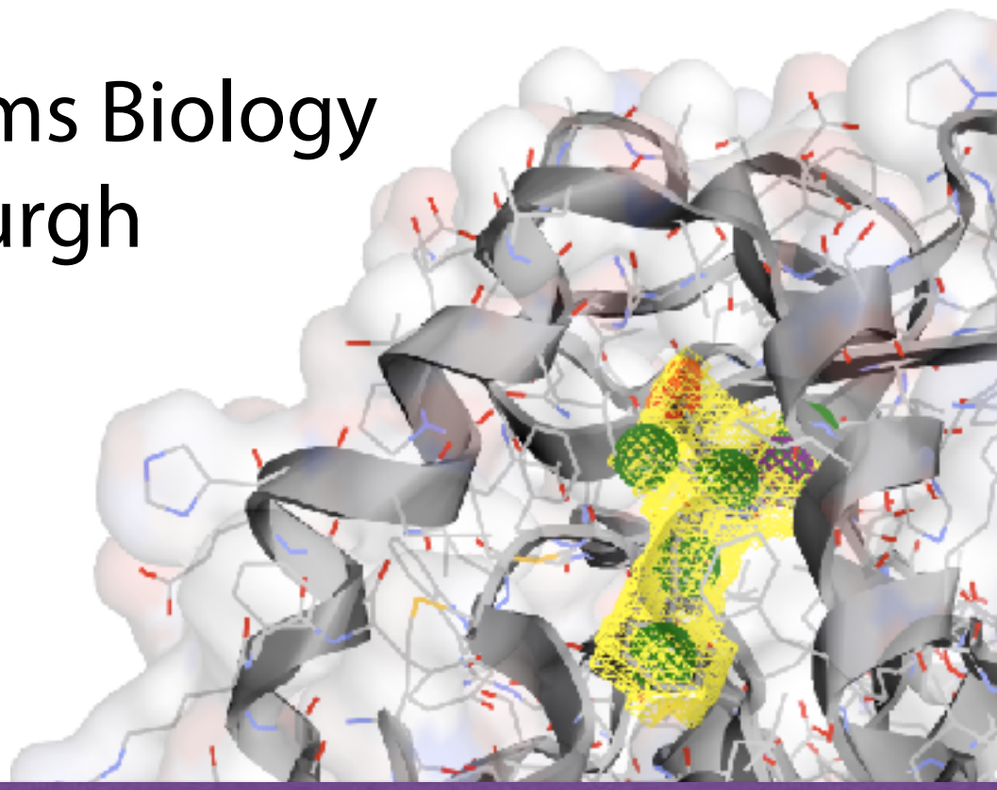
Structure-based search of chemical libraries with

Pharmit

David Ryan Koes

@david_koes

Computational and Systems Biology
University of Pittsburgh



pharmit.csb.pitt.edu/search.html

Search PubChem

Pharmacophore Search -> Shape Filter

Load Receptor... Load Features...

Pharmacophore

- ON **Aromatic** (48.19,39.60,-1.00) Radius 1.1
- ON **HydrogenAcceptor** (47.17,41.33,-5.37) Radius 0.5
- ON **HydrogenAcceptor** (49.17,40.46,-6.38) Radius 0.5
- ON **NegativeIon** (48.21,40.61,-5.92) Radius 0.75
- ON **Hydrophobic** (49.4,41.67,-2.93) Radius 1.0
- ON **Hydrophobic** (52.08,44.85,-2.15) Radius 1.0
- ON **Hydrophobic** (48.19,39.88,-1.38) Radius 1.0
- ON **Hydrophobic** (55.14,47.0,-1.04) Radius 1.0
- ON **Hydrophobic** (50.03,43.31,-5.25) Radius 1.0
- ON **Hydrophobic** (46.4,37.97,-1.95) Radius 1.0
- OFF **Aromatic** (49.4,41.67,-2.93) Radius 1.1
- OFF **Aromatic** (52.08,44.85,-2.15) Radius 1.1

Load Session... Save Session...

Deploy a menu

Pharmacophore Results

Name	RMSD	Mass	RBnds
PubChem-13960682	0.223	392	5
PubChem-23673360	0.223	391	4
PubChem-13960682	0.223	392	5
PubChem-23673360	0.223	391	4
PubChem-13960684	0.243	388	6
PubChem-13960684	0.243	388	6
PubChem-13960684	0.243	388	6
PubChem-13960684	0.250	388	6
PubChem-59810304	0.311	481	8
PubChem-10000399	0.325	389	6
PubChem-10000399	0.327	389	6
PubChem-59081061	0.349	875	15
PubChem-10250942	0.379	387	3
PubChem-23686481	0.379	386	2
PubChem-13960681	0.442	385	7
PubChem-13960681	0.442	385	7
PubChem-13960681	0.444	385	7
PubChem-88181354	0.449	698	10
PubChem-842716	0.462	319	8

Showing 1 to 19 of 38 hits

Previous 1 2 Next

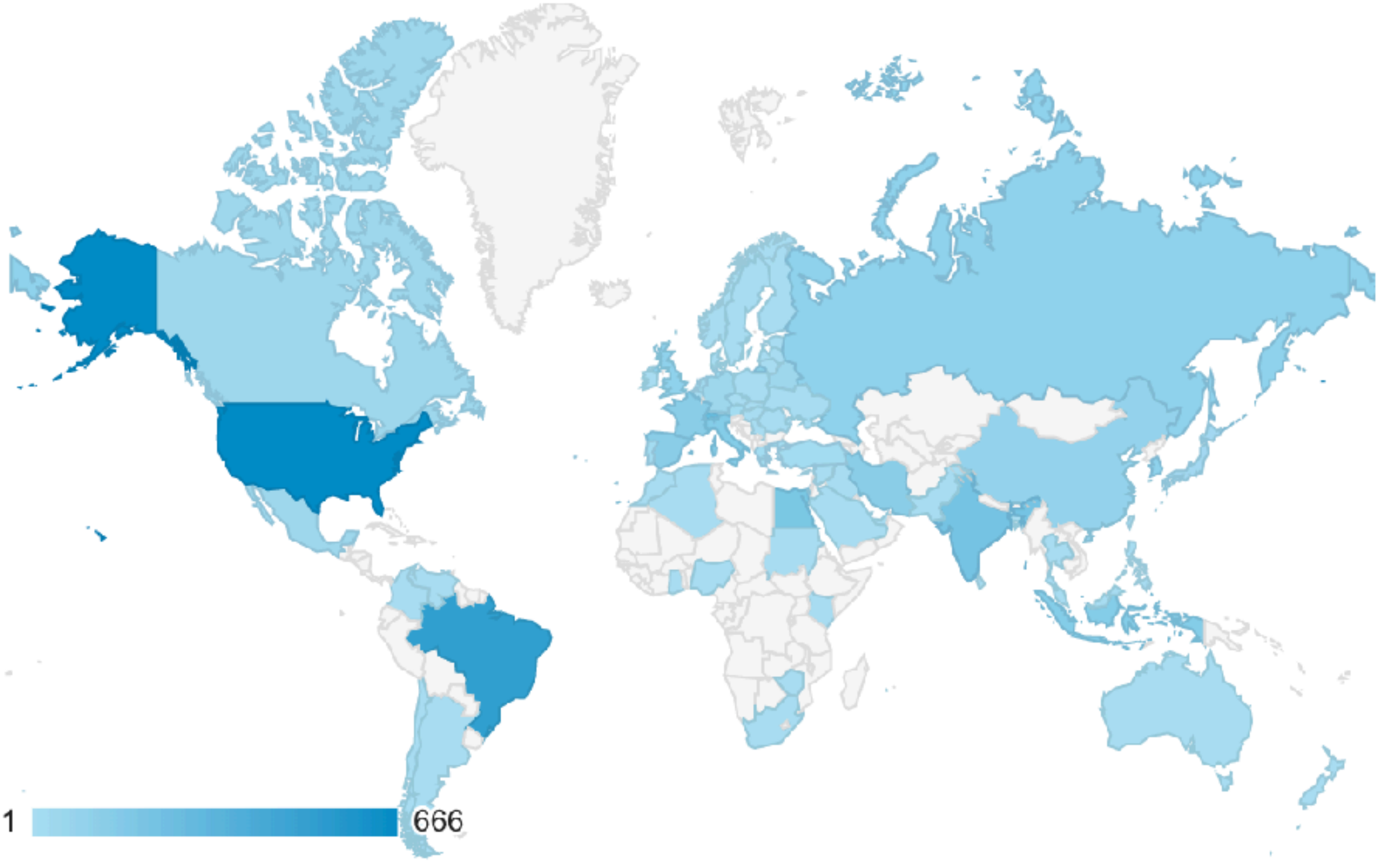
Minimize Save...

http://pharmit.csb.pitt.edu/

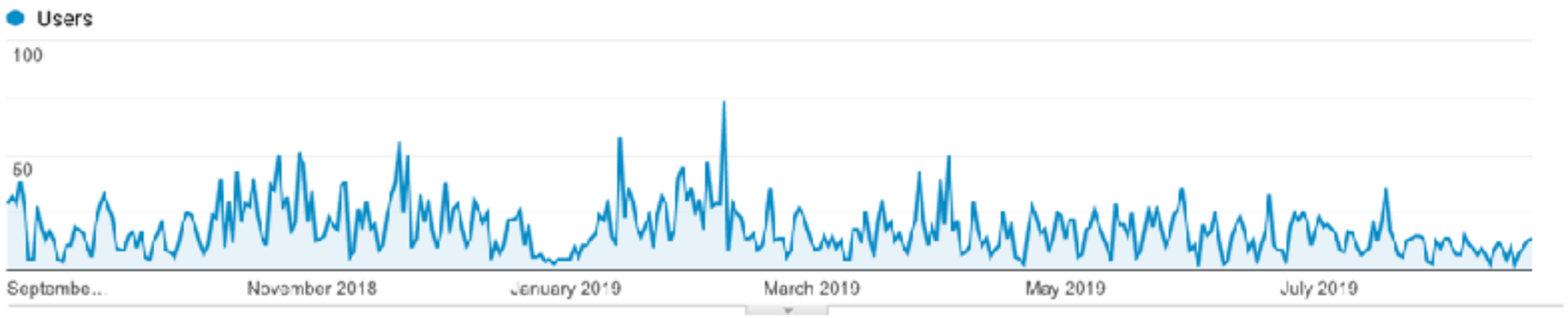
RELAY THERAPEUTICS

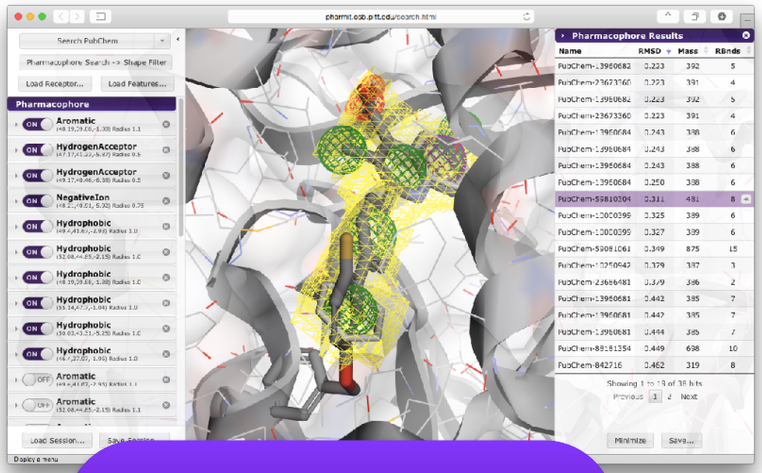
24 x 10 TB HDD
4 TB SSD Cache
512 GB RAM
40 cores

Aug 20, 2018 - Aug 21, 2019



Country	Acquisition			Behavior		
	Users	New Users	Sessions	Bounce Rate	Pages / Session	Avg. Session Duration
	3,444 % of Total: 100.00% (3,444)	3,375 % of Total: 100.12% (3,371)	9,039 % of Total: 100.00% (9,039)	28.99% Avg for View: 28.99% (0.00%)	2.91 Avg for View: 2.91 (0.00%)	00:12:05 Avg for View: 00:12:05 (0.00%)
1. United States	**666** (19.08%)	646 (19.14%)	1,801 (19.92%)	30.82%	2.73	00:12:25
2. Brazil	**489** (14.01%)	480 (14.22%)	1,208 (13.36%)	22.52%	3.20	00:10:30
3. Switzerland	**262** (7.51%)	261 (7.73%)	436 (4.82%)	77.98%	1.58	00:02:22
4. India	**198** (5.67%)	190 (5.63%)	546 (6.04%)	25.82%	2.72	00:09:32
5. Egypt	**185** (5.30%)	182 (5.39%)	437 (4.83%)	27.92%	3.14	00:09:44
6. Italy	**144** (4.13%)	141 (4.18%)	595 (6.58%)	17.82%	2.78	00:14:49
7. Indonesia	**141** (4.04%)	135 (4.00%)	562 (6.22%)	16.55%	3.40	00:15:50
8. France	**130** (3.72%)	130 (3.85%)	357 (3.95%)	15.41%	2.22	00:15:28
9. Spain	**129** (3.70%)	127 (3.76%)	284 (3.14%)	16.20%	3.85	00:14:40
10. Iran	**117** (3.35%)	100 (2.96%)	544 (6.02%)	13.60%	3.79	00:23:58





pharmit.js

JQuery

3Dmol.js

Client

Search

User Libraries

MCULE

ZINC

Chemspace

CHEMBL

PubChem

ChemDiv

NCI

MolPort

Prebuilt Libraries

pharmitserver

OpenBabel

ShapeDB

Pharmer

Minimization

smina

OpenBabel

buildlibs.py

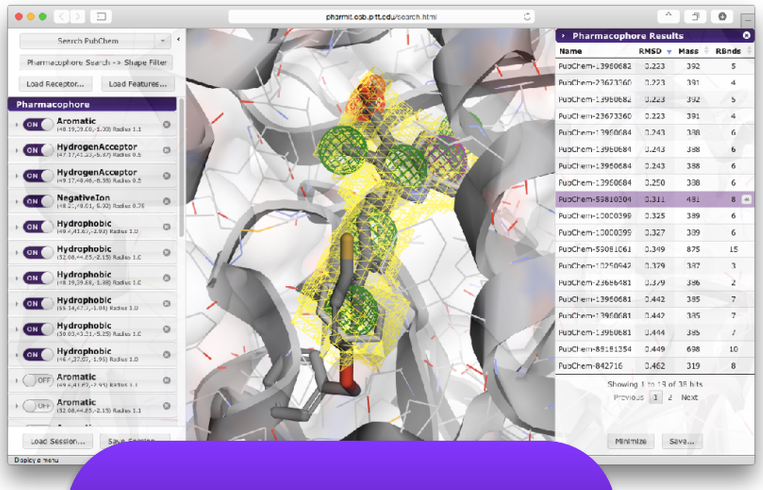
RDKit

OpenBabel

Server

http://pharmit.sf.net

GPL/BSD License



Client

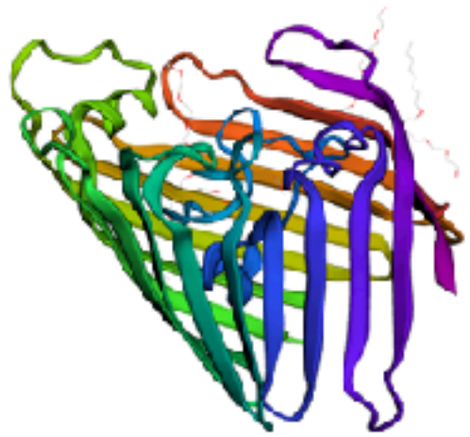
Why web application?

