In silico target profiling

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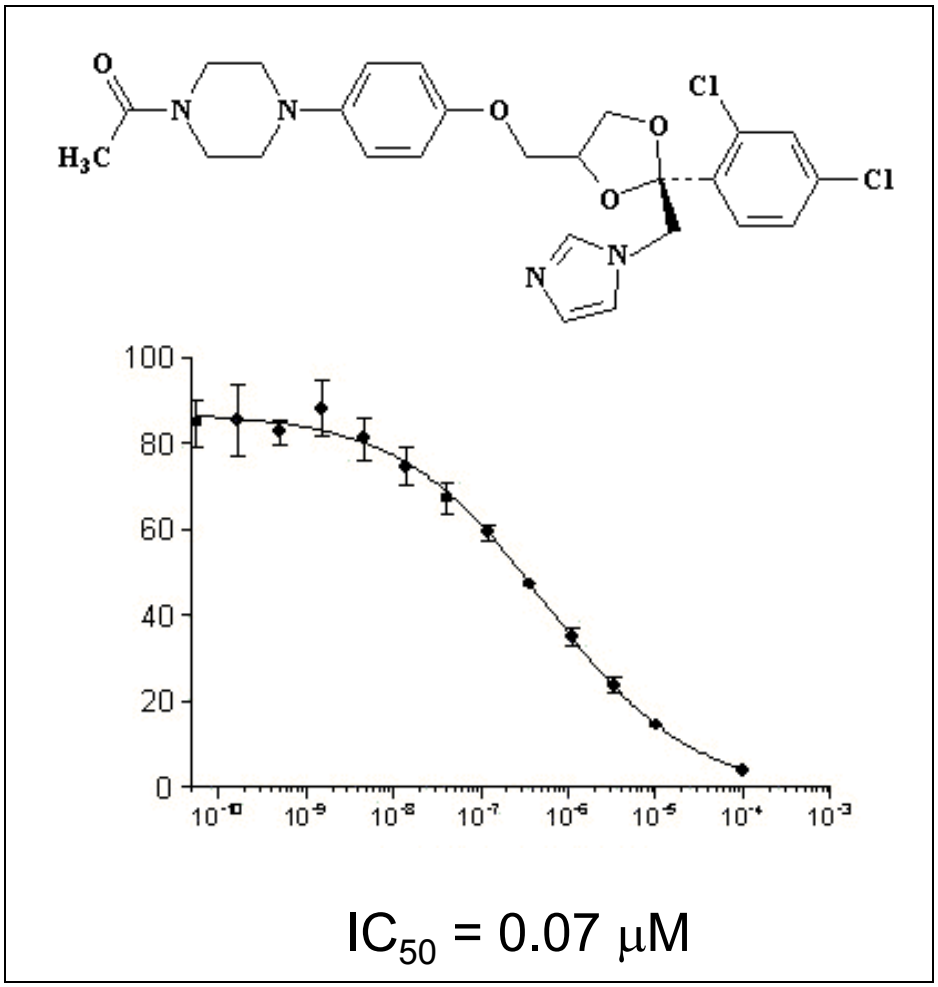
Traditional drug discovery



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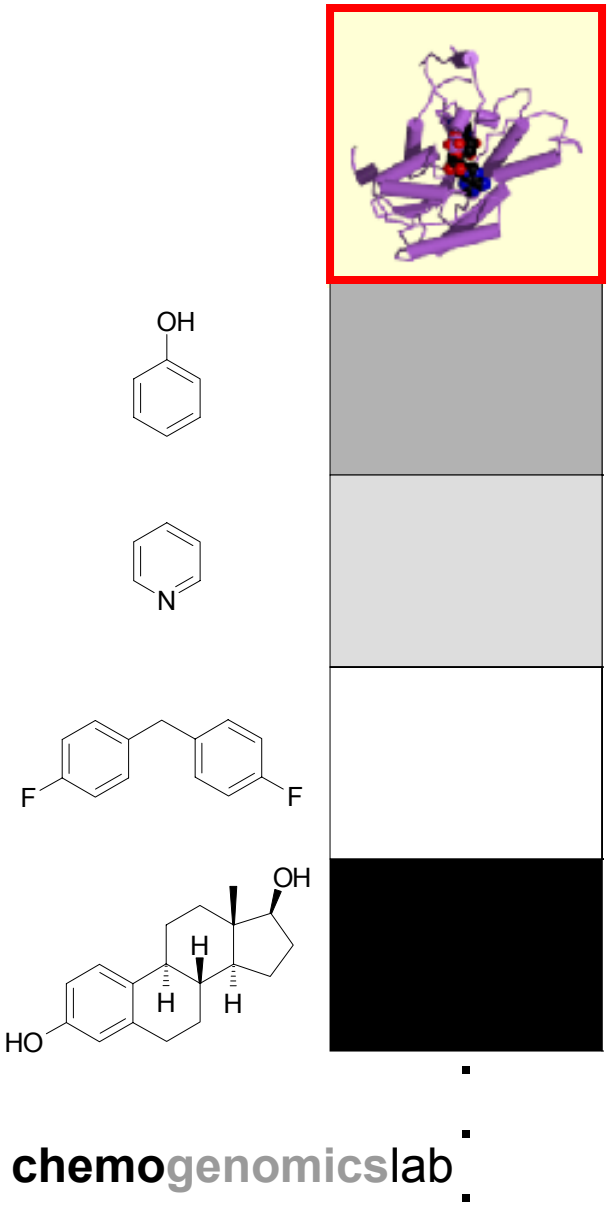
High-throughput screening

Chemical Screening



8,000,000 x 1

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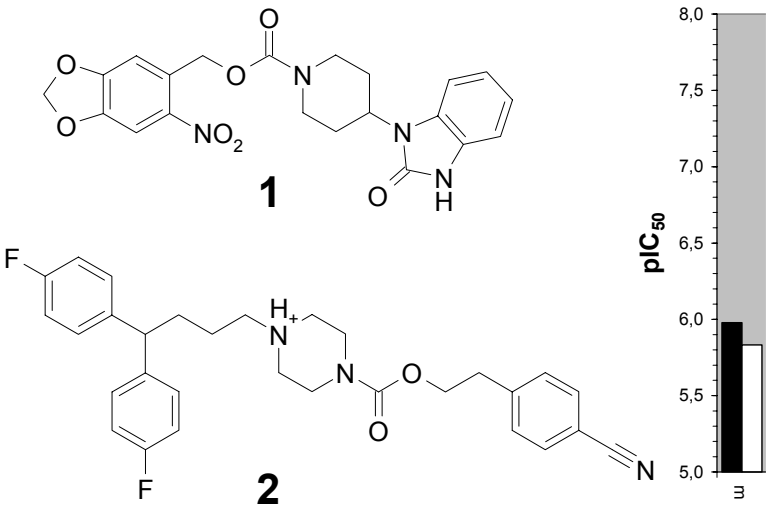
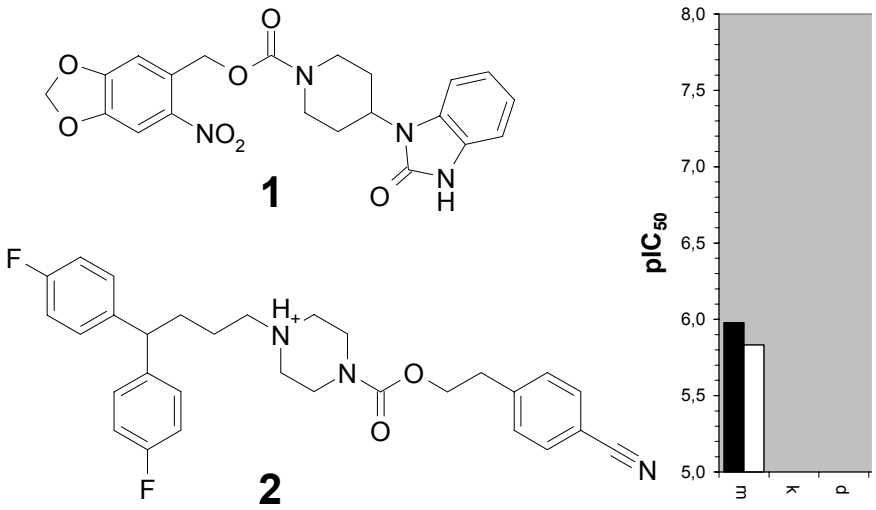
Traditional drug discovery

