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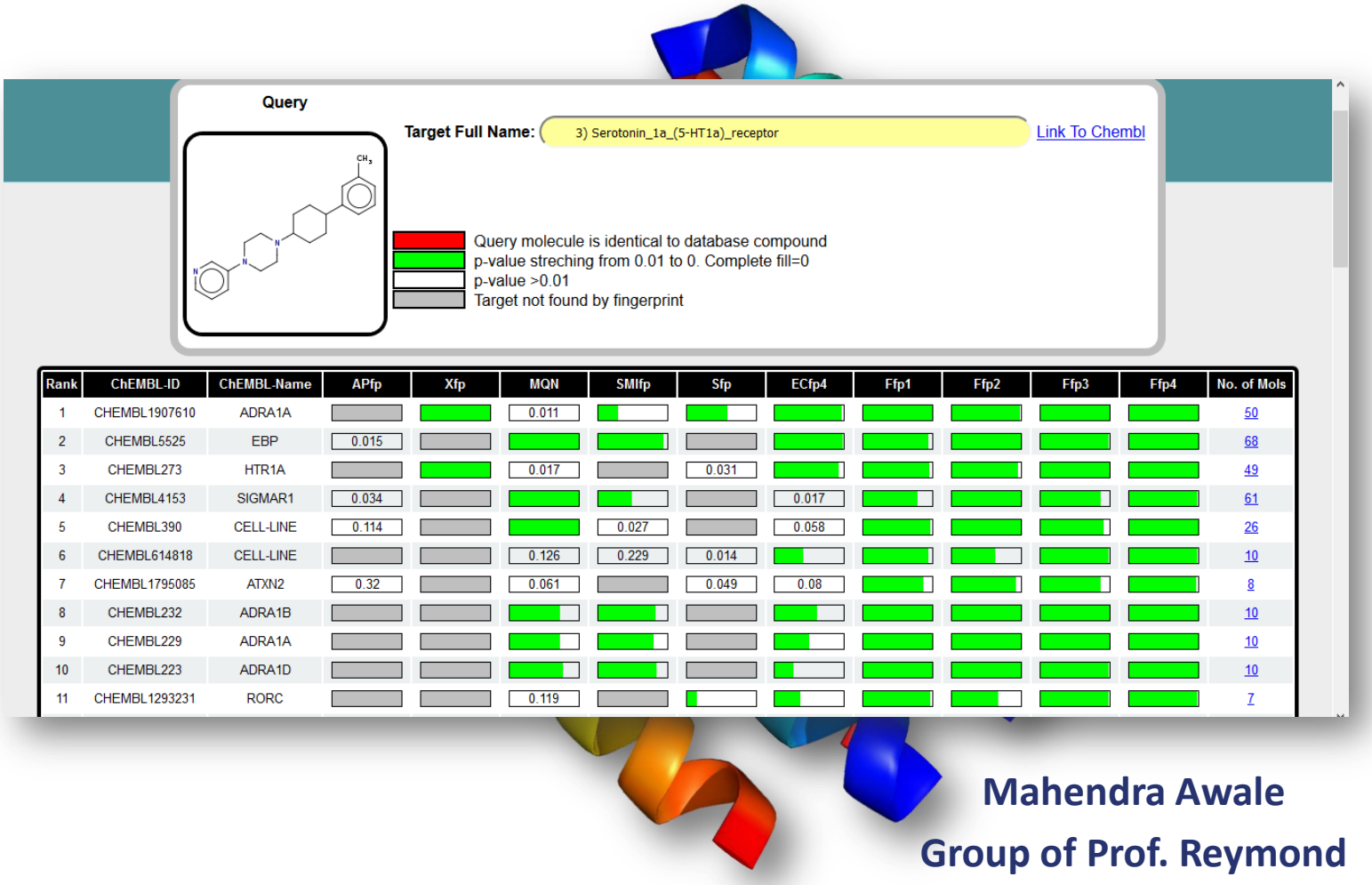
Computational Approaches for Target Prediction



Rank	ChEMBL-ID	ChEMBL-Name	APfp	Xfp	MQN	SMIfp	Sfp	ECfp4	Ffp1	Ffp2	Ffp3	Ffp4	No. of Mols
1	CHEMBL1907610	ADRA1A			0.011								50
2	CHEMBL5525	EBP	0.015										68
3	CHEMBL273	HTR1A			0.017		0.031						49
4	CHEMBL4153	SIGMAR1	0.034					0.017					61
5	CHEMBL390	CELL-LINE	0.114			0.027		0.058					26
6	CHEMBL614818	CELL-LINE			0.126	0.229	0.014						10
7	CHEMBL1795085	ATXN2	0.32		0.061		0.049	0.08					8
8	CHEMBL232	ADRA1B											10
9	CHEMBL229	ADRA1A											10
10	CHEMBL223	ADRA1D											10
11	CHEMBL1293231	RORC			0.119								7

Mahendra Awale

Group of Prof. Reymond

Department of Chem. & Biochem.

University of Berne

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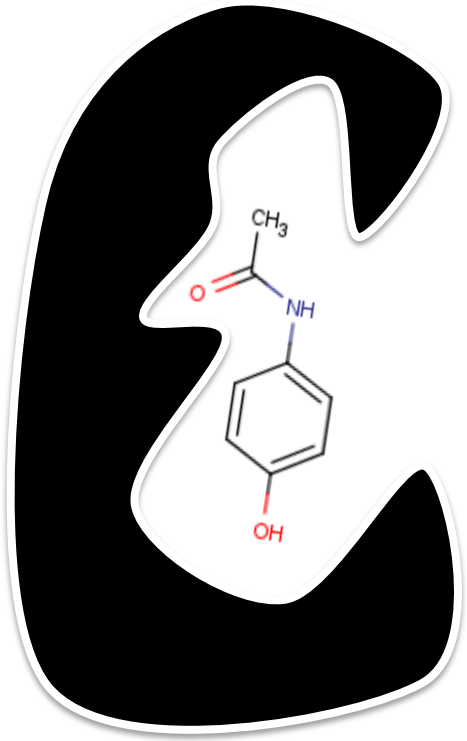
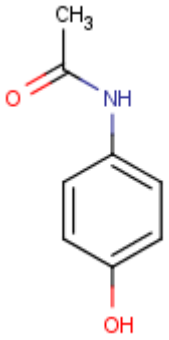
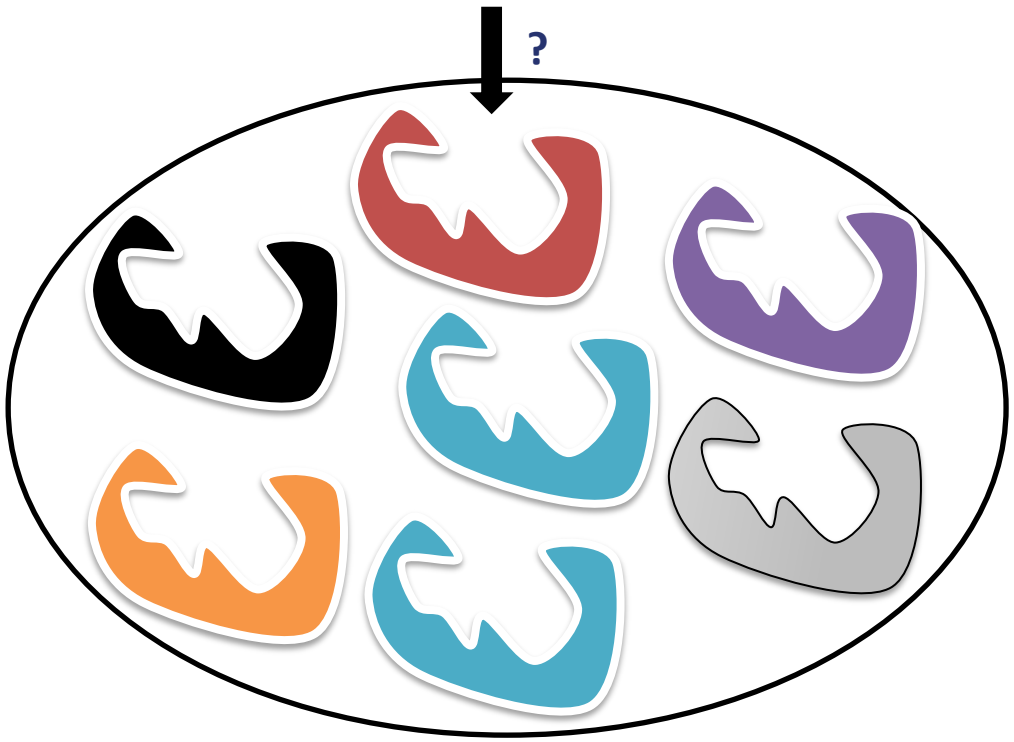
Target Protein Identification



