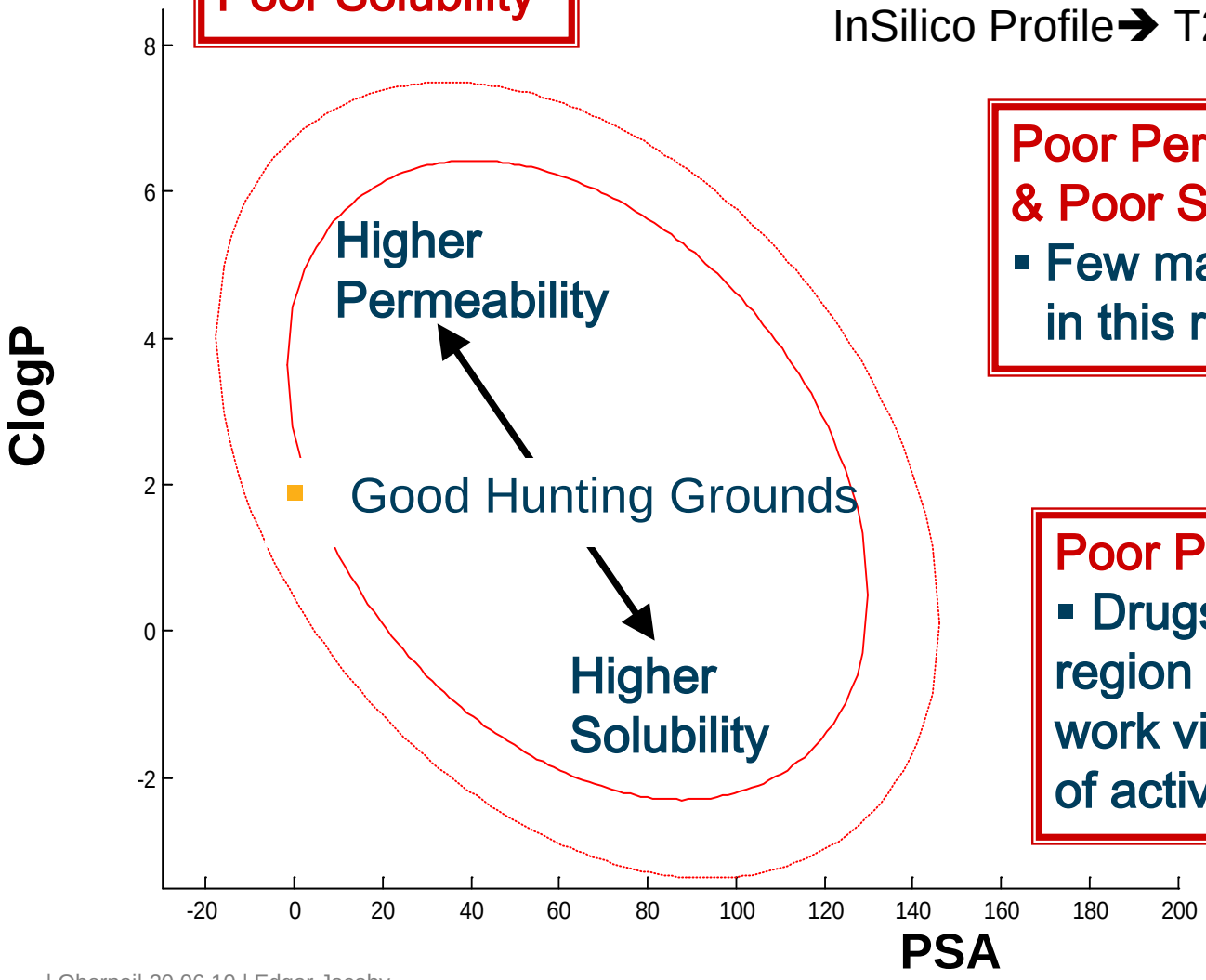
The “Egan Egg”: Statistical Prospectively Useful Model

Poor Solubility

Access Egan Egg via IsisDraw➔
InSilico Profile➔ T2ABS plot



Poor Permeability & Poor Solubility
- Few marketed drugs lie in this region

Poor Permeability
- Drugs in this region usually work via prodrugs of active transport

WJ Egan et al, JMC, 2000

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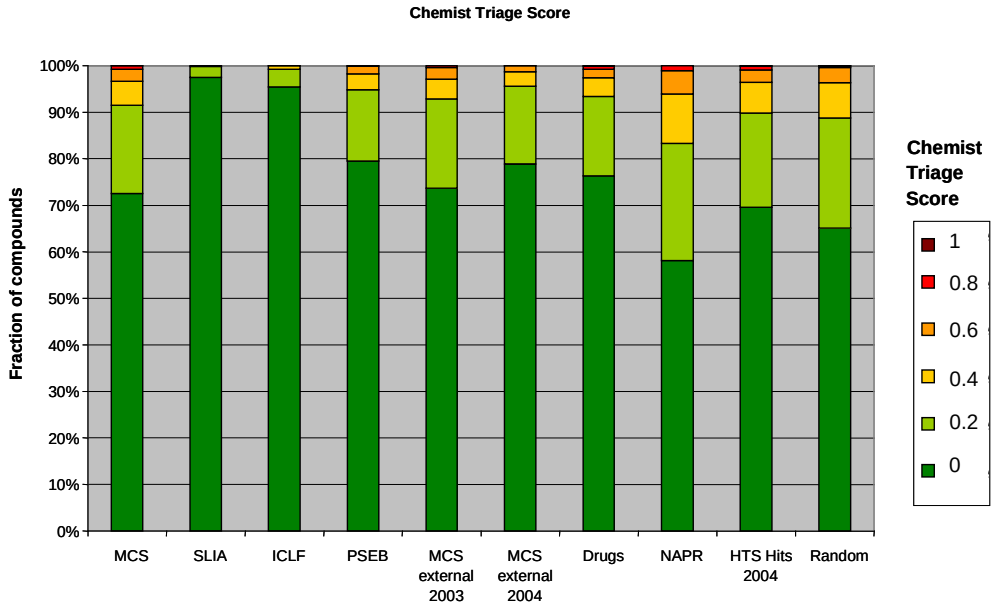
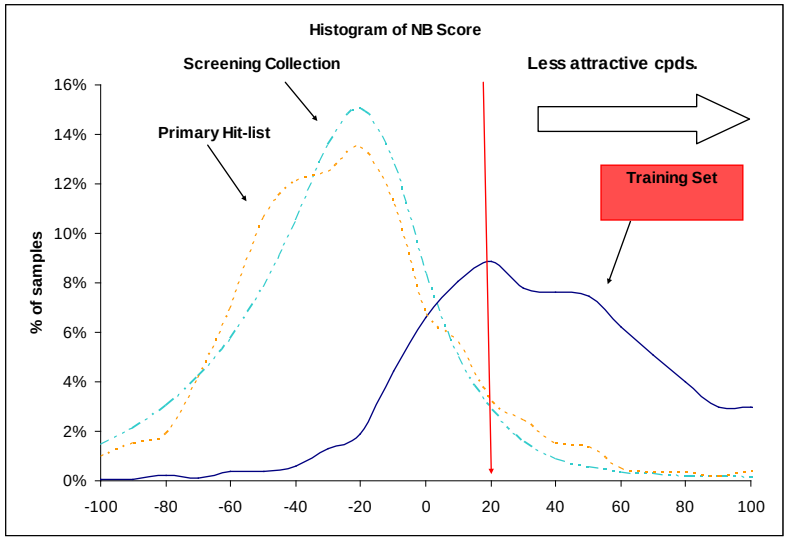
Chemist Triage Score and Naïve Bayesian Models

- Yes/No decision from five individual triaging exercises taken to build one Bayesian models
- All five models are used in a consensus score, fraction of models voting against the molecules





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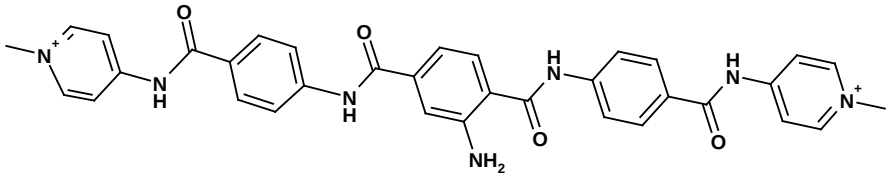
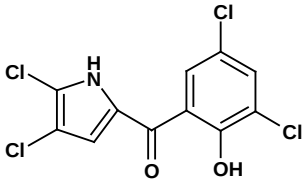
Examples of Unwanted Molecules

ChemistTriageScore: Excluded



1.0



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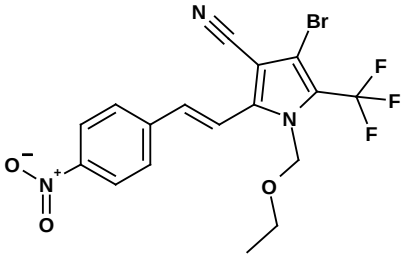

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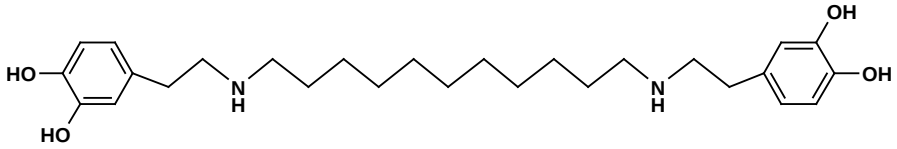
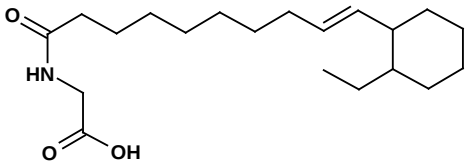
Similog density: Excluded

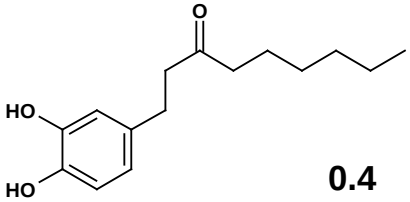


0.0012



0.0017

ChemistTriageScore: Penalized



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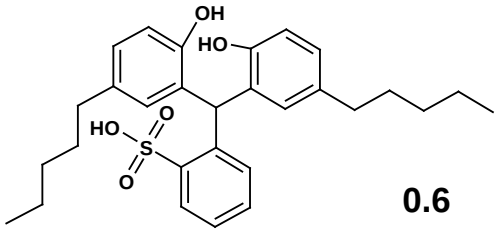
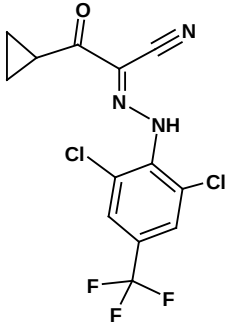


0.6



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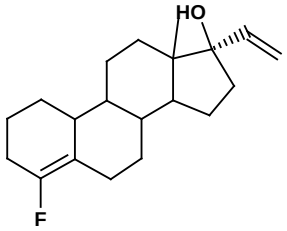
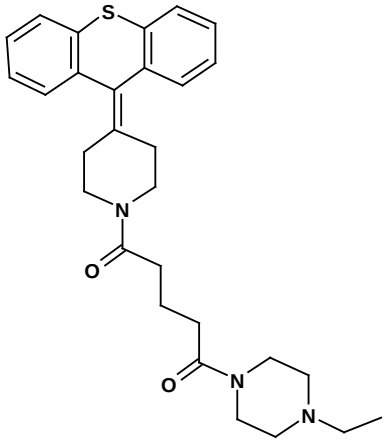
Similog density: Penalized



0.0029



0.0036

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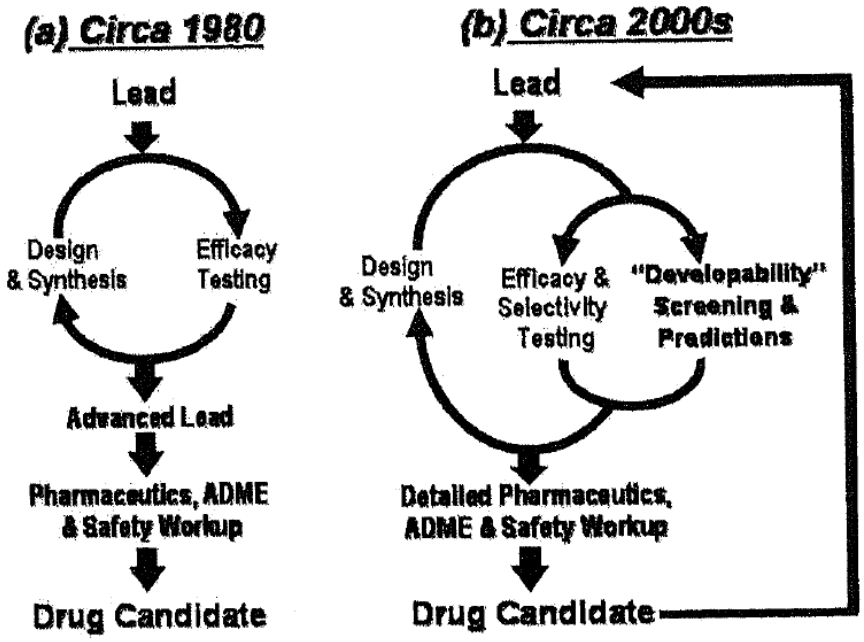
The Challenge of Quality in Candidate Optimization



Assay Type	Cpd #s	Predictivity
In Silico Screen	10^6	Lowest
In Vitro Profiling Screen	10^3	
In Vitro Secondary Assay	Hundreds	
In Vivo Assay	Tens	Highest

Biller S. et al. Biotechnology: Pharmaceutical Aspects, 2004, 413-429.

