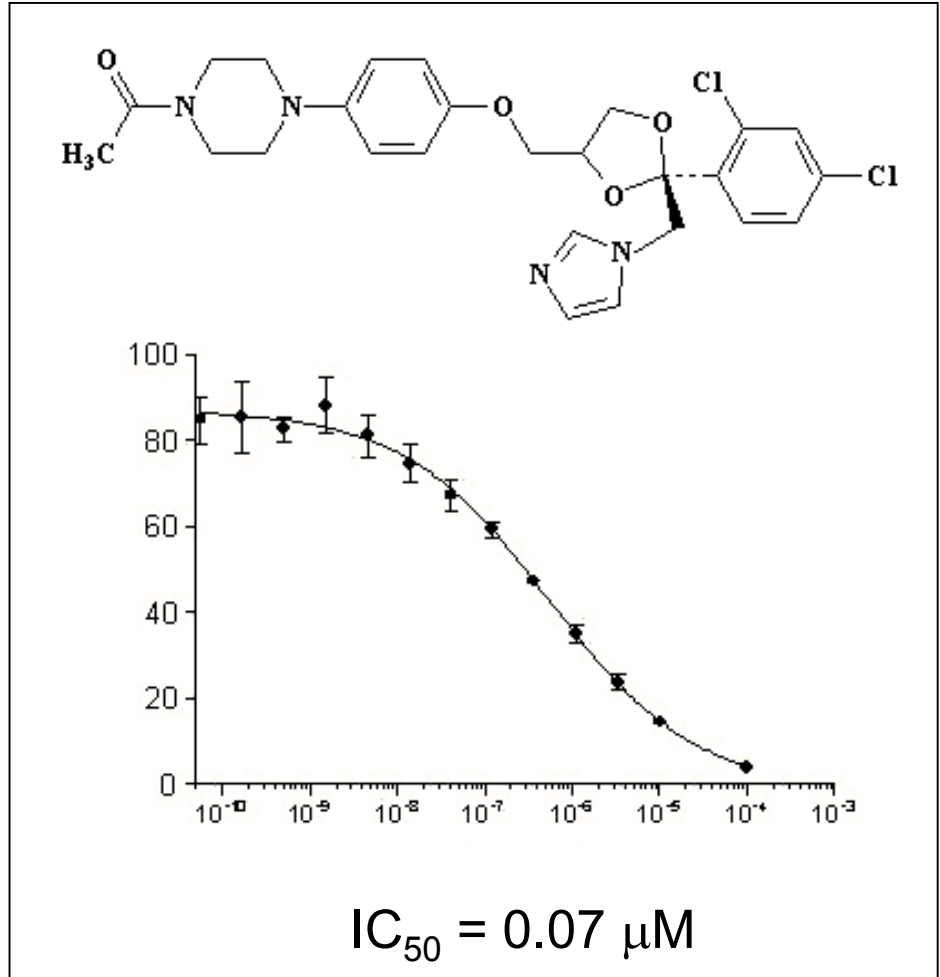


Knowledge-based Approaches to Pharmacological Profiling

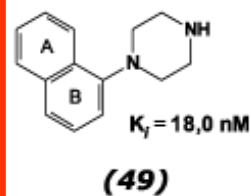
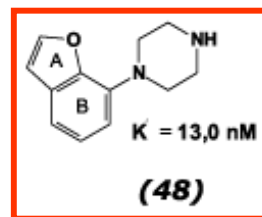
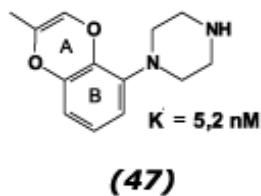
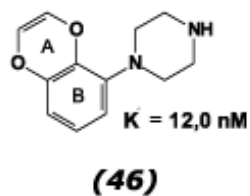
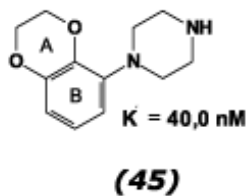
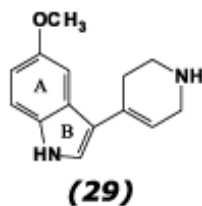
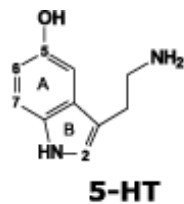
Jordi MESTRES

Chemogenomics Laboratory
Research Unit on Biomedical Informatics (GRIB)
Municipal Institute of Medical Research (IMIM)
Barcelona

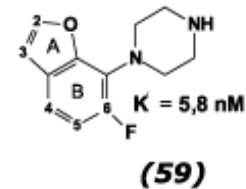
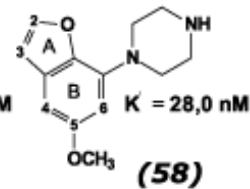
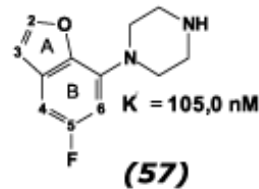
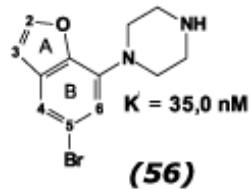
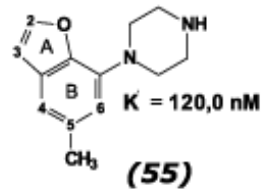
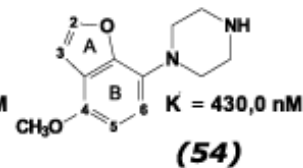
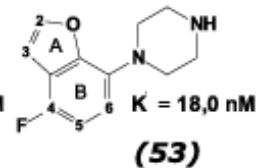
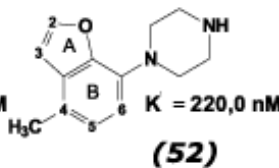
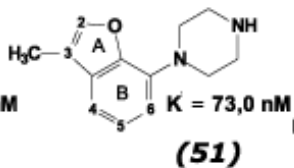
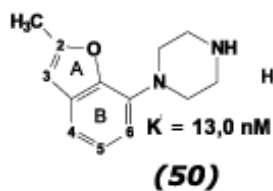
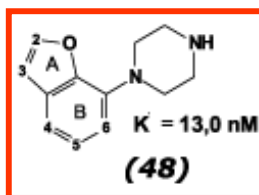
Traditional drug discovery



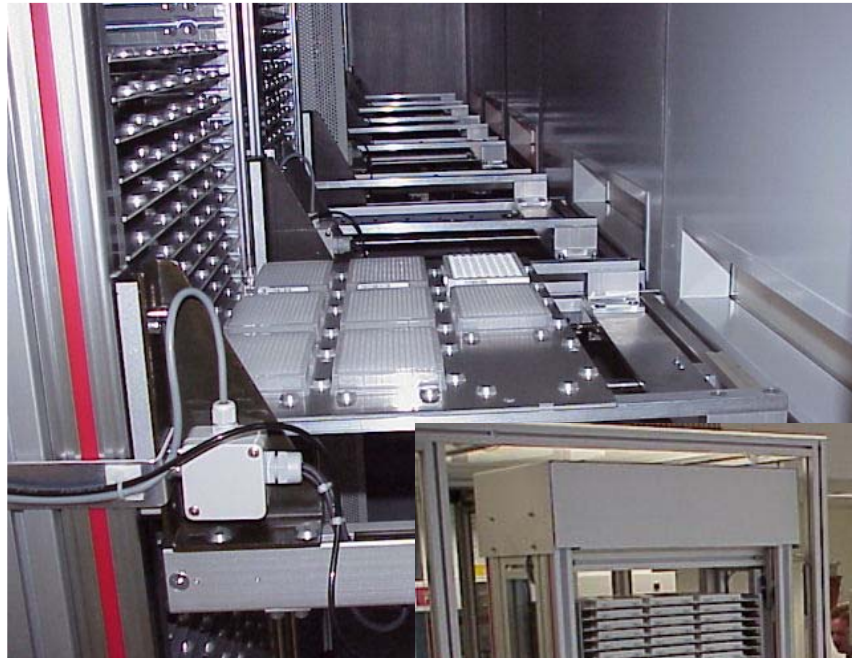
Traditional medicinal chemistry & pharmacology



