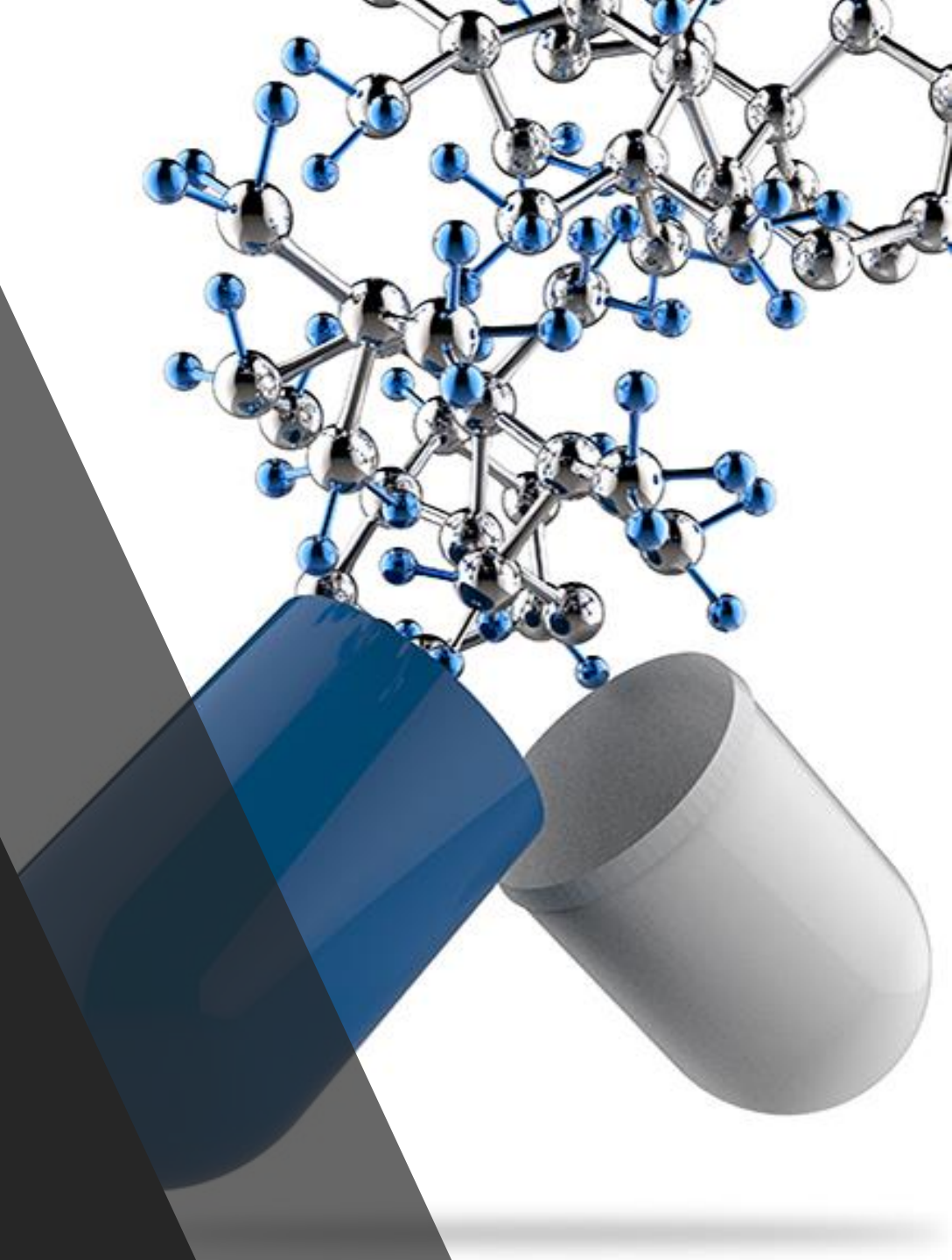
Computer Aided Drug Design

Docking and other Virtual Screening Methods



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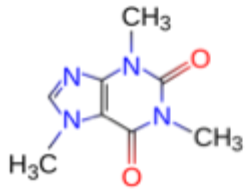
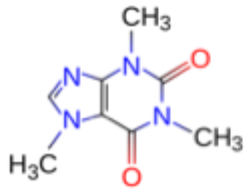