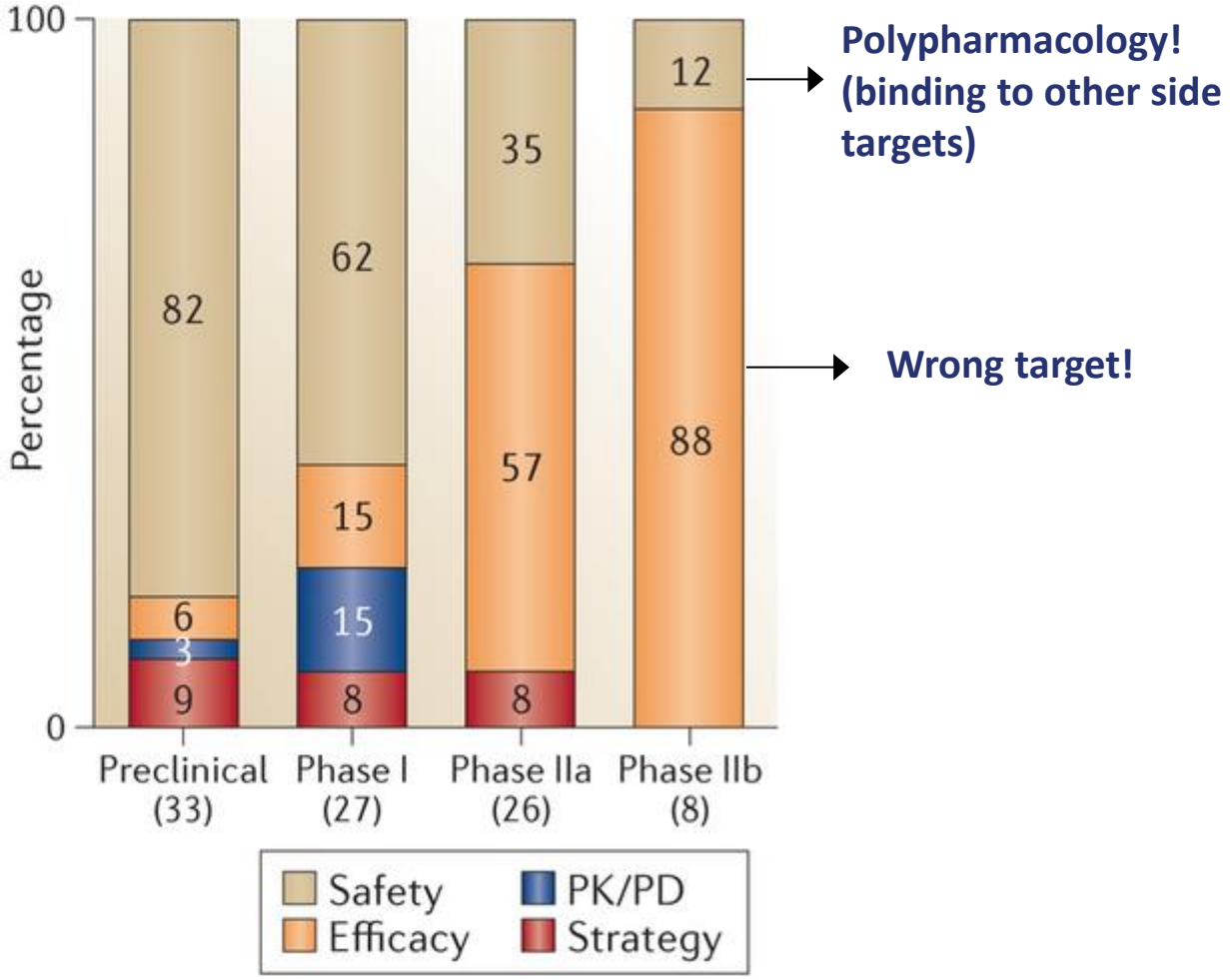
Primary target?
e.g. Compounds from phenotypic screening



Side targets?
(Polypharmacology)



Reasons for project closure at Astrazeneca during 2005-2010



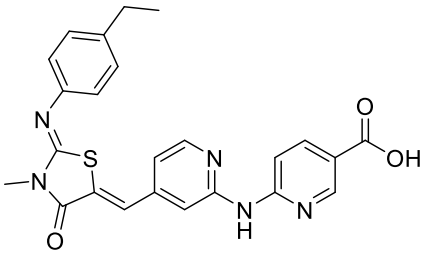
Nature Reviews Drug Discovery 2014, Volume: 13, Pages:419–431

Computational methods for target prediction

Ligand-based target prediction models

Database containing structures of known bioactive compounds

- Chemical similarity searching
- Similarity values based statistical models (e.g Evd)
- Fingerprint based machine learning models (e.g. Naive Bayes)



Query compound

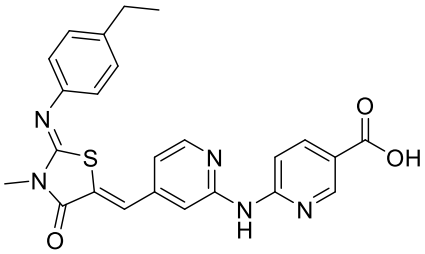
Receptor-based target prediction models

Database containing 3D-structures of target proteins

- Reverse docking
- Receptor-based pharmacophore models

List of predicted targets

Chemical similarity searching for target prediction



Query compound

Calculate similarity

Database

Target A-Ligand set
Target B-Ligand set
Target C-Ligand set
.....

Max. similarity sorting

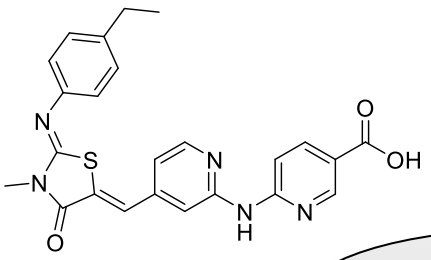
Target A-1 NN score
Target B-1 NN score
Target C-1 NN score
.....

Avg. Similarity sorting

Target A-average score
Target B-average score
Target C-average score
.....

averge similartiy score considering *K* nearest neighbours or all compounds for each target

Chemical similarity searching with Statistical model



Calculate similarity

Database

Target A-Ligand set
Target B-Ligand set
Target C-Ligand set
.....

Max. similarity

Target A-1 NN score
Target B-1 NN score
Target C-1 NN score
.....

P-value sorting

Target A-P-value
Target B-P-value
Target C-P-value
.....

Avg. Similarity

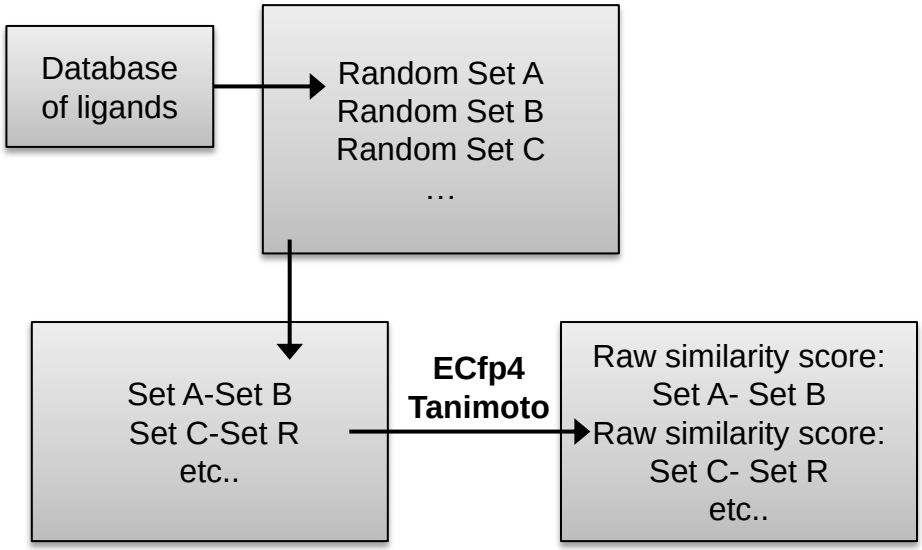
Target A-average score
Target B-average score
Target C-average score
.....