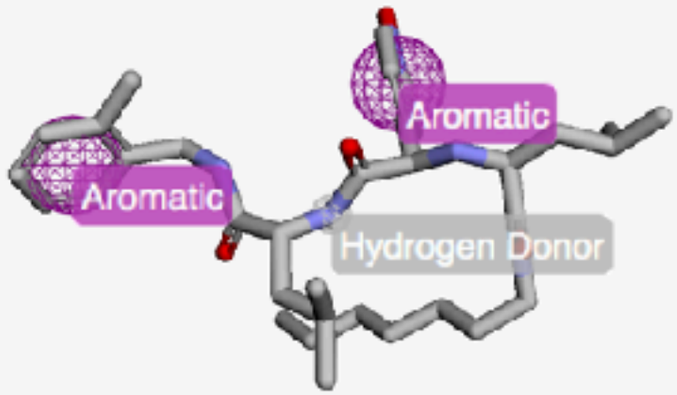
3dmol.csb.pitt.edu

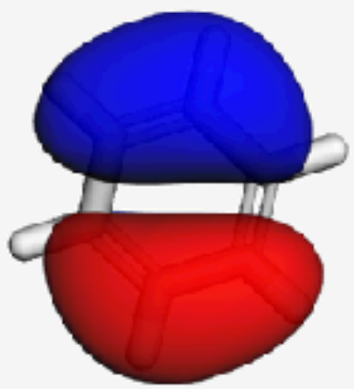
3Dmol.js

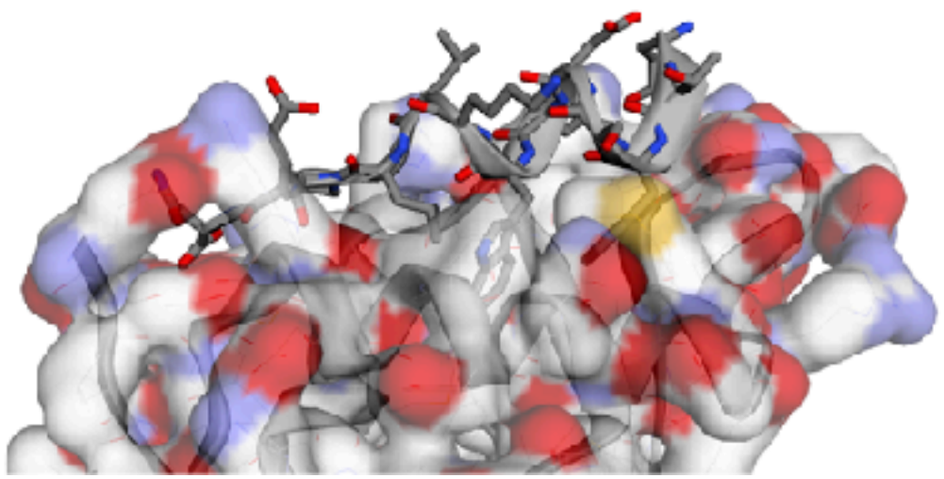
View Embed Jupyter Develop Feedback Download

A modern, object-oriented JavaScript library for visualizing molecular data









http://3dmol.csb.pitt.edu

Rego, N., & Koes, D. (2014). 3Dmol.js: molecular visualization with WebGL. *Bioinformatics*. doi:10.1093/bioinformatics/btu829

Aside:
Molecular Active Learning

Demo

Open Chemistry

Google Summer of Code

Go to this URL: http://3dmol.csb.pitt.edu/viewer.html

Libraries

MCULE

ZINC

Chemspace

CHEMBL

PubChem

ChemDiv

NCI

MolPort

CHEMBL25
23,136,925 conformers of 1,752,844 molecules
Updated: 2019-Jun-03 06:49:19

ChemDiv
21,562,497 conformers of 1,456,120 molecules
Updated: 2019-Jun-05 06:41:23

ChemSpace
250,205,463 conformers of 50,181,678 molecules
Updated: 2019-Jun-19 22:22:08

MCULE
205,592,993 conformers of 41,536,529 molecules
Updated: 2019-Jun-22 12:05:51

MolPort
108,718,272 conformers of 7,546,295 molecules
Updated: 2019-Jun-25 12:37:28

NCI Open Chemical Repository
574,117 conformers of 52,237 molecules
Updated: 2019-Jun-06 13:51:25

PubChem
450,708,705 conformers of 93,067,404 molecules
Updated: 2019-Jun-17 09:23:16

ZINC
123,399,574 conformers of 13,190,317 molecules
Updated: 2019-Jun-02 09:58:08

Contributed Libraries...

Access Private Library...

86% New Compounds

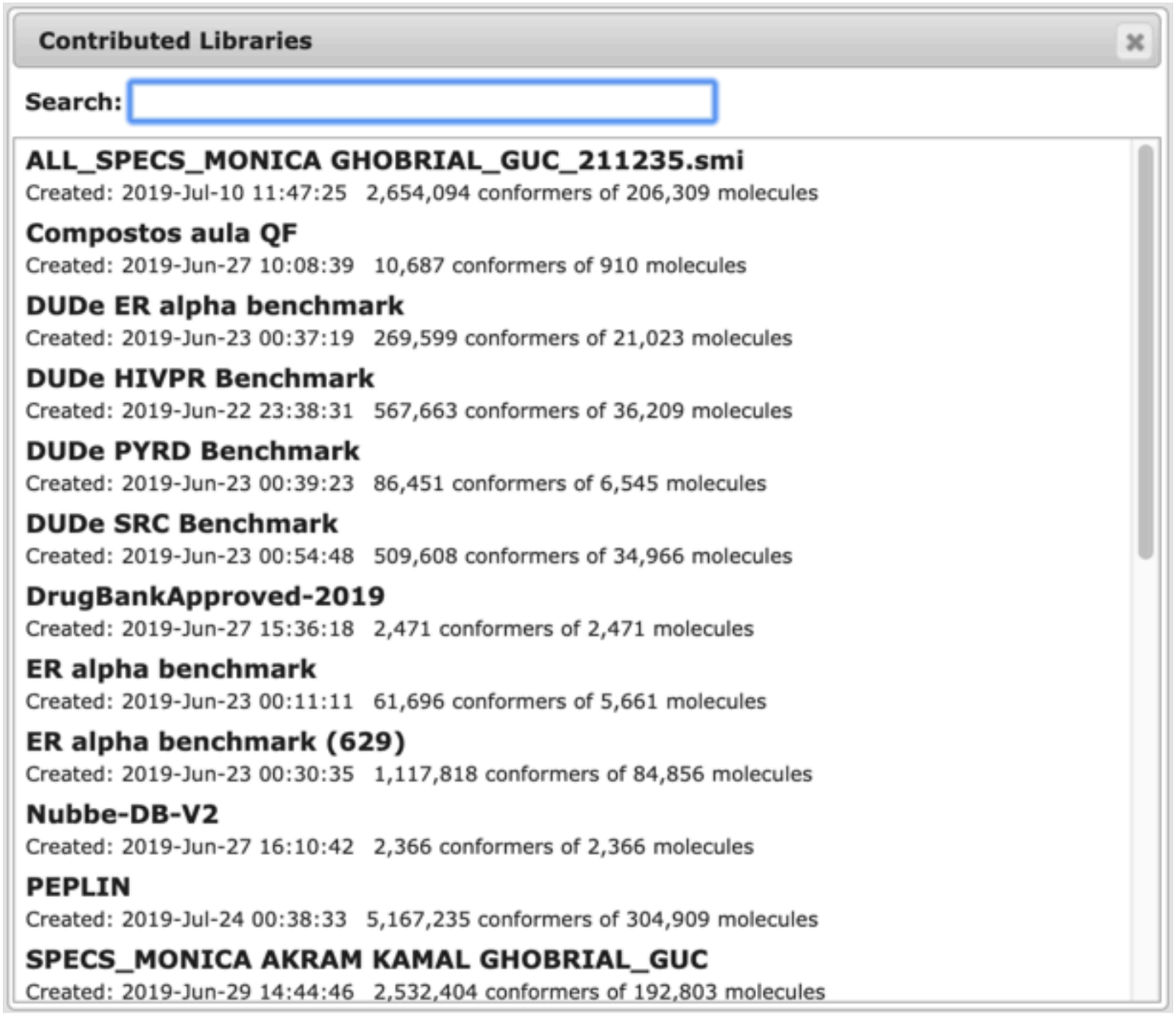
pharmit currently has

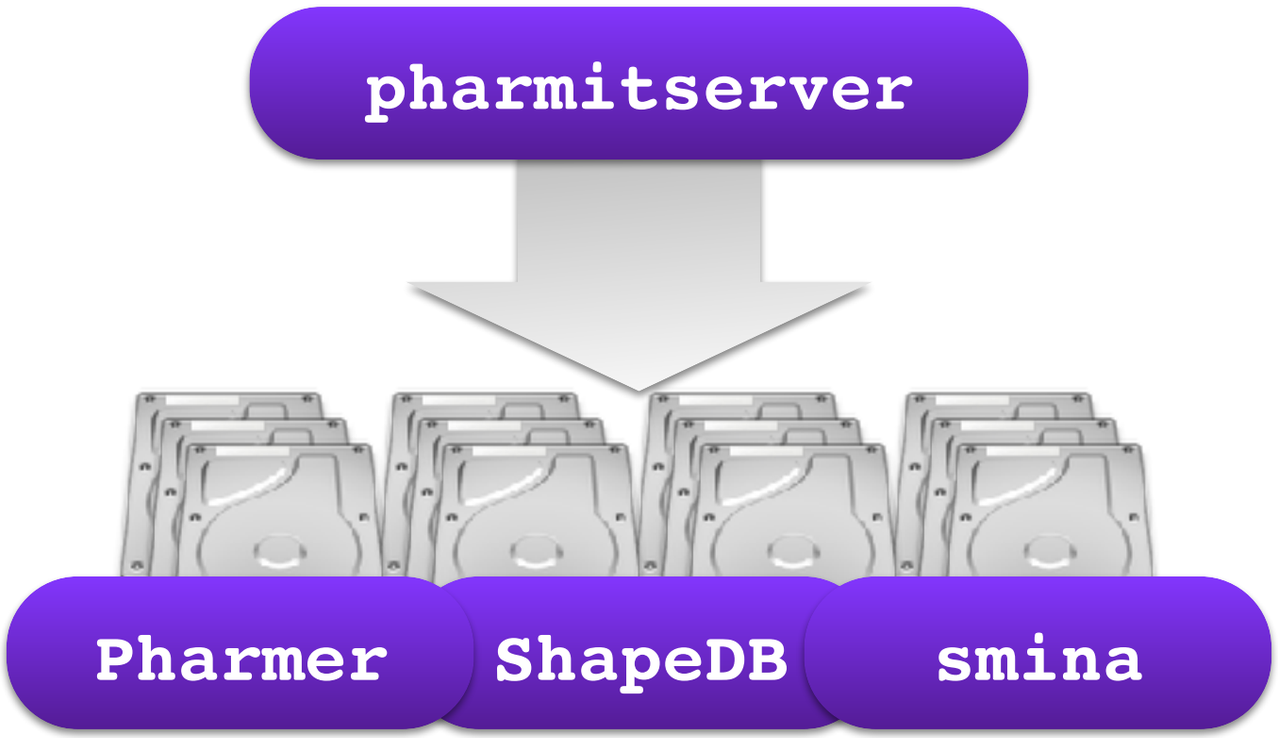
8 built-in libraries containing 1,183,898,546 conformations of 208,783,424 compounds and 30 publicly accessible user-contributed libraries containing 18,932,611 conformations of 1,588,877 compounds.