CH3
N
O
N
N
CH3
H3C
O

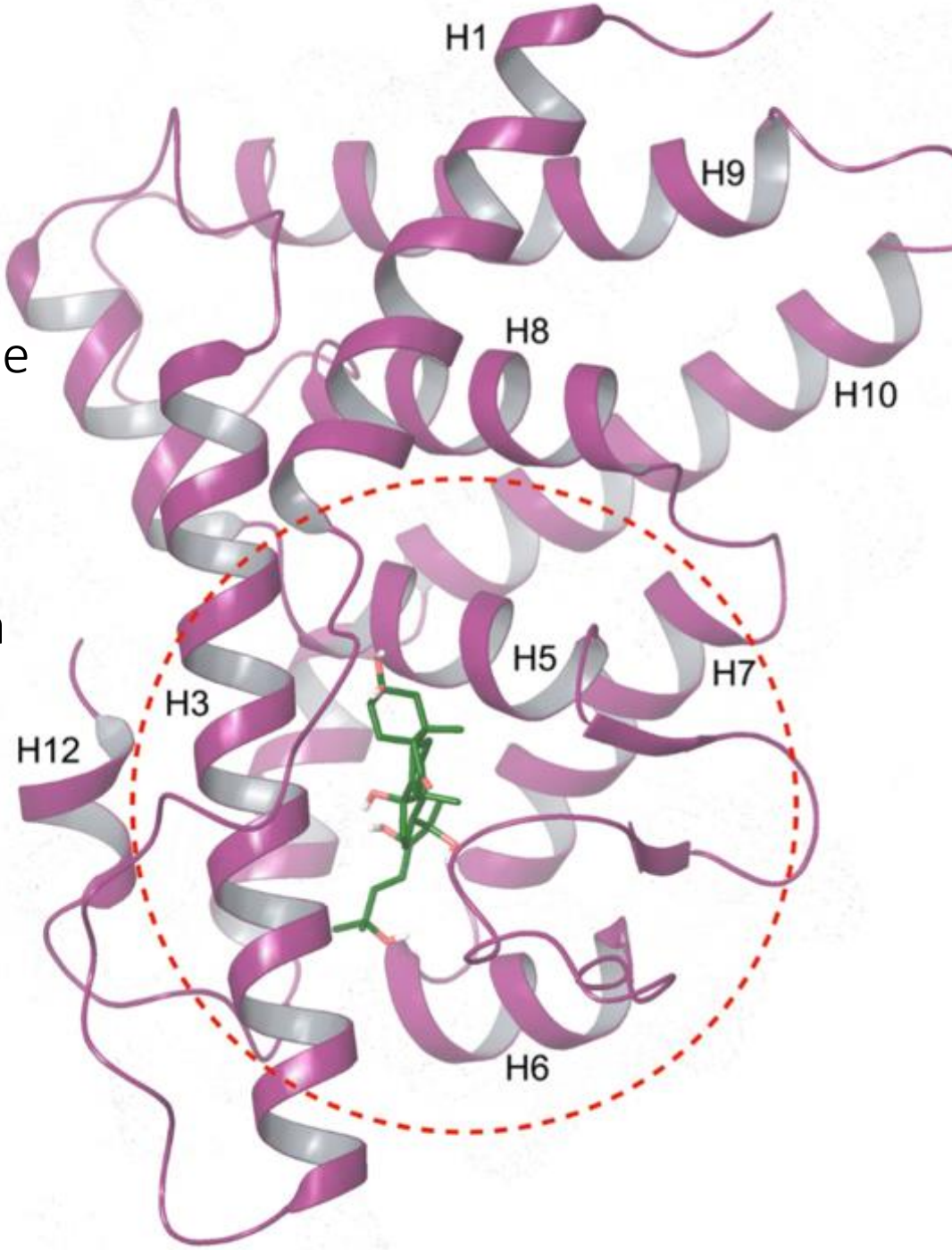
+


CH3
N
O
N
N
N
CH3
H3C
O

→

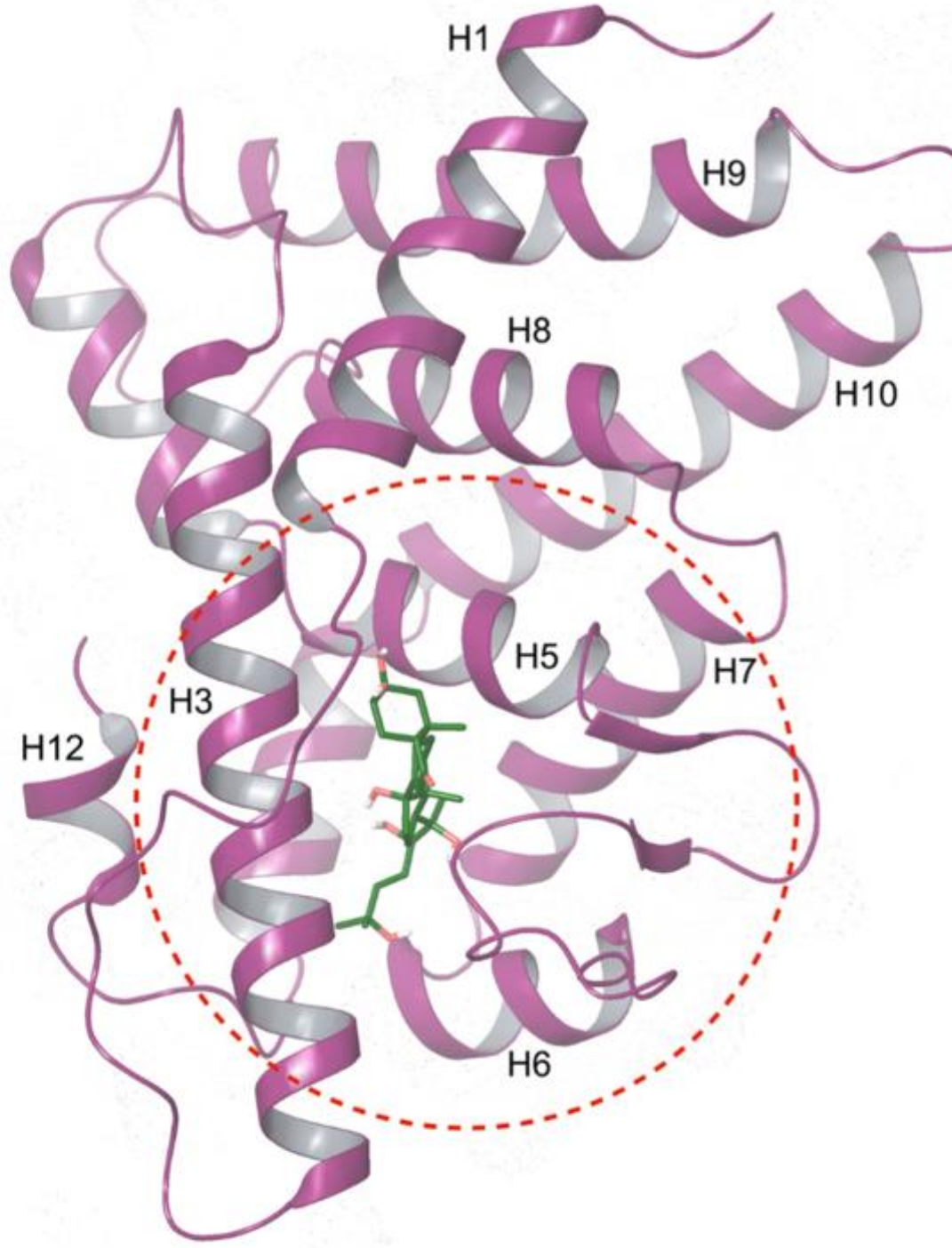
Drug Design Lingo:

- **Target**: any macromolecule whose function can be manipulated/altered to result in disease treatment!
- **Ligand:** compound (typically small molecule) that may bind to a target, with hopes of it serving as a treatment
- **HTS**: High Throughput Screening; experimental method of assaying many (thousands) of compounds for activity
- **Binding Mode:** orientation of ligand in a binding site



Goals/objectives of CADD:

- Find/design ***ligands*** to bind/regulate target ***macromolecules***



Goals/objectives of CADD:

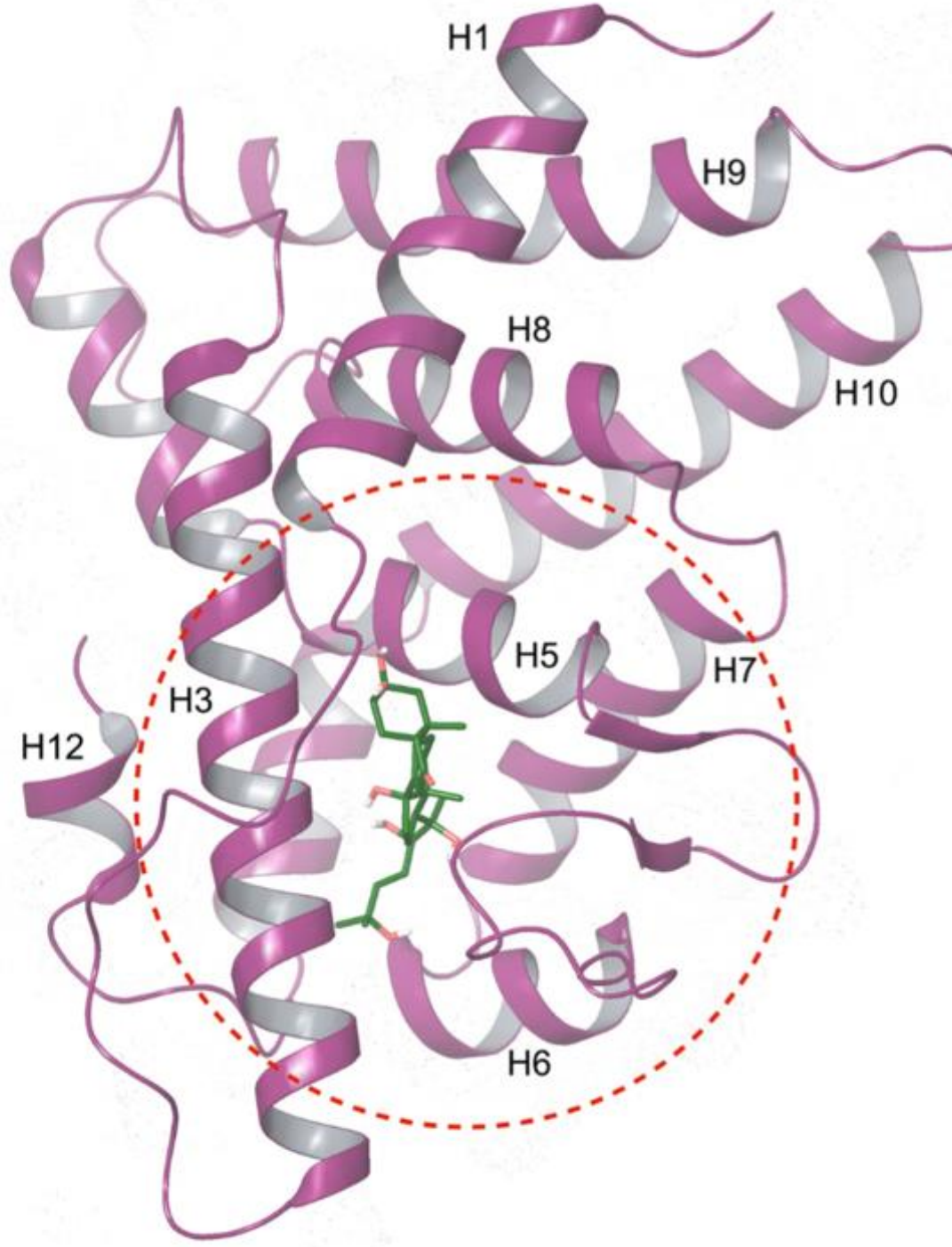
- Find/design ***ligands*** to bind/regulate target ***macromolecules***