Compound	IC50 COX-2 (nM)	IC50 COX-1 (nM)
CN000001	30	500
CN000002	500	1000
CN000003	450	3000
CN000004	2	6000
CN000005	1	4700
CN000006	60	120
CN000007	1000	300
CN000008	30	4400
CN000009	26	2200
CN000010	50	300
CN000011	40	460
CN000012	30	20
CN000013	1200	100
CN000014	380	4470
CN000015	400	370
CN000016	36	1680
CN000017	22	462
CN000018	10	470
CN000019	1	250
CN000020	0,5	1300
CN000021	7	1500
CN000022	10	1600

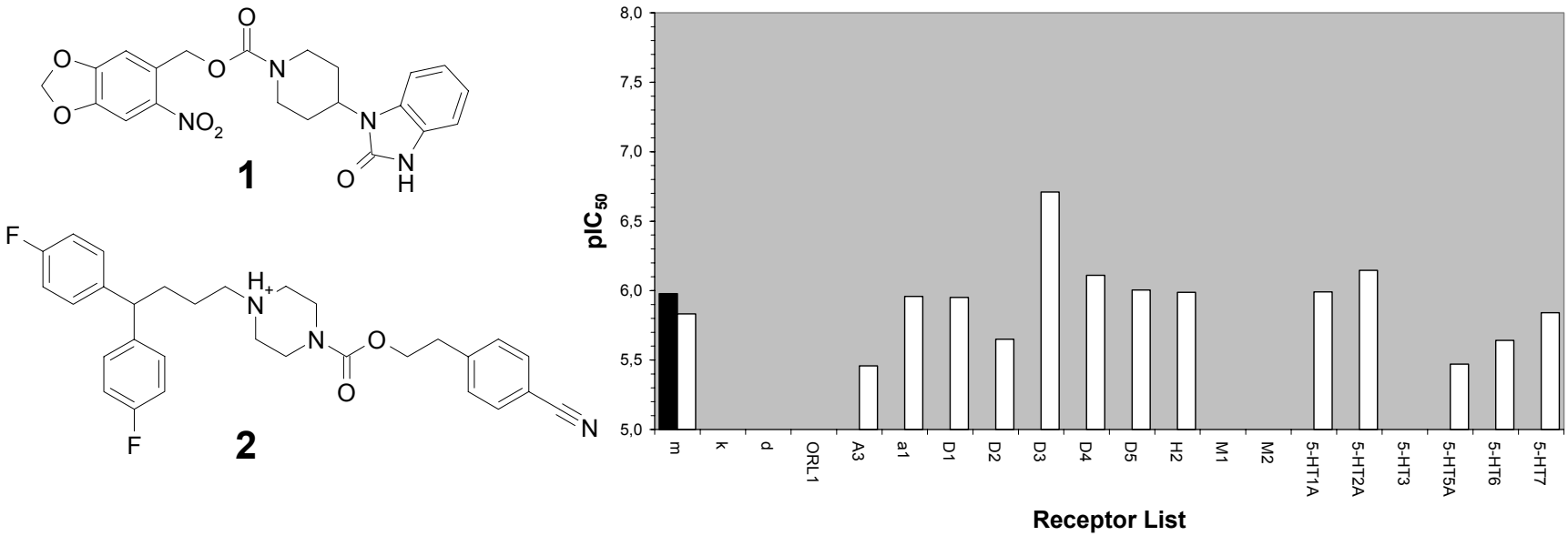
The need to go beyond traditional drug discovery



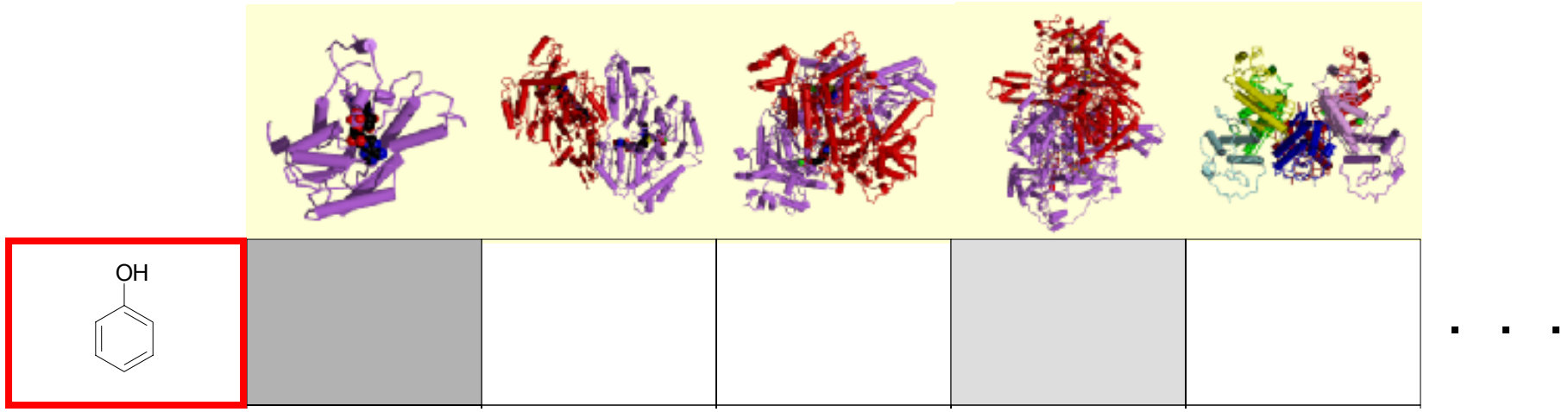
The need to go beyond traditional drug discovery