Traditional medicinal chemistry & pharmacology



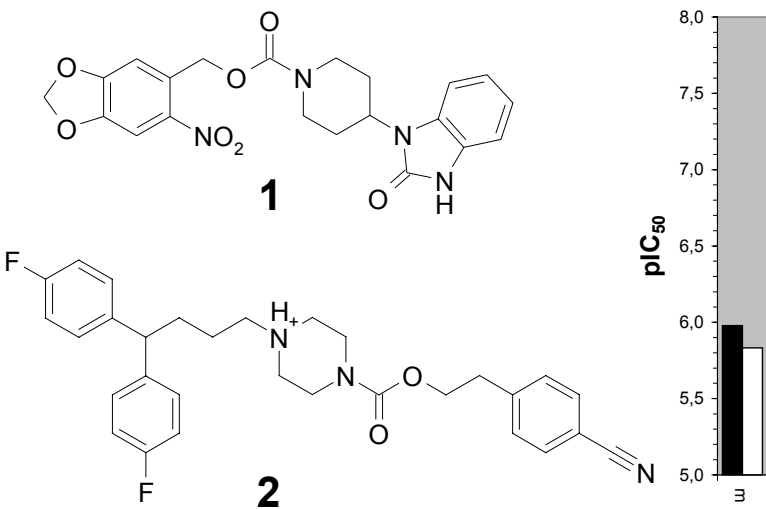
High-throughput screening



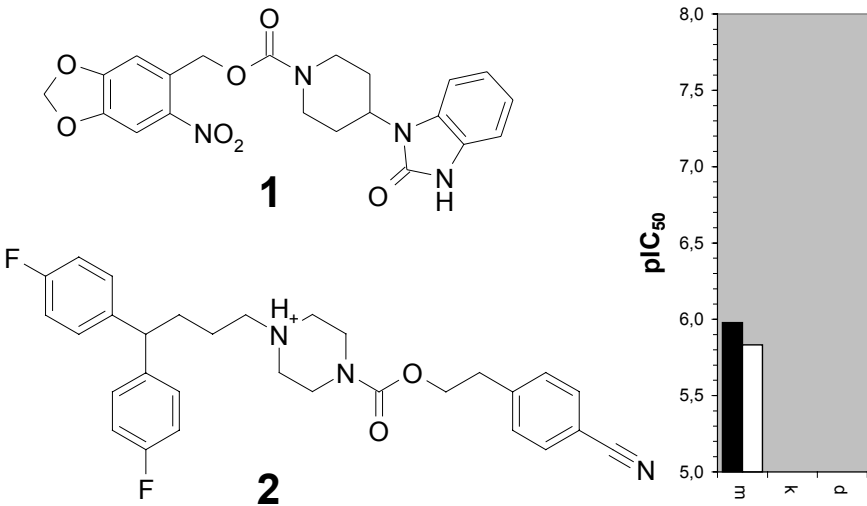
Traditional drug discovery

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

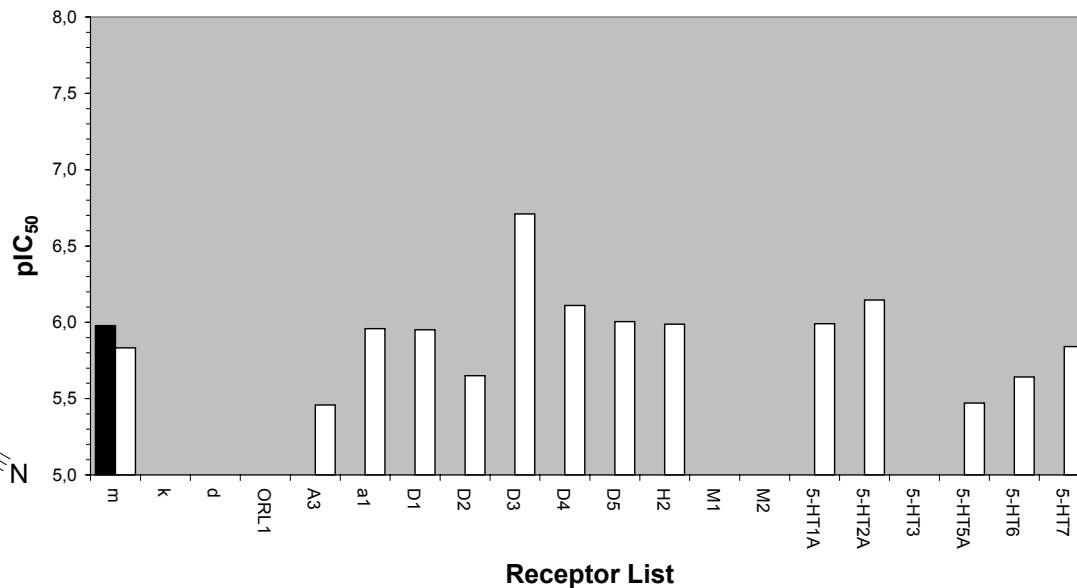
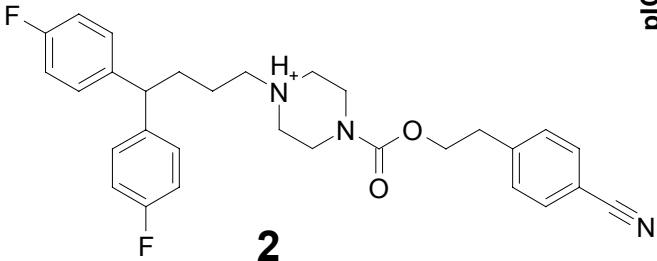
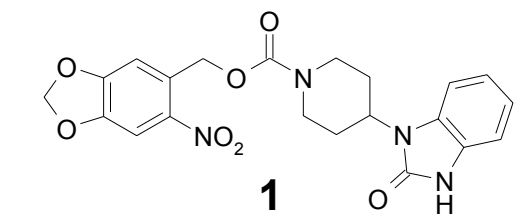
The need to go beyond traditional drug discovery