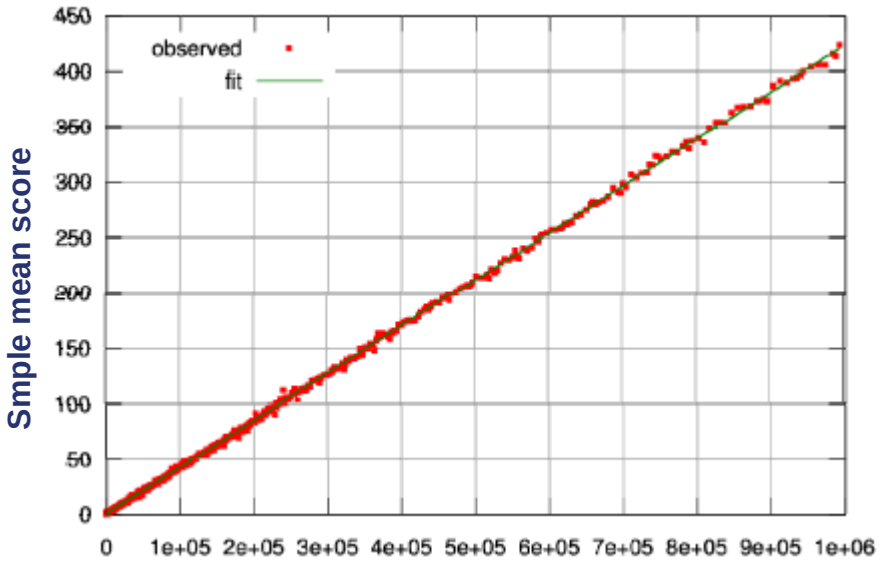
P-value sorting

Target A-P-value
Target B-P-value
Target C-P-value
.....

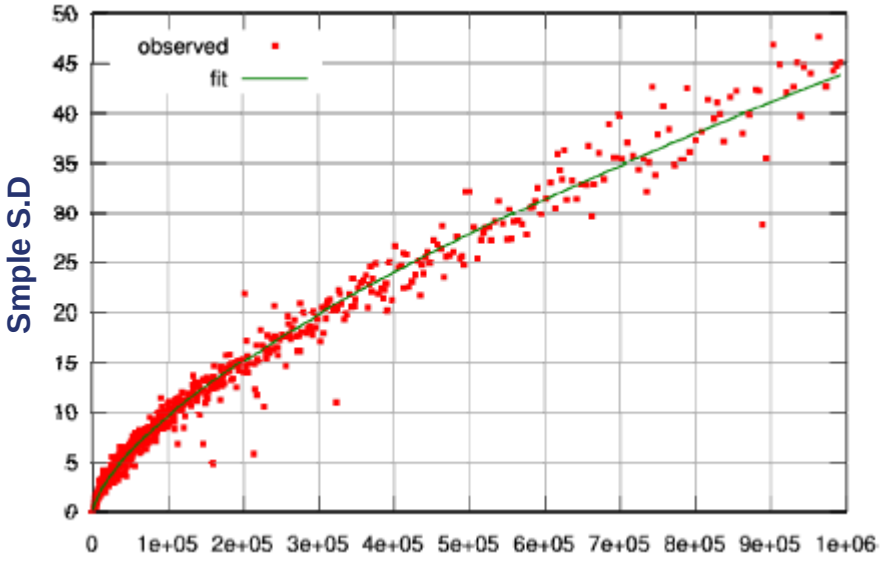
Averge similartiy score considering K nearest neighbours or all compounds for each target

Chemical similarity searching with Statistical model. (Example is shown for SEA method)

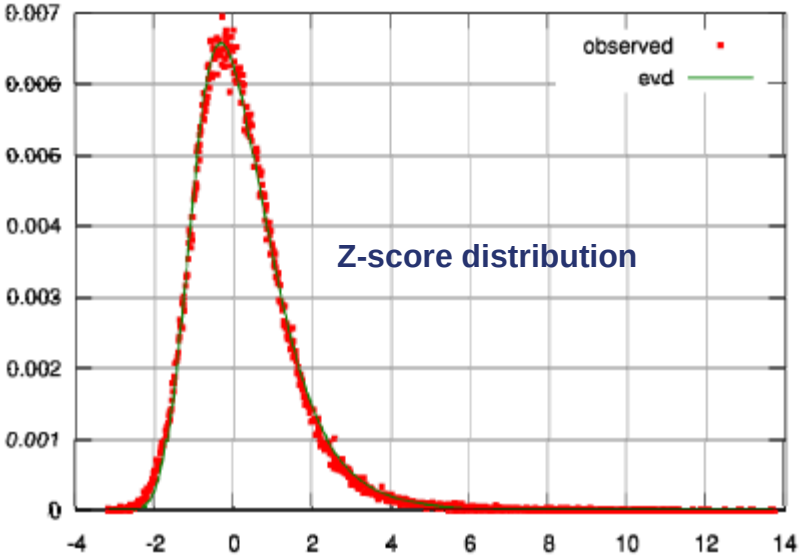




no. of ligands in set A x no. of ligands in set B



no. of ligands in set A x no. of ligands in set B



Chemical similarity searching with Statistical model. (Example is shown for SEA method)