The need to go beyond traditional drug discovery

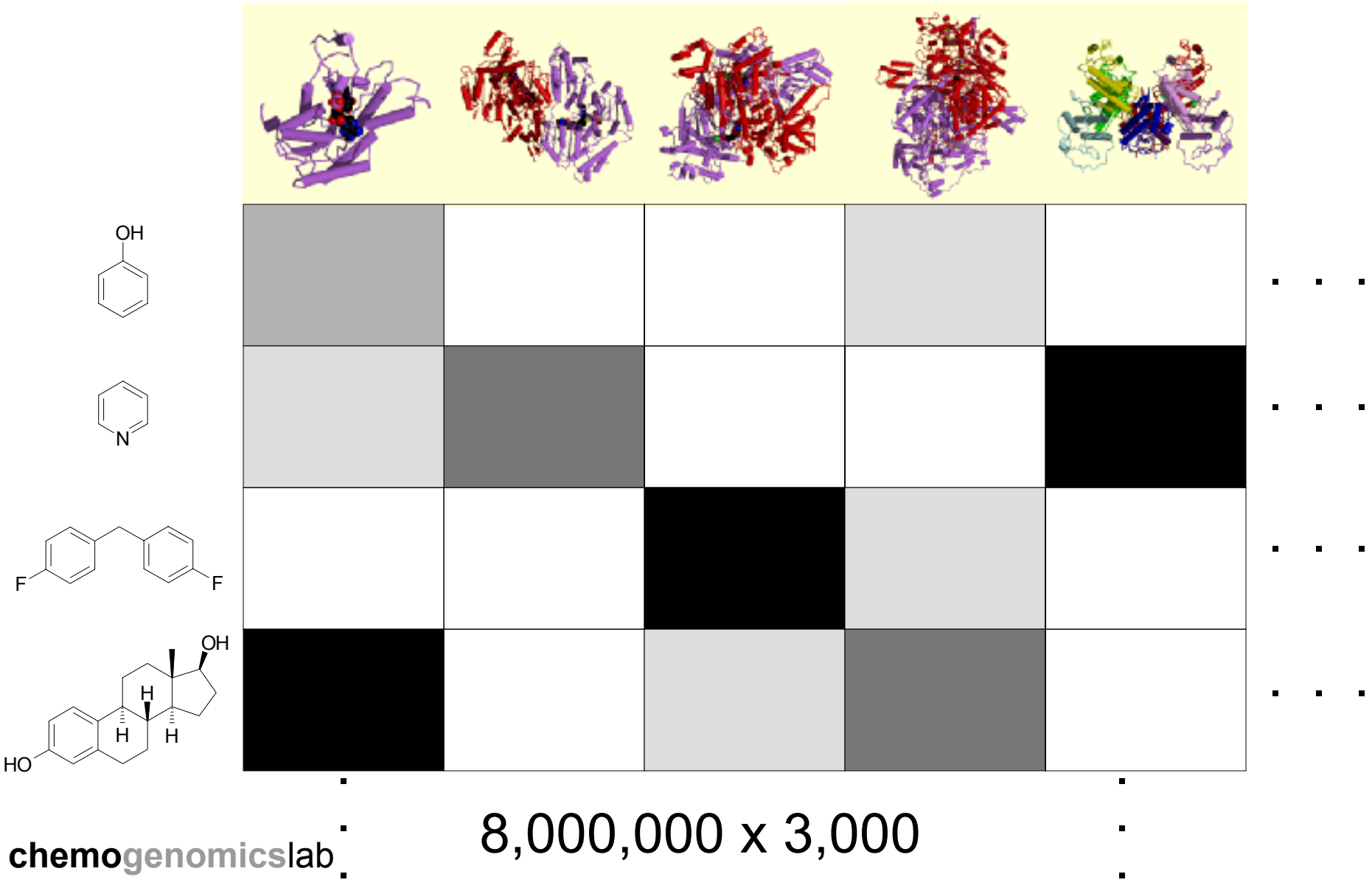


Pharmacological Profiling

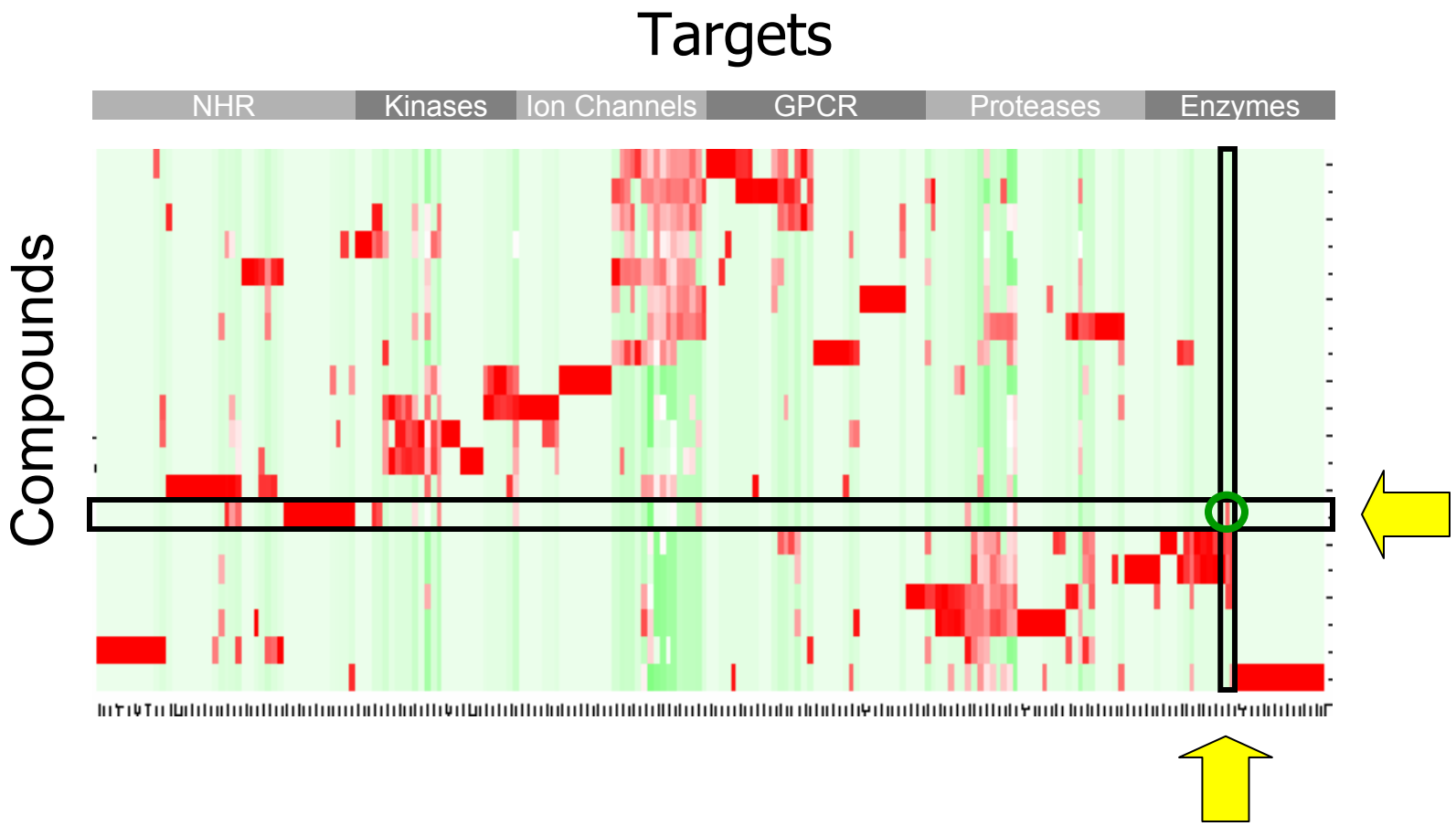


1 x 3,000

Chemogenomic Profiling



Necessary drug discovery



Annotated chemical libraries: WOMBAT

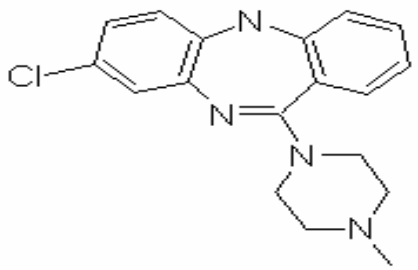
Bioactivity Summary | Target & Biological Information | Computed Chemical Properties

Sunset Molecular Discovery, LLC
www.sunsetmolecular.com

W O M B A T

SMDL-00001128 | 53

structure



CN1CCN(CC1)C2=Nc3cc(ccc3Nc4c2cccc4)Cl

SMDL_ID	molname
1128	clozapine
generic_name: clozapine	drug: 1
reference: Bioorg. Med. Chem. Lett. 12(4)-2002 633-636	
formula: $C_{18}H_{19}ClN_4$	mol_weight: 326.8319
ALogP: 3.8000	ExpLogP: 3.2300
ALogS: -3.2300	ExpLogS