The need to go beyond traditional drug discovery

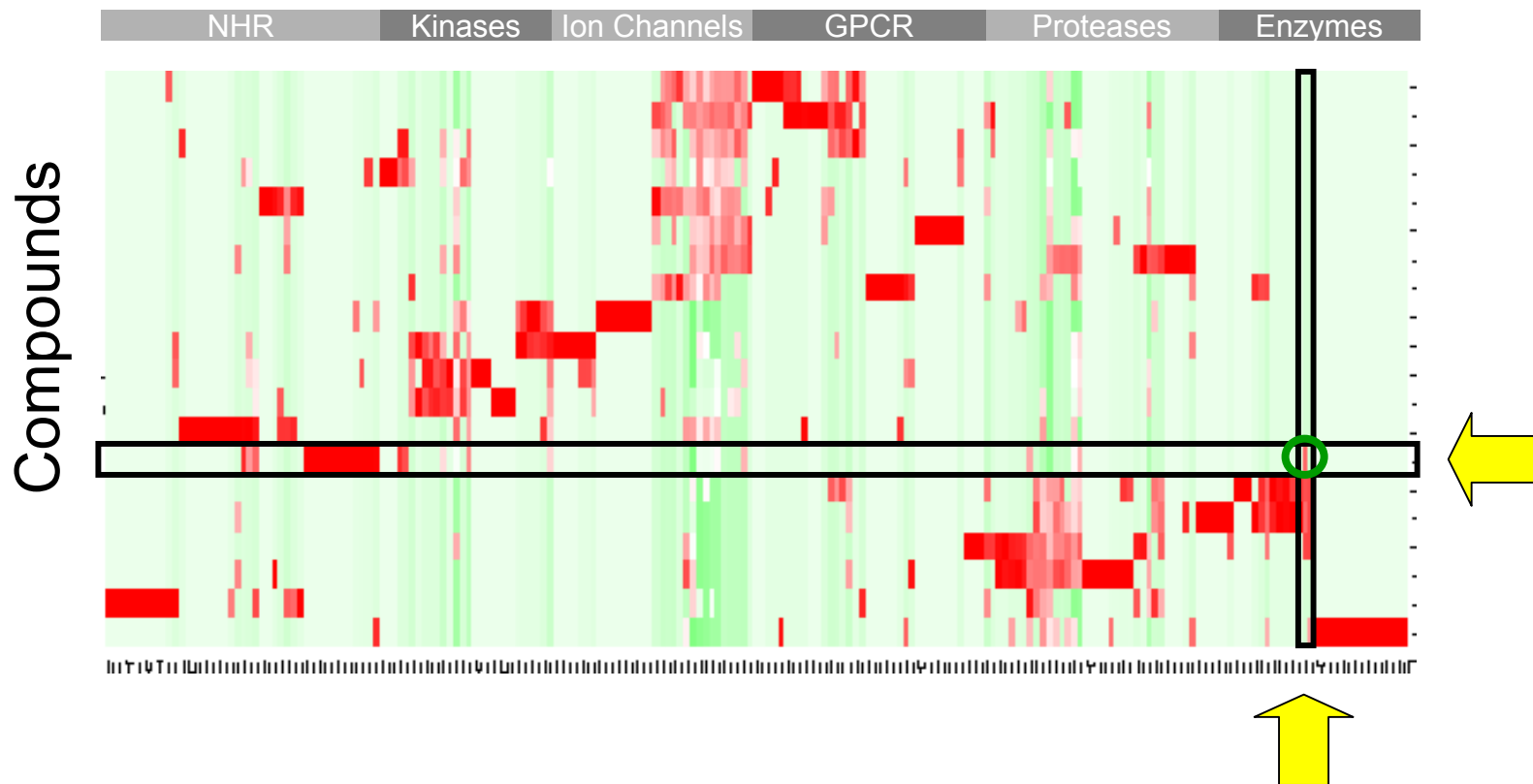


The need to go beyond traditional drug discovery



Necessary drug discovery

Targets

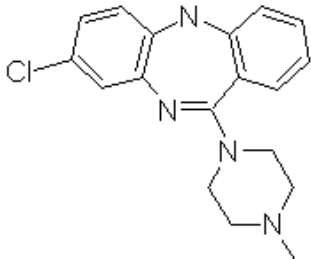


Elements of knowledge-based approaches

- ❑ Collect and store prior knowledge
 - Ligand-based approaches > annotated chemical libraries
 - Structure-based approaches > protein data bank

- ❑ Exploit prior knowledge
 - Ligand-based approaches > molecular descriptors
 - Structure-based approaches > protein-ligand interactions

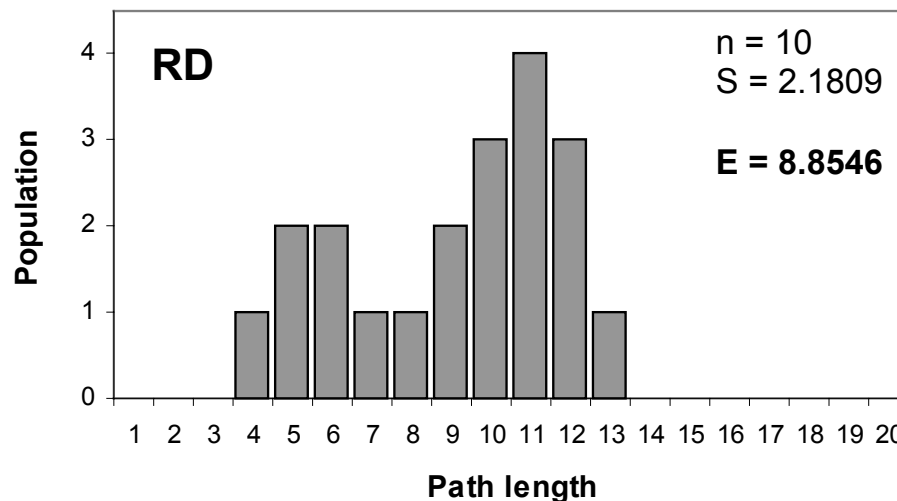
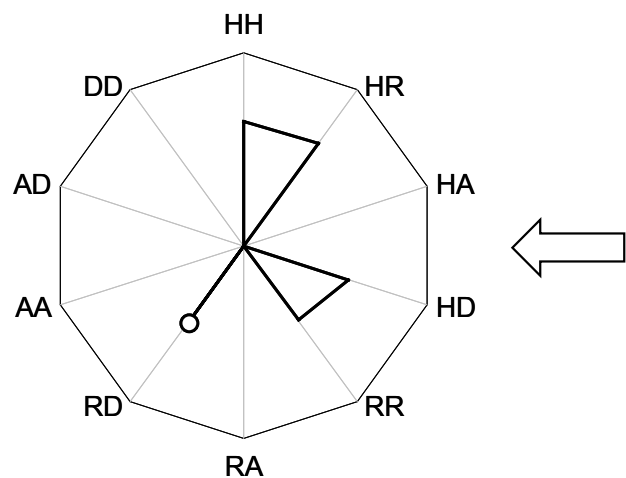
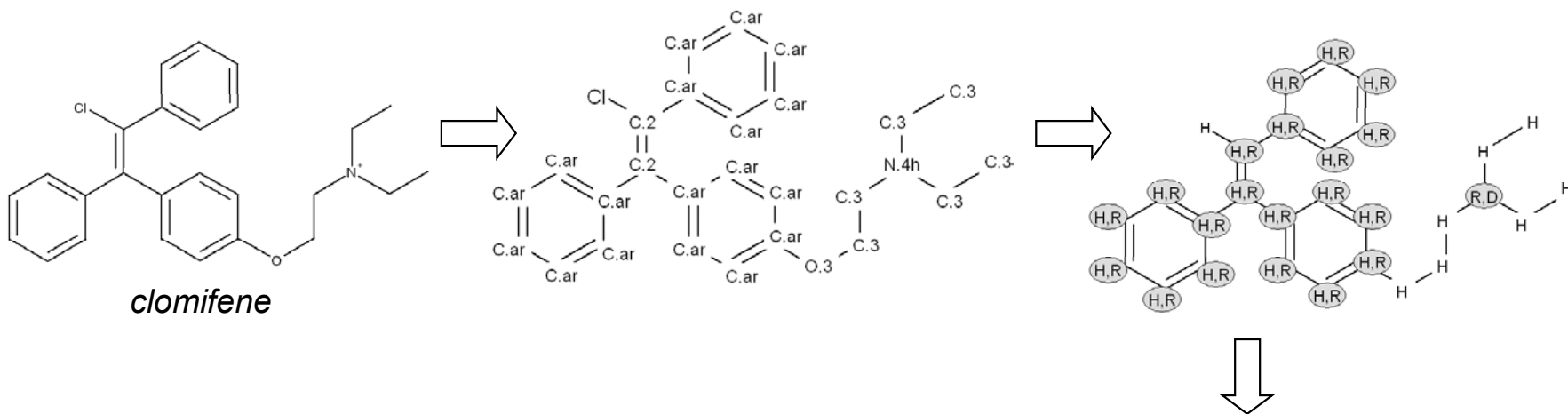
Annotated chemical libraries: WOMBAT

Bioactivity Summary	Target & Biological Information	Computed Chemical Properties																																																												
Sunset Molecular Discovery, LLC www.sunsetmolecular.com		WOMBAT																																																												
		SMDL-00001128																																																												
		53																																																												
structure																																																														
																																																														