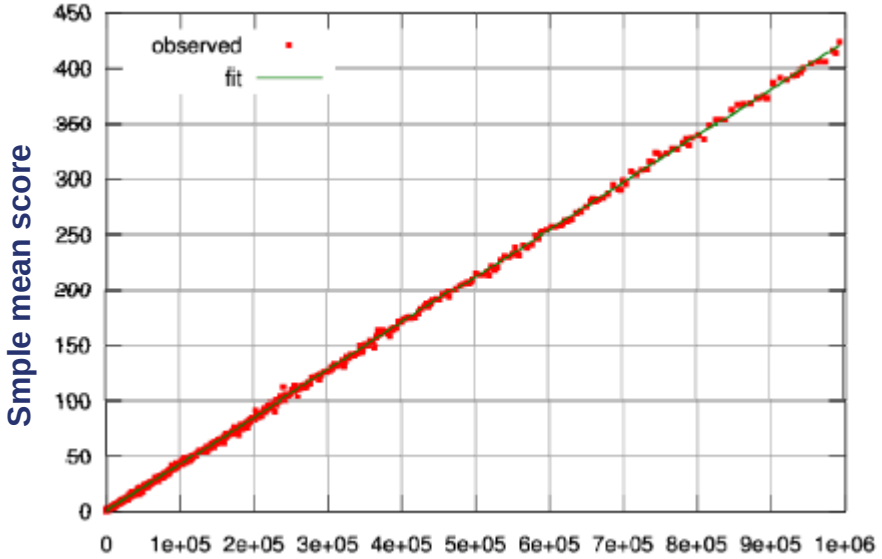
query

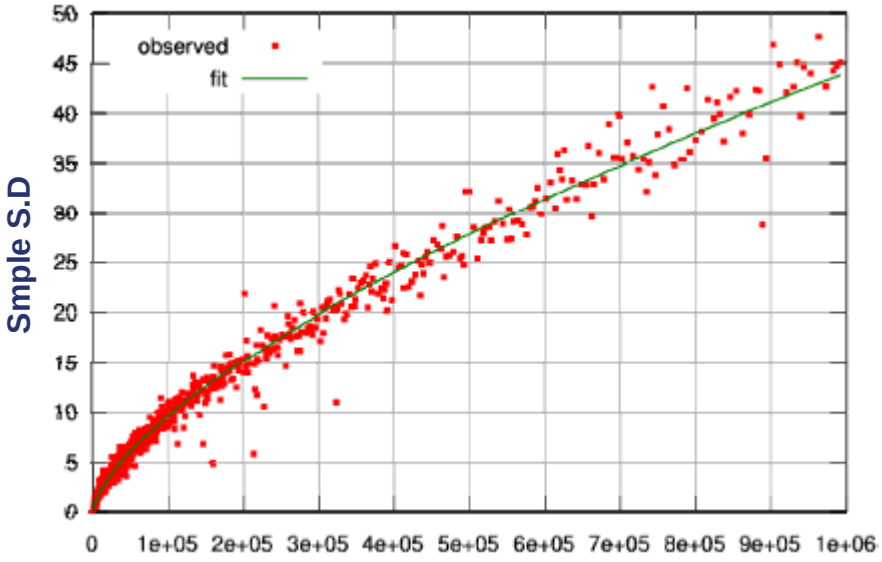
ECfp4 Tanimoto

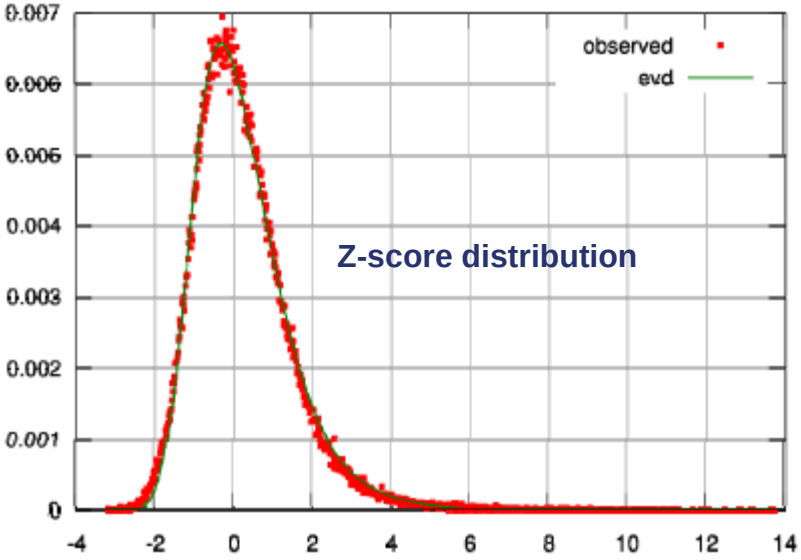
Target A-ligand set
Target B-ligand set
Target C-ligand set
…

Sum up Tanimotos

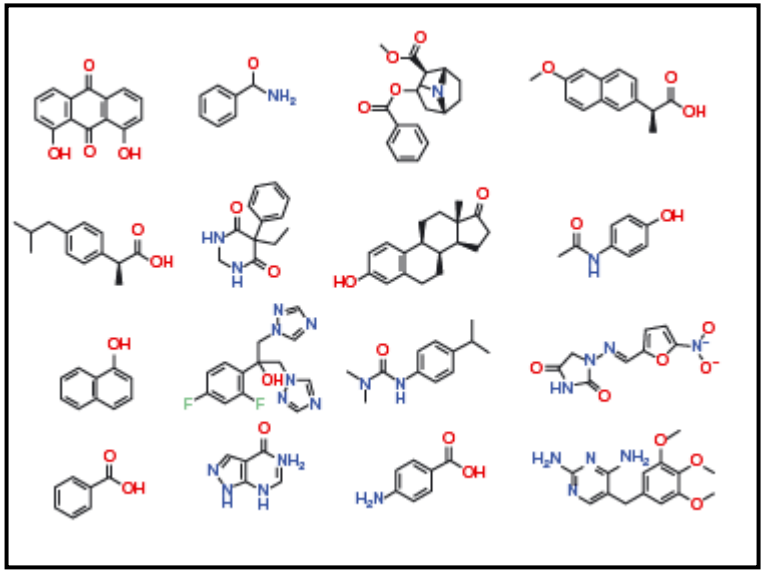
Target A-ligand set raw score
Target B-ligand set raw score
Target C-ligand set raw score
…







Machine Learning Models



Calculate descriptors or fingerprints

Fingerprint space (Predictor variables)

Title	ALogP	ALogp2	AMR	BCUTp-1	BCUTp-1h	fragC	apol	naAromAt	nAtom
Acebutolol	-2.1004	4.41168	67.0727	4.75506	9.76616	2152.06	55.7582	6	52
Amoxicillin	-1.874	3.51188	63.5964	4.78119	12.1043	1516.09	51.0391	6	44
Bendroflumethlazide	-0.8075	0.65206	39.6471	4.24449	12.8541	1147.12	49.7141	12	41
Benzocaine	-0.4883	0.23844	20.5043	4.54796	8.52863	397.03	25.8787	6	23
Benzthlazide	-1.3398	1.79506	50.9651	6.69282	12.9721	1114.11	53.1231	10	40
Clozapine	0.0092	8.46E-05	45.0577	5.92358	11.5903	1519.05	50.9291	12	42
Dibucaine	-0.5602	0.31382	57.7981	5.09923	10.5046	2425.05	59.441	10	54
Diethylstibestrol	-0.2302	0.05299	33.7086	4.85094	11.5338	1301.02	46.6199	12	40
Diflunisal	0.2593	0.06724	11.5289	4.03982	9.84339	423.05	31.7343	12	26
Dipyridamole	-3.3772	11.4055	95.8664	4.30728	11.5724	4981.12	80.9197	10	76
Folic_Acid	-3.3182	11.0105	52.3395	3.83215	9.33155	1817.13	58.6211	12	51
Furosemide	-0.9949	0.98983	33.6078	4.6696	12.2524	669.09	39.7447	11	32
Hydrochlorothiazide	-1.5436	2.3827	35.4327	7.26833	12.8018	404.1	32.1423	6	25
Imipramine	0.091	0.00828	39.2562	5.70631	11.5894	1789.02	51.643	12	45
Indomethacin	0.2922	0.08538	37.8739	4.12177	11.086	1249.06	50.5967	12	41
Ketoprofen	-0.2088	0.0436	21.9194	4.29006	9.91827	814.03	39.9011	12	33
Lidocaine	1.166	1.35956	45.8867	5.09304	9.98654	1249.03	42.3114	6	39
Meclofenamic_acid	1.4704	2.16208	27.2526	4.4468	11.3886	619.05	39.0387	12	30

Target A, Target B,
Target C,
Target D, Target E,
Target F,
Target G, Target H,
Target I
etc.

Target space (Class lables)

Naive Bayes, Support vector machines, Decision trees

Find mathematical functions which correctly mapped fingerprint space to target space