Library Usage

	Event Label	Total Events	Total Events
		59,722 % of Total: 100.00% (59,722)	59,722 % of Total: 100.00% (59,722)
1.	molport	12,280	20.56%
2.	zinc	10,922	18.29%
3.	pubchem	7,948	13.31%
4.	chembl	5,799	9.71%
5.	chemspace	3,628	6.07%
6.	chemdiv	3,056	5.12%
7.	nsc	2,929	4.90%
8.	Public/63ZF8LIDMAU91D1IHYHA	1,222	2.05%
9.	Public/3H0EURBRCF46OWJJ5MAF	1,014	1.70%
10.	Public/LZMM5QOTC3FDQYKGKT5Q	953	1.60%

Contributed Libraries





http://pharmit.sf.net

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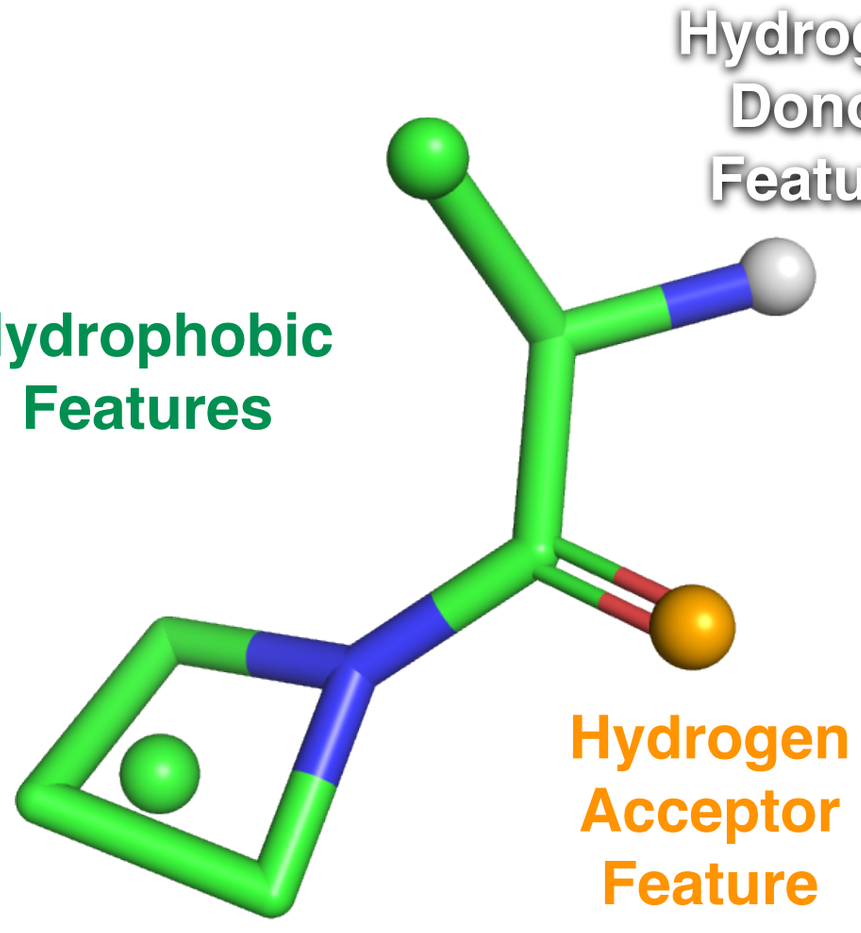
Pharmer

Efficient and Exact Pharmacophore Search



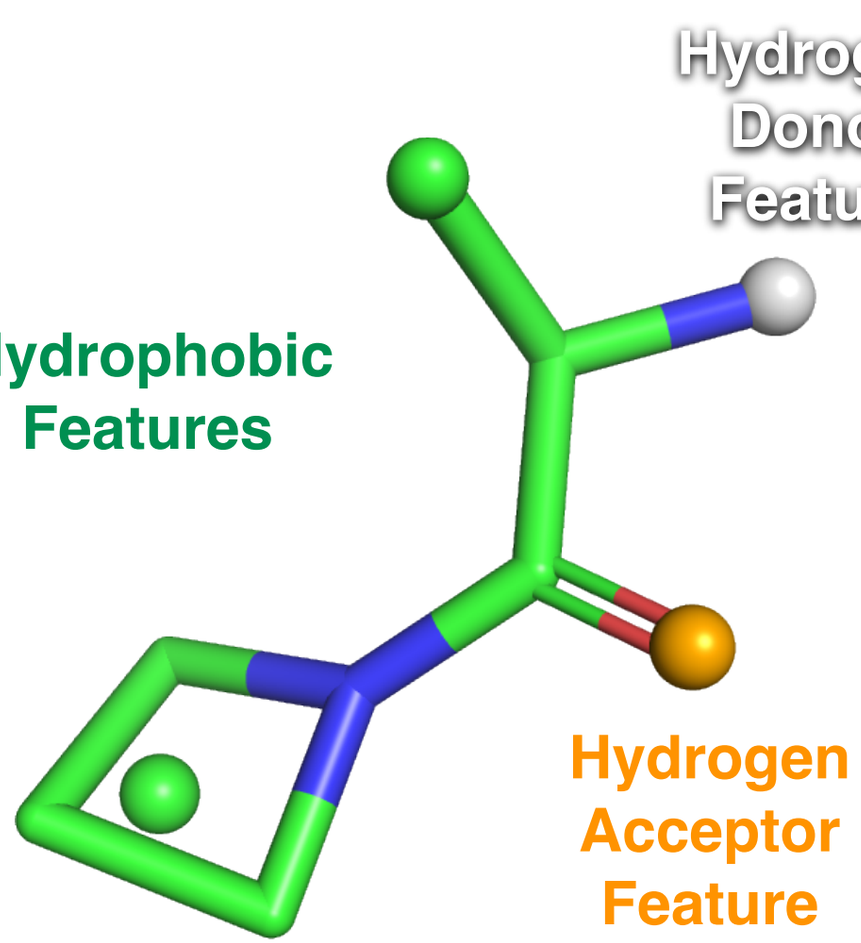
Pharmacophore

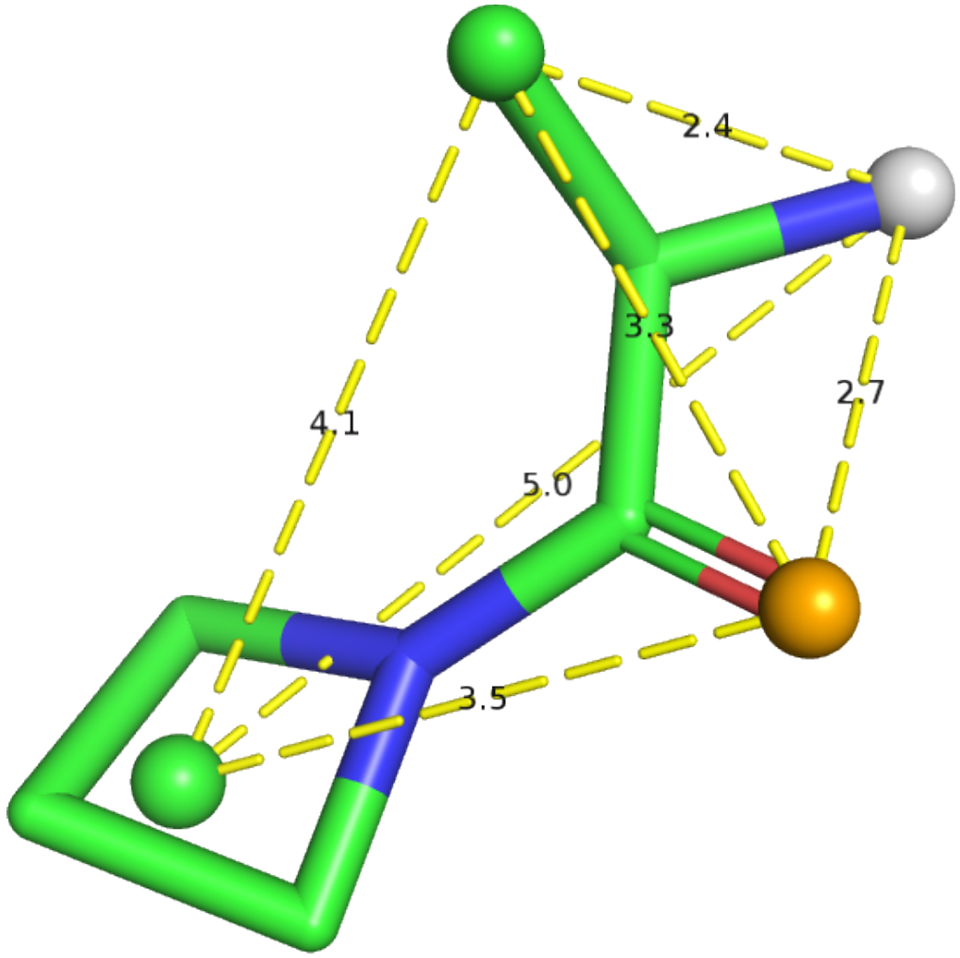
A spatial arrangement of molecular features essential for biological activity

Koes, D. R., & Camacho, C. J. (2011). Pharmer: efficient and exact pharmacophore search. *Journal of Chemical Information and Modeling, 51*(6), 1307-1314. doi:10.1021/ci200097m
Koes, D. R., & Camacho, C. J. (2012). ZINCPharmer: pharmacophore search of the ZINC database. *Nucleic acids research, 40*(Web Server issue), W409-414. doi:10.1093/nar/gks378

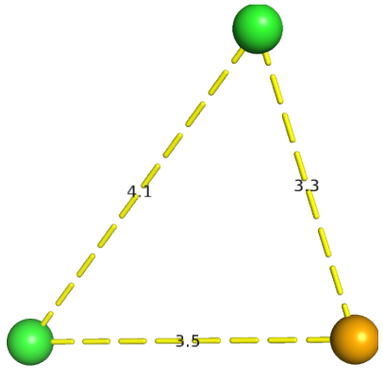
Pharmer

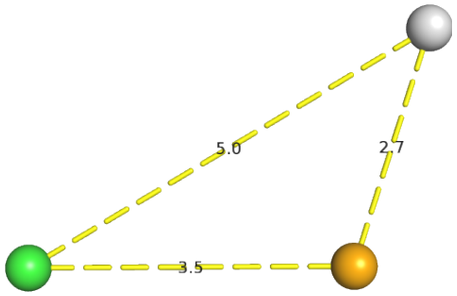
Efficient and Exact Pharmacophore Search

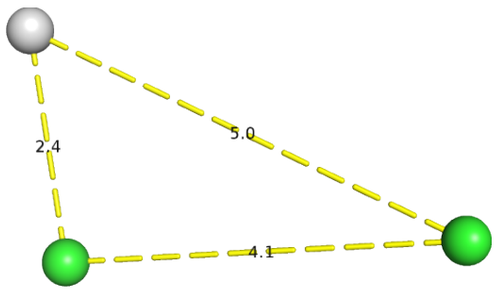


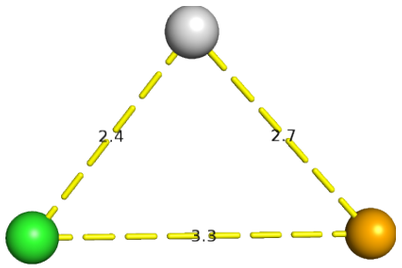


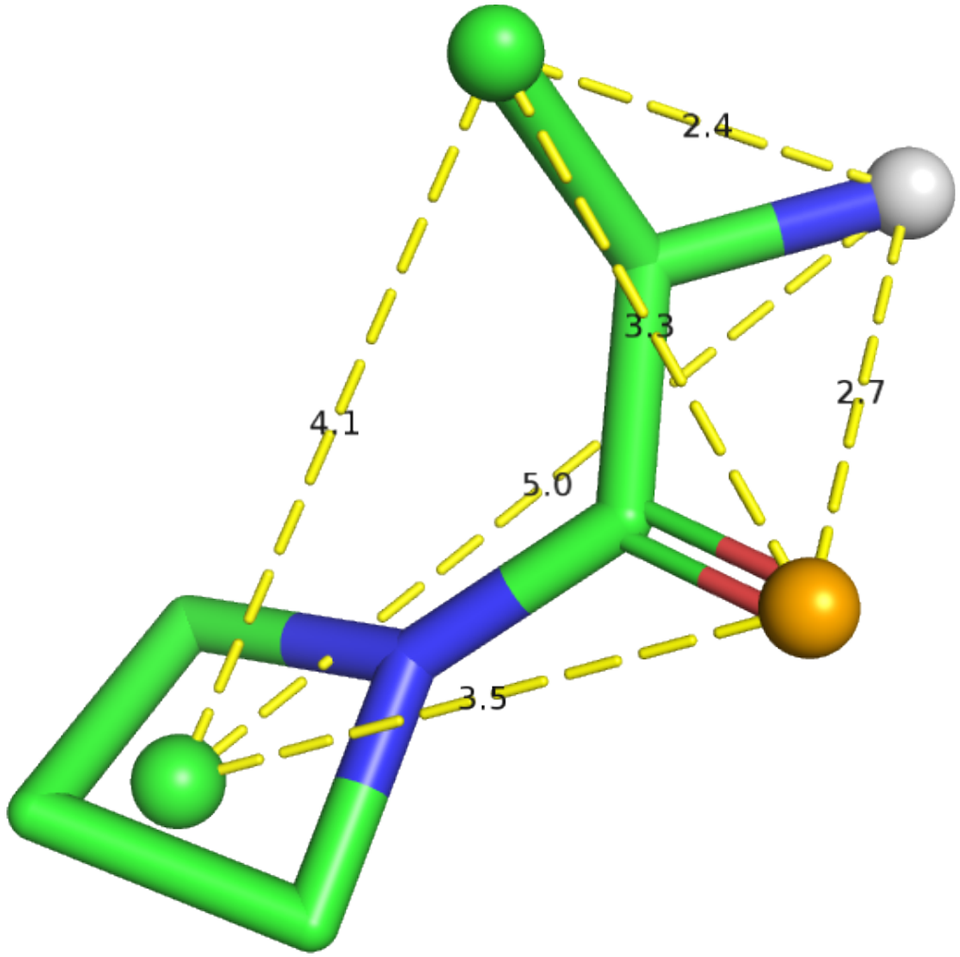
Pharmer Efficient and Exact Pharmacophore Search