<chem>CN1CCN(CC1)C2=Nc3cc(ccc3Nc4c2cccc4)Cl</chem>																																																														
<table border="1"> <thead> <tr> <th>SMDL_ID</th> <th>molname</th> </tr> </thead> <tbody> <tr> <td>1128</td> <td>clozapine</td> </tr> <tr> <th>generic_name</th> <th>drug</th> </tr> <tr> <td>clozapine</td> <td>1</td> </tr> <tr> <th colspan="2">reference</th> </tr> <tr> <td colspan="2">Bioorg. Med. Chem. Lett. 12(4)-2002 633-636</td> </tr> <tr> <th>formula</th> <th>mol_weight</th> </tr> <tr> <td>C₁₈H₁₉ClN₄</td> <td>326.8319</td> </tr> <tr> <th>ALogP</th> <th>ExpLogP</th> </tr> <tr> <td>3.8000</td> <td>3.2300</td> </tr> <tr> <th>ALogS</th> <th>ExpLogS</th> </tr> <tr> <td>-3.2300</td> <td></td> </tr> </tbody> </table>			SMDL_ID	molname	1128	clozapine	generic_name	drug	clozapine	1	reference		Bioorg. Med. Chem. Lett. 12(4)-2002 633-636		formula	mol_weight	C ₁₈ H ₁₉ ClN ₄	326.8319	ALogP	ExpLogP	3.8000	3.2300	ALogS	ExpLogS	-3.2300																																					
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structure_keywords																																																														
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<table border="1"> <thead> <tr> <th>act#</th> <th>targ_type</th> <th>target_name</th> <th>act_type</th> <th>class</th> <th>value</th> <th>min</th> <th>max</th> <th>inhib%</th> <th>lig_eff</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>receptor</td> <td>D1</td> <td>Ki</td> <td>A</td> <td>6.3768</td> <td>6.3768</td> <td>6.3768</td> <td></td> <td>0.3937</td> </tr> <tr> <td>2</td> <td>receptor</td> <td>D2L</td> <td>Ki</td> <td>A</td> <td>7.3872</td> <td>7.3872</td> <td>7.3872</td> <td></td> <td>0.4561</td> </tr> <tr> <td>3</td> <td>receptor</td> <td>D2S</td> <td>Ki</td> <td>A</td> <td>7.5528</td> <td>7.5528</td> <td>7.5528</td> <td></td> <td>0.4663</td> </tr> <tr> <td>4</td> <td>receptor</td> <td>D3</td> <td>Ki</td> <td>A</td> <td>6.0177</td> <td>6.0177</td> <td>6.0177</td> <td></td> <td>0.3715</td> </tr> <tr> <td>5</td> <td>receptor</td> <td>D4</td> <td>Ki</td> <td>A</td> <td>7.7959</td> <td>7.7959</td> <td>7.7959</td> <td></td> <td>0.4813</td> </tr> </tbody> </table>			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
act#	targ_type	target_name	act_type	class	value	min	max	inhib%	lig_eff																																																					
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5	receptor	D4	Ki	A	7.7959	7.7959	7.7959		0.4813																																																					

Biologically-relevant descriptors: SHED

(I)

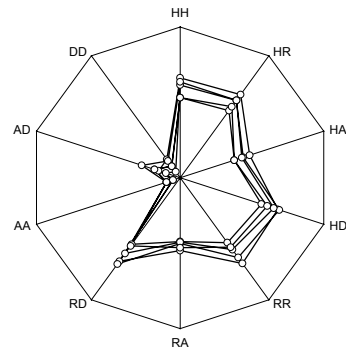
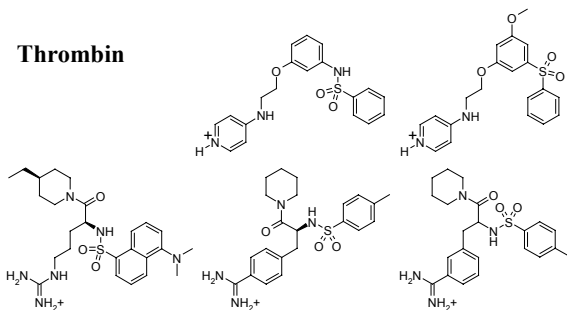
Shannon Entropy Descriptors (SHED)



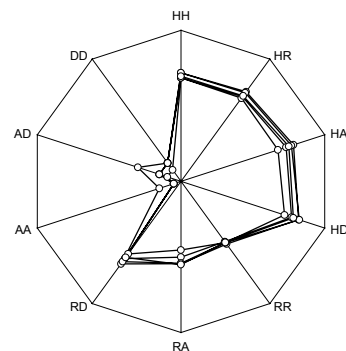
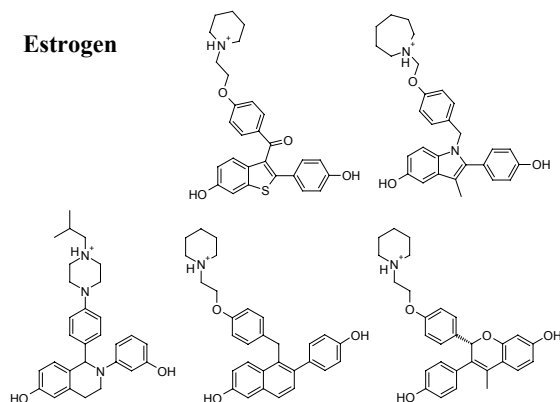
Biologically-relevant descriptors: SHED

(II)

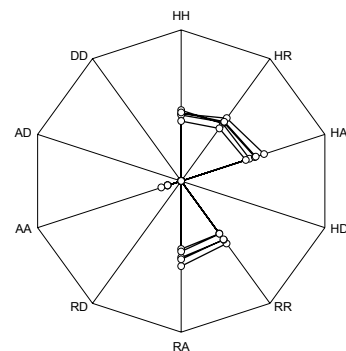
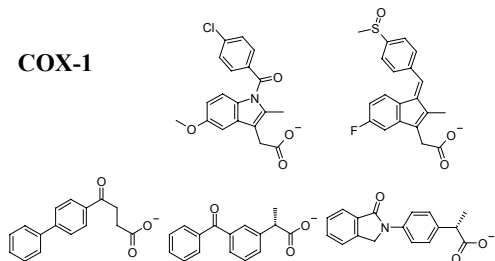
Thrombin



Estrogen

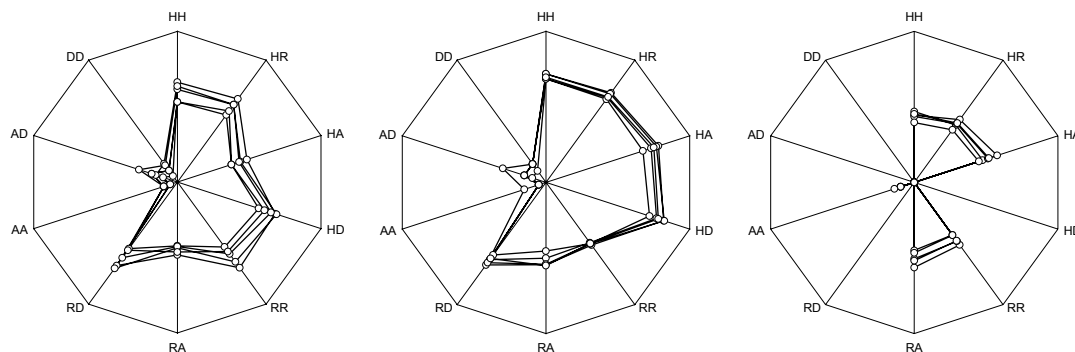


COX-1

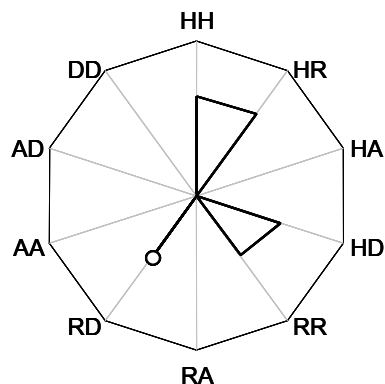


Ligand-based Approach to Chemogenomic Profiling

Targets (Ligand-based Description)