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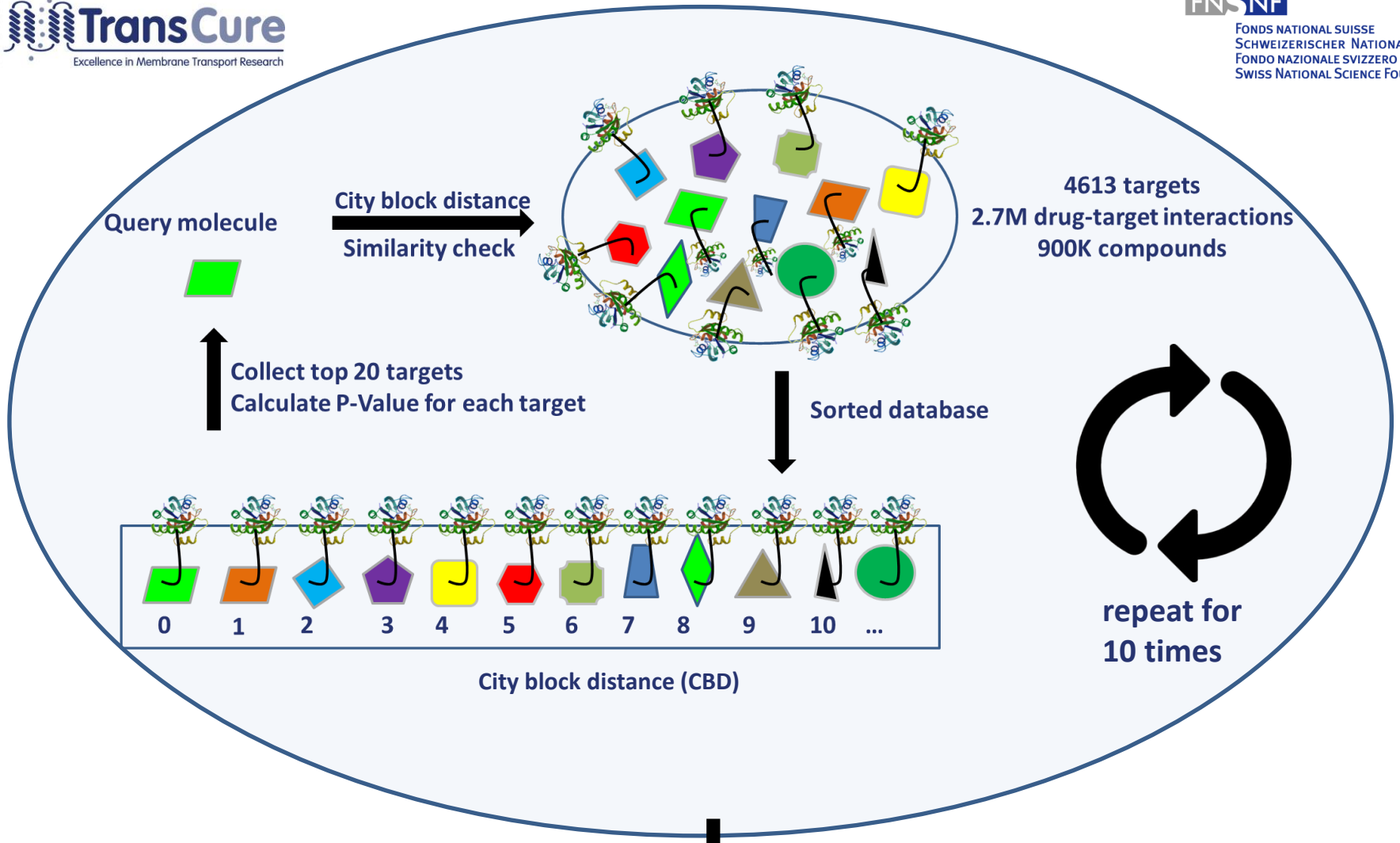
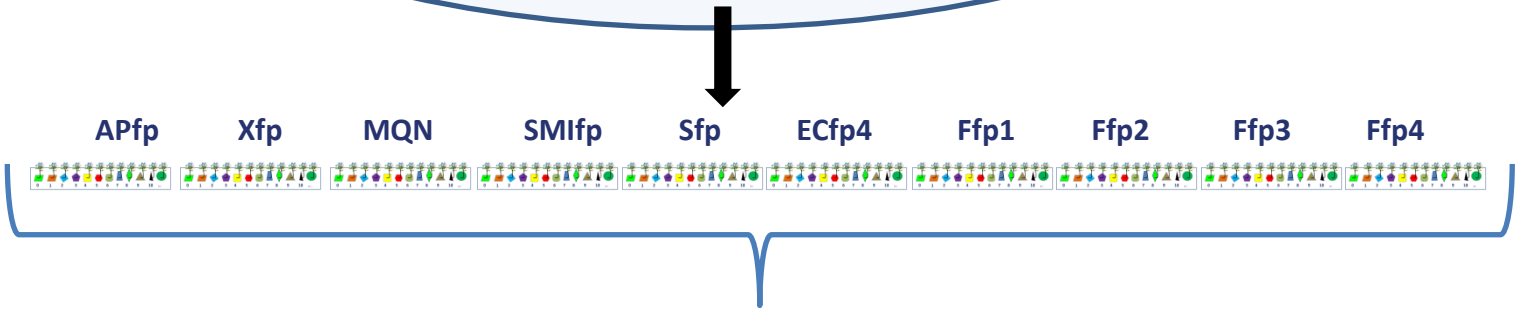
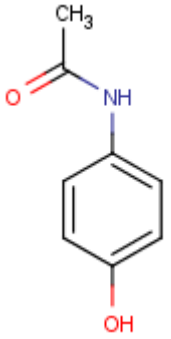
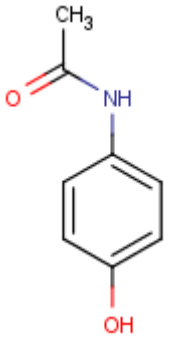




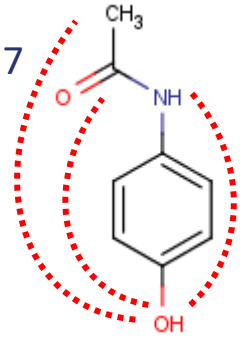
Multi-voting based sorting, Generate combine view

Six types of Molecular Representation





Bond Distance = 7



Bond Distance = 5

MQN (42)

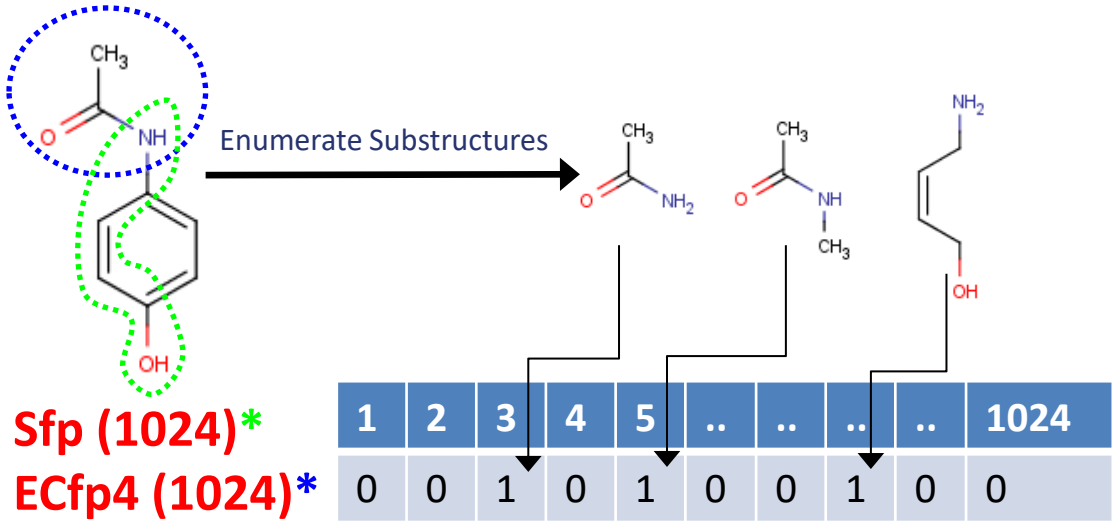
Atom type, Bond type, Ring Count etc.

SMIfp (34)

CC(=O)Nc1ccc(O)cc1
Count different kind of characters in SMILES

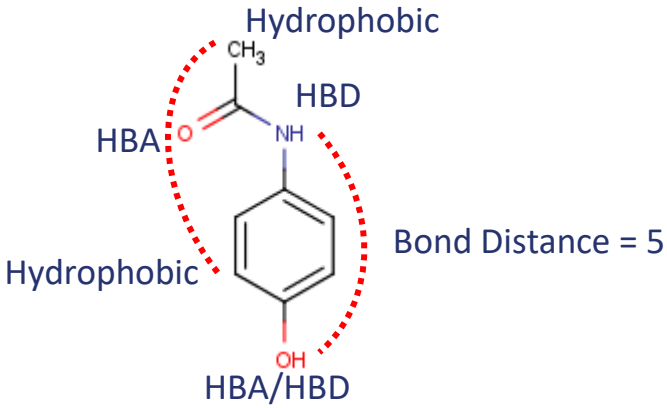
APfp (11)