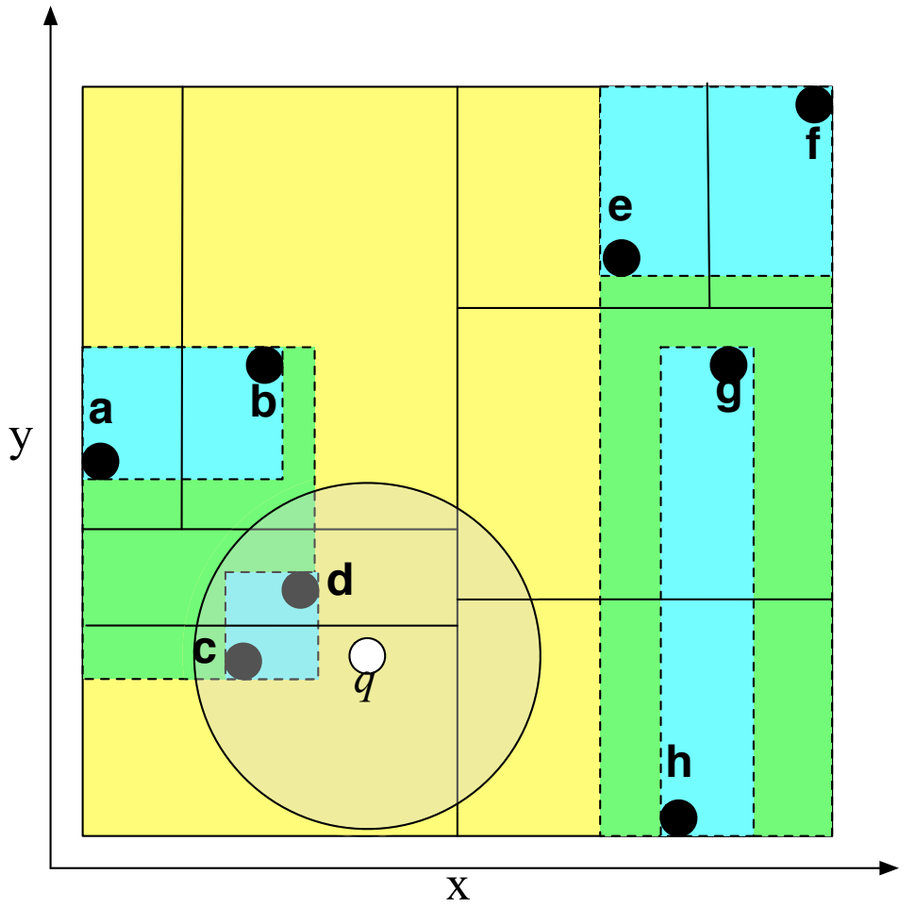


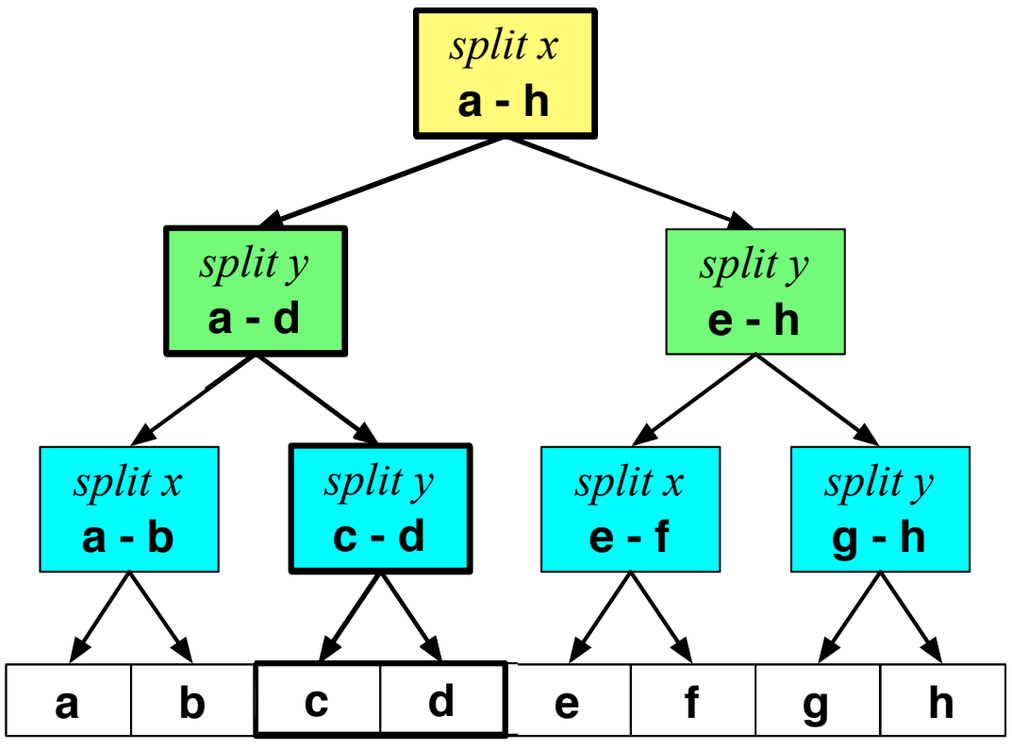


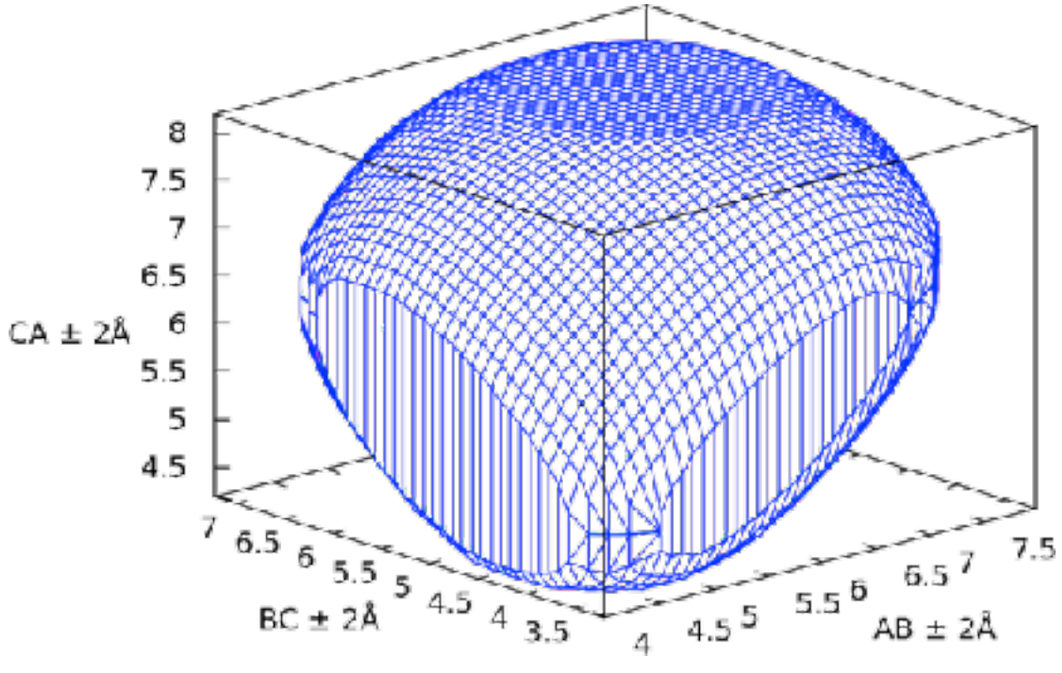


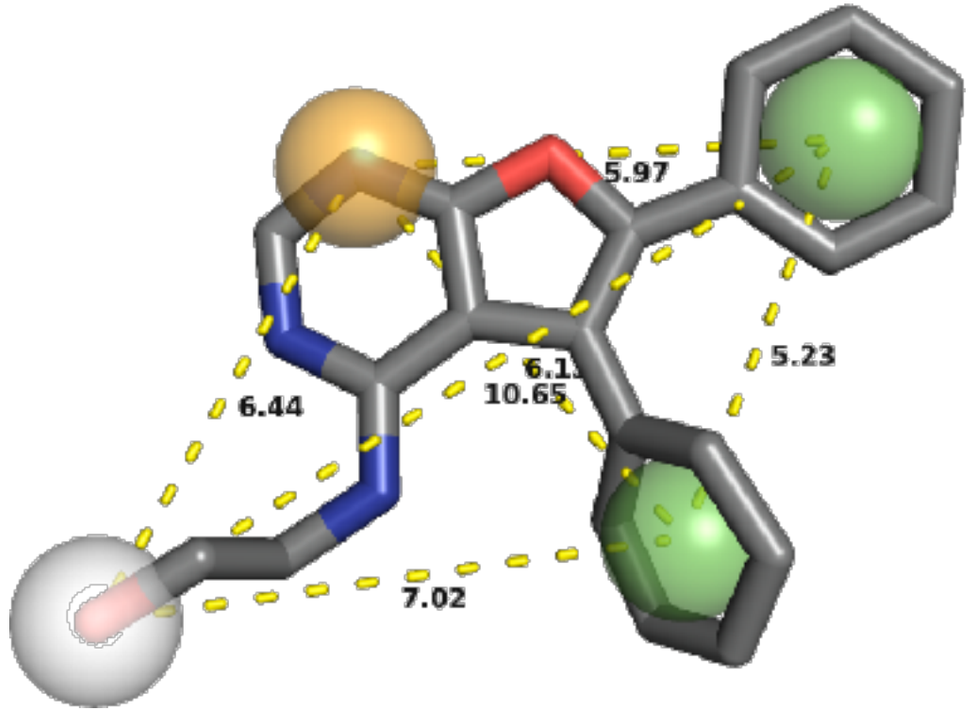
Pharmer

Efficient and Exact Pharmacophore Search



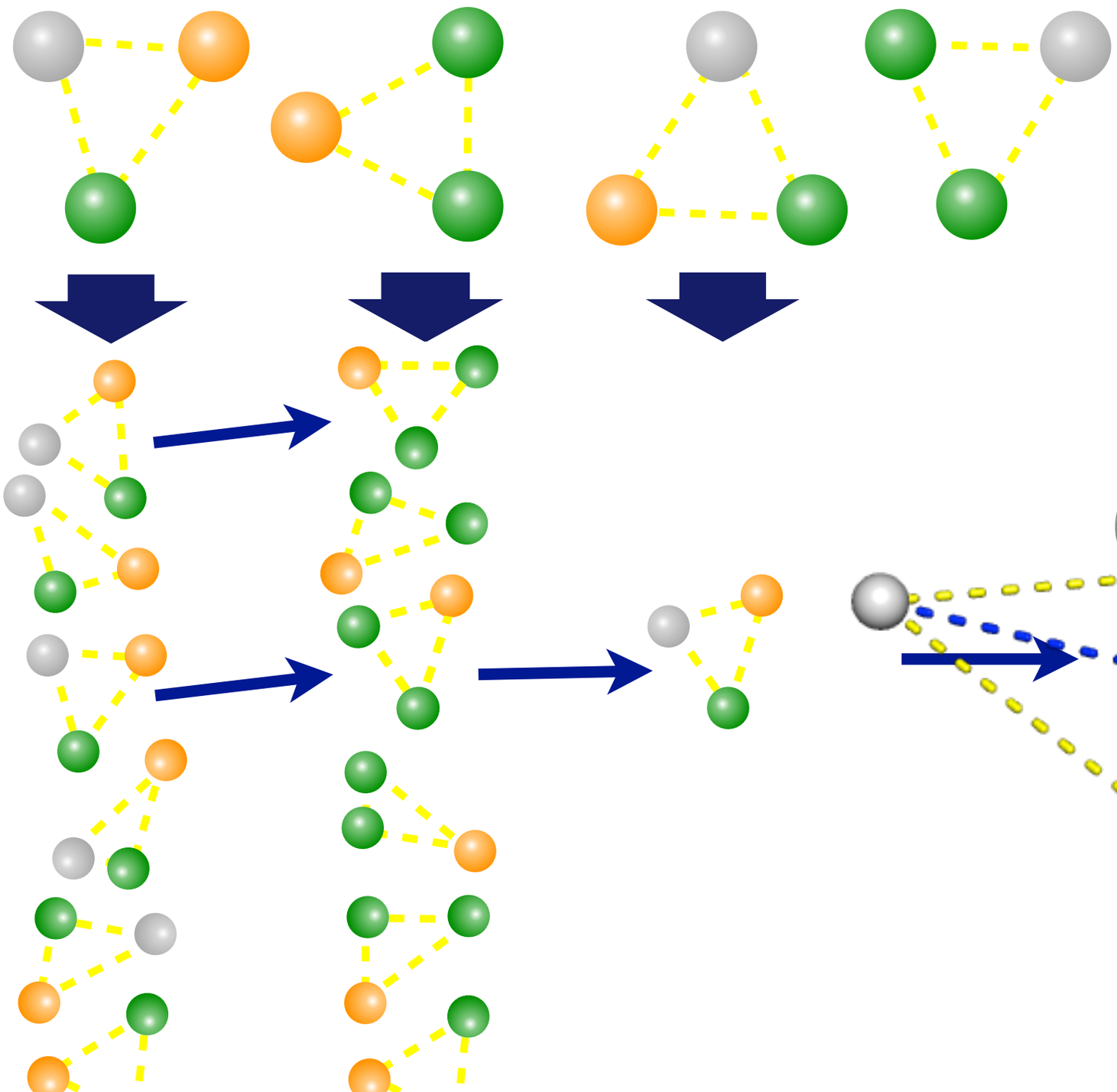


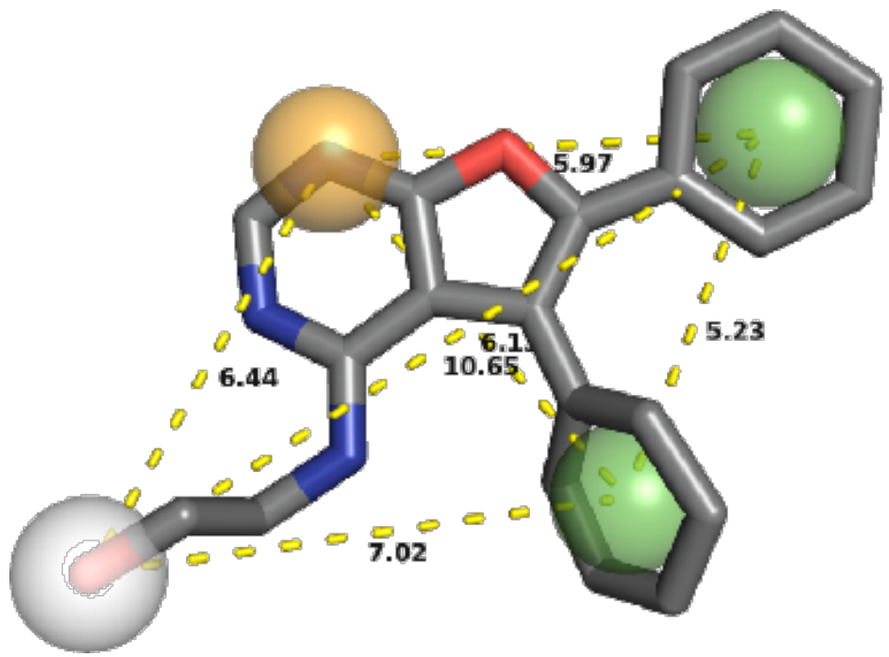




Pharmer

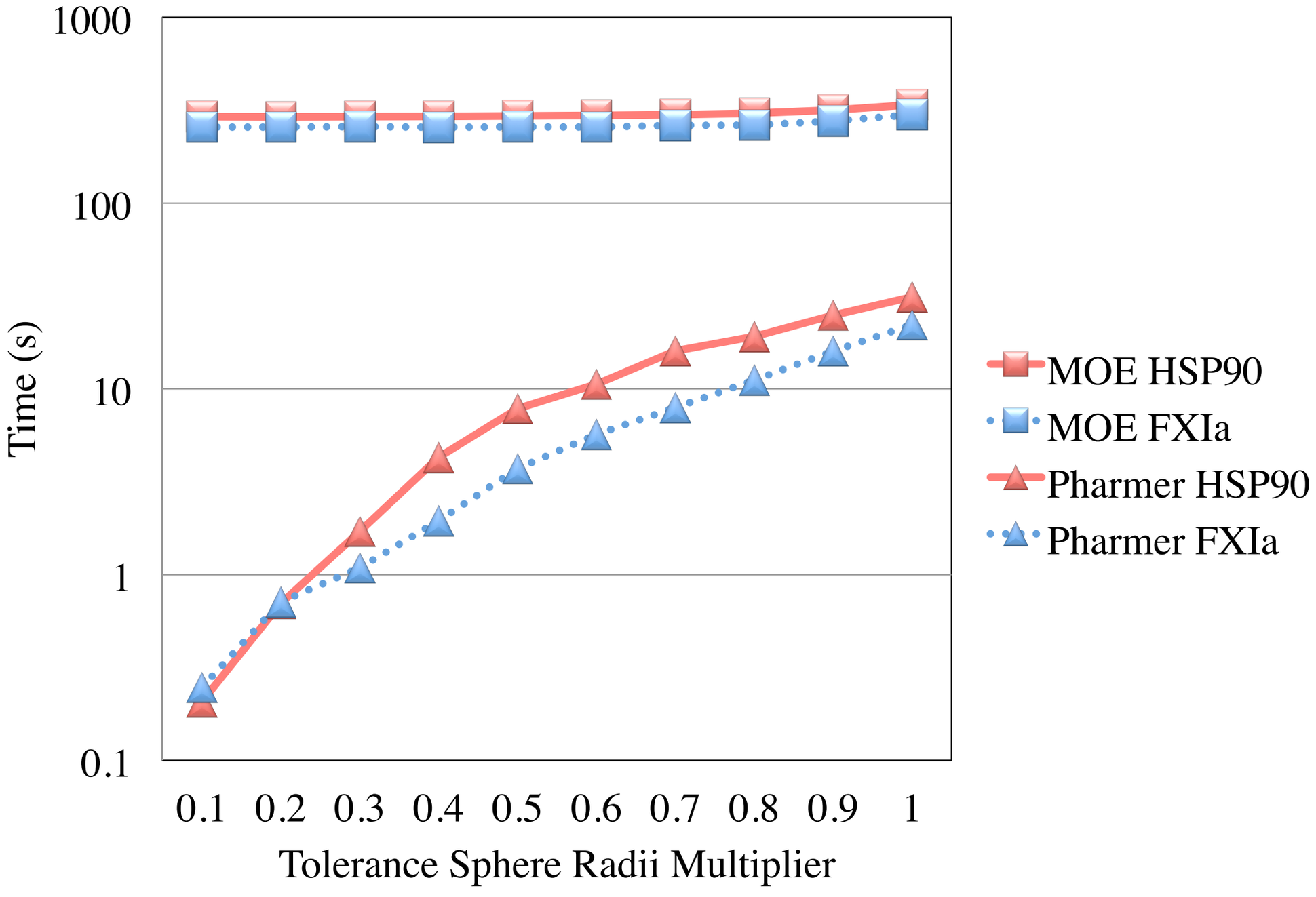