- Virtual High Throughput Screening
  - Thousands+ of ligands/1-2 targets

- Target Structure/Binding Site Prediction
  - 1-2 targets

- Off-path Target Screening
  - 10-20 ligands/10-20 targets

- Binding Mode Analysis/Prediction
  - 10-20 ligands/1-2 targets



Goals/objectives of CADD:

- Find/design ***ligands*** to bind/regulate target ***macromolecules***

- Virtual High Throughput Screening
  - Thousands+ of ligands/1-2 targets

  Docking, Pharmacophore Modeling

- Target Structure/Binding Site Prediction
  - 1-2 targets

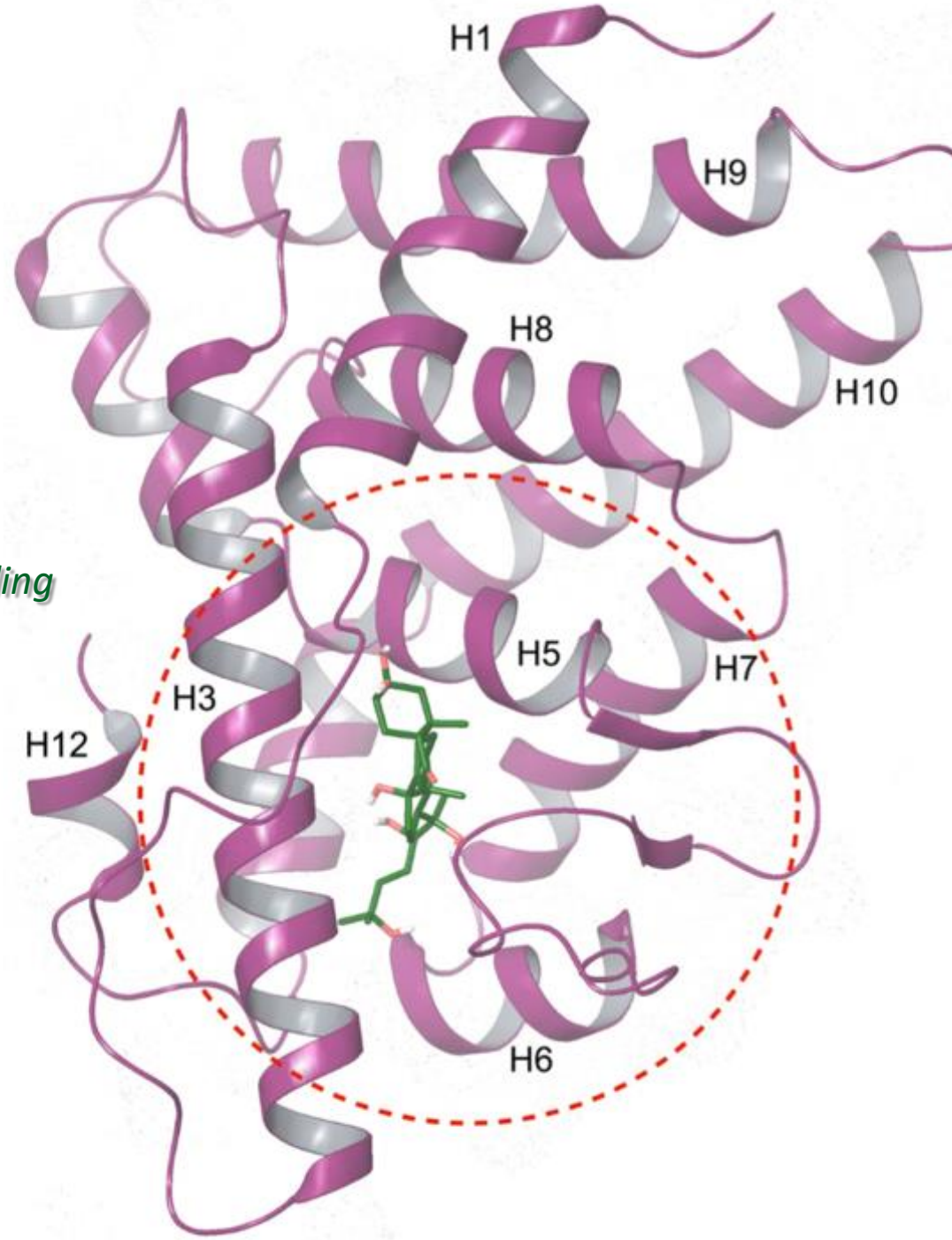
  Homology Modeling, Binding Site Prediction

- Off-path Target Screening
  - 10-20 ligands/10-20 targets

  Binding Site Comparison, Cross-Docking

- Binding Mode Analysis/Prediction
  - 10-20 ligands/1-2 targets

  Flexible Docking



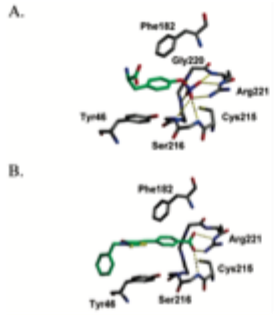
An Example of CADD Success!

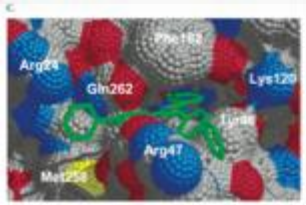
Doman, T. N., et al. Molecular Docking and High-Throughput Screening for Novel Inhibitors of Protein Tyrosine Phosphatase-1B *J. Med. Chem.* **2002.** *45,* 2213-2221

Table 1. Hit Rates from High-Throughput and Docking Screens against PTP1B

technique	compds tested	hits with IC_{50} < 100 μM	hits with IC_{50} < 10 μM	hit rate (%)
HTS	400 000	85	6	0.021
docking	365	127	21	34.8[a]