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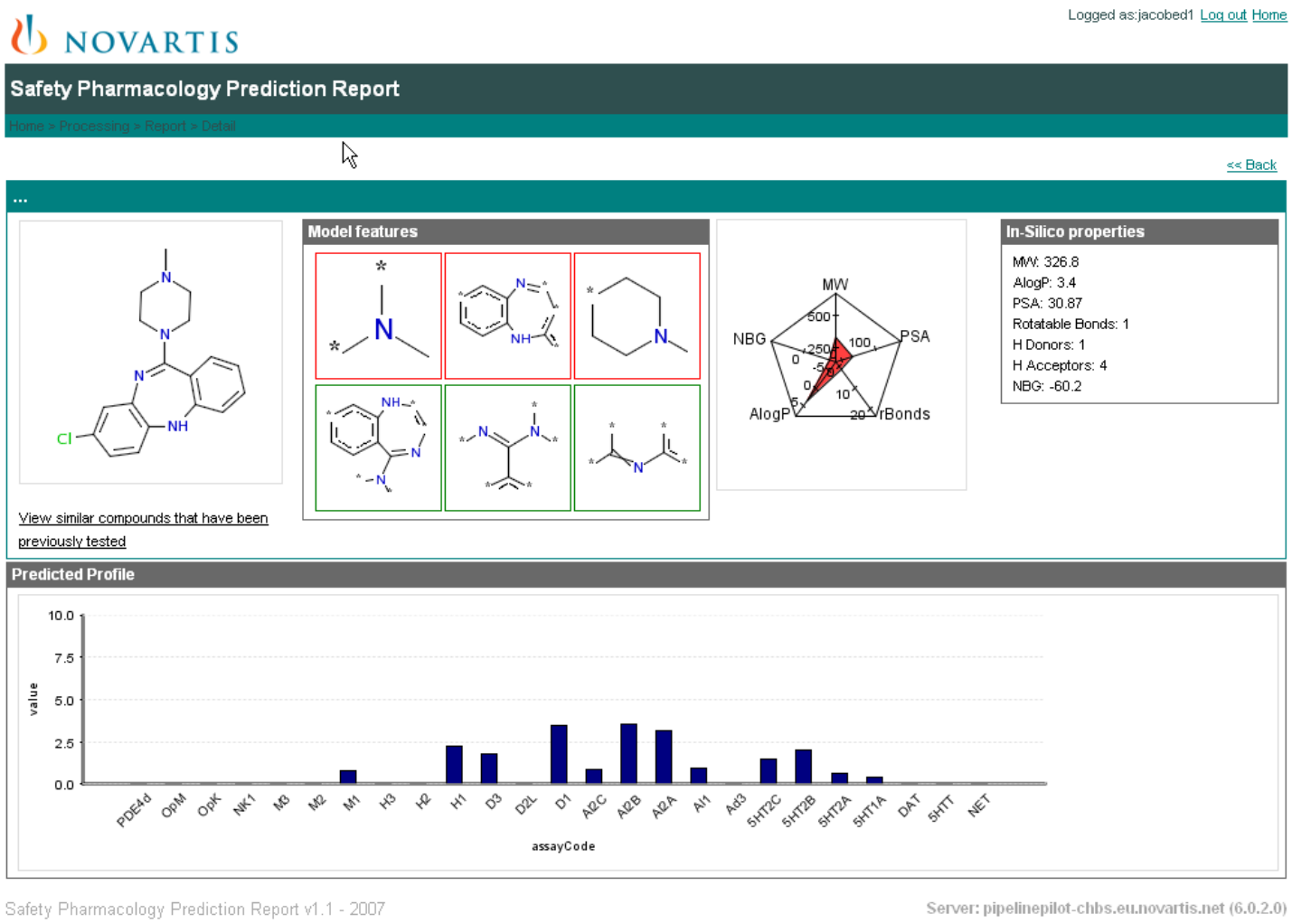
Safety Pharmacology Prediction



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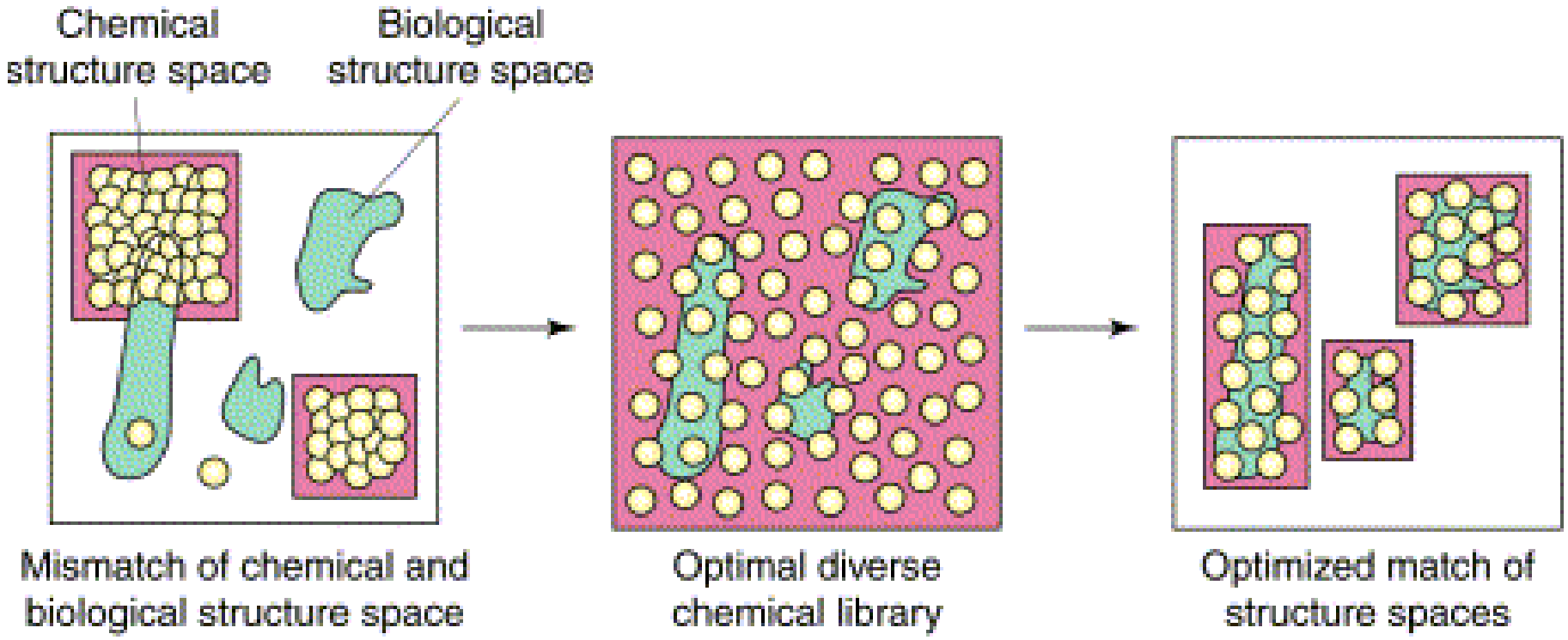
Which Annotated Compound Libraries Make Sense ?

1. Approved drugs – FDA orange book - SOSA
2. Other reference compounds (USAN, INN) with known bioactivity (Tocris, Prestwick, etc.)
3. Compounds processed by profiling
4. Primary metabolites, natural products and derivatives (KEGG, etc.)
5. Target family focused libraries
6. Diversity selection – DOS / BIOS
7. Protein mimetics library: β-turn/α-helix mimetics
8. Fragment library for NMR/Xray screening

Focusing : Optimizing the Overlap Between Chemical and Biological Spaces



Wess DDT 2002, 7, 533-535

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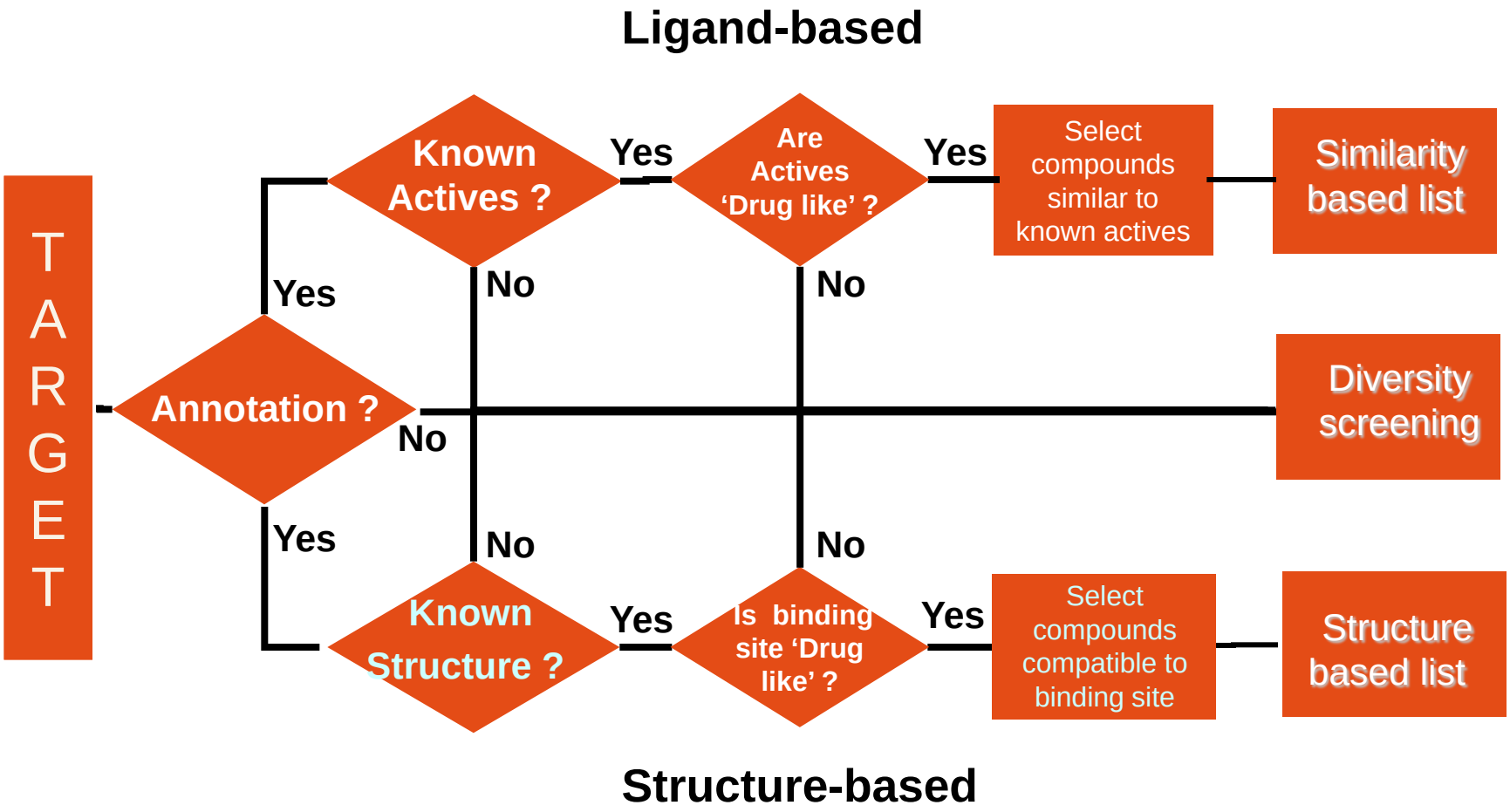
Knowledge-Based Virtual Screening