Molecules



1.7

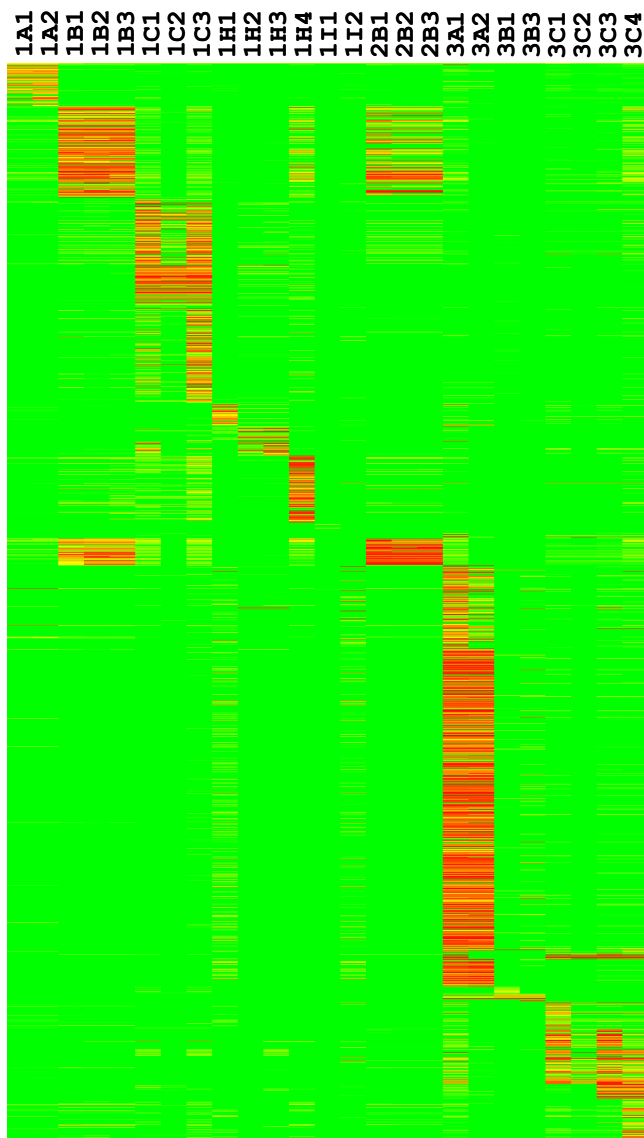
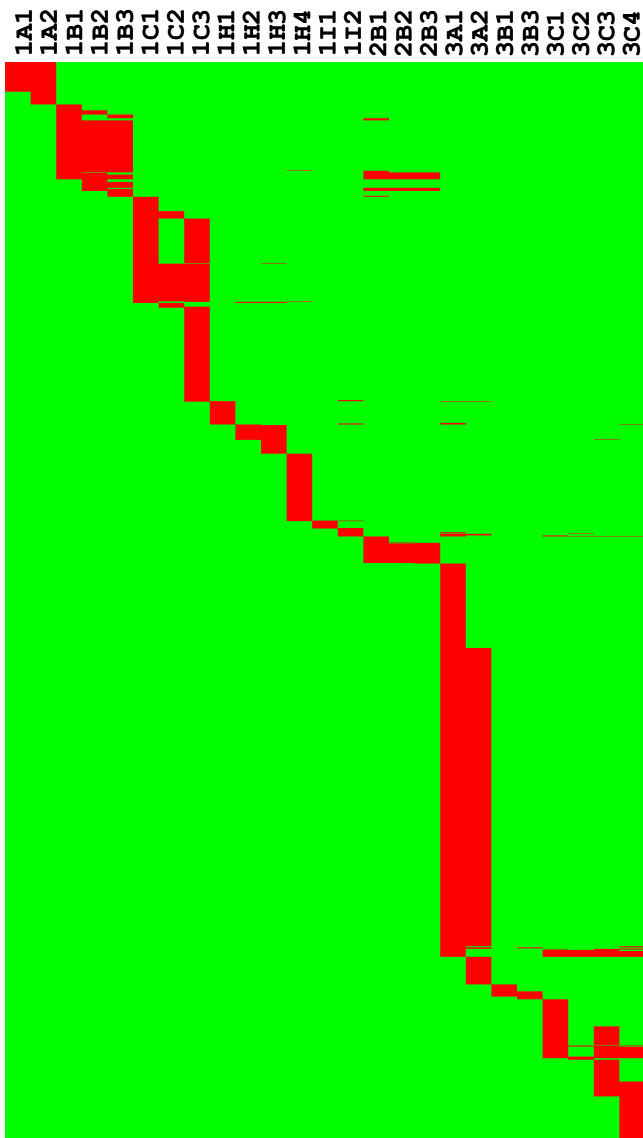
2.6

1.2

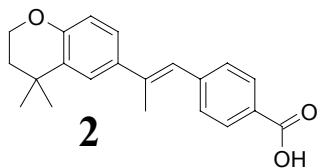
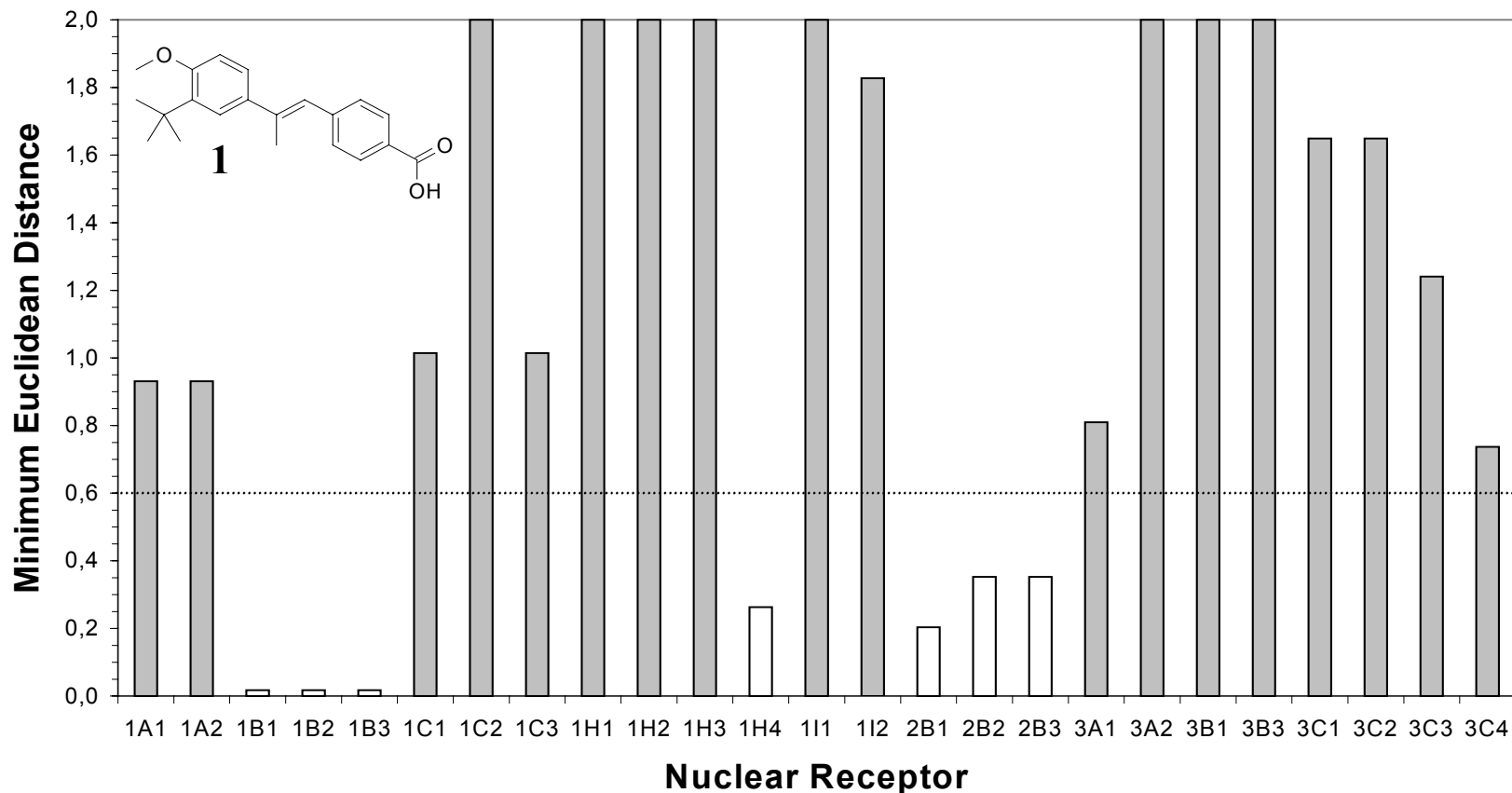
Minimum SHED Euclidean Distance
(closest annotated compound to molecule)