structure_keywords
nc

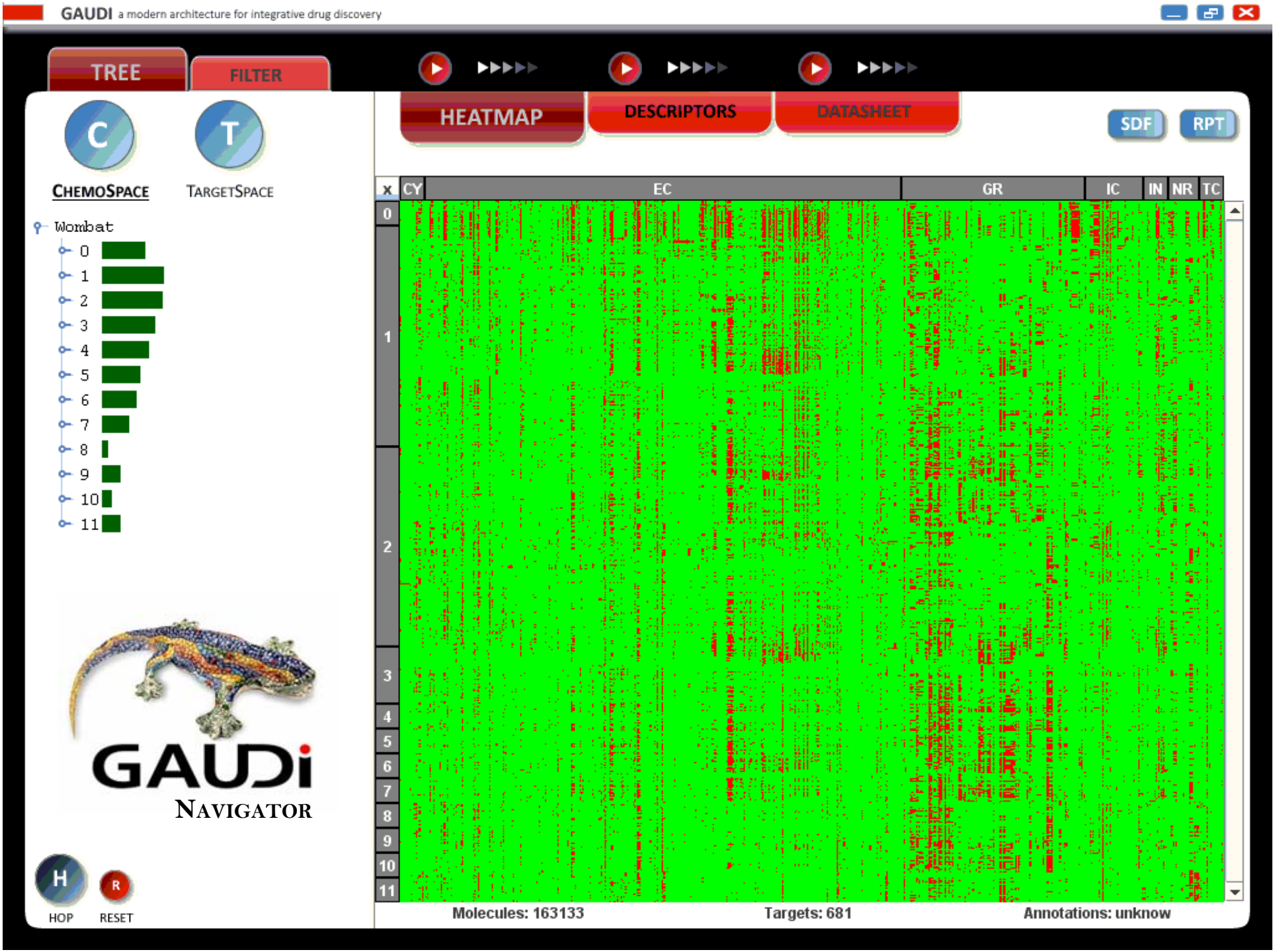
act#	targ_type	target_name	act_type	class	value	min	max	inhib%	lig_eff
1	receptor	D1	Ki	A	6.3768	6.3768	6.3768		0.3937
2	receptor	D2L	Ki	A	7.3872	7.3872	7.3872		0.4561
3	receptor	D2S	Ki	A	7.5528	7.5528	7.5528		0.4663
4	receptor	D3	Ki	A	6.0177	6.0177	6.0177		0.3715
5	receptor	D4	Ki	A	7.7959	7.7959	7.7959		0.4813

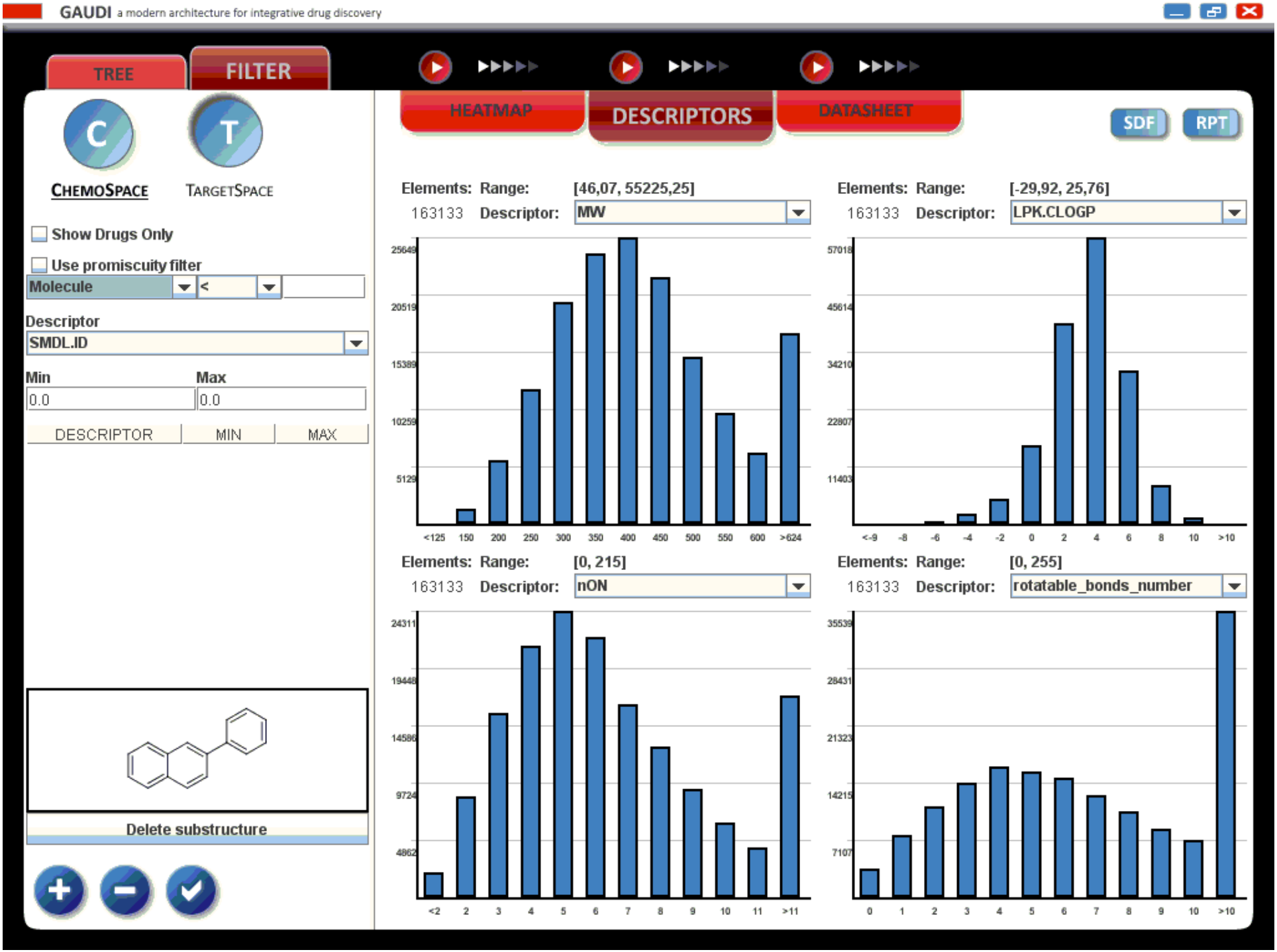
Chemo and Target spaces covered by WOMBAT