Efficient and Exact Pharmacophore Search

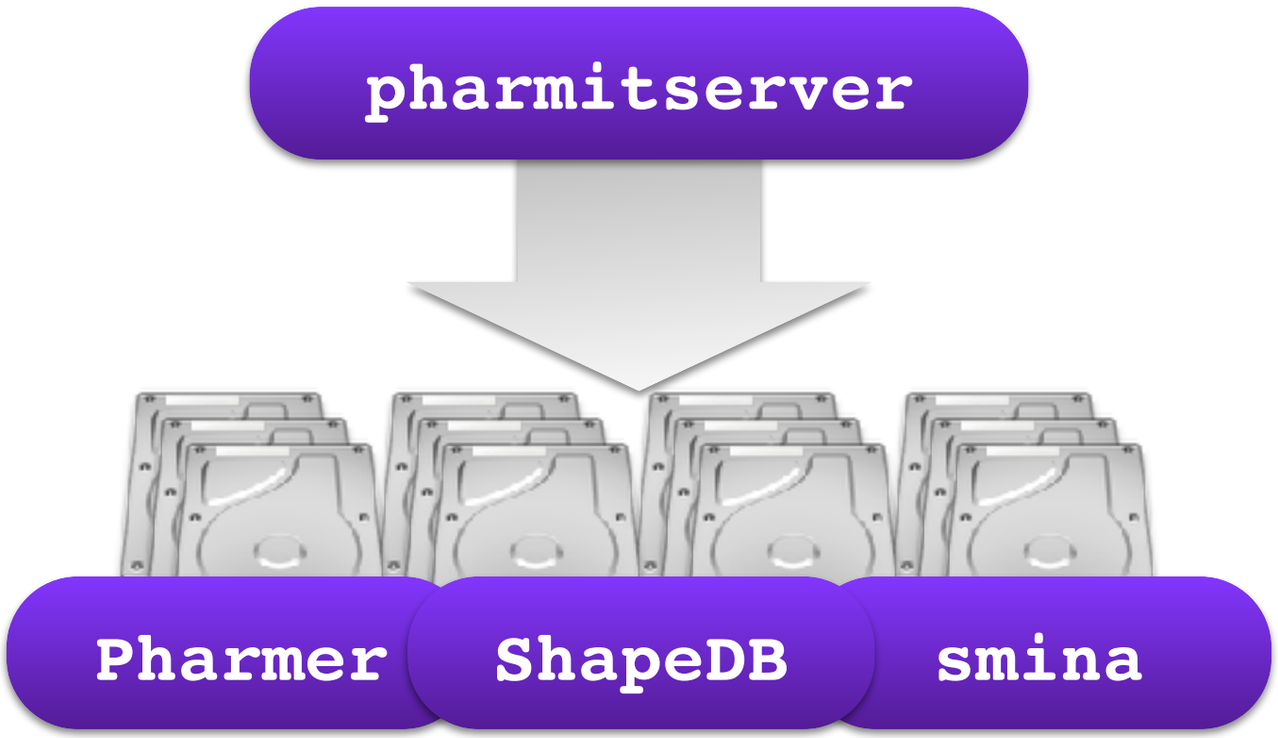




Pharmer

Efficient and Exact Pharmacophore Search





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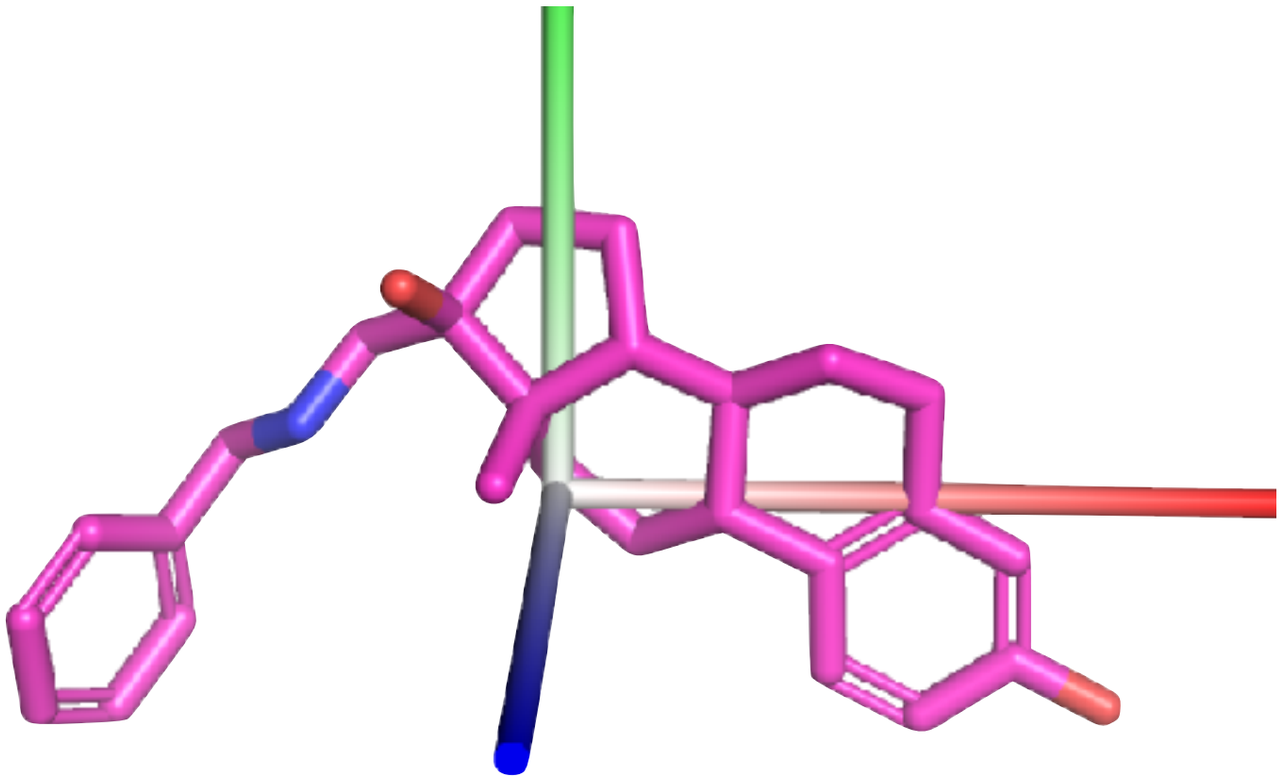
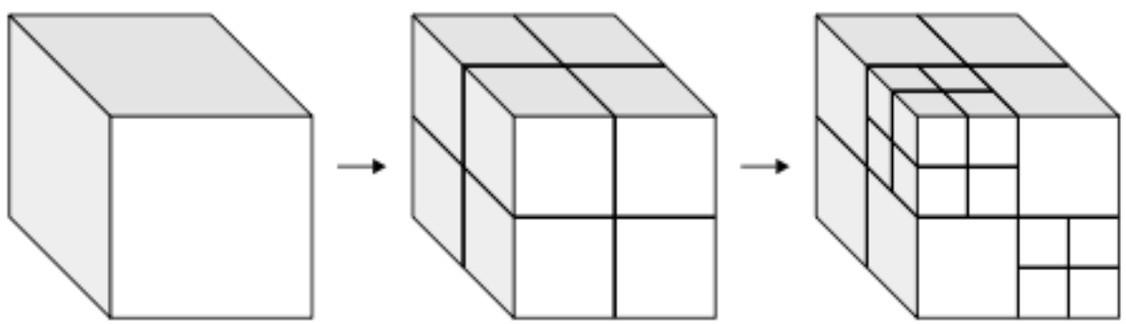
ShapeDB Indexed Search of Molecular Shapes