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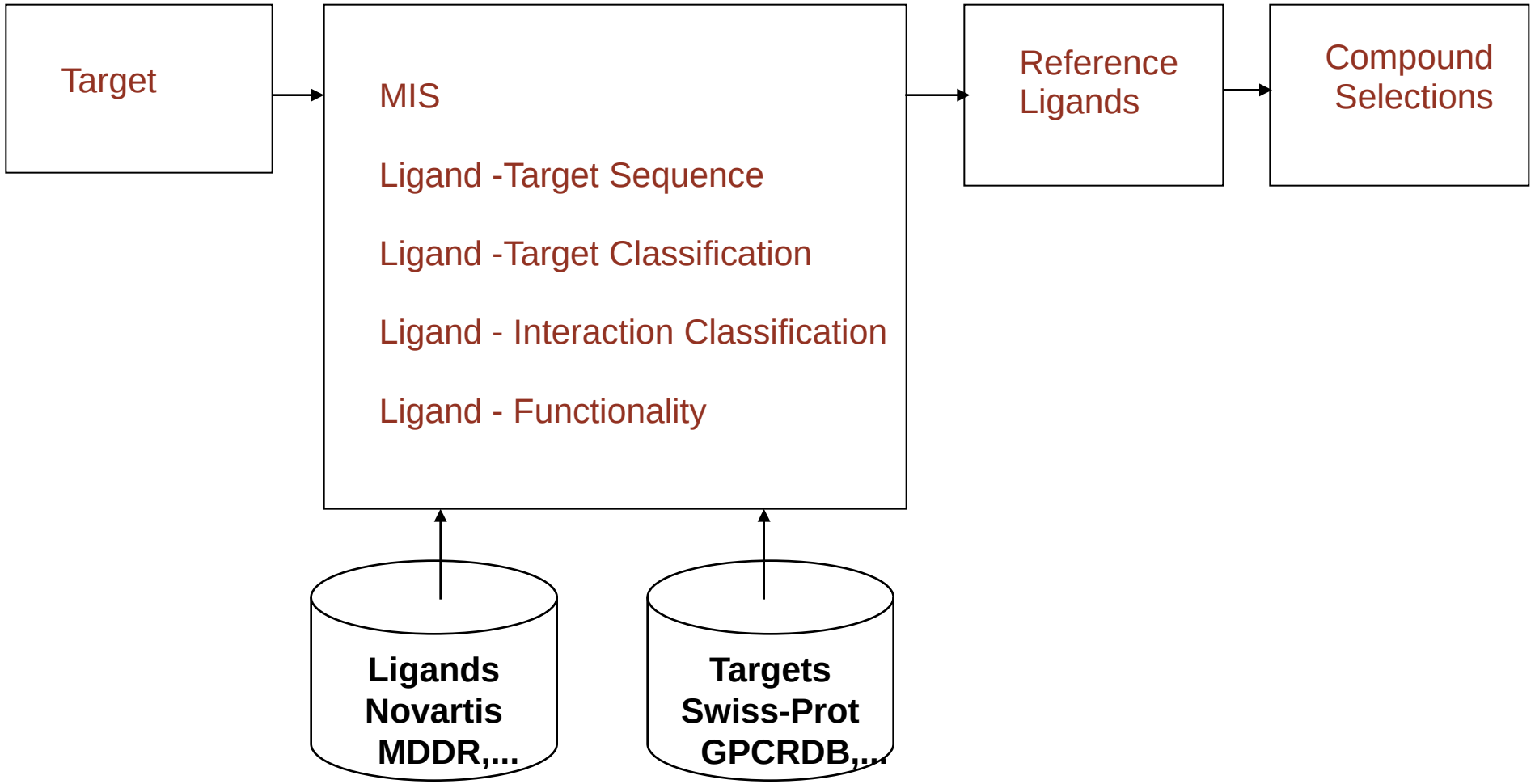
Molecular Information System for Pharmaceutical Ligands of the Main Target Families



Schuffenhauer, A. and Jacoby, E. *BioSilico* (2004), 2, 190-200

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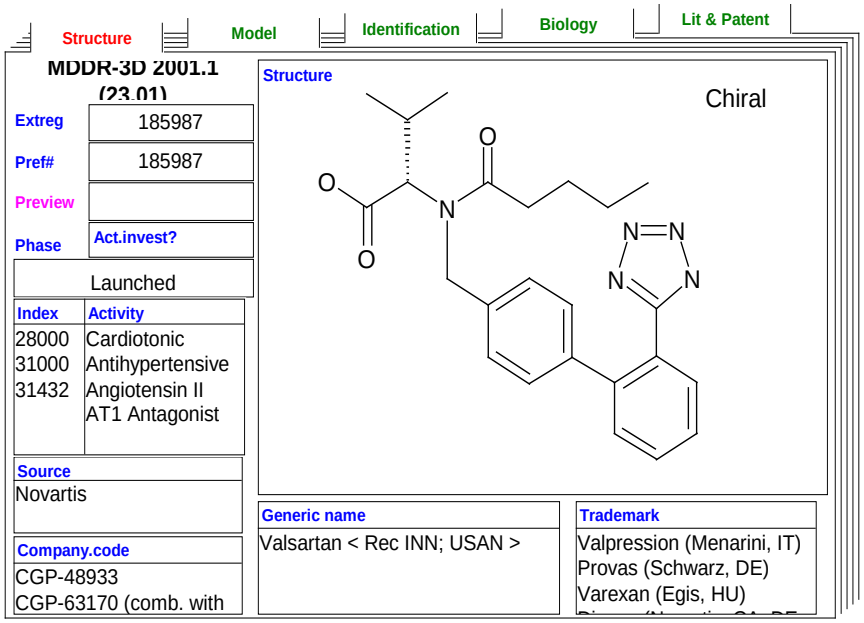
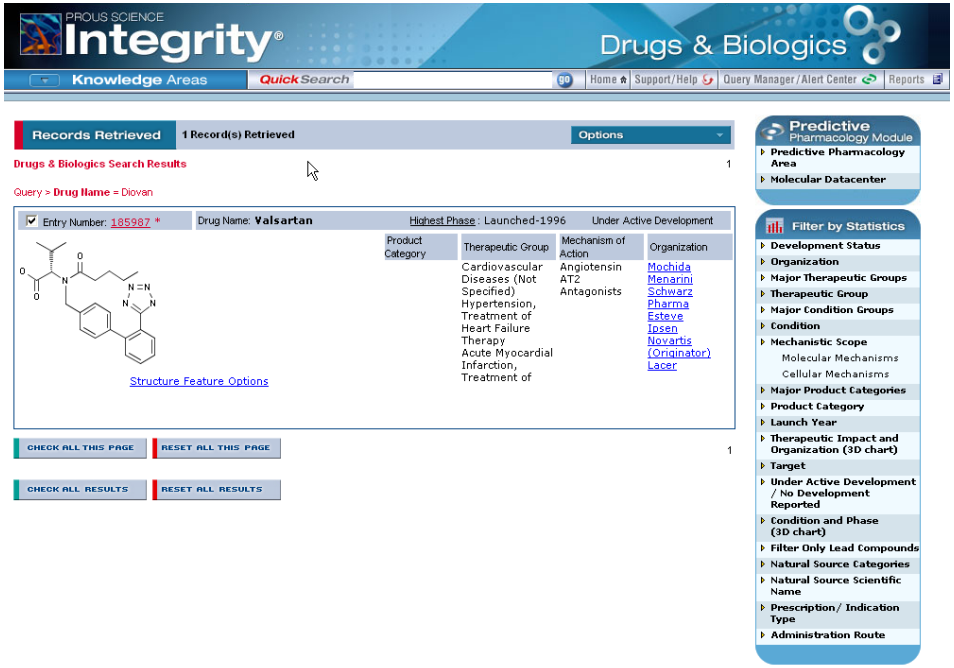
Databases of Known Pharmaceutical Ligands and Drugs





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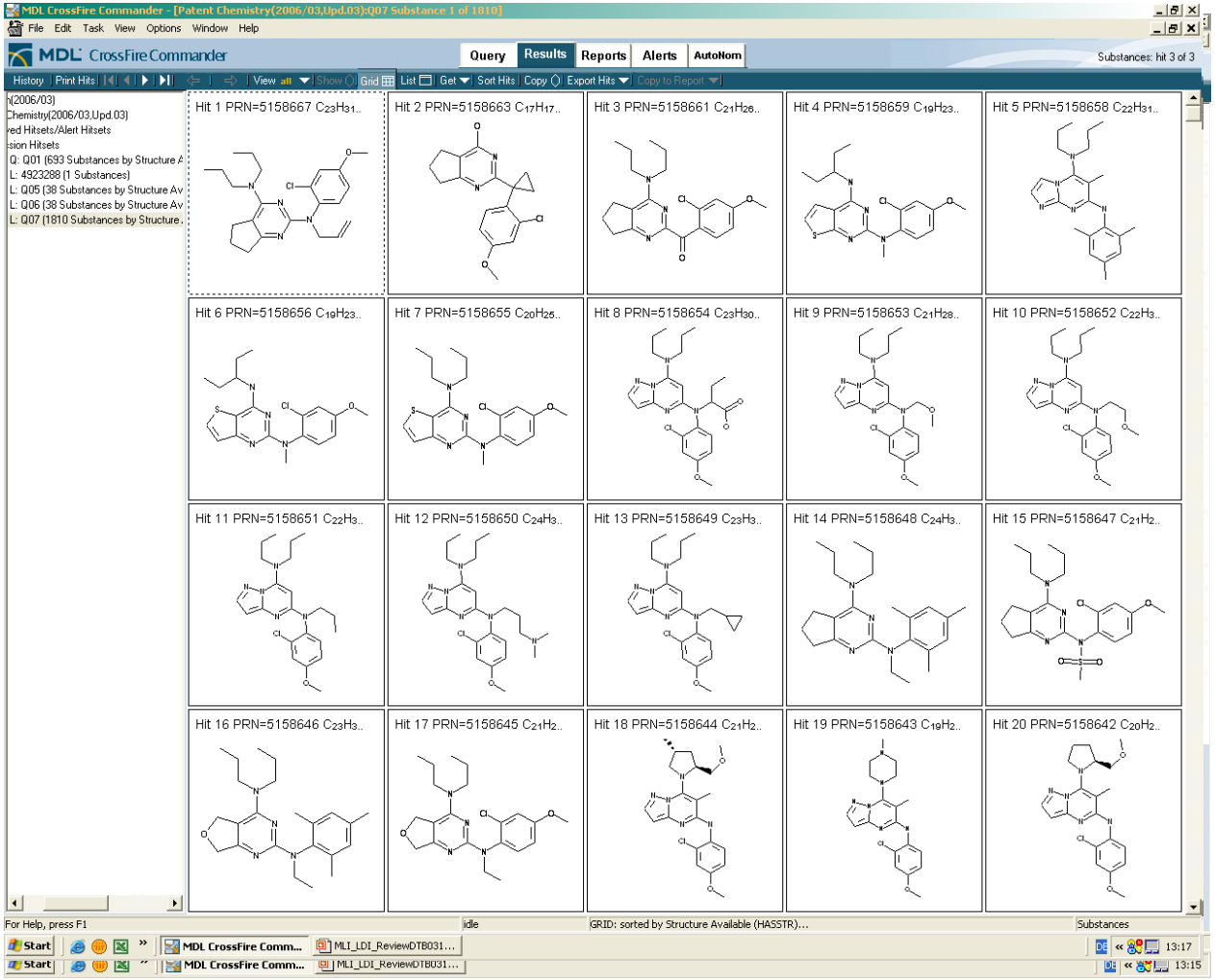
Knowledge Based Approaches : GPCR I

MDL Patent Database



Activity Based Search

⇩

38 Patent Families

⇩

1810 Reference Structures

⇩

Similarity Search

Naïve Bayes Model

⇩

542 SOLAR in silico hits

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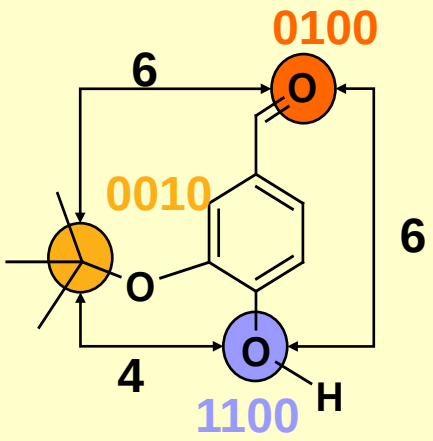
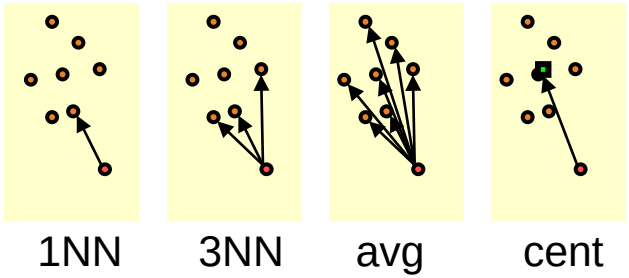
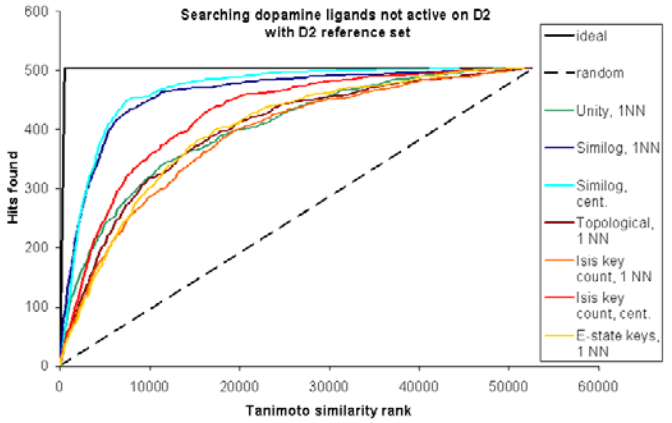
Similarity Searching using Similog Keys

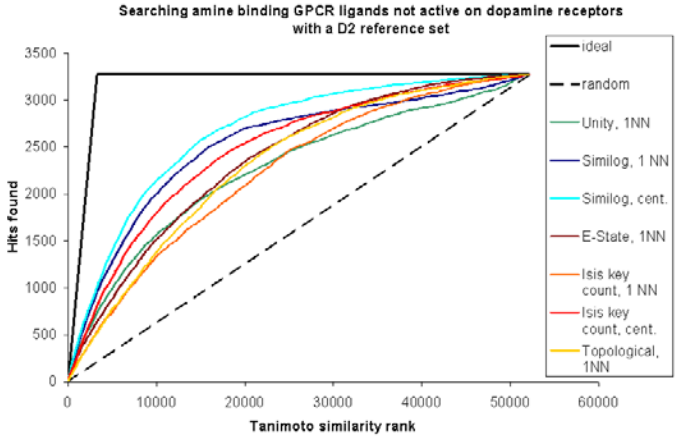
P. Floersheim's Similog keys
counts of DABE triplets in 2D space



0010-4-1100-6-0100-6-







Schuffenhauer, A. *et al. J. Chem. Inf. Comp. Sci. (* 2003), 2, 391-405.