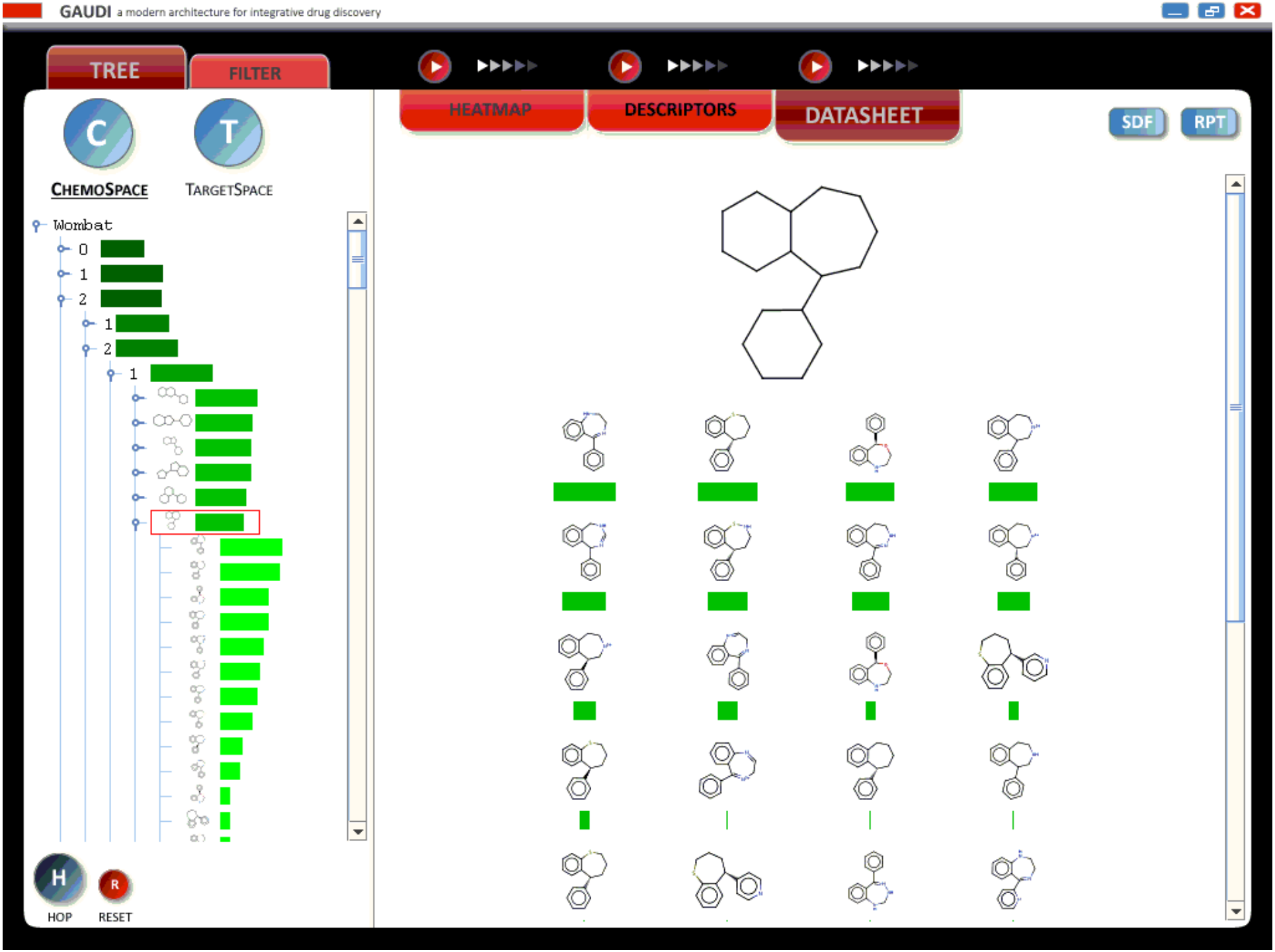
A total of 163134 unique molecules annotated to 681 targets:

- Enzymes: 410
- G protein-coupled receptors: 157
- Ion Channels: 49
- Nuclear receptors: 26
- Transporters: 20
- Cytokines: 11
- Integrins: 8

How can one visualize, classify, and navigate on this Chemo-Target Space?


GAUDI a modern architecture for integrative drug discovery
TREE
FILTER
HEATMAP
DESCRIPTORS
DATASHEET
SDF
RPT
C
T
CHEMOSPACE
TARGETSPACE
Wombat
0
1
2
3
4
5
6
7
8
9
10
11
X
CY
EC
GR
IC
IN
NR
TC
0
1
2
3
4
5
6
7
8
9
10
11
GAUDI
NAVIGATOR
H
R
HOP
RESET
Molecules: 163133
Targets: 681
Annotations: unknow


GAUDI a modern architecture for integrative drug discovery
TREE
FILTER
HEATMAP
DESCRIPTORS
DATASHEET
SDF
RPT
C
T
CHEMOSPACE
TARGETSPACE
Show Drugs Only
Use promiscuity filter
Molecule
<
Descriptor
SMDL.ID
Min
Max
0.0
0.0
DESCRIPTOR
MIN
MAX
Delete substructure
Elements: 163133 Range: [46,07, 55225,25] Descriptor: MW
25649
20519
15389
10259
5129
<125 150 200 250 300 350 400 450 500 550 600 >624
Elements: 163133 Range: [-29,92, 25,76] Descriptor: LPK.CLOGP
57018
45614
34210
22807
11403
<-9 -8 -6 -4 -2 0 2 4 6 8 10 >10
Elements: 163133 Range: [0, 215] Descriptor: nON
24311
19448
14586
9724
4862
<2 2 3 4 5 6 7 8 9 10 11 >11
Elements: 163133 Range: [0, 255] Descriptor: rotatable_bonds_number
35539
28431
21323
14215
7107
0 1 2 3 4 5 6 7 8 9 10 >10


GAUDI a modern architecture for integrative drug discovery
TREE
FILTER
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TARGETSPACE
Wombat
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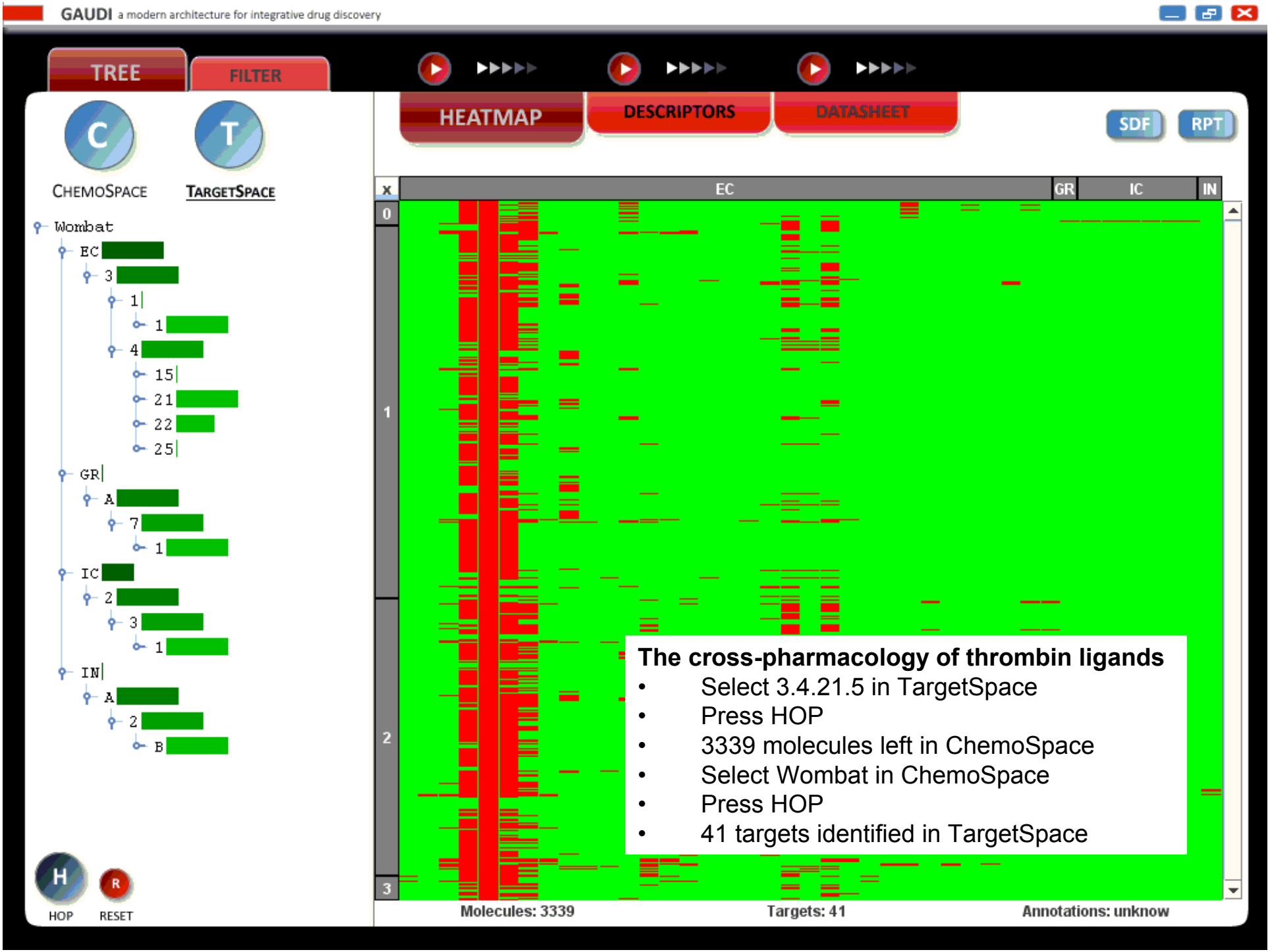
GAUDI a modern architecture for integrative drug discovery
TREE
FILTER
HEATMAP
DESCRIPTORS
DATASHEET
SDF
RPT
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CHEMOSPACE
TARGETSPACE
Wombat
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HOP
RESET
X
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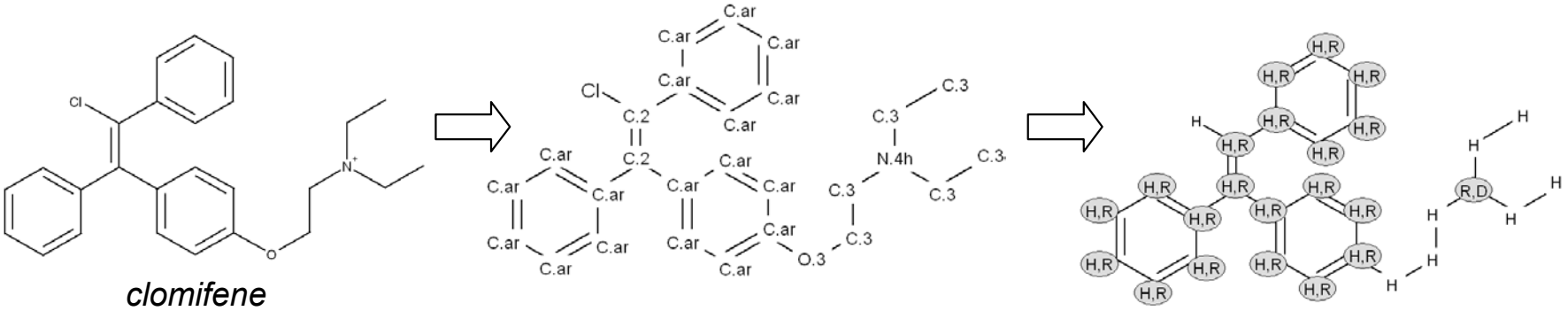
3
The cross-pharmacology of thrombin ligands
• Select 3.4.21.5 in TargetSpace
• Press HOP
• 3339 molecules left in ChemoSpace
• Select Wombat in ChemoSpace
• Press HOP
• 41 targets identified in TargetSpace
Molecules: 3339
Targets: 41
Annotations: unknow