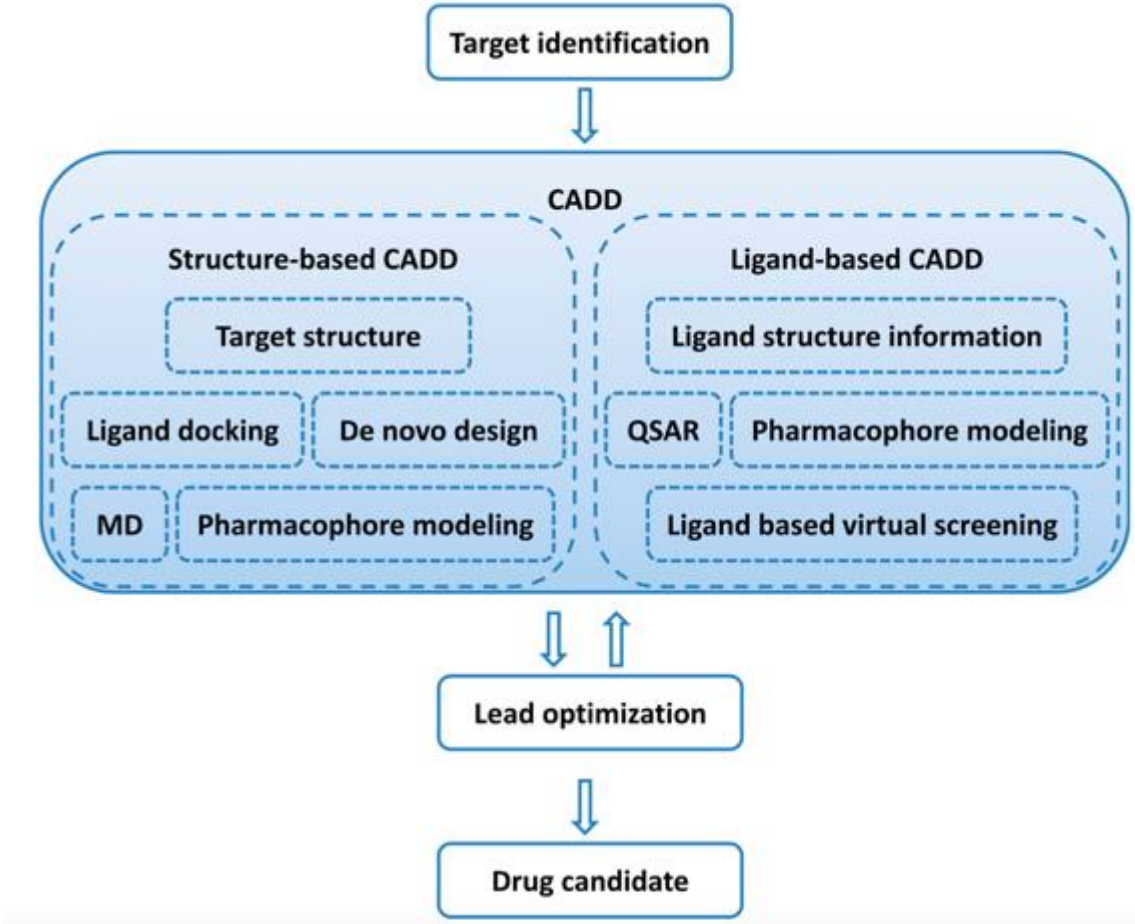
[a] We define hit rate for the docked molecules as 100 times the number of bioactive docked molecules divided by the total number of docked molecules that were bioassayed.





What functionality are you looking for?

- What information do you have??
- What information do you want??
- [Directory of Computer Aided Drug Design Tools]
    - (very great link! cross references functionality by software!)c



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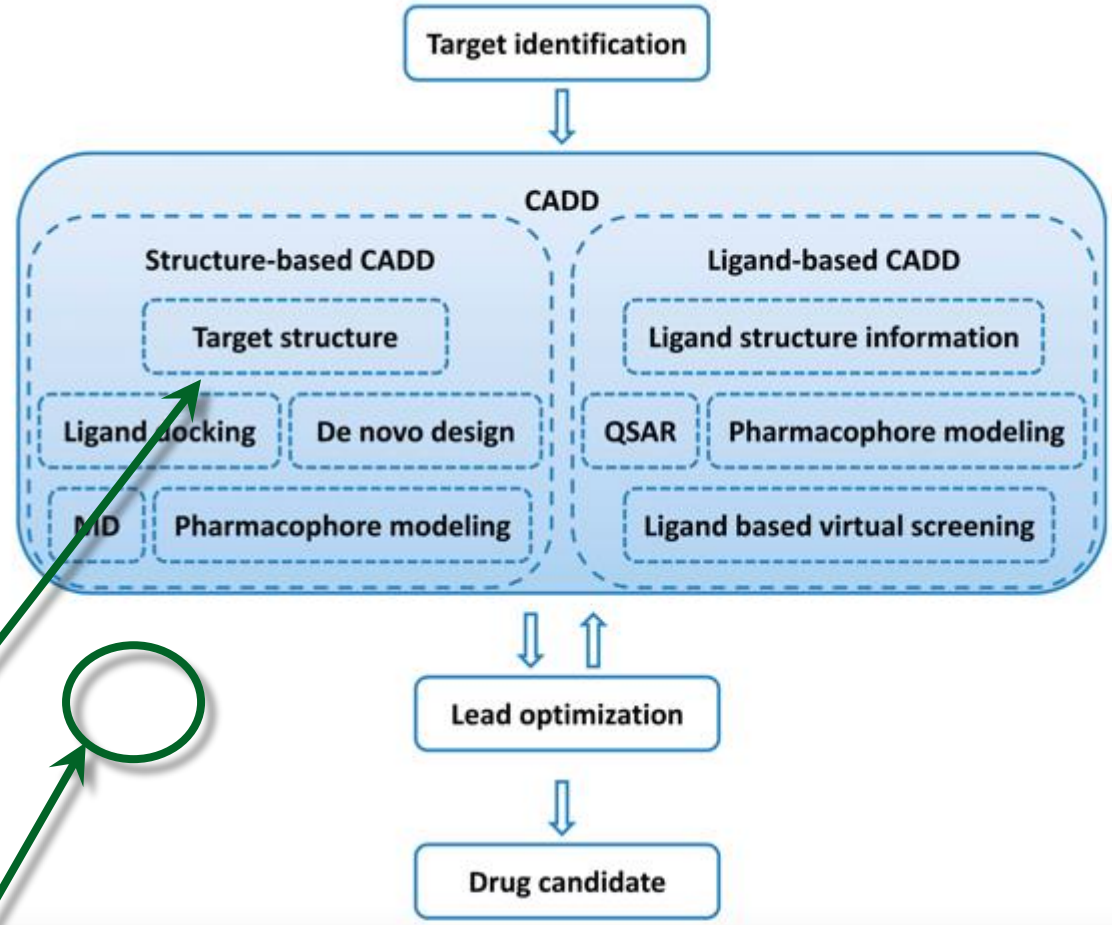


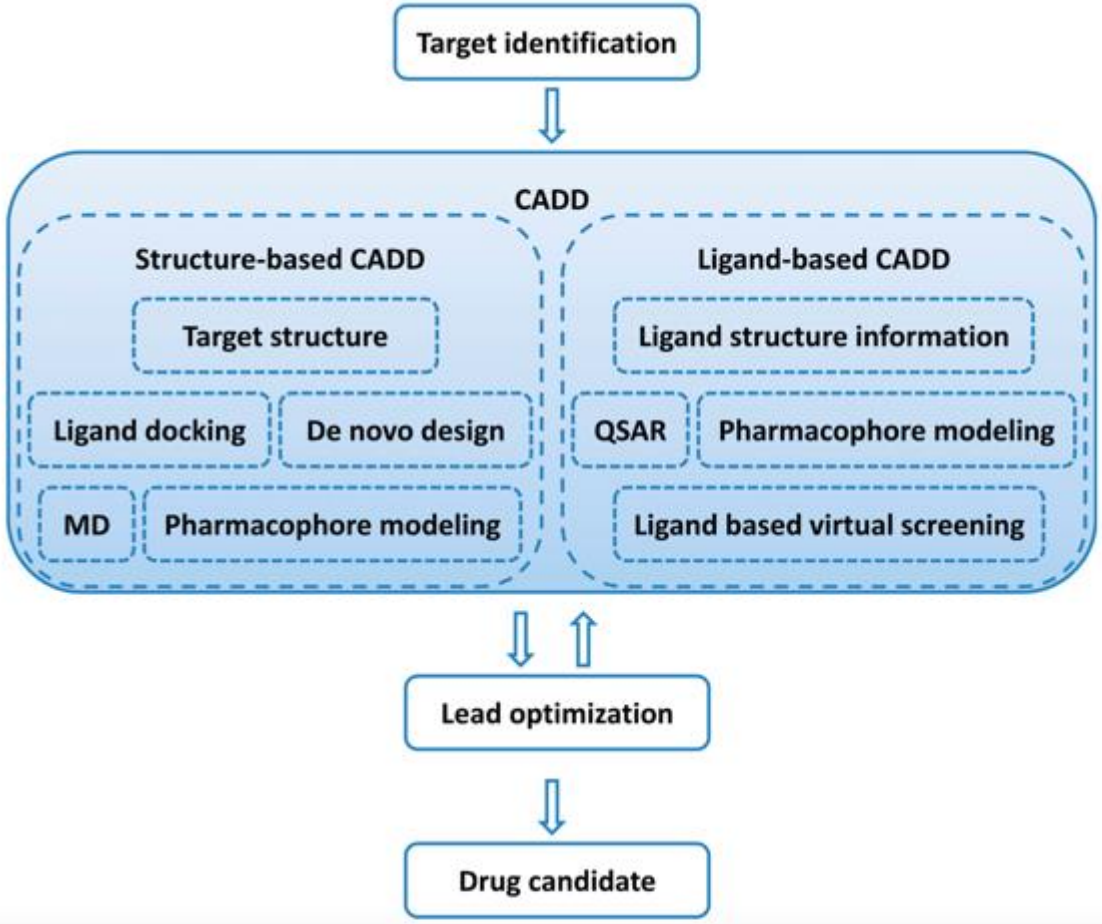
You know the structure of the target binding site!