Count bond distances between atoms



Sfp (1024)*

ECfp4 (1024)*

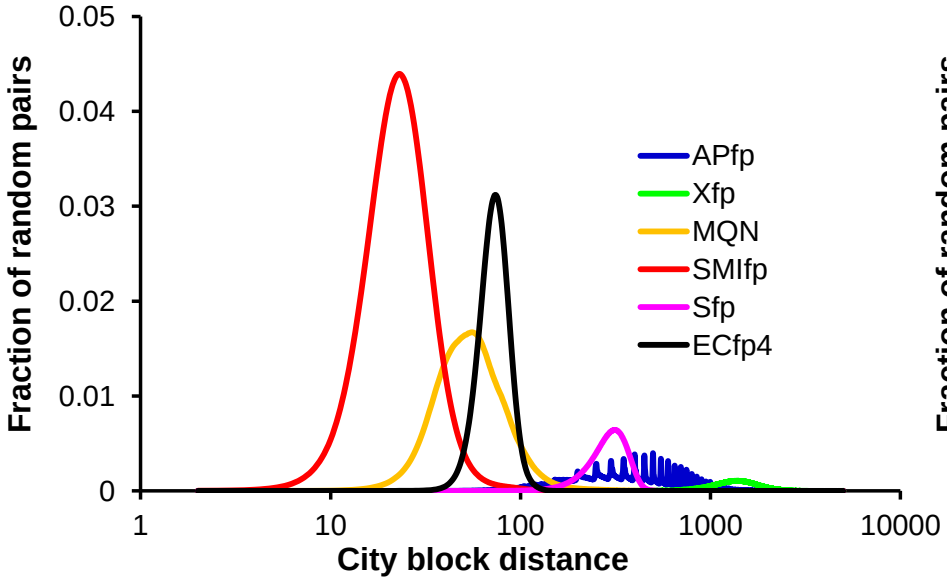


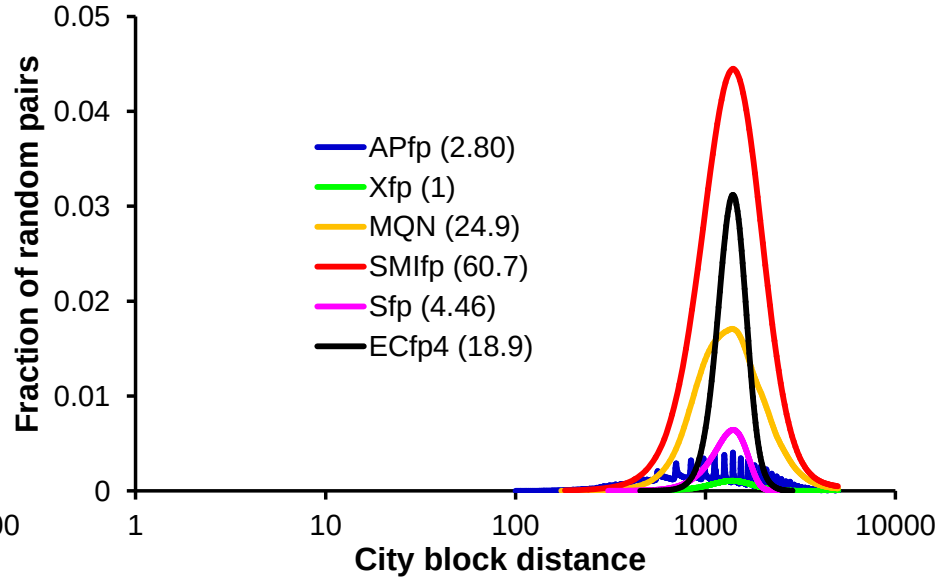
Xfp (55)

Count bond distances between atoms with pharmacophore information

Four similarity fusion methods

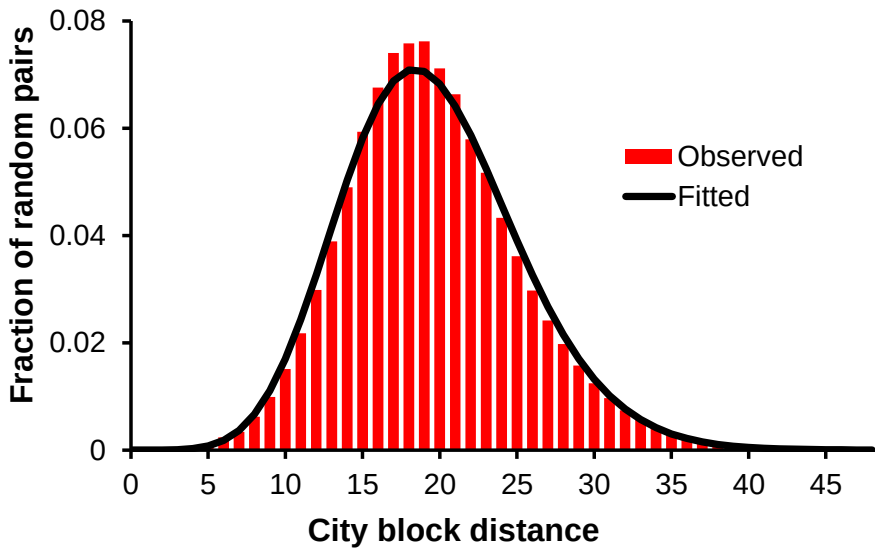
Ffp1 (Xfp_{CBD}+$SMIfp_{CBD}$+Sfp_{CBD})
Ffp2 (Xfp_{CBD}+MQN_{CBD}+$SMIfp_{CBD}$)
Ffp3 (Xfp_{CBD}+$SMIfp_{CBD}$+Sfp_{CBD}+$ECfp4_{CBD}$)
Ffp4 (Xfp_{CBD}+MQN_{CBD}+$SMIfp_{CBD}$+Sfp_{CBD}+$ECfp4_{CBD}$)