Align to Moments of Inertia



Voxelize



Oct-tree

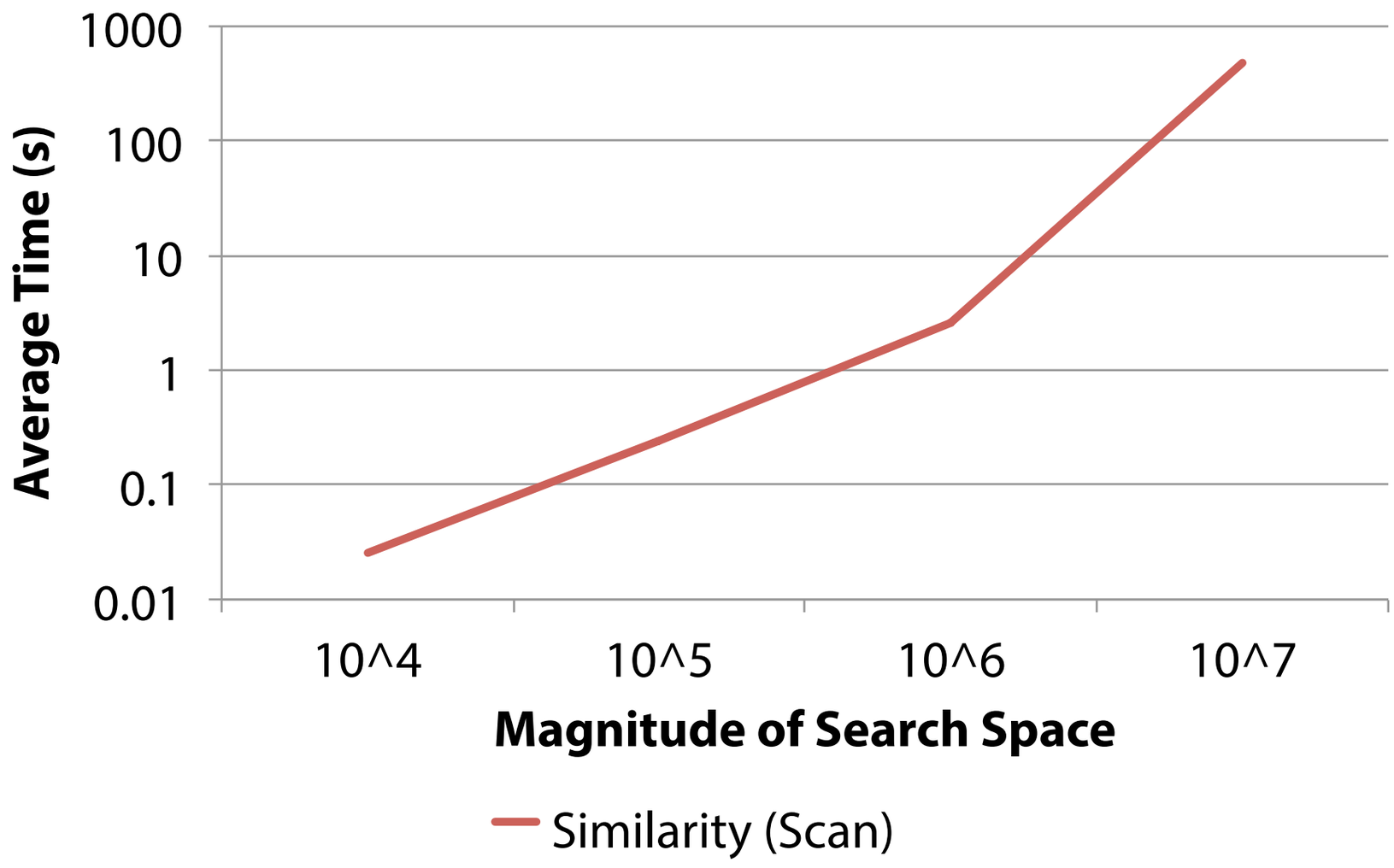
- Scales with Surface Area, not Volume
- Fast Intersection/Union Operations

ShapeDB

Indexed Search of Molecular Shapes

$$\delta(A, B) = \frac{A \cap B}{A \cup B}$$

Performance of Shape Similarity Search



ShapeDB

Indexed Search of Molecular Shapes

MIV

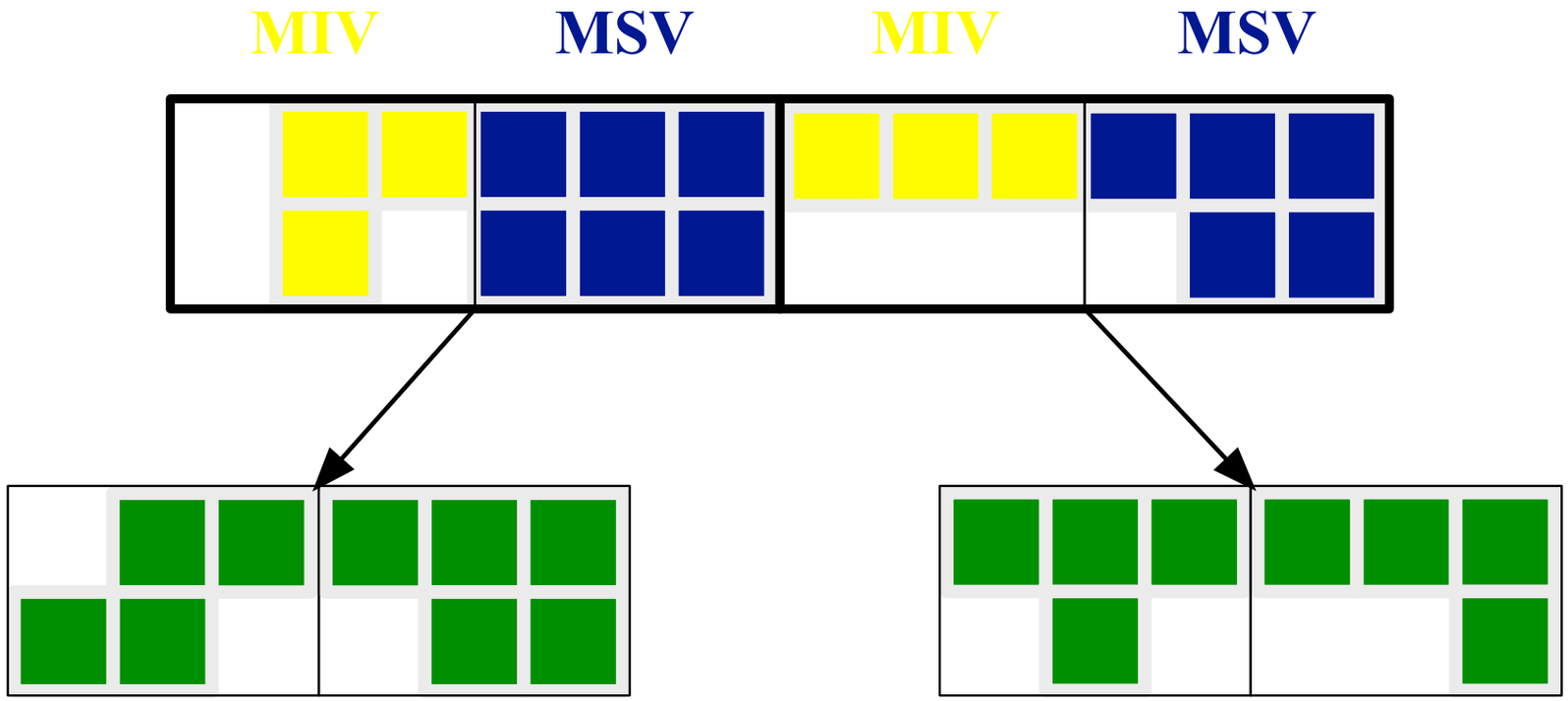
Maximum Included Volume

Intersection

MSV

Minimum Surrounding Volume

Union

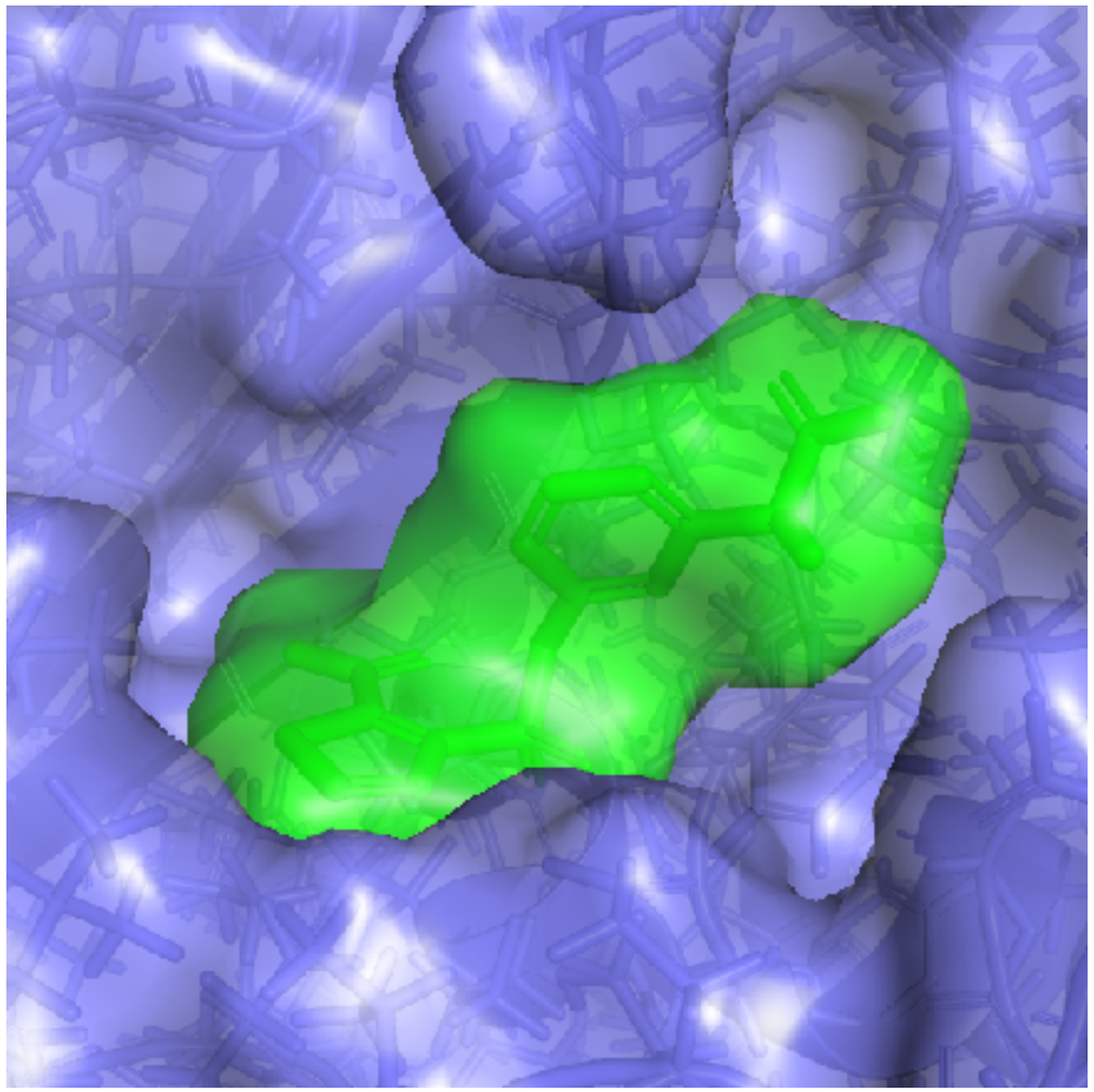


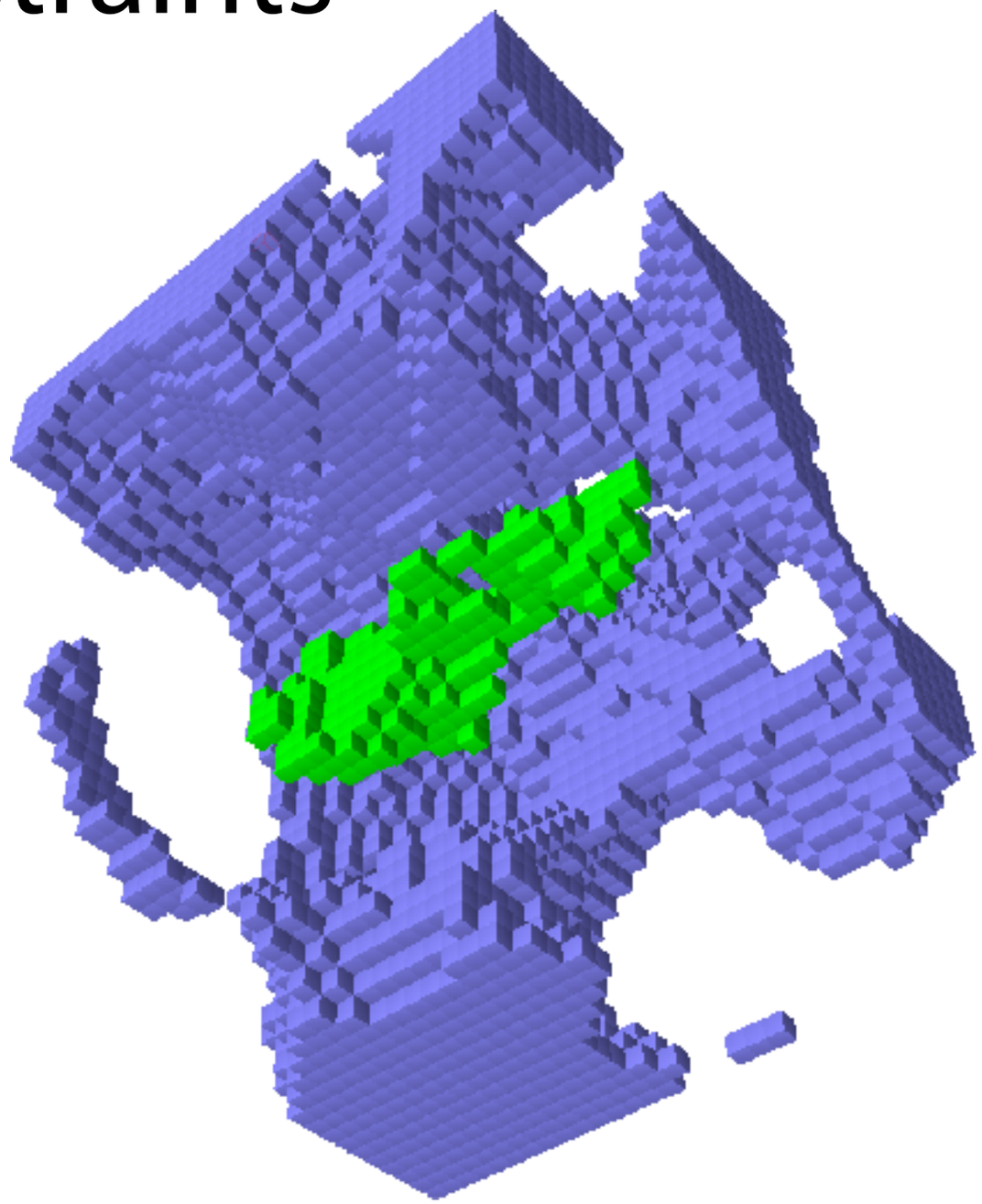
Matching and packing algorithm for efficient and effective initialization