Saturday Morning!!

You know a ligand confirmed to bind target!

What functionality are you looking for?

- What information do you have??
- What information do you want??
- [Directory of Computer Aided Drug Design Tools]
  - (very great link! cross references functionality by software!)c



Let's take 5 minutes, to all follow this link separately… you might find something that interests you!

Molecular Docking Simulations:

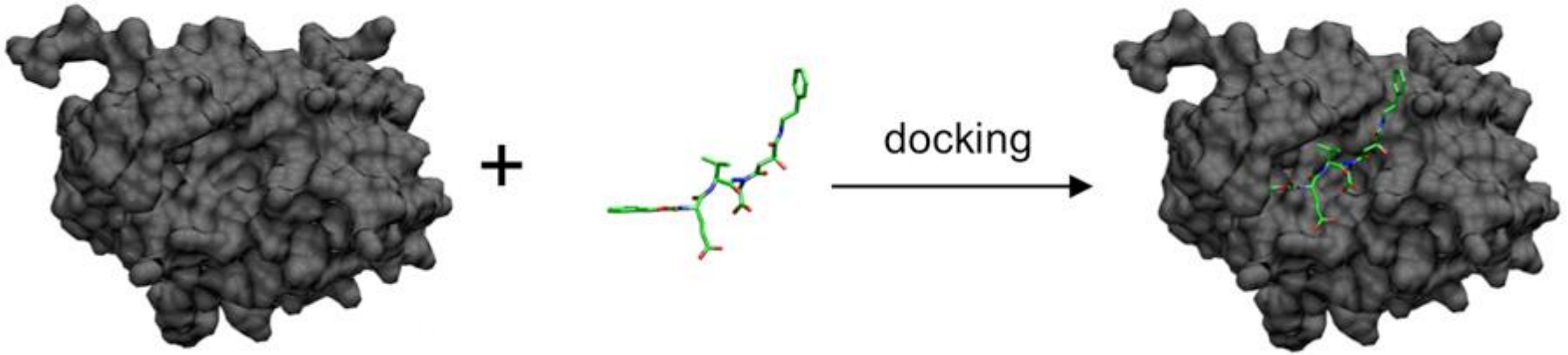
Introduction and Tutorial

Docking… What is it??

"In the field of molecular modeling, **docking** is a method which **predicts the preferred orientation** of one molecule to a second when bound to each other to **form a stable complex.** Knowledge of the preferred orientation in turn may be used to predict the **strength of association or binding affinity** between two molecules using, for example, **scoring functions**." (from Wikipedia)





ΔG_{bind}

https://en.wikipedia.org/wiki/Docking_(molecular)

Lengauer T, Rarey M. *Computational methods for biomolecular docking.* **1996.** *6*(3), 402-406

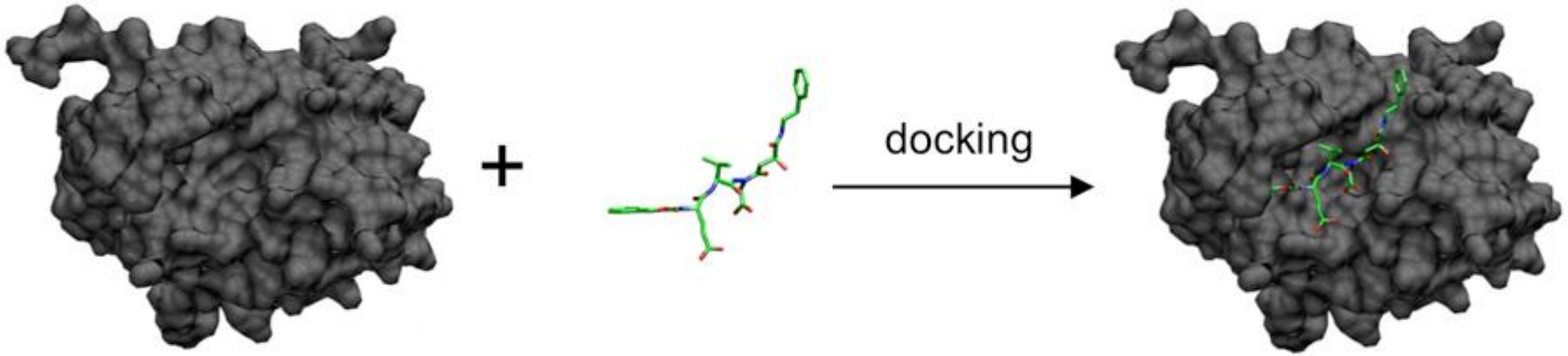
"In the field of molecular modeling, **docking** is a method which **predicts the preferred orientation** of one molecule to a second when bound to each other to **form a stable complex.** Knowledge of the preferred orientation in turn may be used to predict the **strength of association or binding affinity** between two molecules using, for example, **scoring functions**." (from Wikipedia)



fun + sunshine



get into school lockers



ΔG_{bind}

https://en.wikipedia.org/wiki/Docking_(molecular)

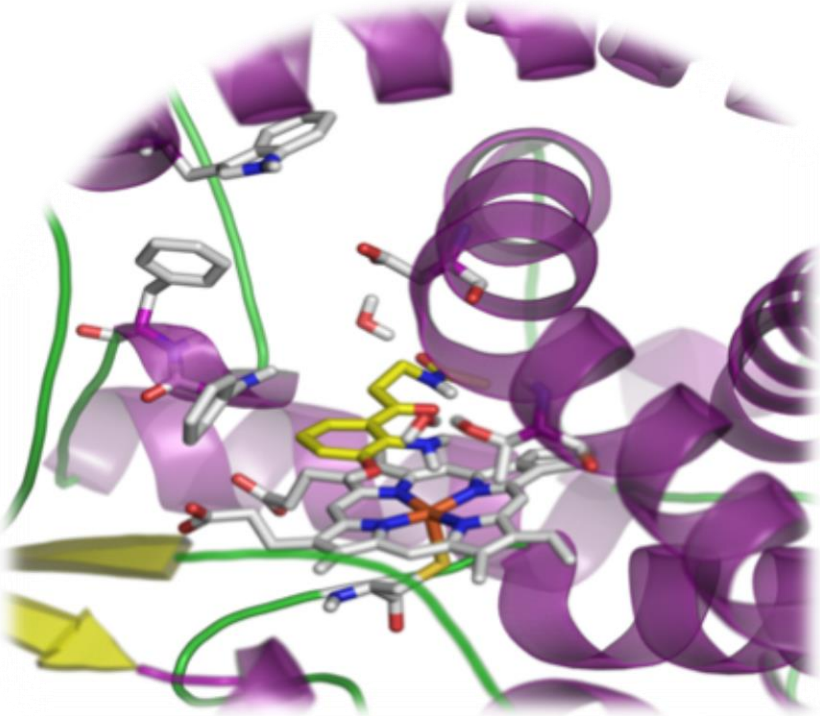
Lengauer T, Rarey M. *Computational methods for biomolecular docking.* **1996.** *6*(3), 402-406