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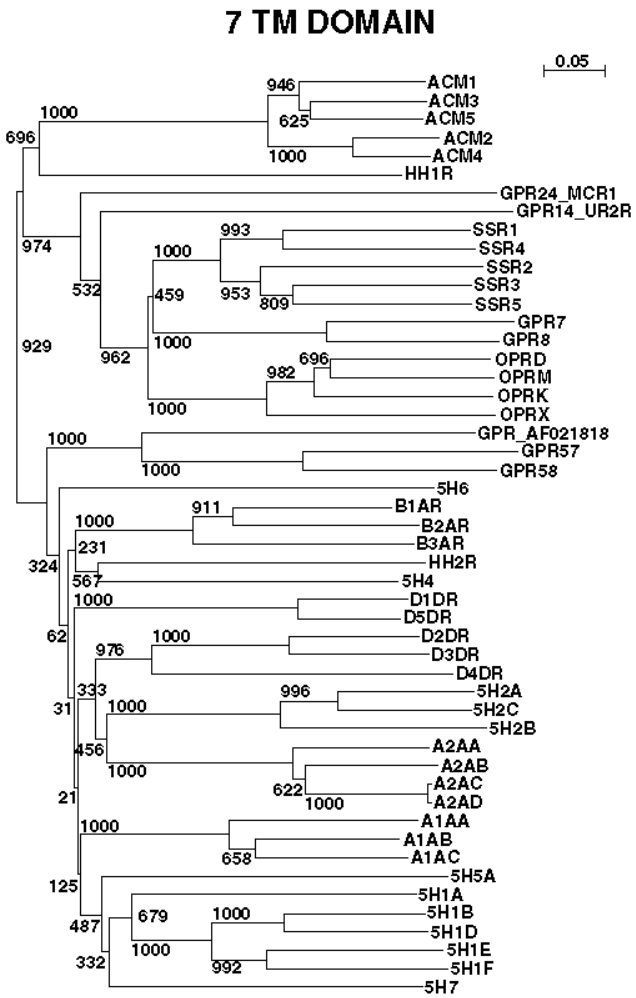
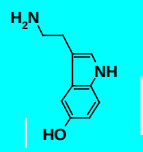
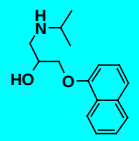
Design of TAM Libraries for Monoamine-Related GPCRs



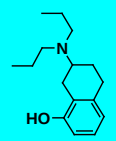
Known Reference Architectures



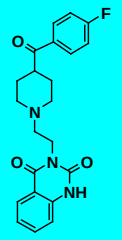
Serotonin
5HT ago.



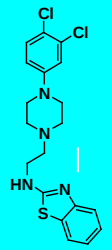
Propranolol
β antago.



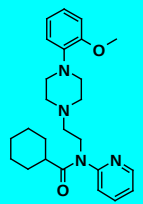
8-OH-DPAT
5HT1A part. ago.



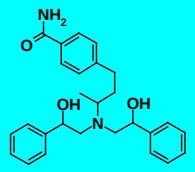
Ketanserin
5HT2A antago.



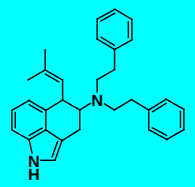
Janssen_1
D4 antago.



WAY-100635
5HT1A antago.

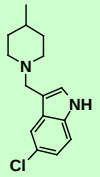


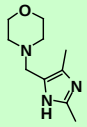
RO-16814
β ago.

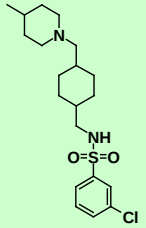


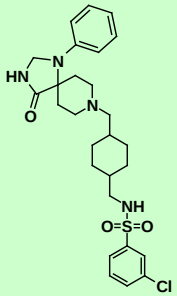
Kissei_1
D2 antago.

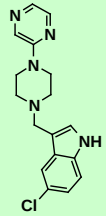
Novel Prototypes

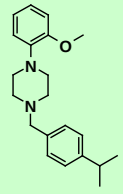




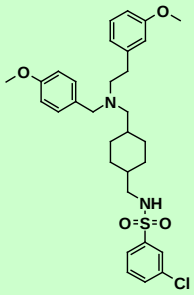


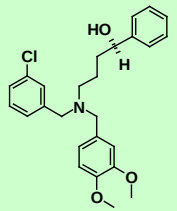






5HT7 antago.
pKB = 7.25





Jacoby, E. *Quant. Struct. Activity. Relations.* (2001) 20, 115-123.

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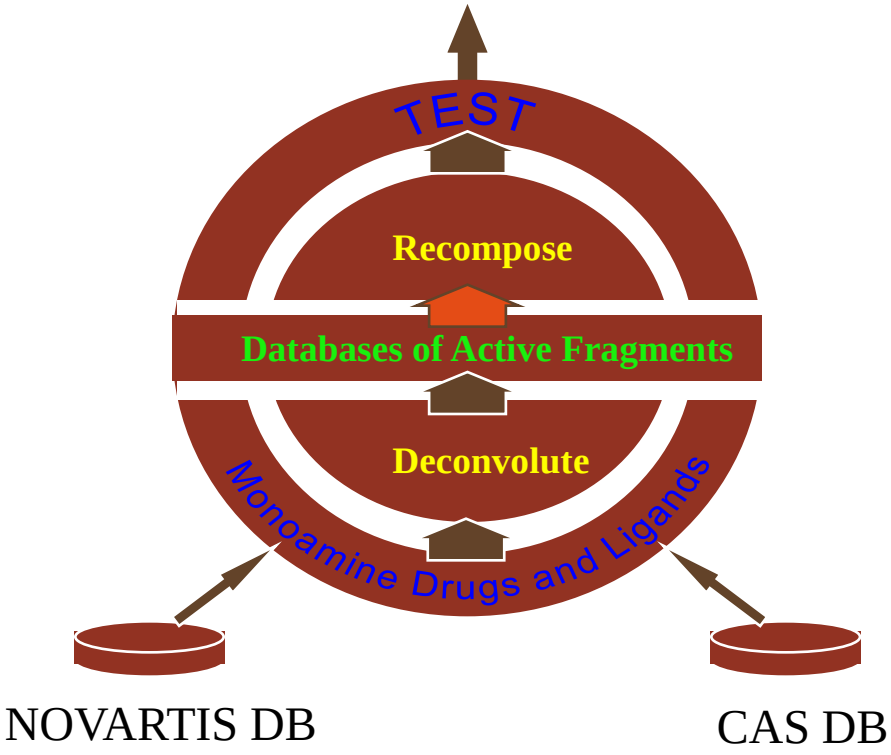
Deconvolute and recombine : Drug like molecules

Currently applied knowledge-based strategy

New Leads + New Affinity Profiles



Jacoby *et al.* Drug News Perspect. (2003),16, 93-102.

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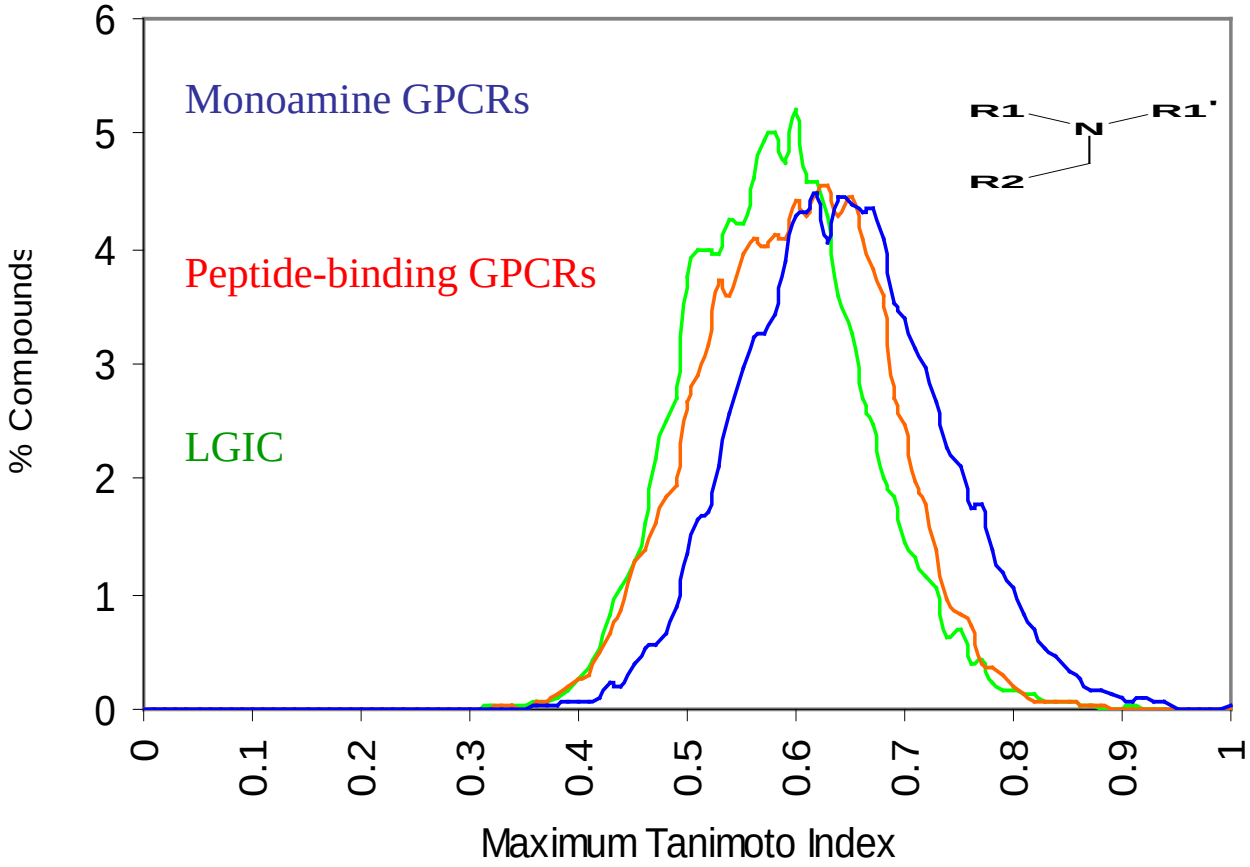
Ligand selectivity in a subfamily with conserved molecular recognition

pKi	α2A	α2B	α2C	β1	β2	D2.L	D3	D4.2	5HT1A	5HT1D	5HT1E	5HT1F	5HT2A	H1
Sumatriptan	< 6	< 6	< 6	< 6	< 6	< 6	< 6	< 6	6.4	8.4	< 6	7.8	< 6	
Alniditan	7.4	6.8	7.7	< 6	< 6	< 6	6.5	7.1	8.4	9.4	6.6	6.4	< 6	< 6
Haloperidol	< 6	6 .3	6.2	< 6	< 6	8.7	8.1	7.9	< 6	6.6	< 6	< 6	6.7	6.1
Pipamperone	6.1	7.5	6.5	< 6	< 6	6.9	6.6	8.3	< 6	6.8	< 6	< 6	8.3	< 6
Clozapine	7.3	7.7	8.1	< 6	< 6	6.7	6.6	7.4	6.9	6.4	6.4	6.9	8.0	9.6
Olanzapine	6.3	6.7	6.7	< 6	< 6	7.5	7.3	7.6	< 6	6.2	< 6	6.5	8.6	9.2

Do we understand and master the principles of profile composition in terms of molecular recognition ?

Focus of TAM library – Similarity Histograms



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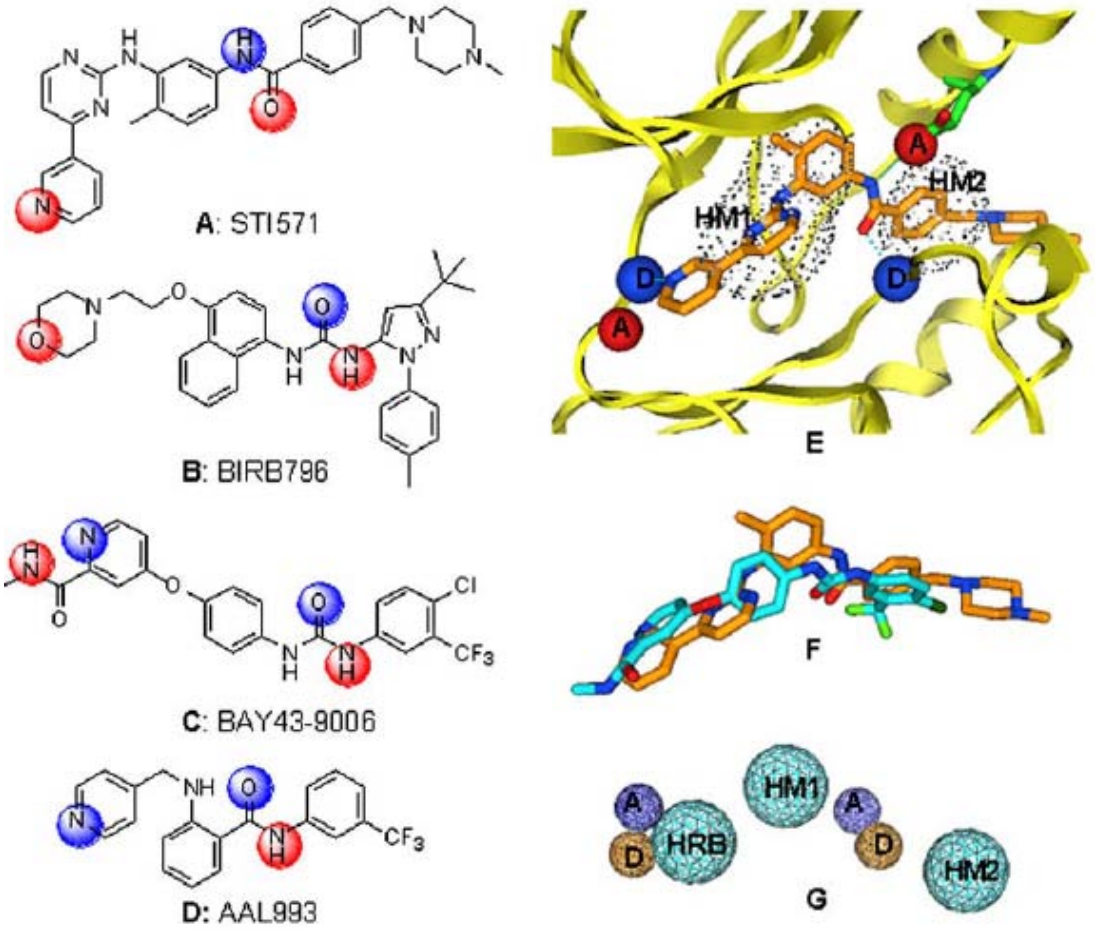
A general strategy for creating “inactive” conformation kinase inhibitors - ABL