Biologically-relevant descriptors: SHED (I)

Shannon Entropy Descriptors (SHED)



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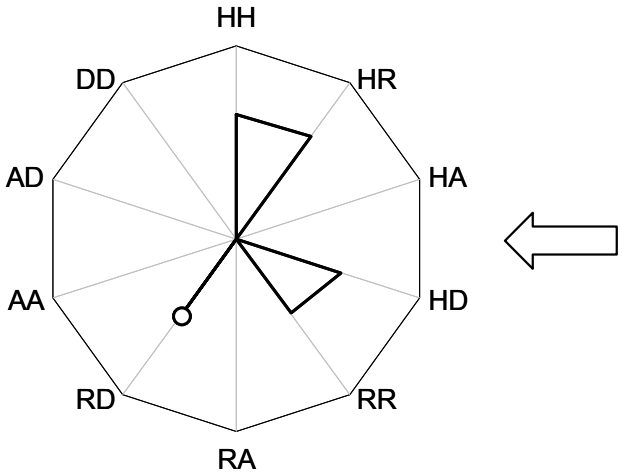
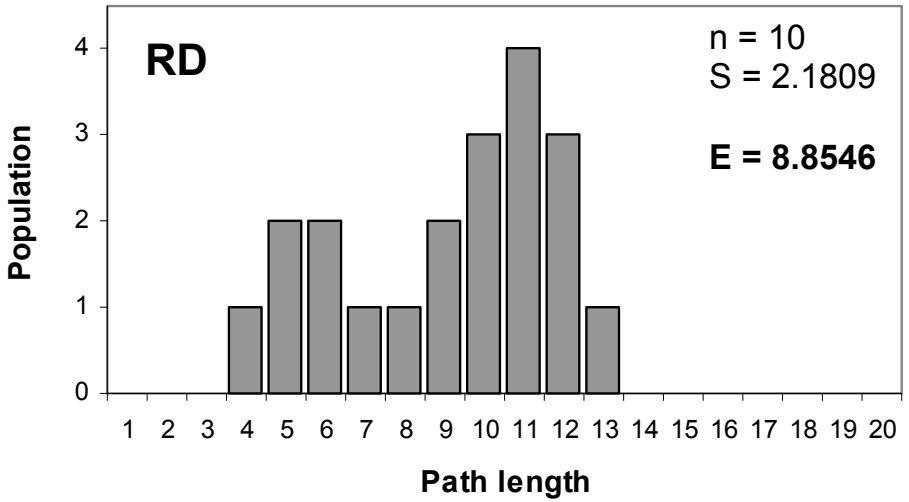
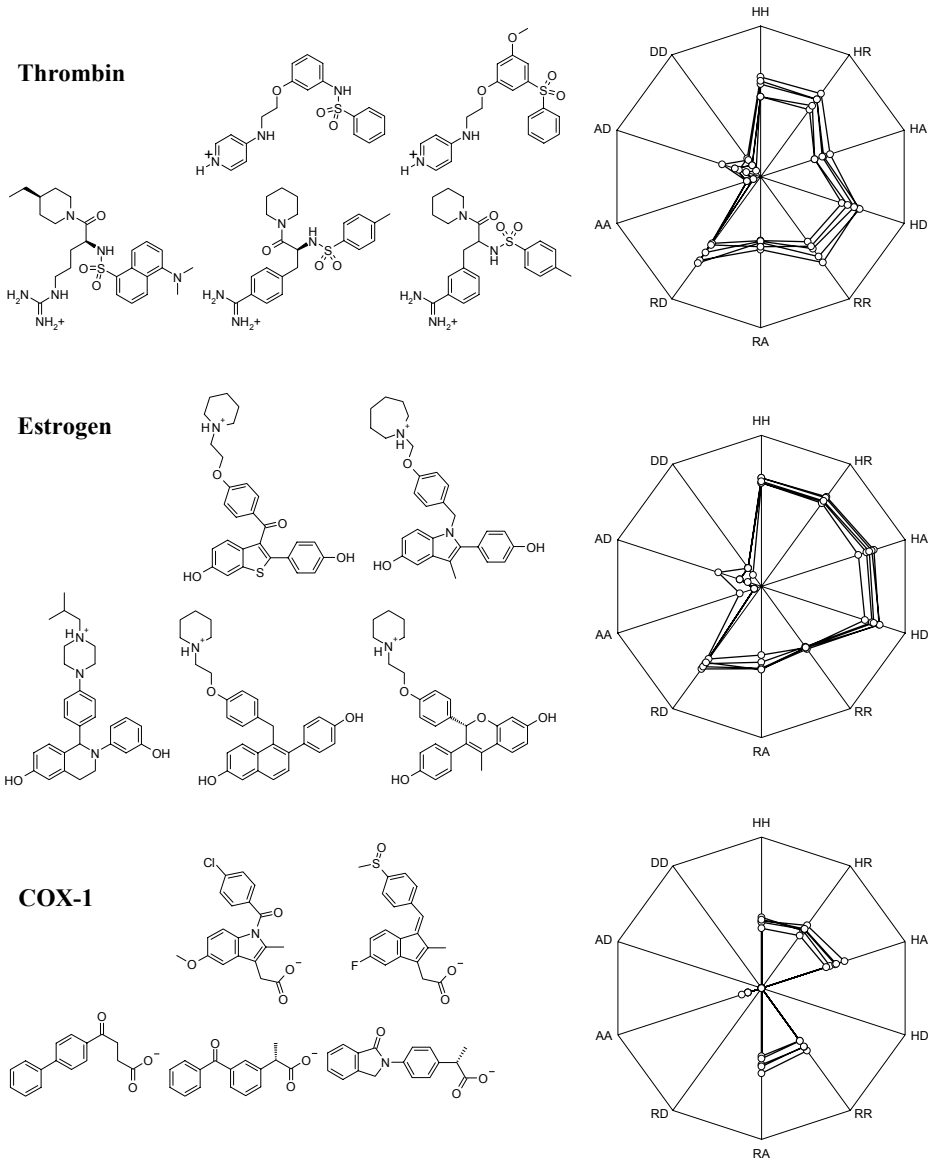




J Chem Inf Model 2006; 46: 1615-1622

Biologically-relevant molecular descriptors



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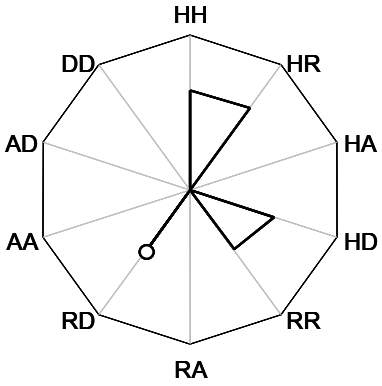
J Chem Inf Model 2006; 46: 1615-1622

Ligand-based approach to in silico pharmacology

Targets (Ligand-based Description)

. . .