Docking Goals:

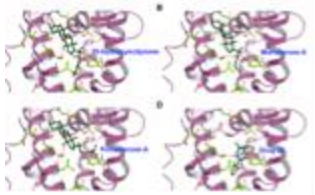
1. Identify false positives and false negatives before experimental screening (narrow compound library)

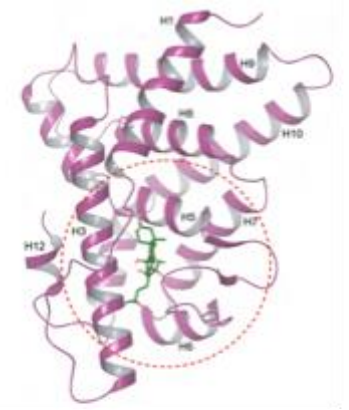
2. Predict binding modes & relative binding affinity

3. Suggest possible successful compounds

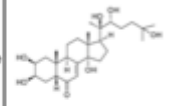
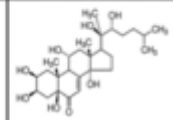
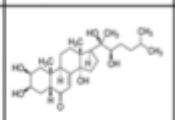
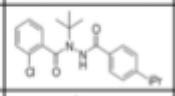
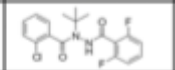
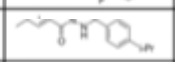


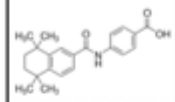
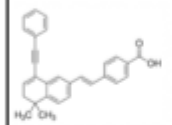
Docking can predict binding modes as well as possible binders!





Number of Compound	Ligand PubChem ID Number	Docking Score (kcal/mol)
1	5287509	-14.70727
2	49837867	-13.31776
3	56603803	-12.93604
4	16214849	-12.65447
5	445460	-12.346
6	25166350	-12.34432
7	9909190	-12.2792
8	10436120	-12.08685
9	6398761 (Maxacalcitol)	-11.69114
10	ChemSpider ID: 146693	-11.60698
11	11352536	-11.49709
12	5289548	-11.38218
13	9935197	-11.37474
14	4469124	-11.35766
15	5289501	-11.05898
16	5288670 (Lexacalcitol)	-11.0335
17	44192388	-10.9312
18	44141919	-10.80572
19	46901277	-10.75546
20	2126	-10.68504
21	2418	-10.49947
22	56844264	-10.07298
23	49817357	-9.211291
24	44141920	-8.99854
25	10180805	-7.881713

Compound	Structure	EC_{50} in μM
20-Hydroxyecdysone		2.347
Muristerone		0.05
Ponasterone A		0.041
Drug 18		3.687
Drug 28		0.735
		
Drug 38		0.996

Drug name	Structure	EC_{50} in μM
AM580		38.1
BMS493		33.7

JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

pubs.acs.org/jcim

How Does Catalase Release Nitric Oxide? A Computational Structure–Activity Relationship Study

Sai Lakshmana Vankayala, Jacqueline C. Hargis, and H. Lee Woodcock*

Department of Chemistry, University of South Florida, 4202 E. Fowler Avenue, CHE205, Tampa, Florida 33620-5250, United States

JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

pubs.acs.org/jcim

Open Access on 08/24/2015

Fragment-Based Docking: Development of the CHARMMing Web User Interface as a Platform for Computer-Aided Drug Design

Yuri Pevzner,[†] Emilie Frugier,[‡] Vinushka Schalk,[†,§] Amedeo Caflisch,[‡] and H. Lee Woodcock*[,†]

[†]Department of Chemistry, University of South Florida, 4202 E. Fowler Ave., CHE205, Tampa, Florida 33620-5250, United States
[‡]Department of Biochemistry, University of Zurich, CH-8057 Zurich, Switzerland
[§]Department of Natural Sciences, New College of Florida, Sarasota, Florida 34243, United States

JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

pubs.acs.org/jcim

Unlocking the Binding and Reaction Mechanism of Hydroxyurea Substrates as Biological Nitric Oxide Donors

Sai Lakshmana Vankayala, Jacqueline C. Hargis, and H. Lee Woodcock*

Department of Chemistry and Center for Molecular Diversity in Drug Design, Discovery, and Delivery, University of South Florida, Tampa, Florida 33620, United States

Journal of Molecular Graphics and Modelling xxx (2016) xxx–xxx

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journal homepage: www.elsevier.com

Elucidating a chemical defense mechanism of Antarctic sponges: A computational study

Sai Lakshmana Vankayala[a, 1], Fiona L. Kearns[a, 1], Bill J. Baker[a], Joseph D. Larkin[b], H. Lee Woodcock[a, *]

[a] Department of Chemistry, University of South Florida, 4202 E. Fowler Ave., CHE205, Tampa, FL 33620, USA
[b] Department of Chemistry, Eckerd College, 4200 54th Avenue South, St. Petersburg, FL 33711, USA

ARTICLE INFO

ABSTRACT

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Identification of Ecdysone Hormone Receptor Agonists as a Therapeutic Approach for Treating Filarial Infections

Amruta S. Mhashilkar[1], Sai L. Vankayala[2], Canhui Liu[1], Fiona Kearns[2], Priyanka Mehrotra[2], George Tzertzinis[3], Subba R. Palli[4], H. Lee Woodcock[2], Thomas R. Unnasch[1]*

1 Department of Global Health, College of Public Health, University of South Florida, Tampa, Florida, United States of America, 2 Department of Chemistry, University of South Florida, Tampa, Florida, United States of America, 3 New England Biolabs, Ipswich, Massachusetts, United States of America, 4 Department of Entomology, University of Kentucky, Lexington, Kentucky, United States of America

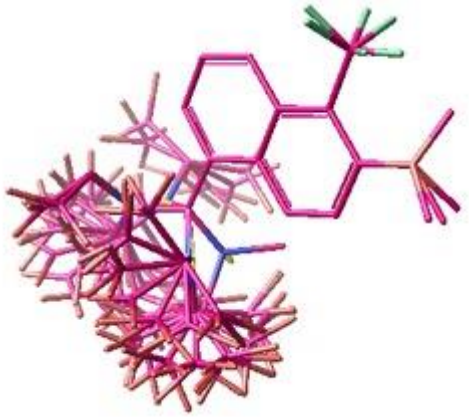
* tunnasch@health.usf.edu

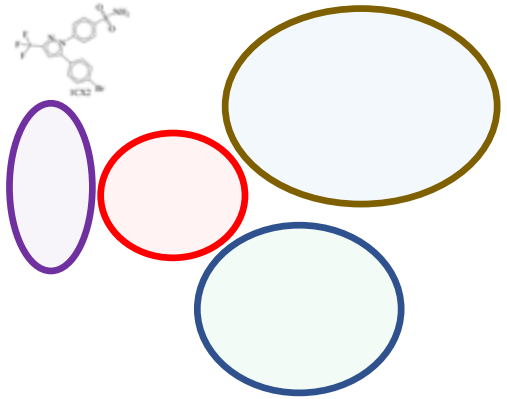
There are many docking programs….