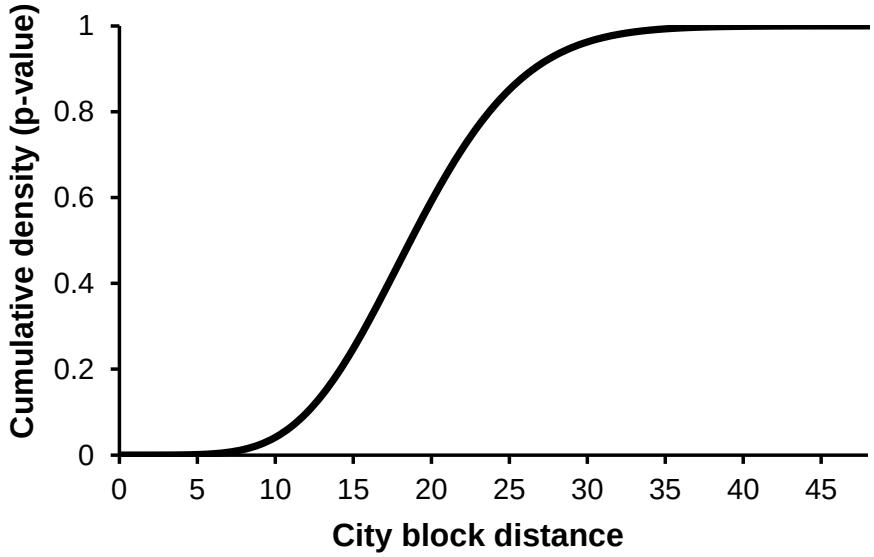




p-value calculation

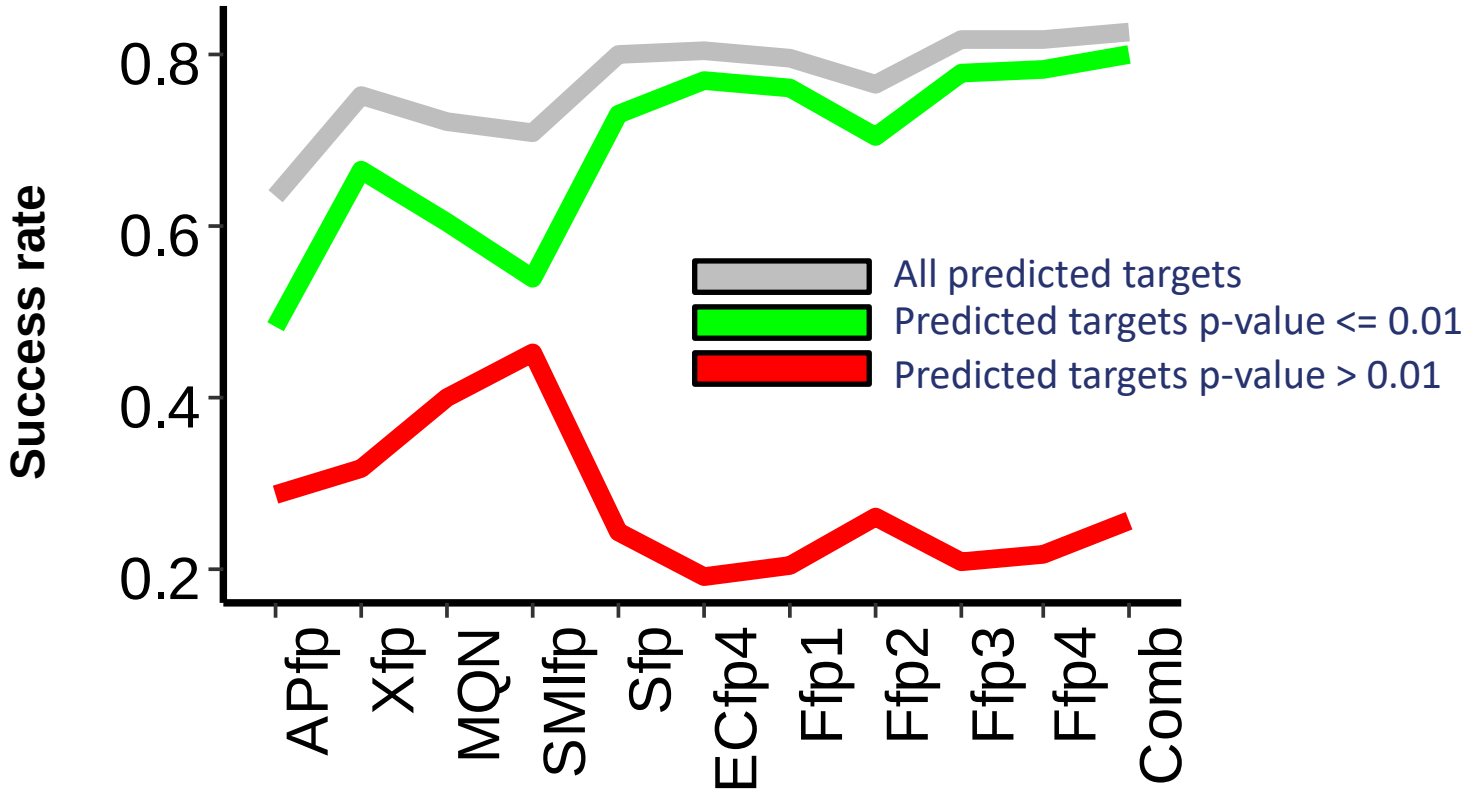
for the muscarinic acetylcholine receptor M1 (CHRM1)
in MQN fingerprint space





46,130 distributions: (4,613 targets*10 fingerprints)

Validation Study: 670 Drugs



Success rate to find at least one of the known targets of drug in top 5 predicted targets

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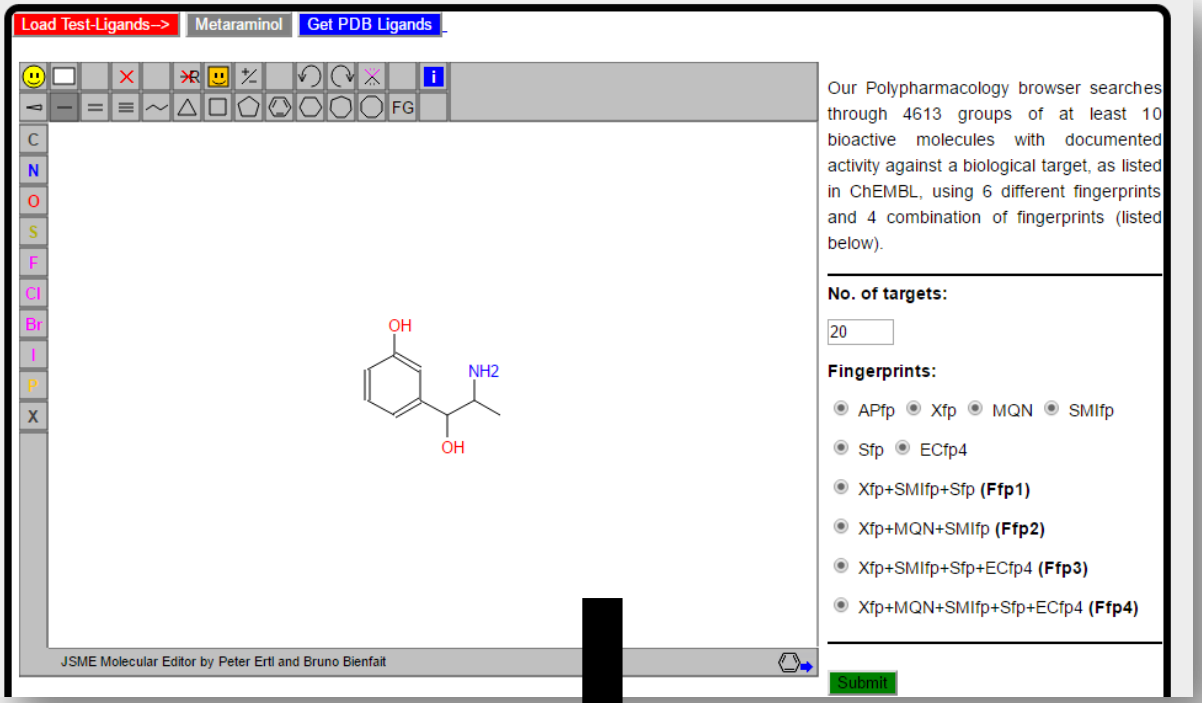

SAVE

Query

Target Full Name: 5) Adrenergic_receptor_alpha-1 Link To Chembl

Query molecule is identical to database compound
p-value streching from 0.01 to 0. Complete fill=0
p-value >0.01
Target not found by fingerprint

Rank	ChEMBL-ID	ChEMBL-Name	APfp	Xfp	MQN	SMIfp	Sfp	ECfp4	Hyp1	Hyp2	Hyp3	Hyp4	No. of Mols
1	CHEMBL1293235	LMNA											19
2	CHEMBL1697668	SLCO1B1											17
3	CHEMBL4261	HIF1A											19
4	CHEMBL1743121	SLCO1B3											22
5	CHEMBL1907610	ADRA1A				0.027							10
6	CHEMBL6035	TXNRD1			0.083	0.167							9
7	CHEMBL2007624	PMP22				0.011							8
8	CHEMBL2093864	ADRA2C				0.013							16
9	CHEMBL4096	TP53			0.133	0.195							8

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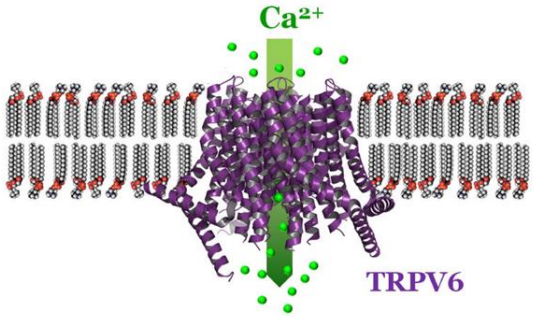
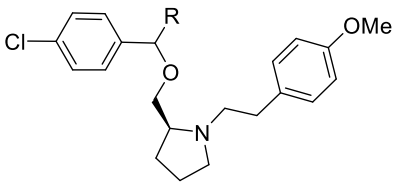
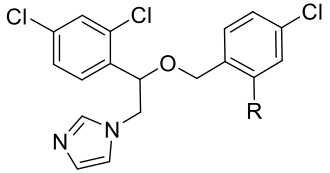
xLOS Virtual Screening for TRPV6

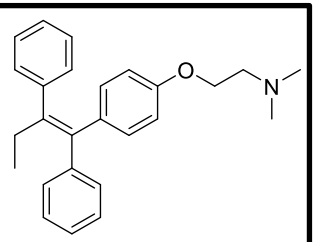




1 (R = H) IC_{50} = 90 μM
2 (R = Ph) IC_{50} = 675 μM

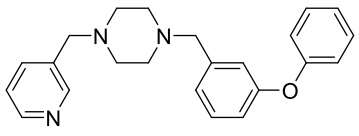


3 (R = H, econazole) IC_{50} = 190 μM
4 (R = Cl, miconazole) IC_{50} = 200 μM

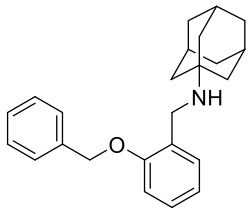


5 (tamoxifen) IC_{50} = 8 μM

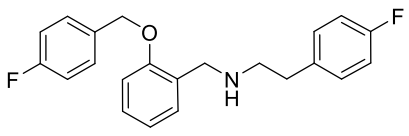
1) xLOS Screening
12M compounds
2) 133 compounds purchased
3) FLIPR calcium assay