Molecules

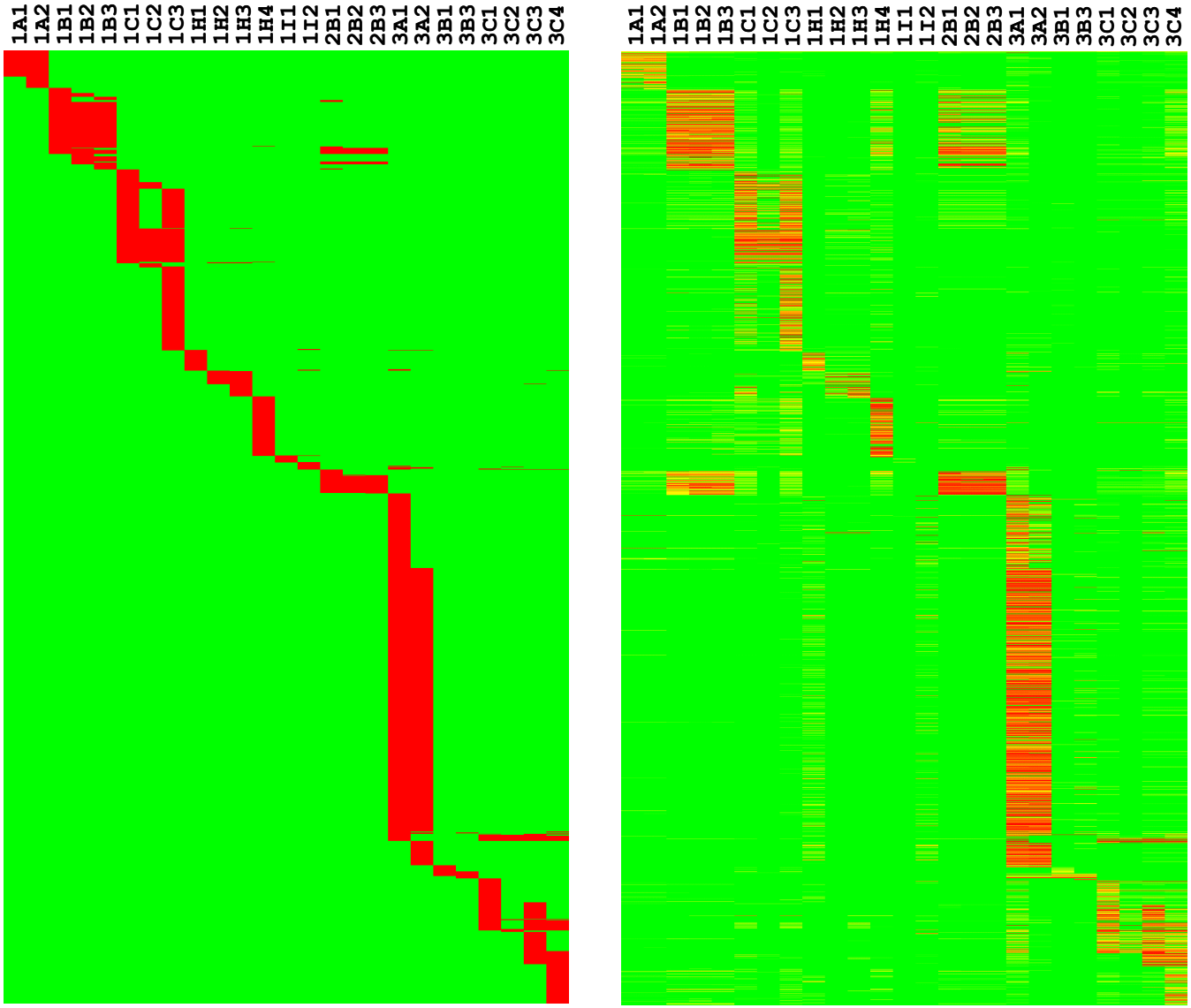


1.7 **2.6** **1.2**

Closest distance to target descriptors

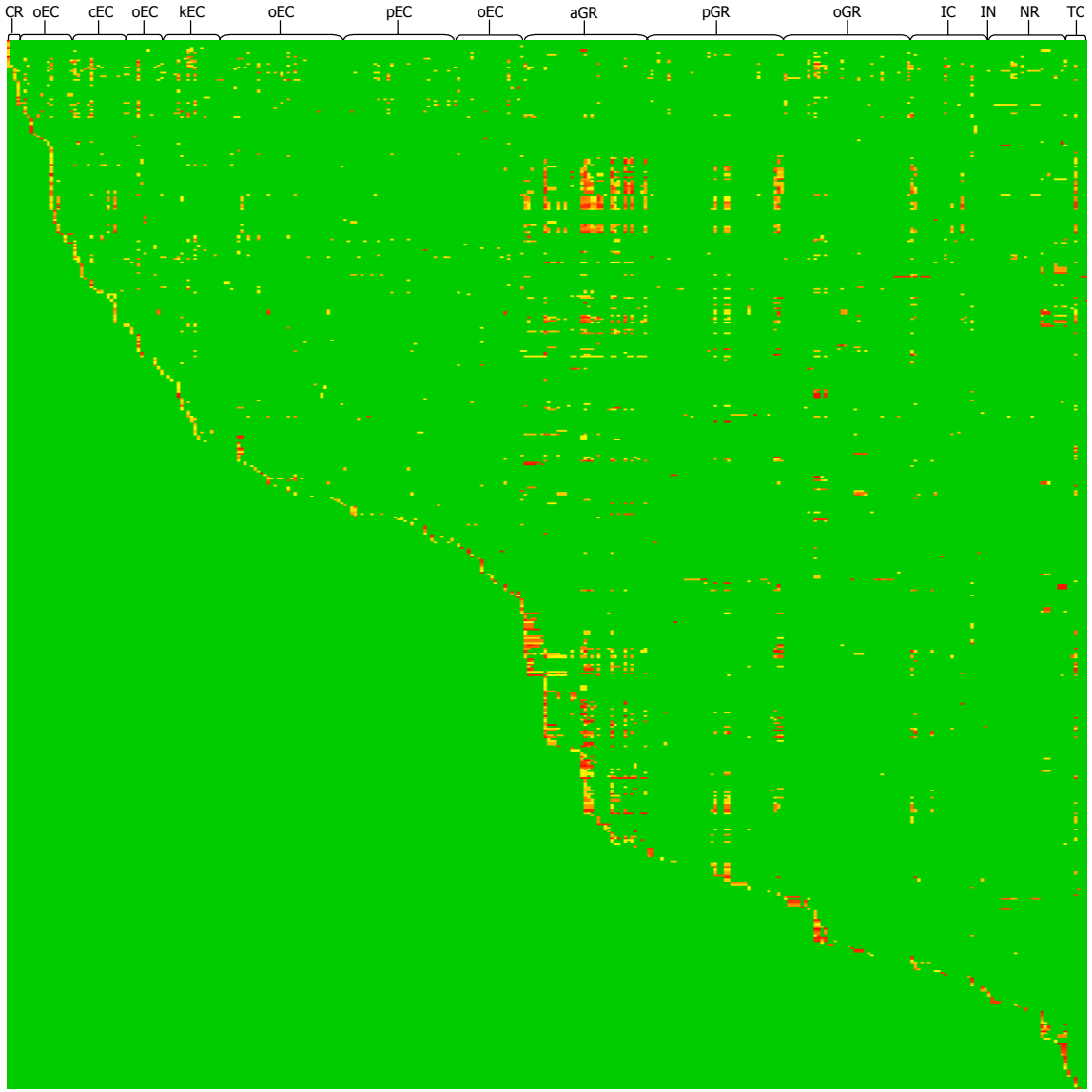
. . .