1-Click Docking
AADS
ADAM
AutoDock
AutoDock Vina
BetaDock
Blaster
BSP-SLIM
CIF-DOCK
DARWIN
DIVALI
DOCK
DockingServer
DockVision
EADock
eHITS
EUDOC
FDS
FlexAIS
FlexPepDock
FlexX
FLIPDock
FLOG
FRED
FTDOCK
GEMDOCK
Glide
GOLD
GPCRautomodel
HADDOCK
ICM-Dock
idTarget
iScreen
Lead Finder
LigandFit
LigDockCSA
LIGIN
MCDock
MOE
MolDock
MS-DOCK
ParDOCK
PatchDock
PLANTS
PLATINUM
PRODOCK
PSI-DOCK
PSO@AUTODOCK
PythDock
Q-Dock
QXP
rDock
SANDOCK
Score
smina
SODOCK
SOFTDocking
Surflex-Dock
SwissDock
VoteDock
YUCCA

Why so many different docking programs??

- **Protein, Ligands, etc.**
  - **Ligand**
    - Whole molecule
    - Fragment Based
  - **Protein**
    - Rigid Docking
    - Flexible Receptor Docking
    - Semi-flexible docking
    - Full Protein Flexible Docking
  - **Water / co-factors / metals**
    - Explicit
    - Implicit

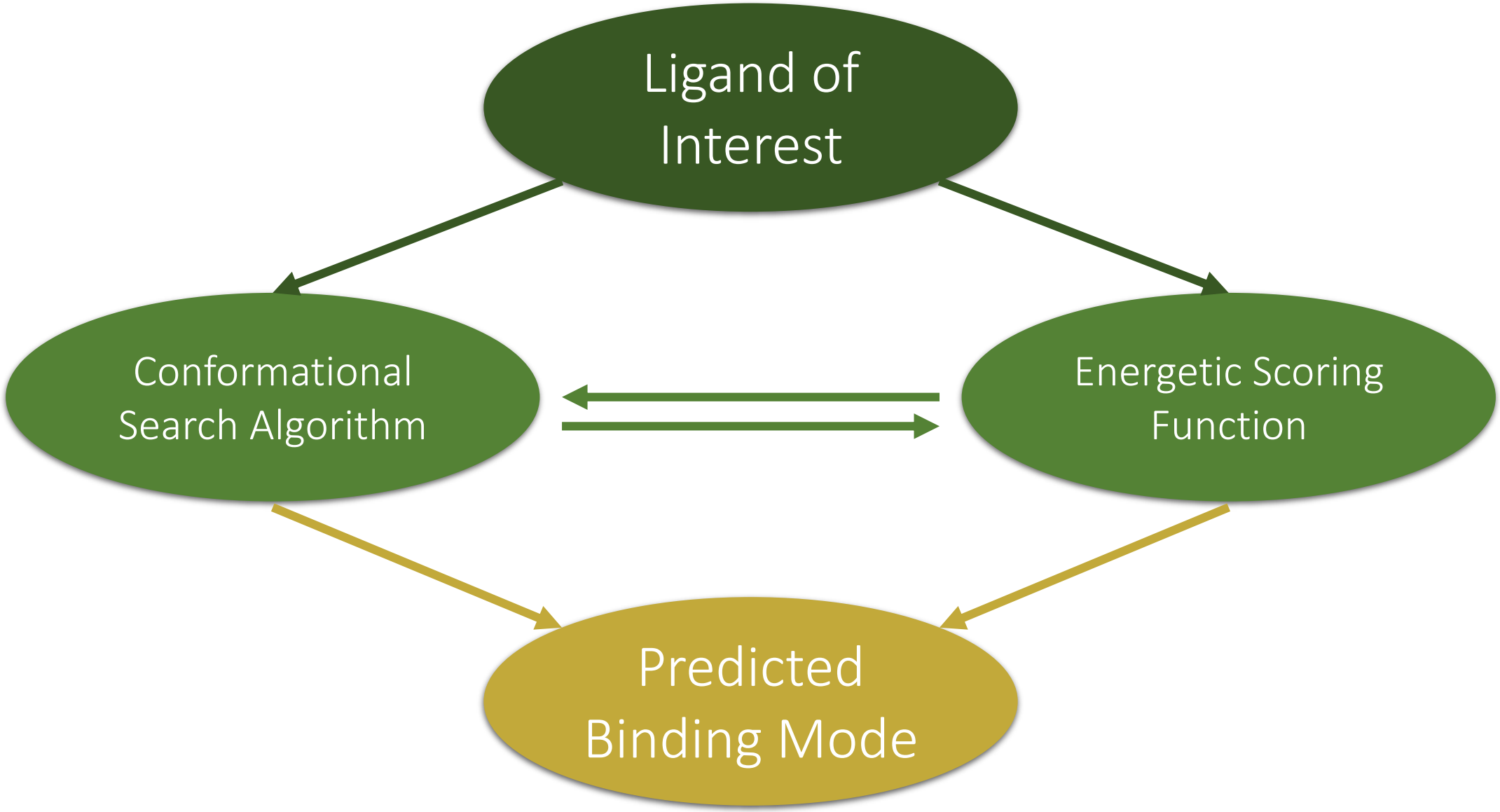




- **Scoring Function**
  - Empirical
  - Force Field
  - Knowledge Based
  - Consensus

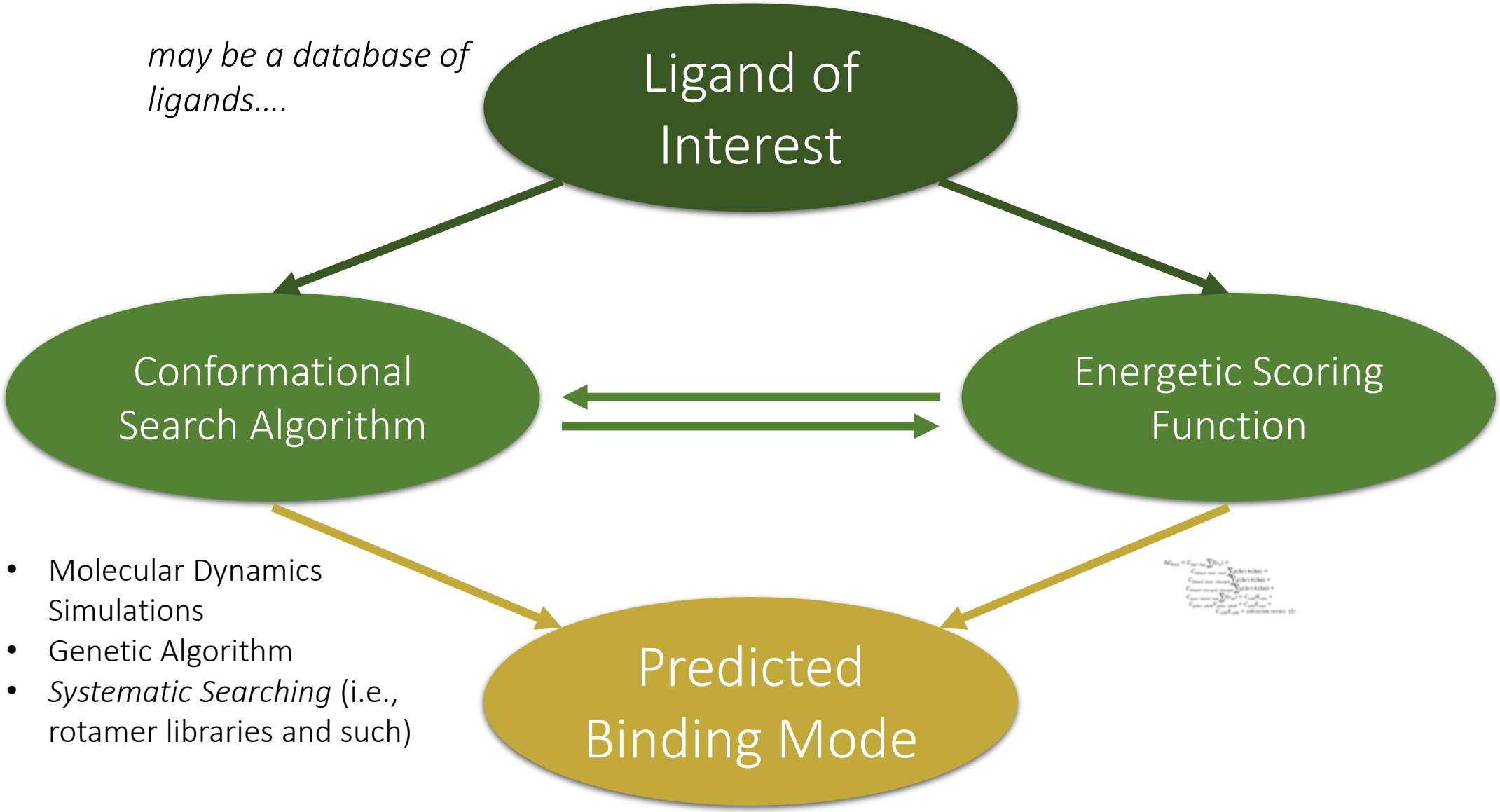
$$\Delta G_{SDOCK,score} = E_{intra}^{protein} + E_{intra}^{ligand} + E_{vdw} + E_{elec} + \Delta G^{complex} + \Delta G^{complex}$$