•
•
•

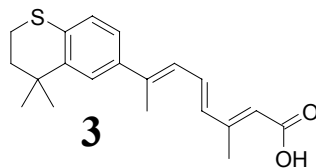
Application to nuclear receptor profiling



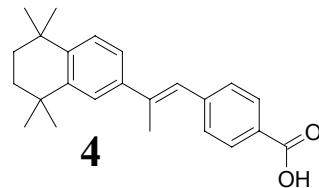
Application to nuclear receptor profiling



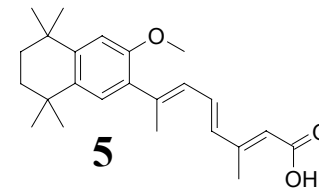
1B1,1B2,1B3



1B1,1B2,1B3,2B1

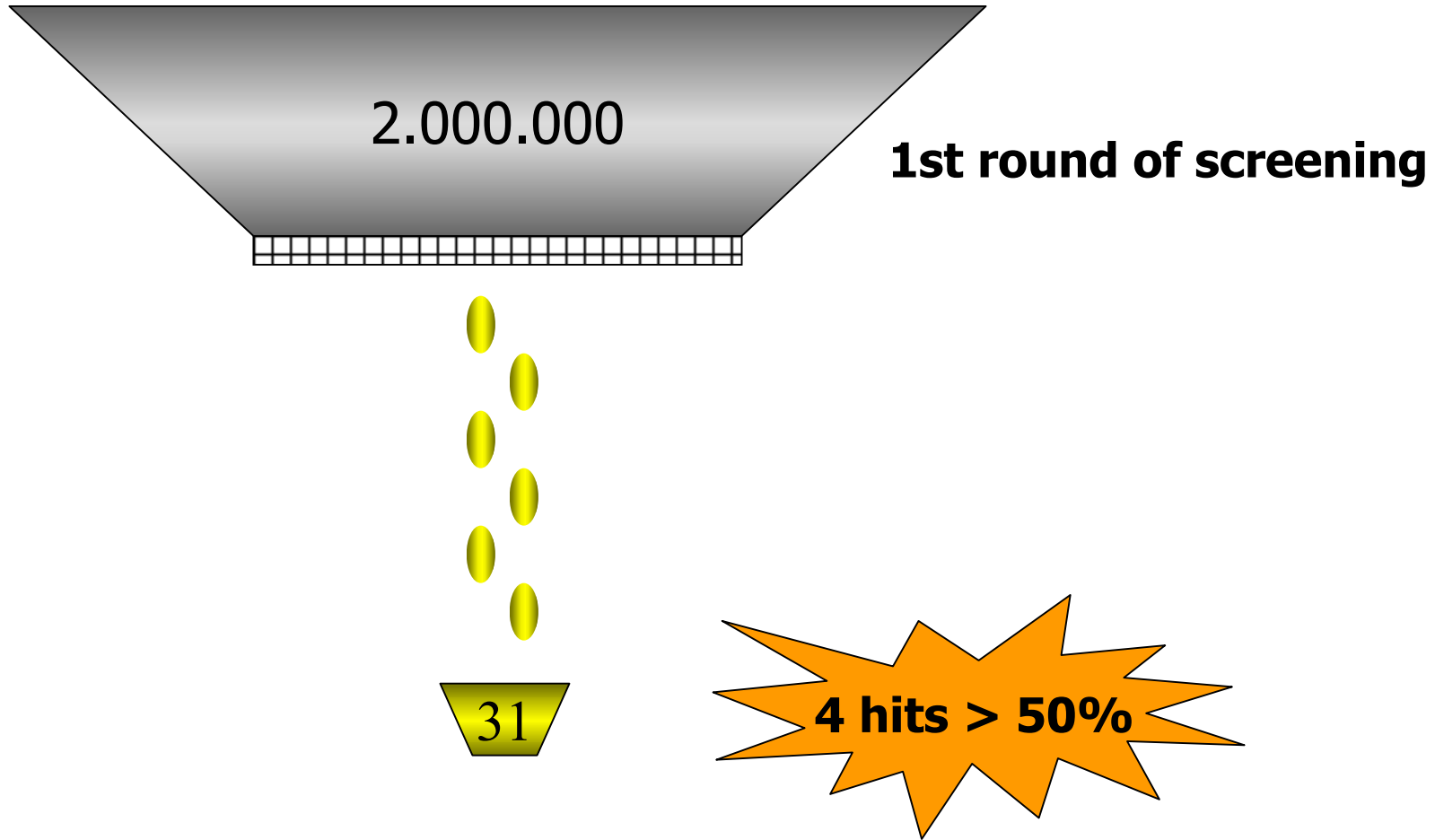


1B1,1B2,1B3,1H4

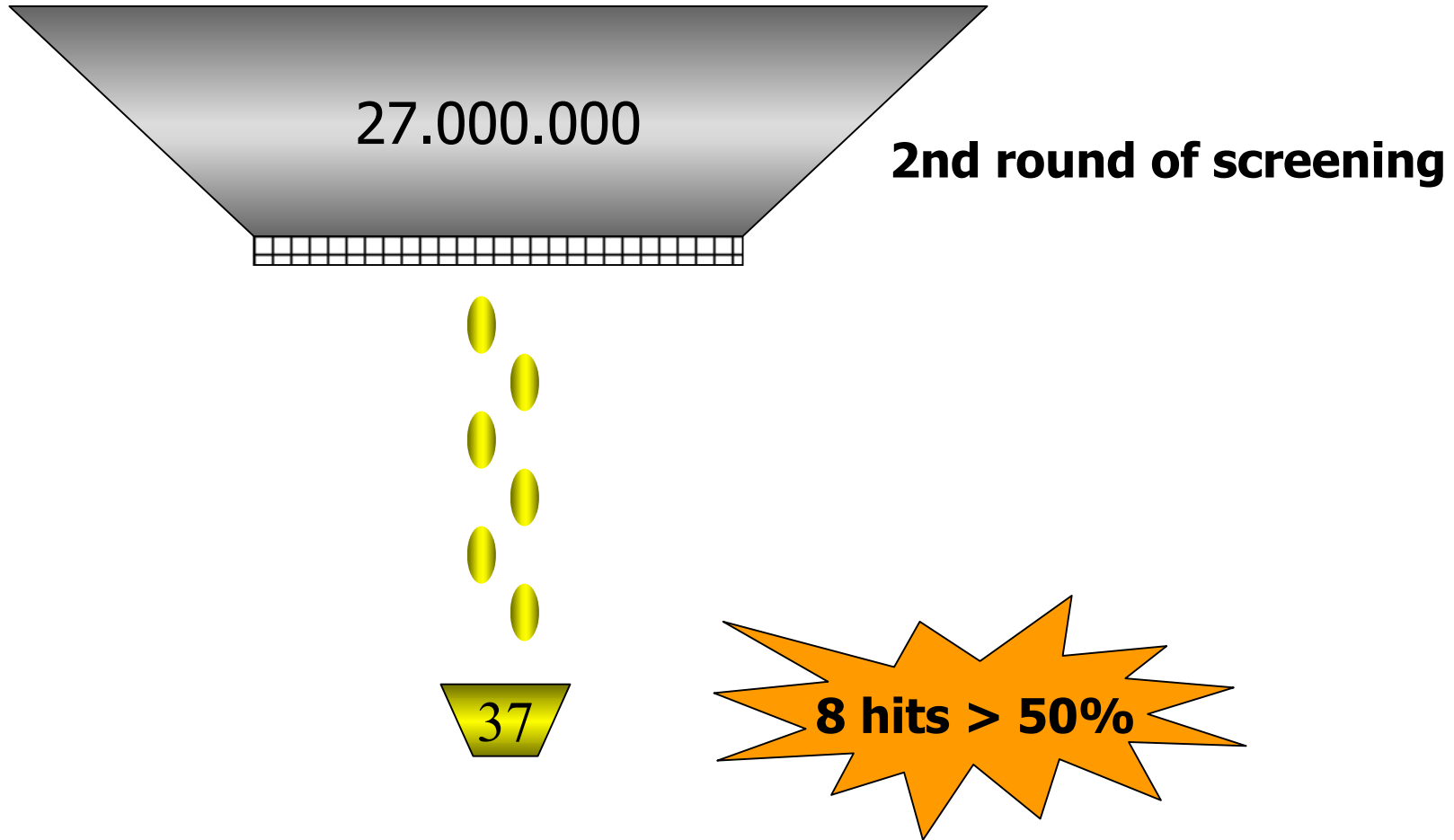


1B1,1B2,1B3,2B1,2B2,2B3