Okram et al. Chemistry & Biology 2006, 13, 779–786

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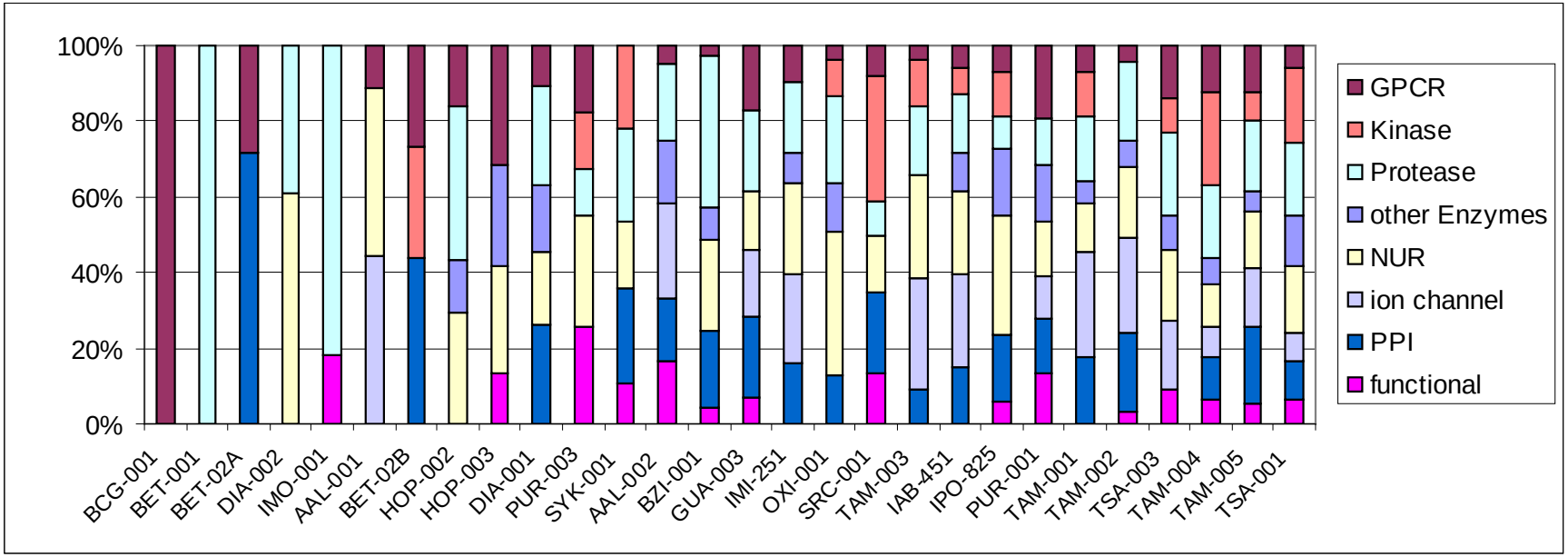
Selectivity Analysis of Combinatorial Libraries



Is Target Family Focus a Myth ?

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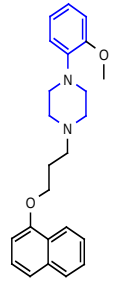
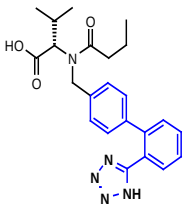
Extend Knowledge-based Approaches

- Target family based approaches
- BIOS – Protein domain based designs
- Privileged Scaffolds
- Protein Secondary Structure Mimetics: α-helix/β-turn
- Co-factor mimetics: ATP, NADP, FAD, Co-A, SAM, etc.

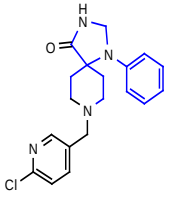
Privileged structures / Scaffold target matrix



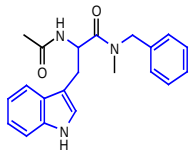
Naftopidil
α_1 antagonist



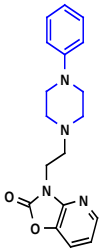
Diovan
AT_1 antagonist



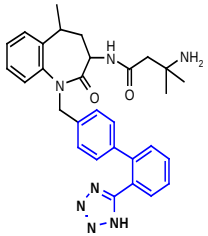
Meiji Seko
μ_1 agonist / D_2 antagonist



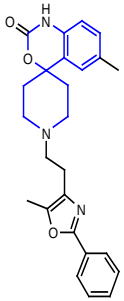
Merck_1
NK_1 antagonist



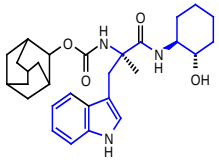
Servier_1
NK_1 antagonist



Merck_2
GHr agonist

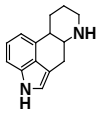


RS504393
α_{1A} / CCR_{2b} antagonist



Pfizer_1
CCK antagonist

	5HT1A	5HT1B	5HT1D	5HT1F	5HT2A	5HT2B	5HT2C	5HT4	A1A	A2A	B1	B3	D1	D2	D3	D4	M1	M3	H2	Frequency
PS1	0	0	0	0	2	0	0	0	0	4	0	0	1	11	0	0	0	0	0	4
PS2	0	0	0	0	0	1	1	0	0	0	0	0	0	2	0	14	0	0	0	4
PS3	6	0	0	0	3	3	3	0	0	0	0	0	0	0	0	0	0	0	0	4
PS4	2	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	4
PS5	2	0	0	0	0	0	0	0	1	0	0	0	0	2	1	0	0	0	0	4
PS6	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	3	0	0	0	4
PS7	2	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	0	0	0	4



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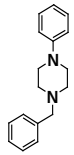

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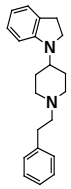
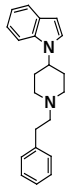


PS3



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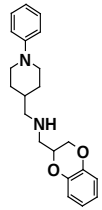
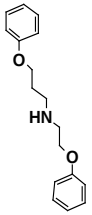


PS5



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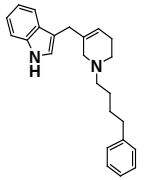

PS7

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Privileged structures GPCRs

The 2-aryl-indole case

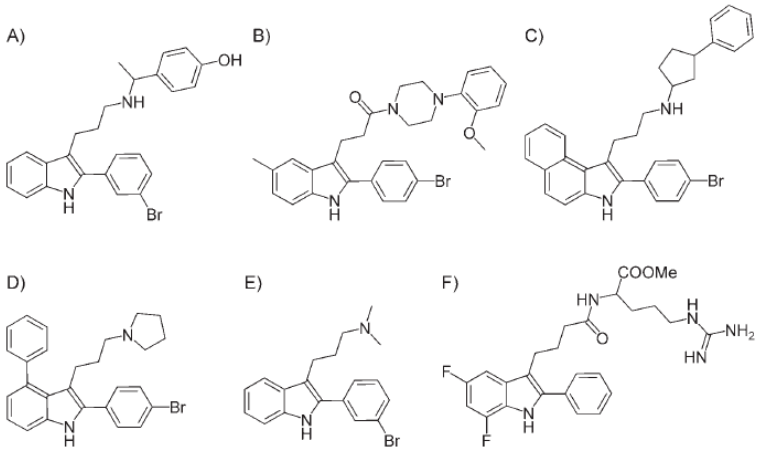

Figure 4. Examples of GPCR-active compounds based on the 2-arylindoles privileged scaffold identified from a focused combinatorial library at Merck. Screening of the library against several GPCRs led to the discovery of receptor antagonists toward A) NPY_5 (IC_{50} = 0.8 nM); B) NK_1 (IC_{50} = 0.8 nM); C) chemokine CCR_3 (IC_{50} = 920 nM) and CCR_5 (IC_{50} = 1190 nM); D) serotonin $5HT_{2A}$ (IC_{50} = 10 nM); E) serotonin $5HT_6$ (IC_{50} = 0.7 nM); and F) SST_4 (K_i = 0.7 nM).[91]

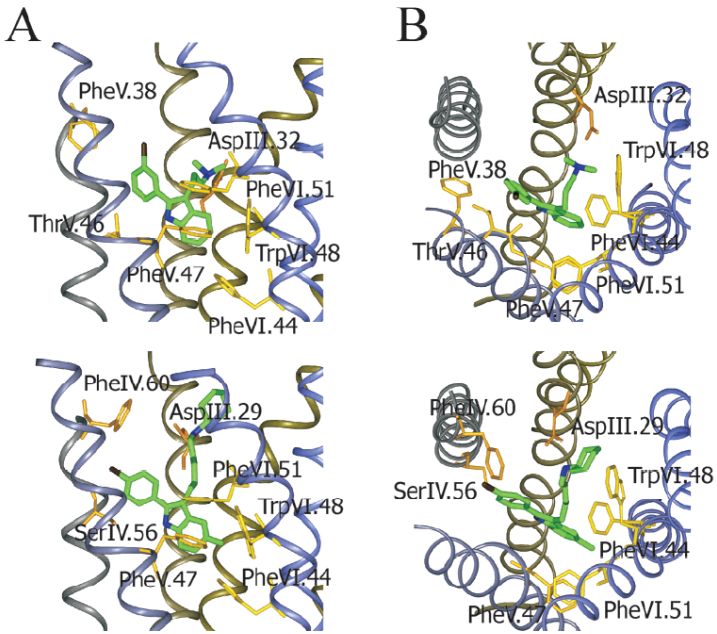

Figure 4. The ligand binding pocket of the (**1**)-5HT6 receptor (top) and (**2**)-MC4 receptor complexes (bottom). (A) Side view from with TM 5, 6, and 7 in front, and (B) top view from the extracellular side. Ligand atoms are color-coded according to atom types: carbon, green; oxygen, red; nitrogen, blue; and bromine, dark green. Receptor atoms are shown in yellow and TMs are shown in shades of brown (TM1) to blue (TM7).

C. A. Willoughby, S. M. Hutchins, K. G. Rosauer, M. J. Dhar, K. T. Chapman, G. G. Chicchi, S. Sadowski, D. H. Weinberg, S. Patel, L. Malkowitz, J. Di Salvo, S. G. Pacholok, K. Cheng, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 93–96.

K. Bondensgaard, M. Ankersen, H. Thørgersen, B. S. Hansen, B. S. Wulff, R. P. Bywater, *J. Med. Chem.* **2004**, *47*, 888–899.

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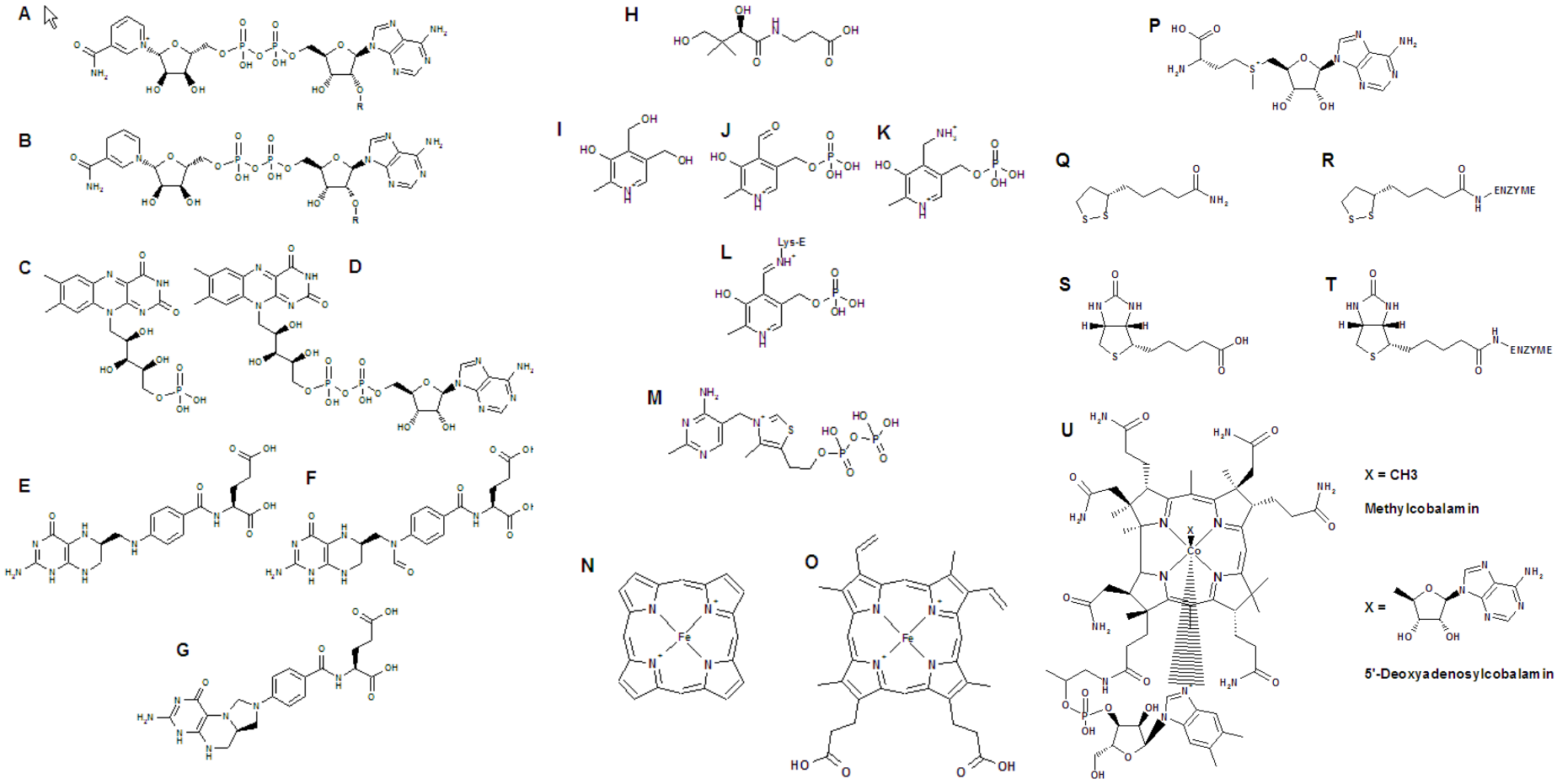
Co-factors