Koes, D. R., & Camacho, C. J. (2014). Shape-based virtual screening with volumetric aligned molecular shapes. *J Comput Chem, 35*(25), 1824-1834. doi:10.1002/jcc.23690

Koes, D., & Camacho, C. (2014). Indexing volumetric shapes with matching and packing. *Knowledge and Information Systems*, 1-24. doi:10.1007/s10115-014-0729-z

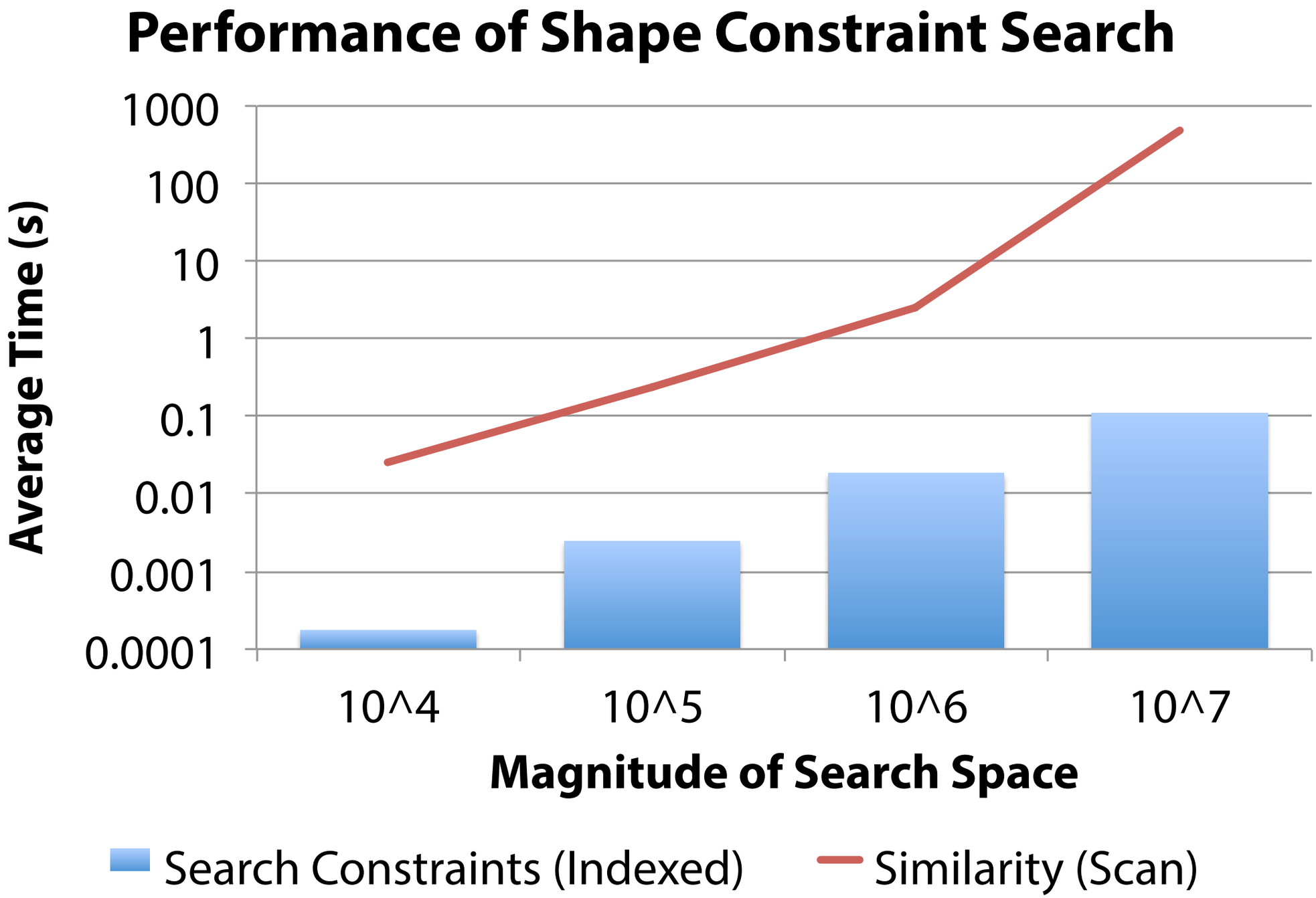
Shape Constraints

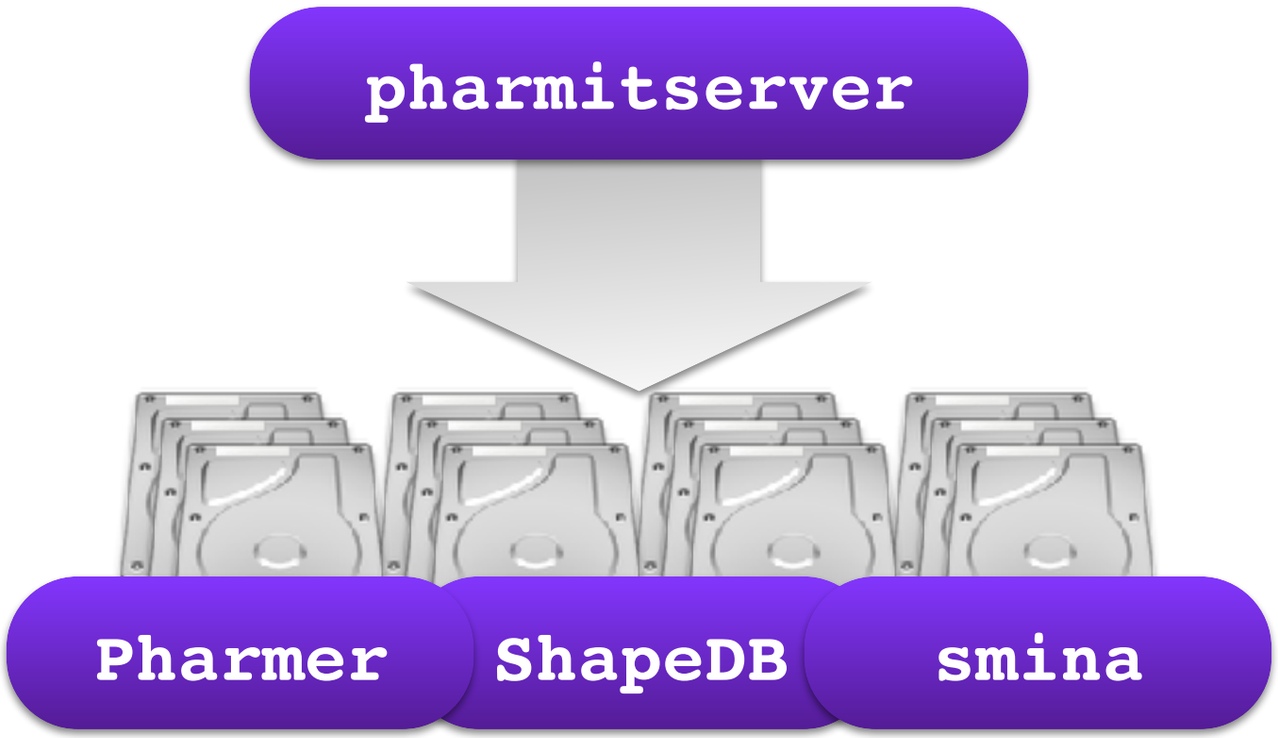




ShapeDB

Indexed Search of Molecular Shapes





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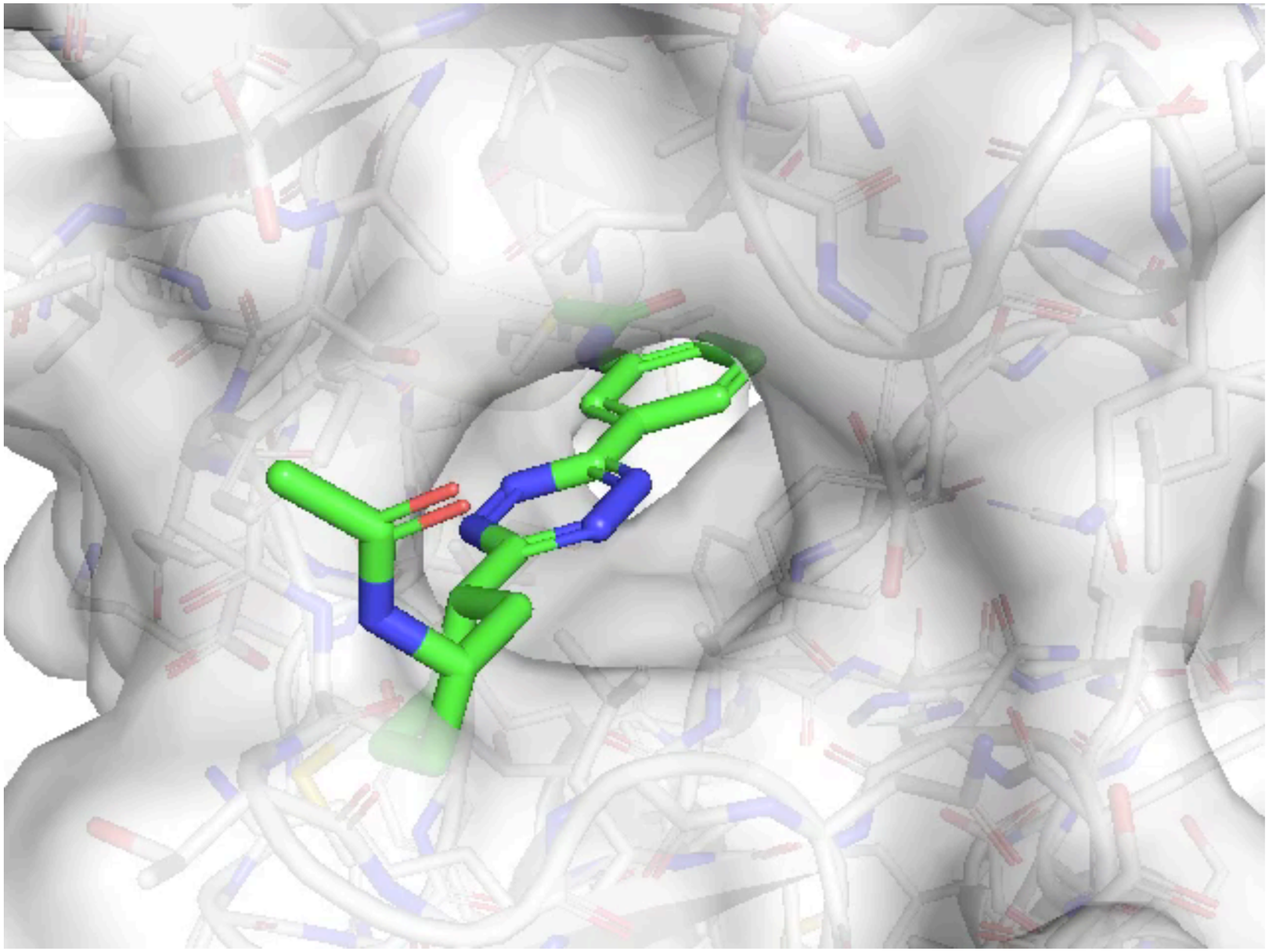
GPL/BSD License

smina

Scoring and Minimization with AutoDock Vina



Improved energy minimization

Facilities for scoring function development

Custom format with precomputed torsion tree

Implementation of server protocol

Koes, D. R., Baumgartner, M. P., & Camacho, C. J. (2013). Lessons Learned in Empirical Scoring with smina from the CSAR 2011 Benchmarking Exercise. *Journal of Chemical Information and Modeling, 53*(8), 1893-1904. doi:10.1021/ci300604z

Case Study:

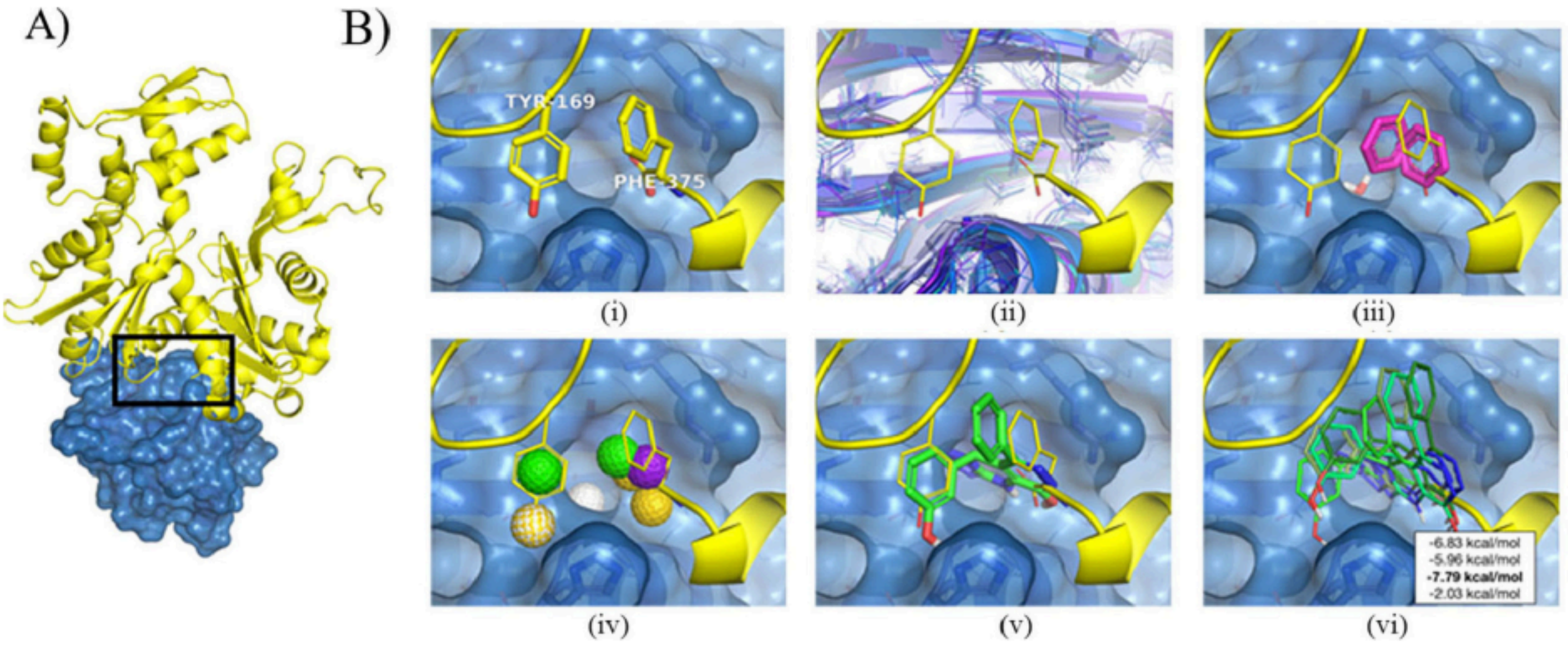
Profilin

Structure-based virtual screening identifies a small-molecule inhibitor of the profilin 1–actin interaction