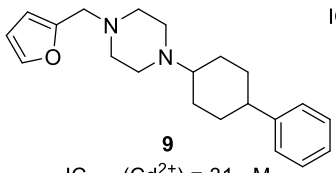
6
IC_{50} (Cd^{2+}) = 26 μM
IC_{50} (Ca^{2+}) = 17 μM



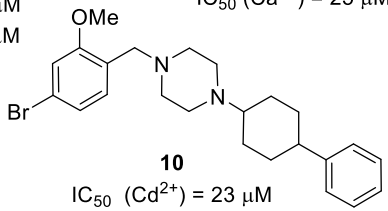
7
IC_{50} (Cd^{2+}) = 26 μM
IC_{50} (Ca^{2+}) = 21 μM



8
IC_{50} (Cd^{2+}) = 37 μM
IC_{50} (Ca^{2+}) = 25 μM

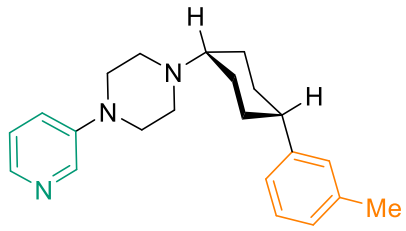


9
IC_{50} (Cd^{2+}) = 31 μM
IC_{50} (Ca^{2+}) = 26 μM



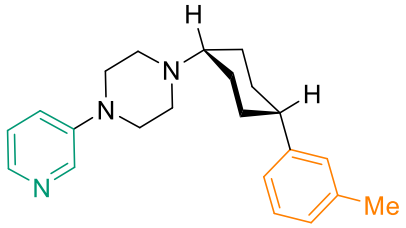
10
IC_{50} (Cd^{2+}) = 23 μM
IC_{50} (Ca^{2+}) = 15 μM

1) xLOS Screening
2) Synthesis (>50 compounds)
3) FLIPR calcium assay



cis-**22a**
IC_{50} = 0.32 ± 0.12 μM

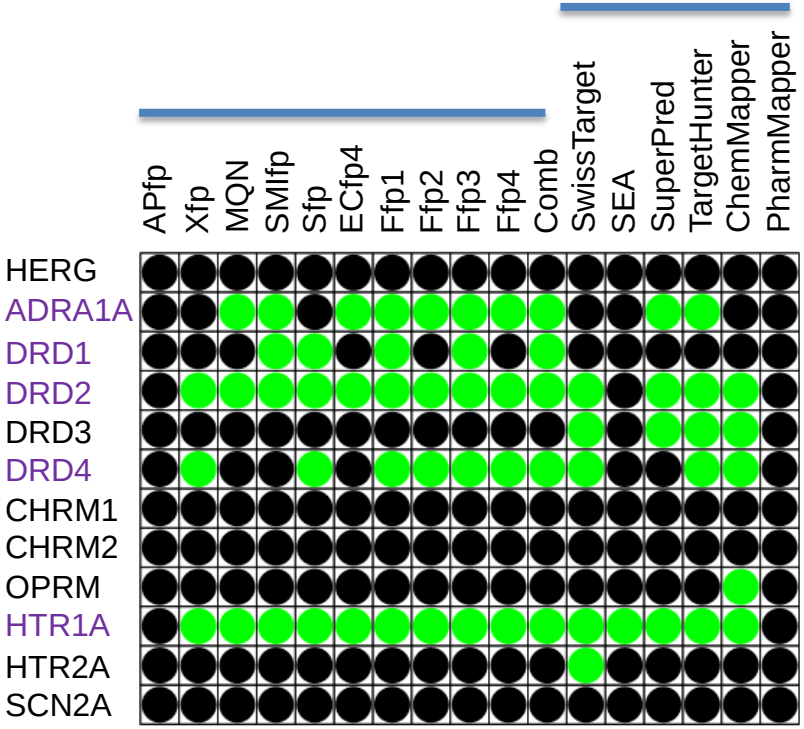
Polypharmacology Profile of CIS22a



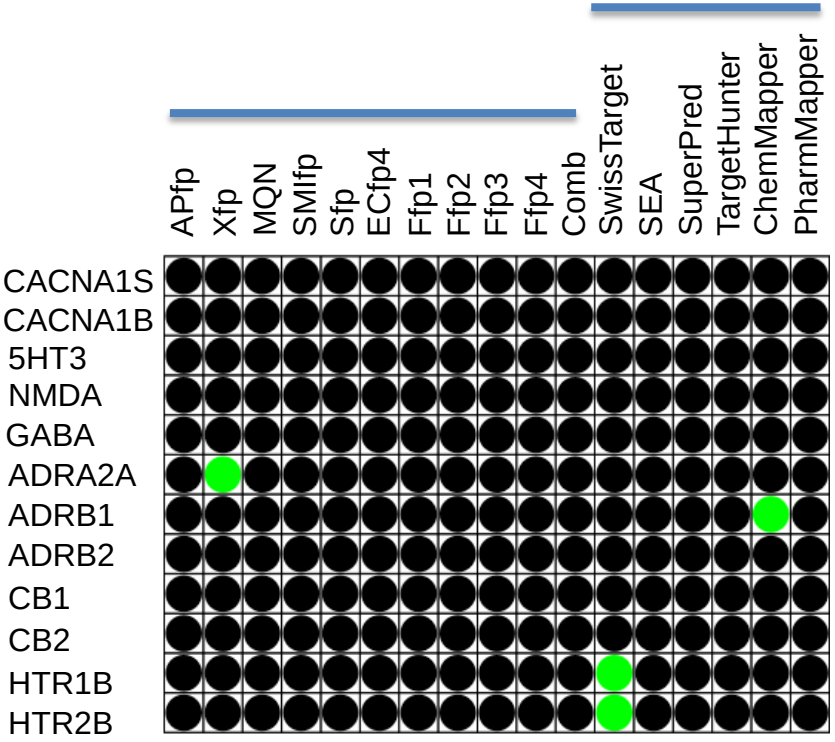
cis-**22a**

IC_{50} = 0.32 ± 0.12 μM

True positive targets
(significant binding)



True negative targets
(no significant binding)



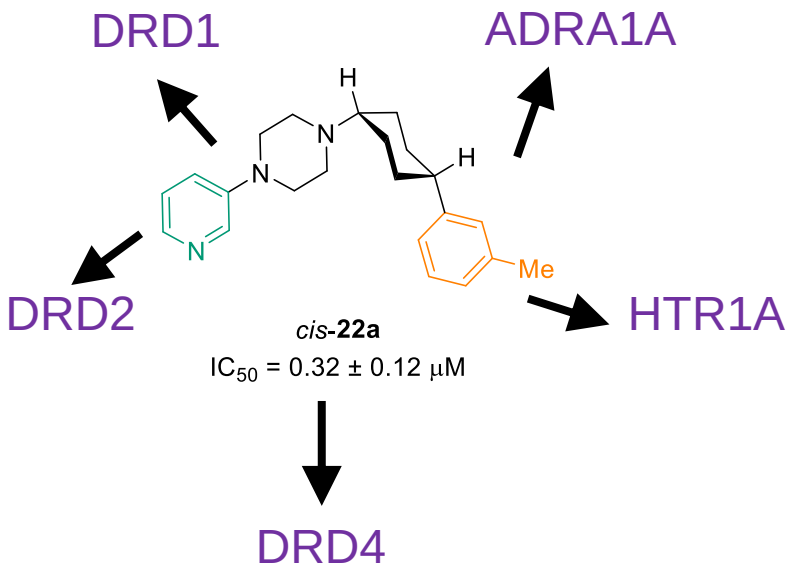
In collaboration with CEREP Pvt. Ltd.

Summary

Chemical similarity searching

Similarity values based statistical models

Fingerprint based machine learning models



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Thank you