Bioactive Motifs with Conserved Binding Sites in Enzymes



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Ligands vs. domains and folds that bind them

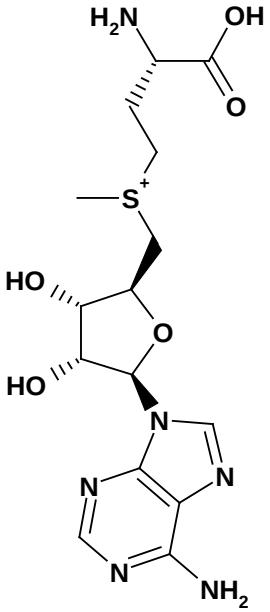
Analysis of PDB – Cofactor Binding Sites Open Large Potential Target Space

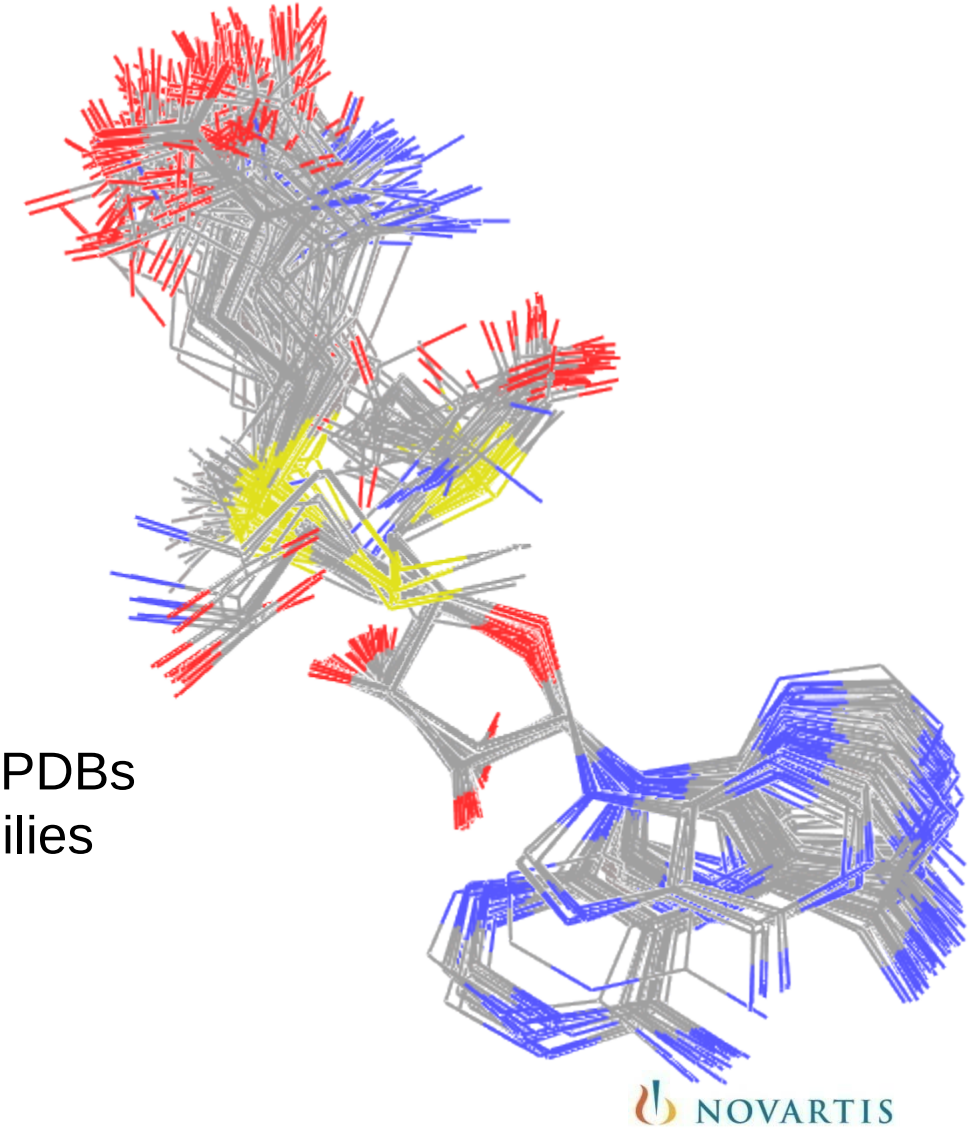
Ligands	Full name of ligands	Number of domains	Number of folds
PLP	Pyridoxal-5'-phosphate	17	10
TDP	ThiaminDiphosphate	36	10
SAM	S-adenosylmethionine	41	13
COA	CoenzymeA	29	14
GTP	Guanosine-5'-triphosphate	26	15
AMP	AdenosineMonophosphate	29	15
NAP	NadpNicotinamide-adenine-dinucleotidePhosphate	73	16
FMN	FlavinMononucleotide	122	16
NDP	NadphDihydro-nicotinamide-adenine-dinucleotidePhosphate	44	18
ANP	PhosphoaminophosphonicAcid-adenylateEster	59	19
FAD	Flavin-adenineDinucleotide	152	21
NAD	Nicotinamide-adenine-dinucleotide	149	27
GDP	Guanosine-5'-diphosphate	86	29
ADP	Adenosine-5'-diphosphate	137	31
ATP	Adenosine-5'-triphosphate	97	35

Distribution patterns of small-molecule ligands in the protein universe and implications for origin of life and drug discovery
Hong-Fang Ji , et al.
Genome Biology 2007, 8:R176doi:10.1186/gb-2007-8-8-r176

Sam: S-Adenosylmethionine

Jack of all Trades and Master of Everything?





Conformational Analysis of 252 SAM PDBs
3 main Clusters – Pharmacophorfamilies
(J. Priestle MLI)

Loenen WA.
Biochem Soc Trans. 2006 Apr;34(Pt 2):330-3

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Knowledge-Based Virtual Screening – MDM4/2

Compounds From In-house MDM2 Assays and Similars

- Hit-finding and Hit-to-lead assays - compounds with IC50 < 50 µM (650)
- FCFP4 similarity search (1873)
- Hopfen QSAR (5000)

Literature and Patent Mining

- WOMBAT Literature Data and 14 Patent families from MDL Patent Database
- FCFP4 similarity search (675) and NB model (5000)
- FEPOPS (1000) similarity search, Substructure search (1707)

HTD

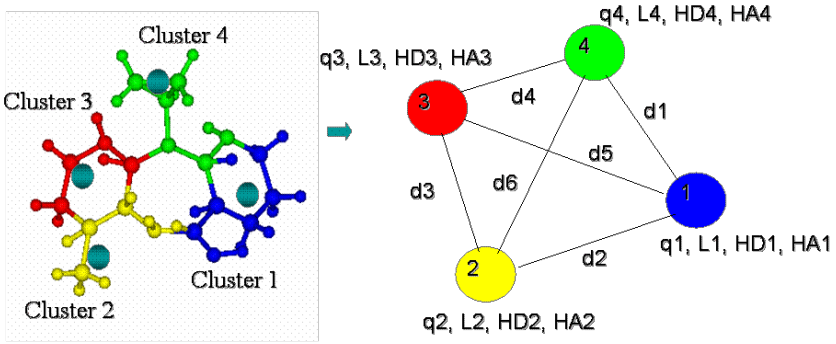
- Homology model based on SPIRO-OXINDOLE and NUTLIN MDM2 structures
- Constrained SP Glide docking
- Selection of top 20000 Compounds

UNITY Searching

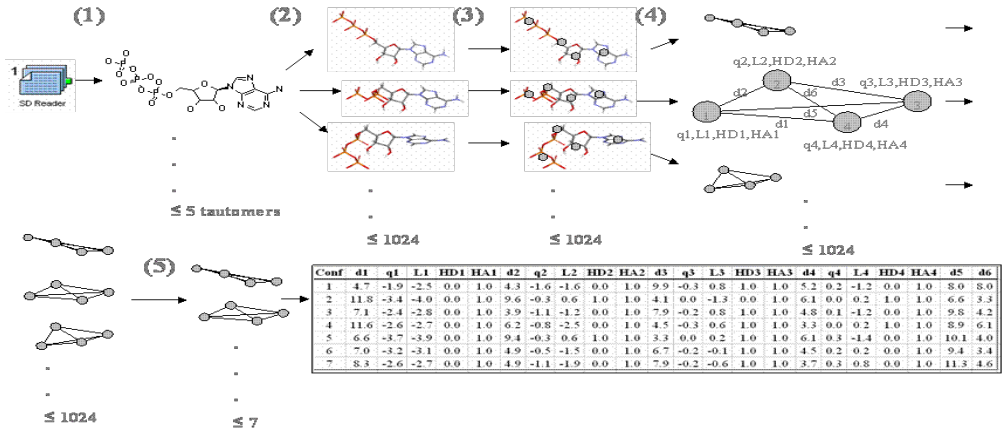
- Homology model based on SPIRO-OXINDOLE and NUTLIN MDM2 structures
- Constrained search: Hydrophobic centers and HBonds (49305)
- Constrained SP Glide docking
- Selection of top 20000 Compounds

MDM4 HIT SET 46511

FEPOPS 3D similarity searching



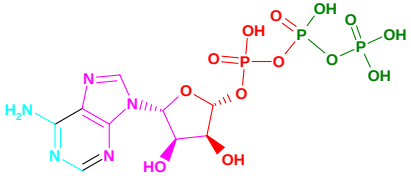
4 feature centroids and distances



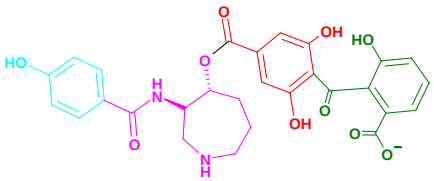
Conf	d1	q1	L1	HD1	HA1	d2	q2	L2	HD2	HA2	d3	q3	L3	HD3	HA3	d4	q4	L4	HD4	HA4	d5	d6
1	4.7	-1.9	-2.5	0.0	1.0	4.3	-1.6	-1.6	0.0	1.0	9.9	-0.3	0.8	1.0	1.0	5.2	0.2	-1.2	0.0	1.0	8.0	8.0
2	11.8	-3.4	-4.0	0.0	1.0	9.6	-0.3	0.6	1.0	1.0	4.1	0.0	-1.3	0.0	1.0	6.1	0.0	0.2	1.0	1.0	6.6	3.3
3	7.1	-2.4	-2.8	0.0	1.0	3.9	-1.1	-1.2	0.0	1.0	7.9	-0.2	0.8	1.0	1.0	4.8	0.1	-1.2	0.0	1.0	9.8	4.2
4	11.6	-2.6	-2.7	0.0	1.0	6.2	-0.8	-2.5	0.0	1.0	4.5	-0.3	0.6	1.0	1.0	3.3	0.0	0.2	1.0	1.0	8.9	6.1
5	6.6	-3.7	-3.9	0.0	1.0	9.4	-0.3	0.6	1.0	1.0	3.3	0.0	0.2	1.0	1.0	6.1	0.3	-1.4	0.0	1.0	10.1	4.0
6	7.0	-3.2	-3.1	0.0	1.0	4.9	-0.5	-1.5	0.0	1.0	6.7	-0.2	-0.1	1.0	1.0	4.5	0.2	0.2	0.0	1.0	9.4	3.4
7	8.3	-2.6	-2.7	0.0	1.0	4.9	-1.1	-1.9	0.0	1.0	7.9	-0.2	-0.6	1.0	1.0	3.7	0.3	0.8	0.0	1.0	11.3	4.6

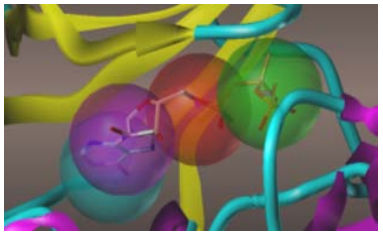
Jenkins *et al. J. Med. Chem.* (2004), 47, 6144-6159.