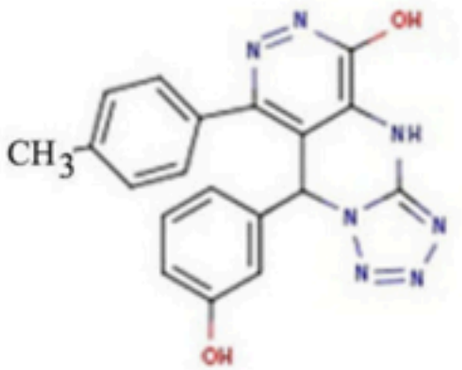
Received for publication, July 27, 2017, and in revised form, December 8, 2017 Published, Papers in Press, December 27, 2017, DOI 10.1074/jbc.M117.809137

David Gau[‡1], **Taber Lewis**[§], **Lee McDermott**[¶], **Peter Wipf**[‡§], **David Koes**[¶], **and Partha Roy**[‡‖**2]

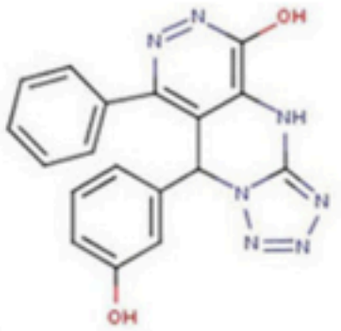
From the Departments of [‡]*Bioengineering,* [§]*Chemistry,* [¶]*Computational and Systems Biology,* [‖]*Cell Biology, and* [**]*Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania 15219*



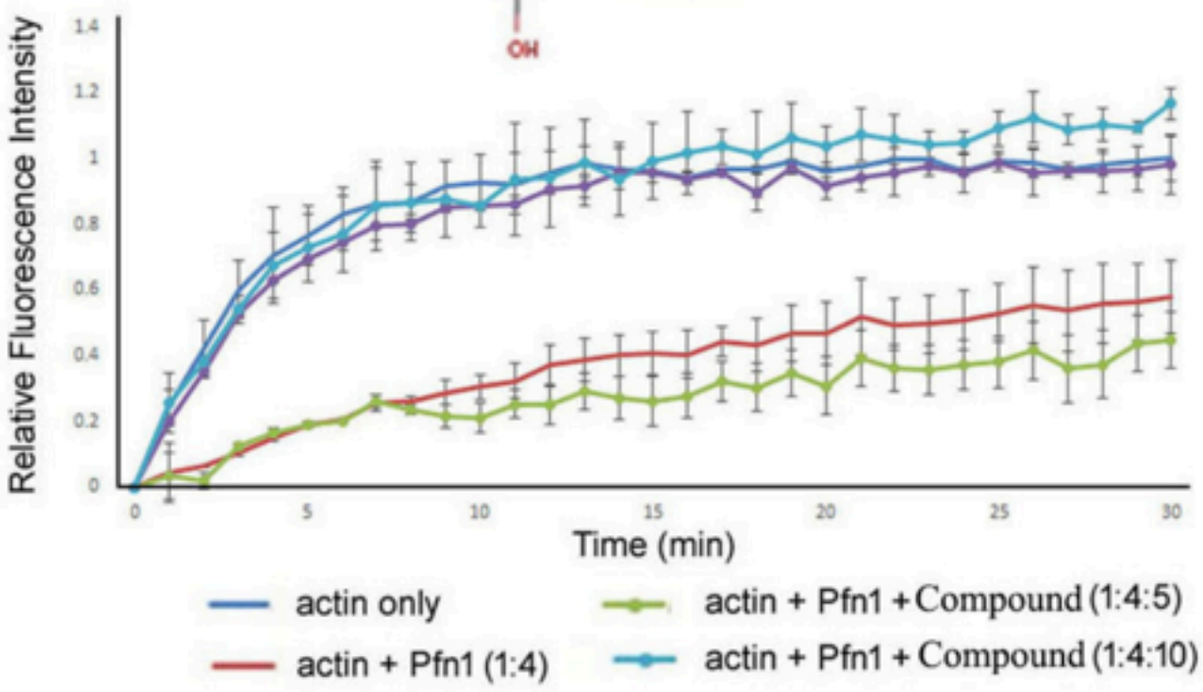
Top 20 compounds purchased

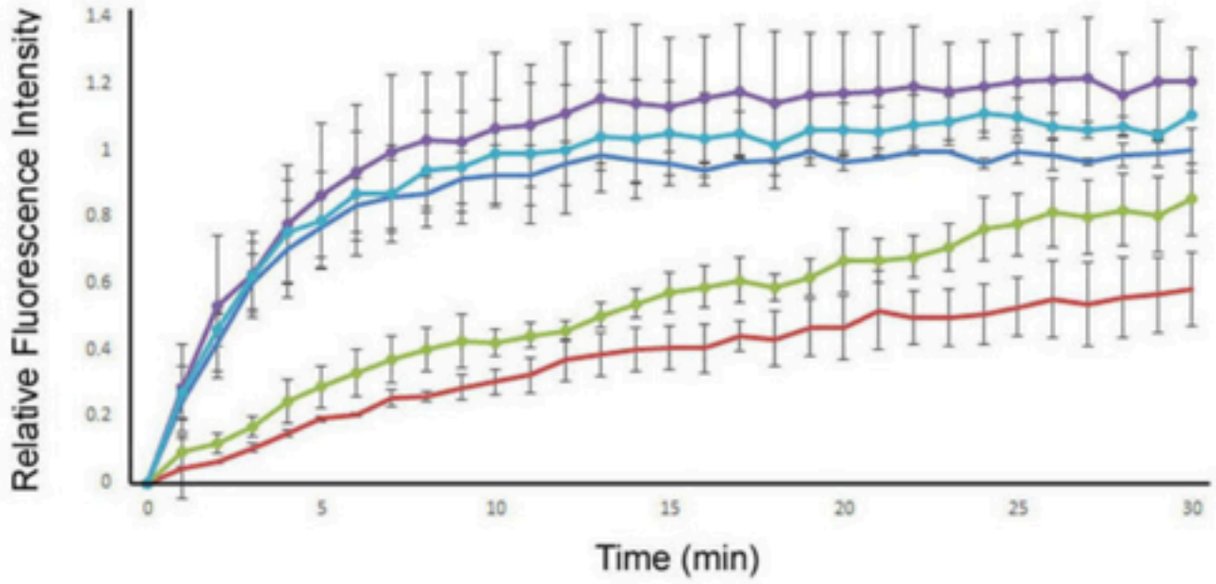

CH3
OH
NH
N
N
N
N
OH

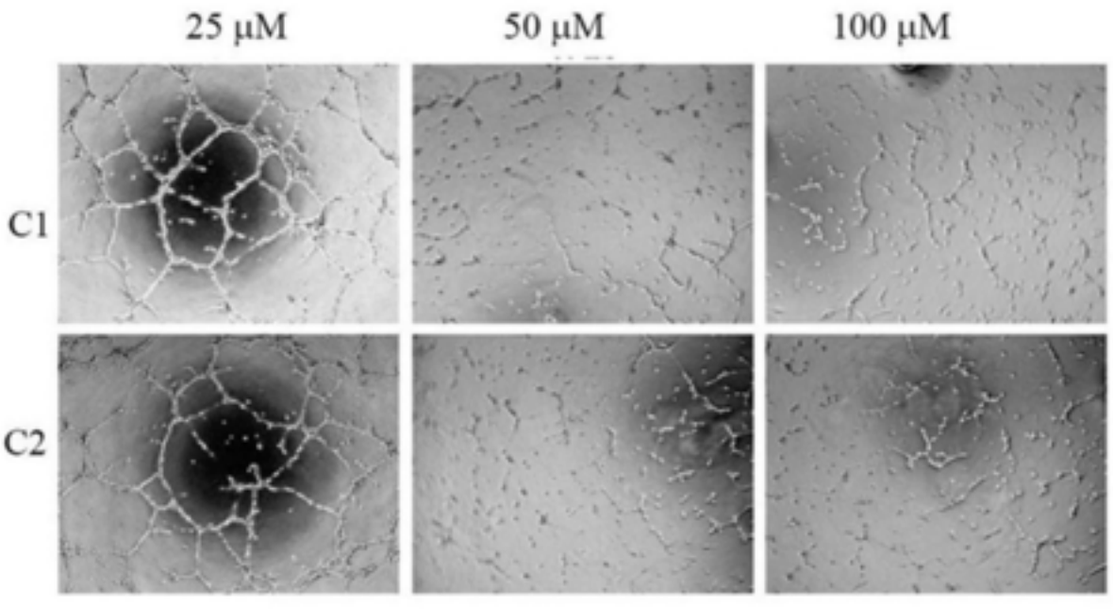
C1

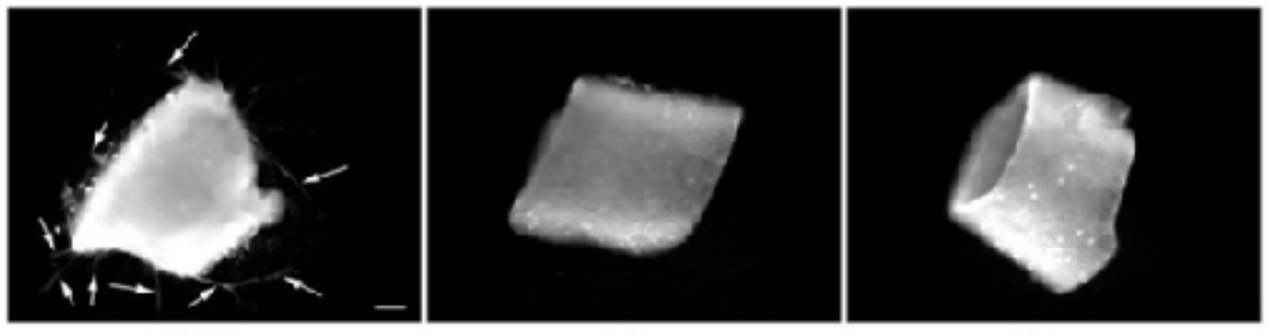

OH
NH
N
N
N
N
OH

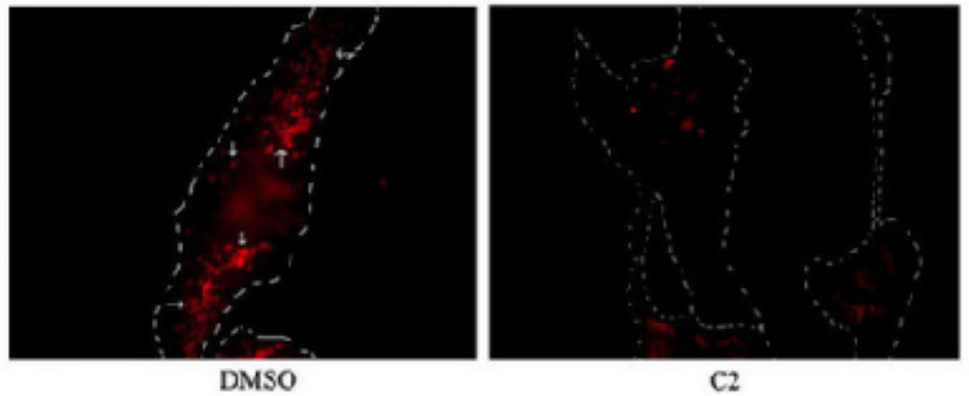
C2


Relative Fluorescence Intensity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
Time (min)
actin only
actin + Pfn1 (1:4)
actin + Pfn1 + Compound (1:4:5)
actin + Pfn1 + Compound (1:4:10)
actin + Compound (1:10)


Relative Fluorescence Intensity
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
Time (min)


25 μM
50 μM
100 μM
C1
C2


DMSO
C1
C2


DMSO
C2

Acknowledgements

http://pharmit.csb.pitt.edu

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RELAY THERAPEUTICS

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@david_koes

Questions?

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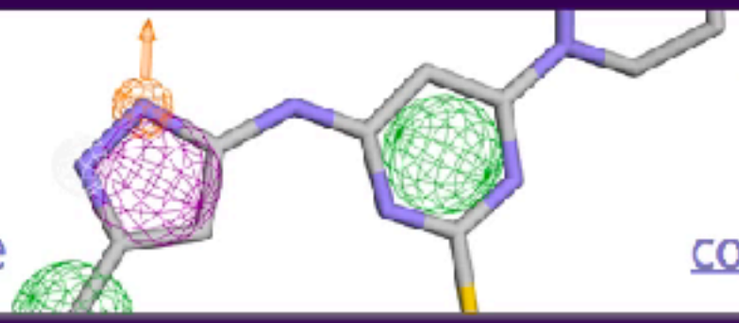
pharmit beta

interactive exploration of chemical space



code

help

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search

virtual screening in your browser

enter pharmit search

start from PDB: ligand

binding site waters: ignore

submit

examples

create

submit your own chemical libraries

log in to manage libraries

email:

password:

log in

register new account

log in as guest

pharmit currently has

5 built-in libraries containing 1,039,706,461 conformations of 75,076,775 compounds and

7 publicly accessible user-contributed libraries containing