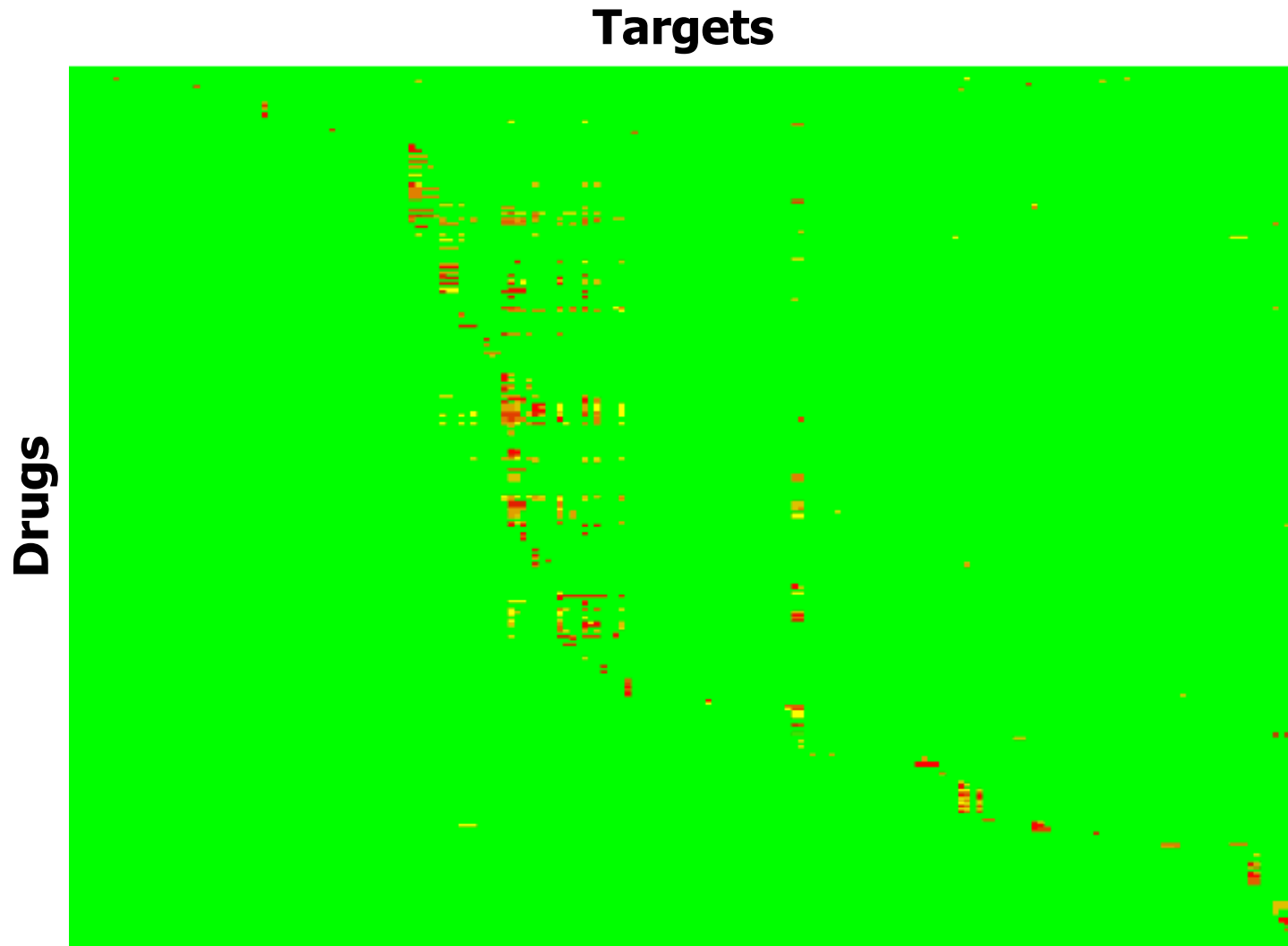
Hit ID case: multiple targets – overactive bladder



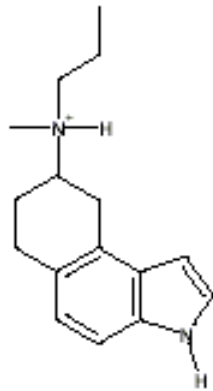
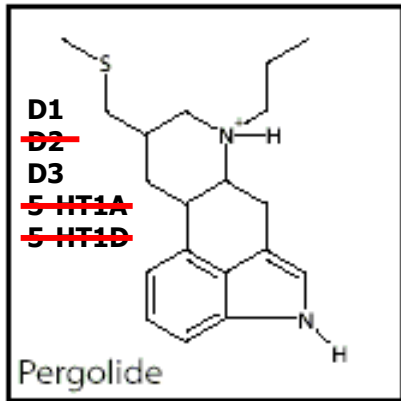
Hit ID case: multiple targets – overactive bladder



Drug repurposing case: 322 drugs x 199 targets



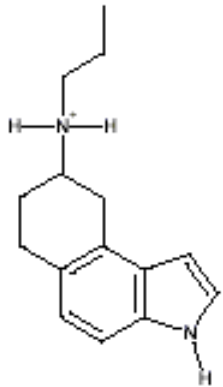
Drug repurposing case: 322 drugs x 199 targets