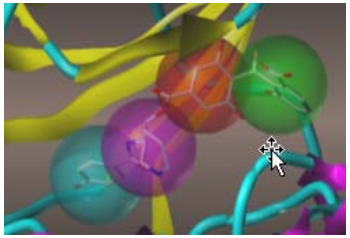
ATP



Balanol PKC inhibitor







Balanol low 2D similarity to ATP

High similarity in FEPOPS as in Xray

Computational Procedure

1. Generate conformers
2. Calculate FPs and properties
3. Compute fingerprints
4. Search based on fingerprints

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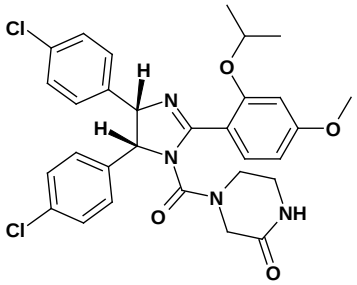
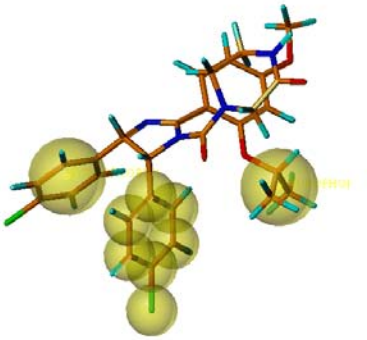
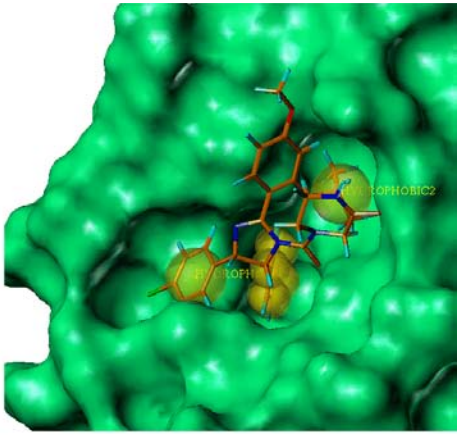
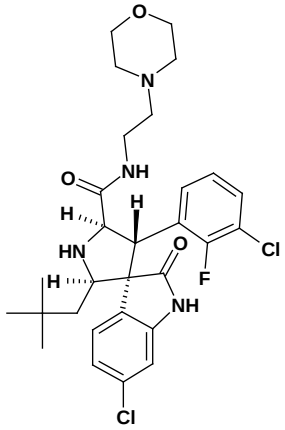
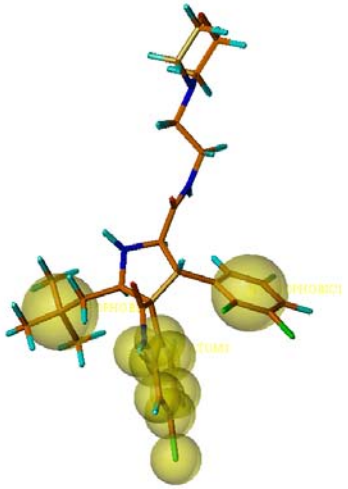
Pharmacophore Screening – MDM4/2

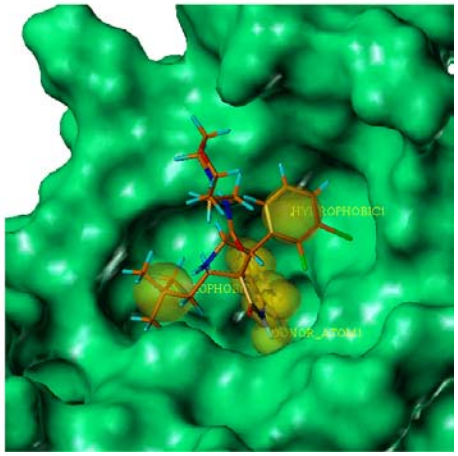












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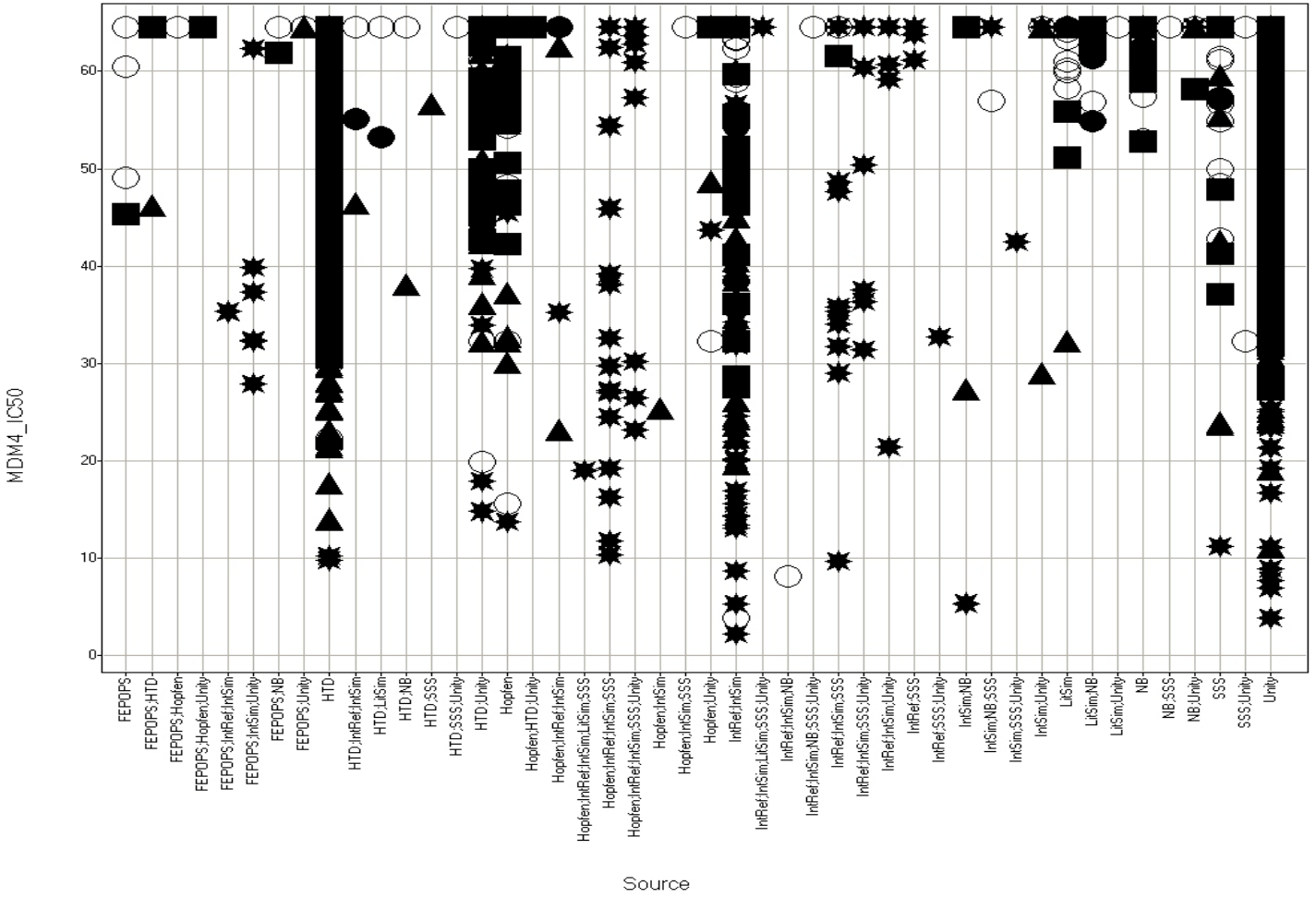
Knowledge-Based Virtual Screening – MDM4/2



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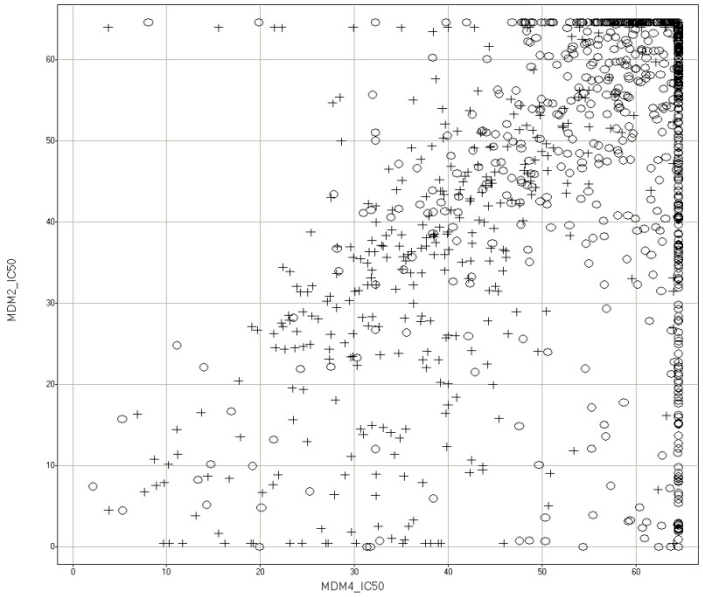
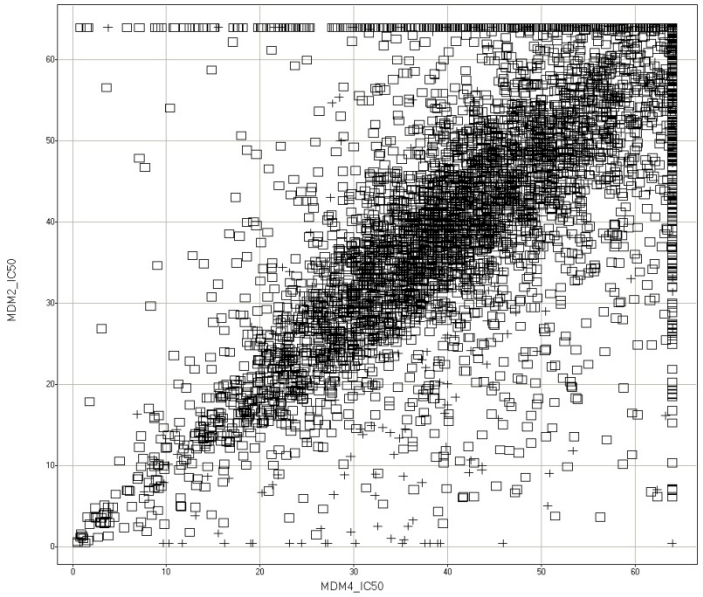
Comparing HTS and Virtual Screening – MDM4/2



Virtual Screen



HTS

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Comparing HTS and virtual screening – MDM4/2

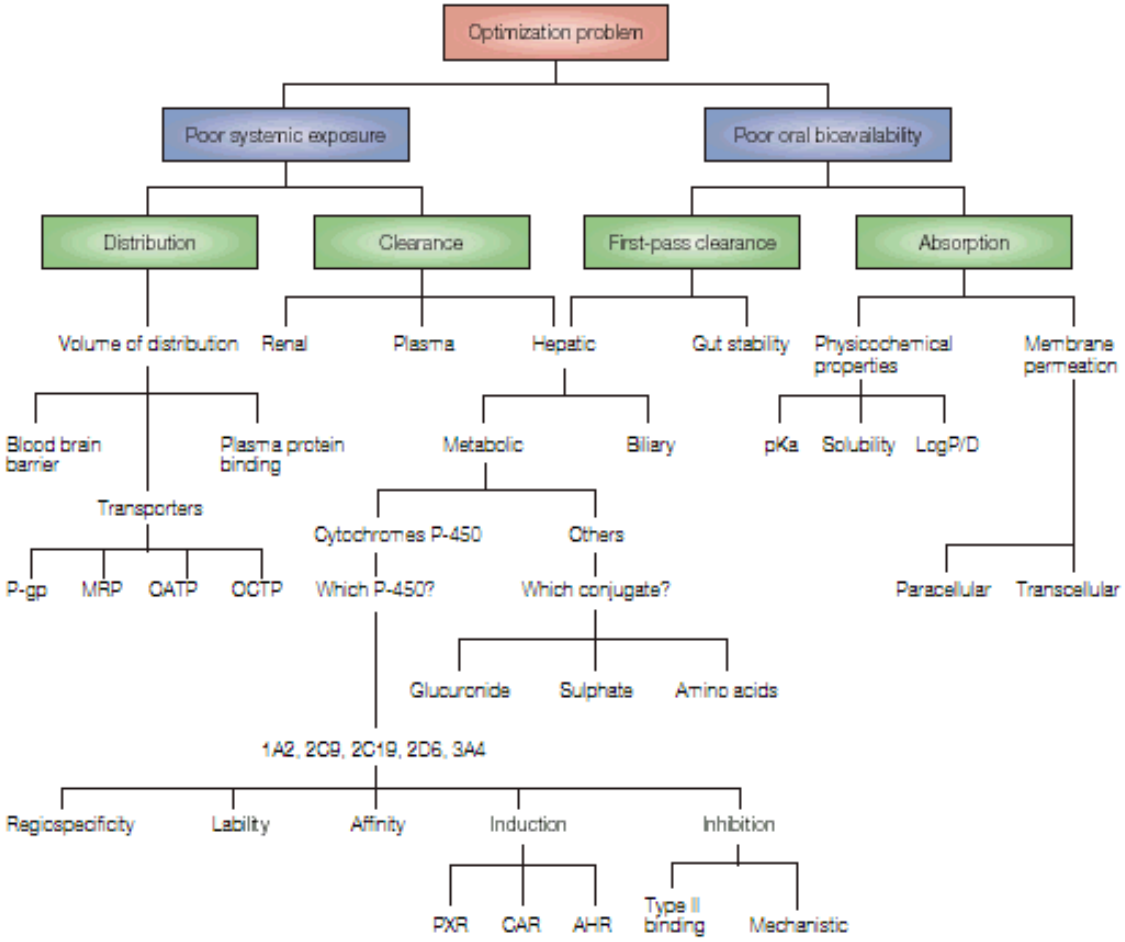
Key parameters for HTS and VS approaches at different concentration thresholds of the MDM4 and MDM2 assays

Assay/Threshold	HTS	VS	HTS/VS	HR HTS %	HR VS %	Enrichment	FN HTS %
MDM4 < 64 μM	4,062	455	326	0.366	1.679	5	9
MDM4 ≤ 60 μM	3,876	336	318	0.350	1.406	4	7
MDM4 ≤ 40 μM	1,974	79	196	0.181	0.591	3	4
MDM4 ≤ 20 μM	327	13	26	0.029	0.084	3	4
MDM2 < 64 μM	3,945	538	316	0.355	1.836	5	11
MDM2 ≤ 60 μM	3,768	446	309	0.340	1.623	5	10
MDM2 ≤ 40 μM	2,034	186	207	0.187	0.845	5	8
MDM2 ≤ 20 μM	444	84	78	0.044	0.348	8	14

HTS and VS are, respectively, the number of hits found exclusively in the HTS and VS experiments; HTS/VS is the number of hits found in the overlap. The hit rate (HR) is defined by the number of hits divided by the total number of compounds screened. The enrichment factor is defined by the VS hit rate divided by the HTS hit rate. The false negative hit rate (FN) is defined by the number of VS hits divided by the total number of hits.