Validation example: nuclear receptor family



J Chem Inf Model 2006; 46: 2725-2736

Target ID case #1: Drug profiling (767 drugs x 684 targets)



Comb Chem High Through Screen (in press)

Target ID case #1: Drug profiling (767 drugs x 684 targets)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation

René Schade, M.D., Frank Andersohn, M.D., Samy Suissa, Ph.D., Wilhelm Haverkamp, M.D., Ph.D., and Edeltraut Garbe, M.D., Ph.D.

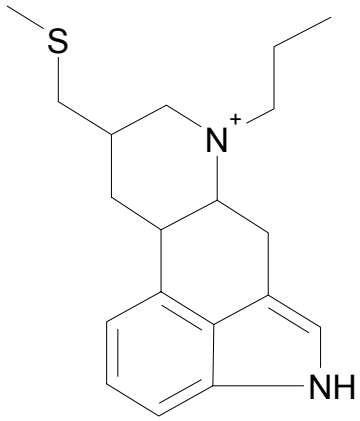
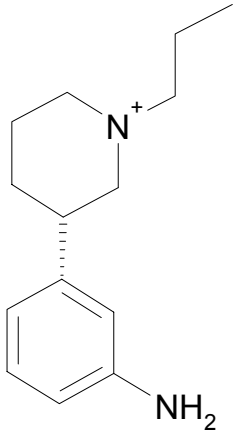
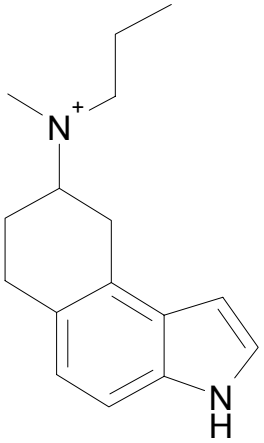
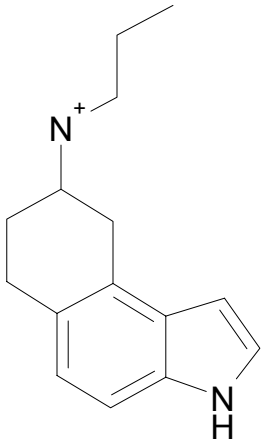
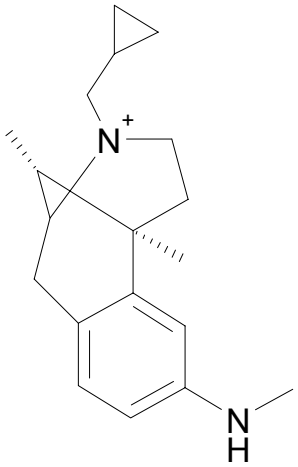
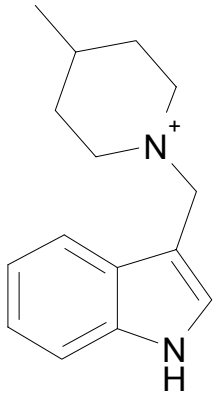
ABSTRACT

BACKGROUND

Case reports and echocardiographic studies suggest that the ergot-derived dopamine agonists pergolide and cabergoline, used in the treatment of Parkinson's disease and the restless legs syndrome, may increase the risk of cardiac-valve regurgitation.

5-HT$_{2B}$ agonism!

Target ID case #1: Drug profiling (767 drugs x 681 targets)

Pergolide 	D_2, 5-HT_{1A} 0.29 	D_3, 5-HT_{1D} 0.31 
5-HT_{1B} 0.34 	δ, κ, μ opioid 0.50 	D_4 0.51 

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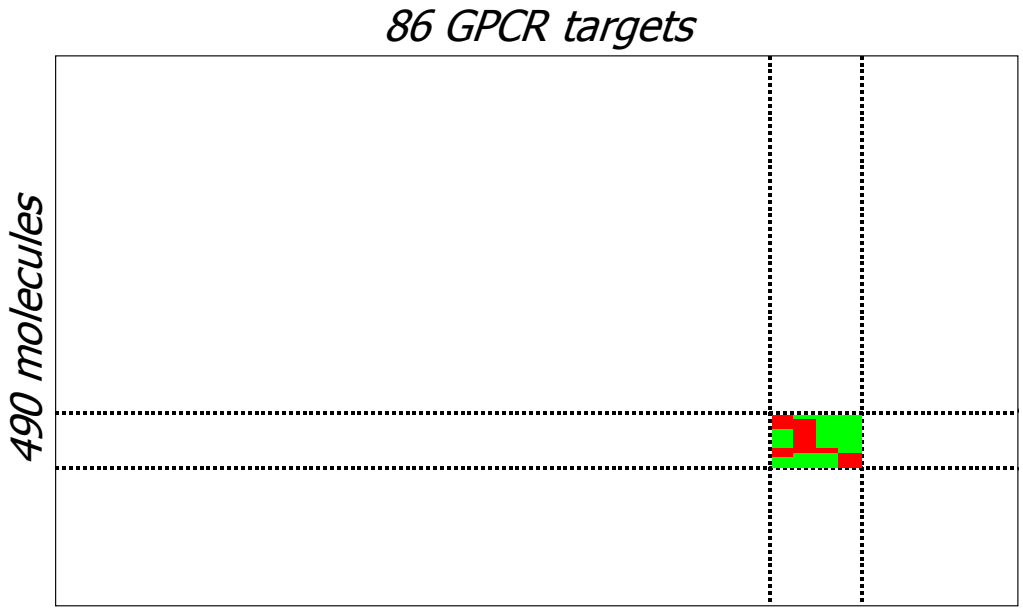
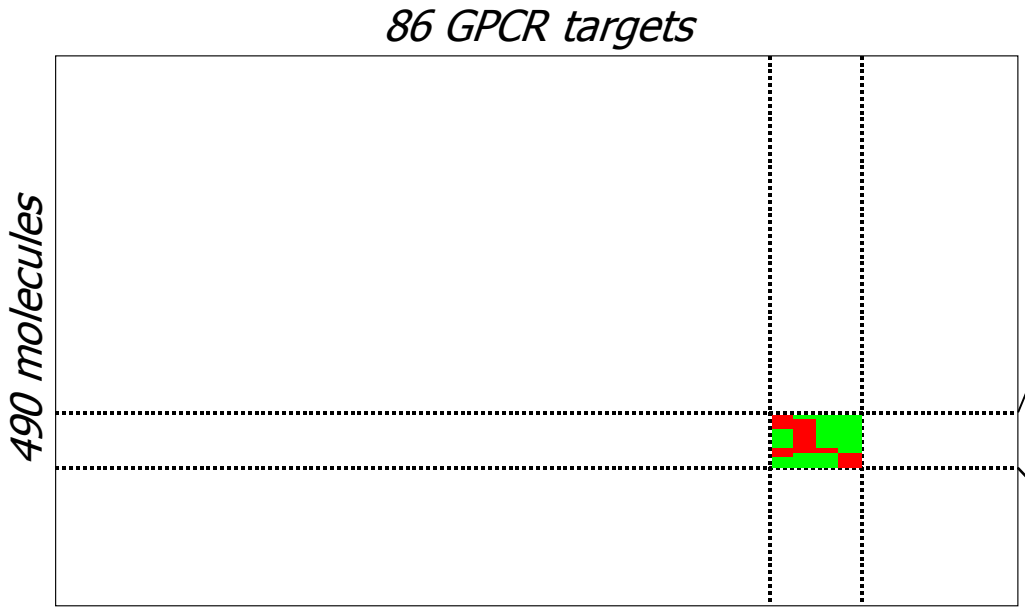
Target ID case #2: Targeted chemical biology



Target ID case #2: Targeted chemical biology



A1	A2a	A2b	A3
15	3	14	29
11	23	0	0
26	5	0	23
1	0	0	15
8	6	0	3
19	5	3	32
7	14	0	0
27	15	**55**	26
38	20	0	**71**
10	15	0	2
0	10	10	28

Target ID case #2: Targeted chemical biology