Euclidean distance : 0.3050

Annotated to : D2

5-HT 1A

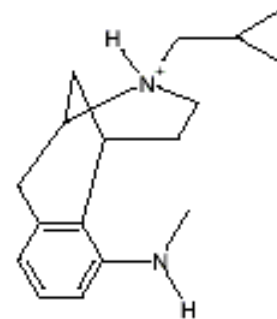


Euclidean distance : 0.3382

Annotated to : D2

5-HT 1A

5-HT 1D



Euclidean distance : 0.5031

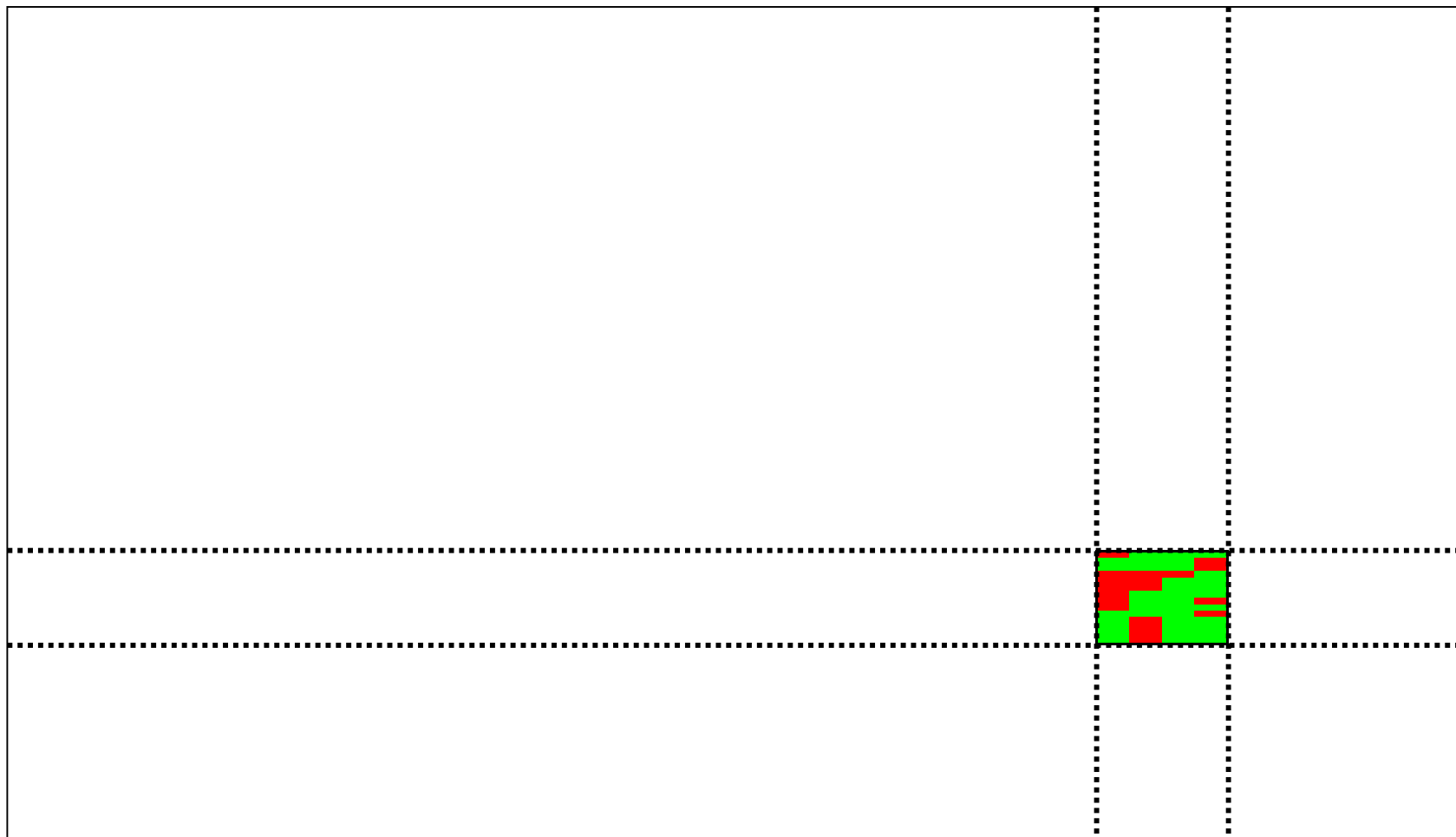
Annotated to : kappa
mu



Target ID case: GPCRs

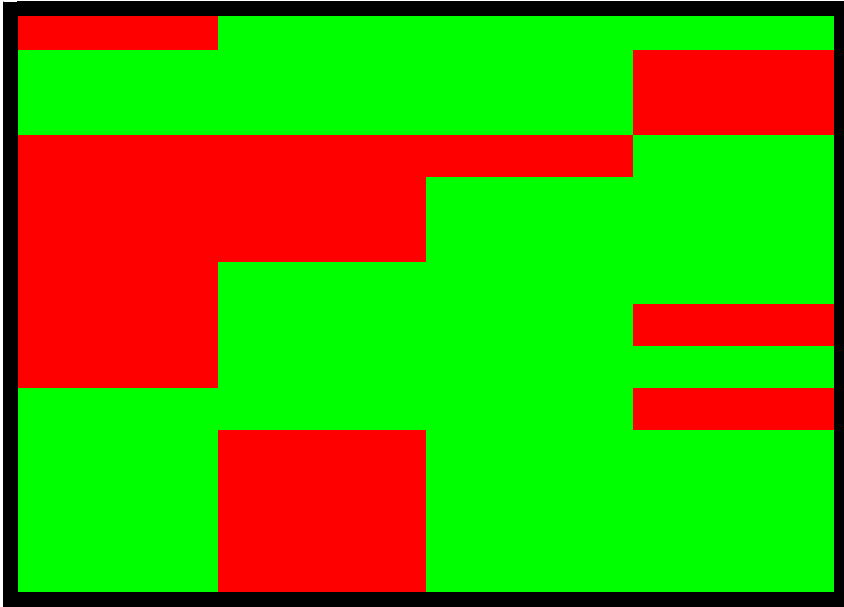
86 targets

490 molecules

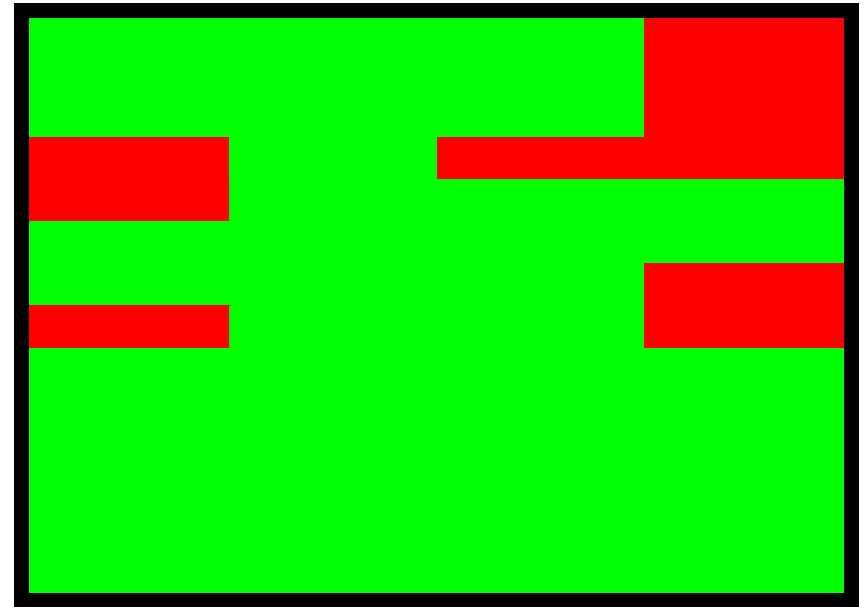


Target ID case: GPCRs

In silico



In vitro



3 hits > 50%

Summary

- We have developed an in silico pharmacology platform that is able to profile millions of compounds on over 400 targets
- The in silico platform is applicable to:
 - hit identification
 - drug repurposing
 - target fishing
 - safety profiling