Chemoinformatics: Quo vadis?

Towards prediction paradise?



Van de Waterbeemd, H. et al. Nat Rev Drug Discov. 2003,192-204

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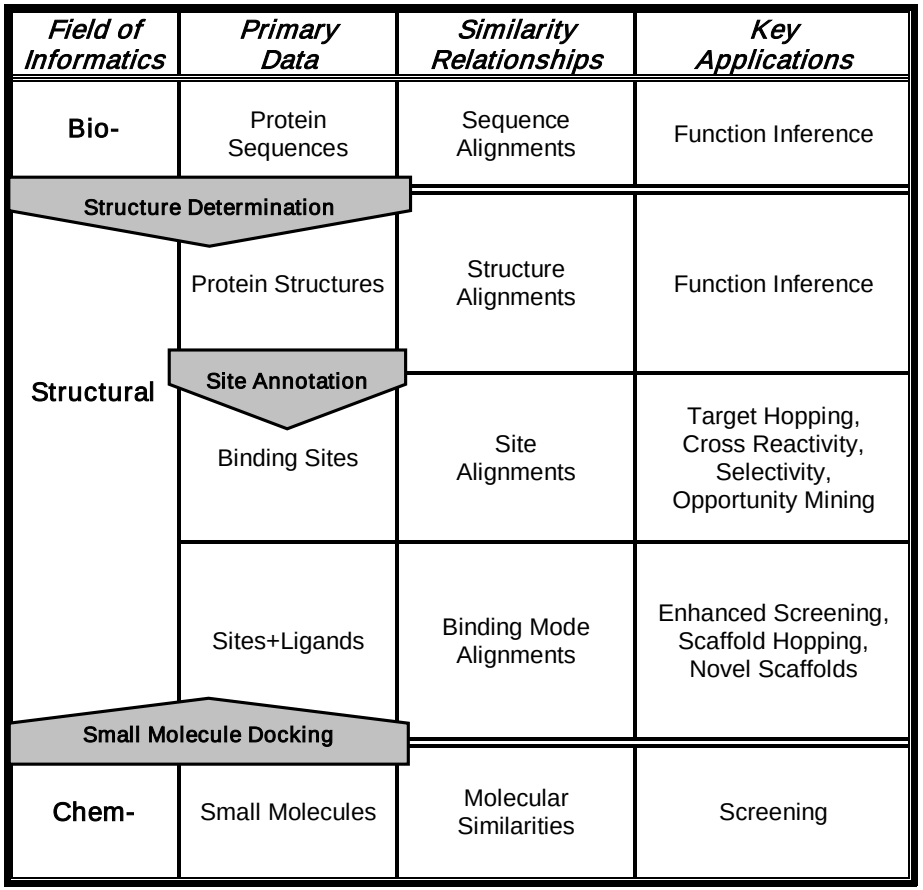
Chemoinformatics: Quo vadis?

Molecular Informatics



Courtesy of Dr. D. Debe, Eidogen-Sertanty

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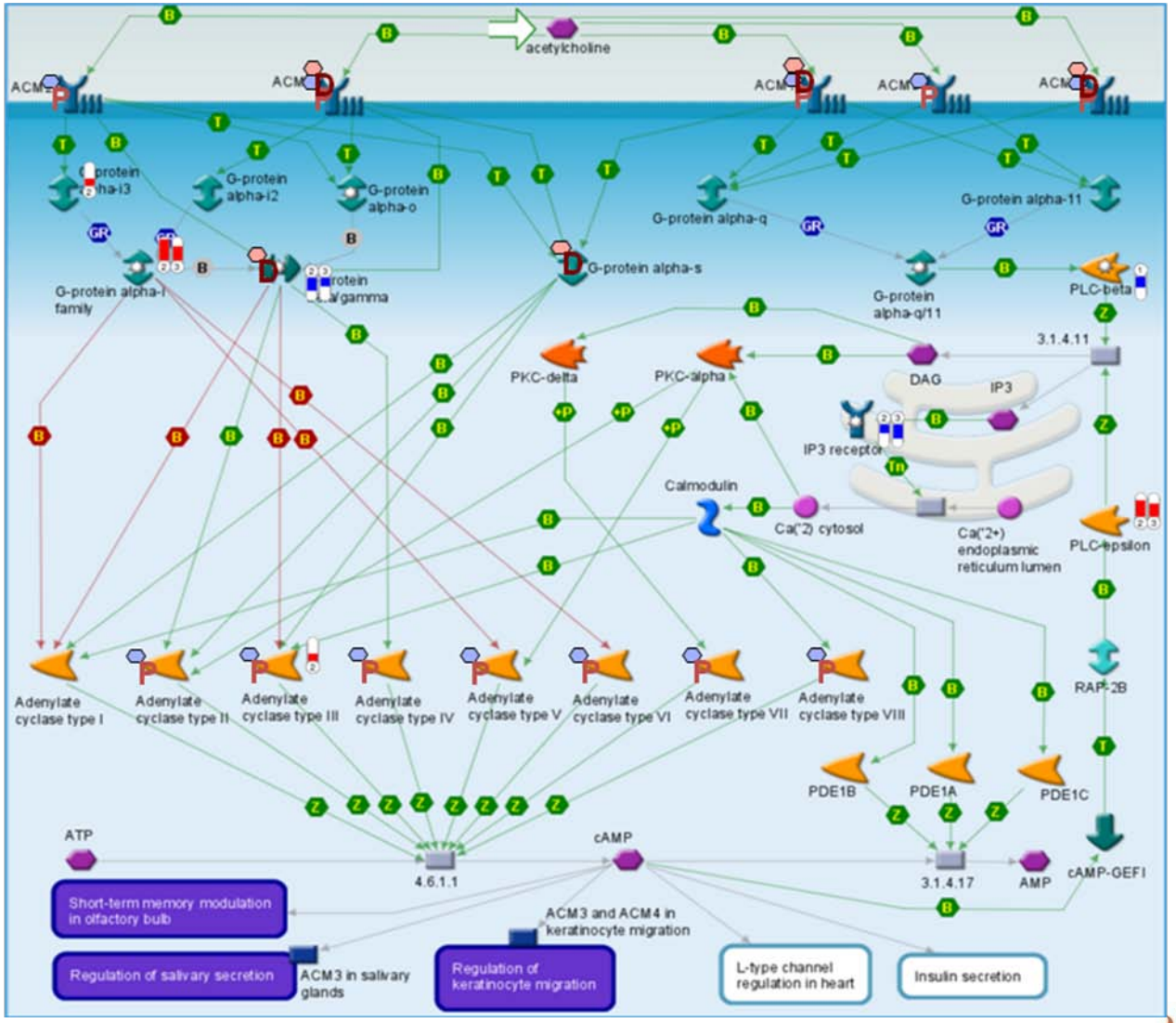
Chemoinformatics: Quo vadis?

Chemical Systems Biology – Compound-pathway maps



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- Maxim Popov
- Kamal Azzaoui
- Joerg Muehlbacher
- Jeremy Jenkins
- Meir Glick
- Bill Egan
- Peter Ertl
- Bernard Faller
- Hans-Joerg Roth
- Peter Fuerst

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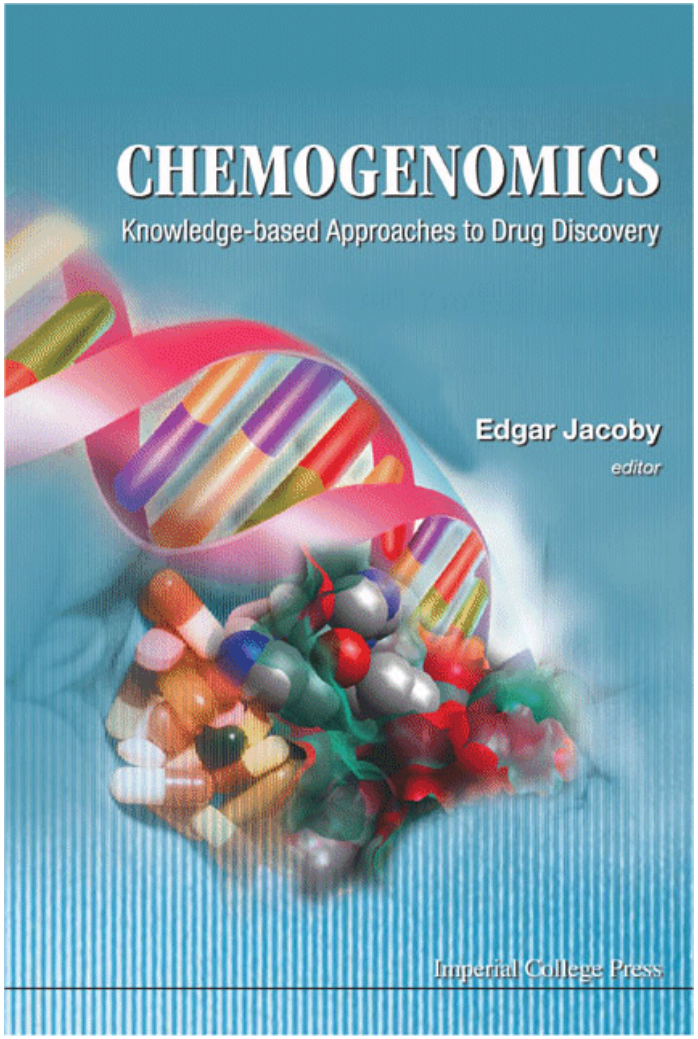
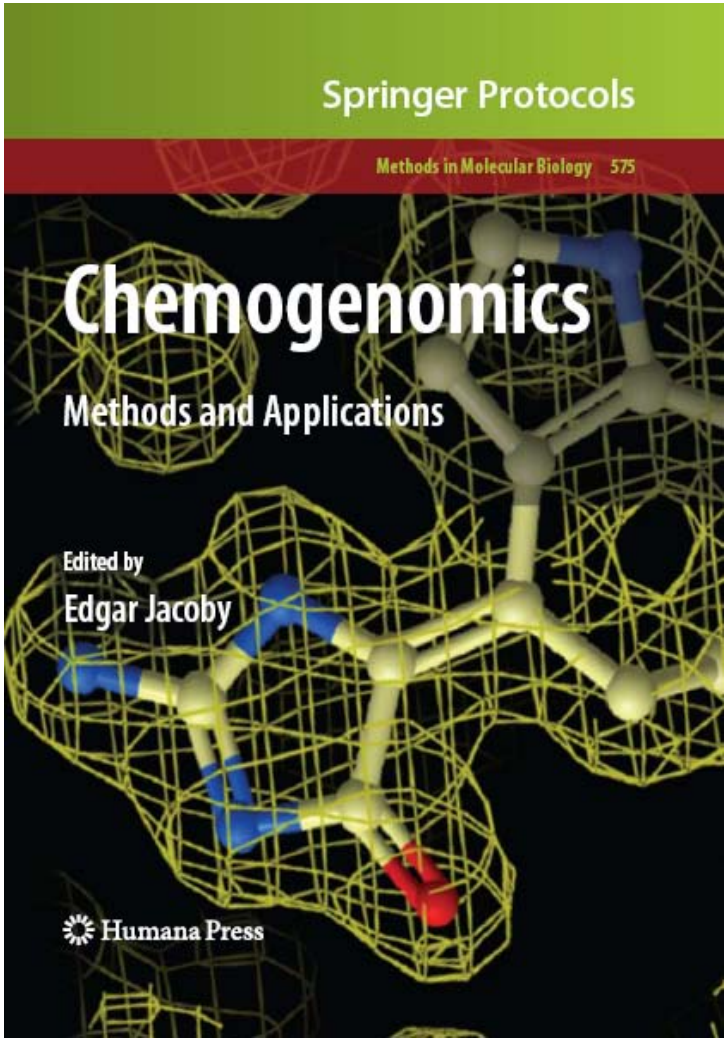
Recent Publications





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