The Specifics: What do we need to *predict* a binding mode?



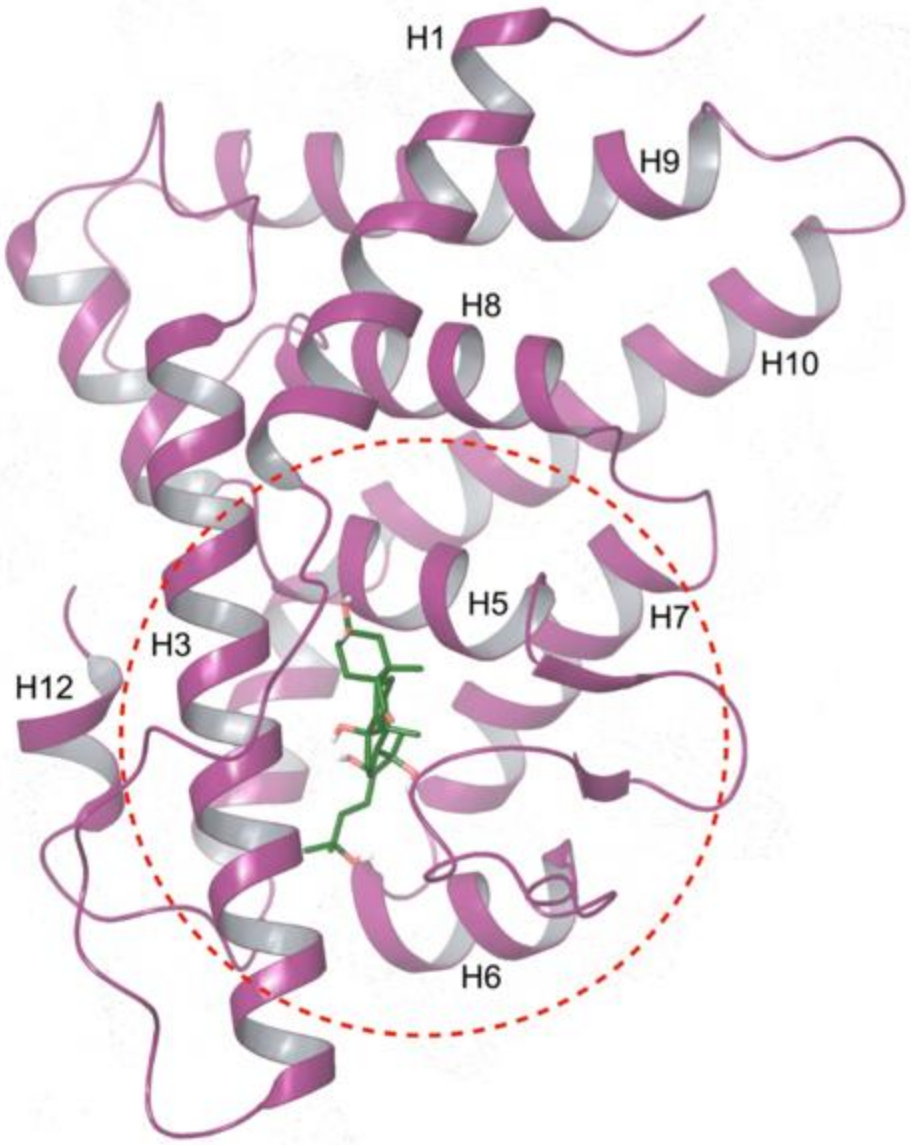
The Specifics: What do we need to *predict* a binding mode?

may be a database of ligands….



- Molecular Dynamics Simulations
- Genetic Algorithm
- *Systematic Searching* (i.e., rotamer libraries and such)

AutoDock Vina: A Rigid, Grid-based Docking Procedure



Vina represents shape and properties of the receptor as a *grid of points*, where each point in space is assigned a value in a field! (ligand = flexible, protein = rigid)

(draw grid here on board)

The non-bonded energetic terms of a docked ligand are then minimized within this grid/field, rather minimized via explicit atom-atom calculations.

Is “rigid” the *best* model for receptor/ligand interaction?

Is “rigid” the *best* model for receptor/ligand interaction?

Results: “Canonical” Cross Docking Test Set

	Cross-dockings		Schrödinger		Accelrys	SCARE	Fleksy	CIF Dock
	PDB		RMSD's (Å)					
Enzyme family	Ligand	Protein	Rigid	IFD	Flexible			
Aldose Reductase	1AH3	2ACR	6.5	0.9	-	1.1	-	0.7
Antibody DB3	1DBB	1DBA	7.6	0.3	-	0.7	0.6	0.5
CDK2	1DM2	1BUH	6.4	1.1	-	-	1.0	0.8
	1DM2	1AQ1	0.6	0.8	0.9	1.0	1.2(2)	1.2
	1AQ1	1DM2	6.2	0.8	0.7	0.6(5)	1.4	1.5
COX-2	1CX2	3PGH	11.1	1.0	1.9	1.0	1.0	0.9
	3PGH	1CX2	6.6	0.5	2.0	0.9	2.0	1.3
Estrogen Receptor	1ERR	3ERT	2.3	1.0	1.0	1.5	1.4	1.8
	3ERT	1ERR	5.3	1.0	1.2	1.5	1.1	0.9
Factor-XA	1XKA	1KSN	9.3	1.5	2.0	1.0	1.4	3.1
	1KSN	1XKA	5.3	1.5	2.0	0.5	2.2	1.2
HIV-RT	1RTH	1C1C	12.0	2.5	-	1.2(6)	5.4	0.8
	1C1C	1RTH	2.5	1.3	-	0.7	6.1	1.2
Neuraminidase	1A4Q	1NSC	3.9	0.8	1.6	0.8	1.5	1.6
	1NSC	1A4Q	1.0	1.7	1.7	0.4	0.5	1.4
PPARgama	2PRG	1FM9	9.1	1.8	-	1.7(3)	1.8(7)	1.5
	1FM9	2PRG	9.8	1.5	-	1.6	10.0	-
Thermolysin	1KR6	1KJO	3.5	3.2	3.0	-	7.7	2.7
	1KJO	1KR6	1.1	1.3	1.2	-	1.1	1.0
Thymidine Kinase	1KI4	1KIM	4.7	0.4	1.2	0.5	0.4	0.5
	1KIM	1KI4	0.5	1.2	1.2	1.3	1.1	1.1

“Lock and key” → implies some element of rigidity



“Hand and glove” model → implies receptor and ligand are both flexible



Thus we need:

“Lock and key” → implies some element of rigidity



“Hand and glove” model → implies receptor and ligand are both flexible



Thus we need:

“Lock and key” → implies some element of rigidity



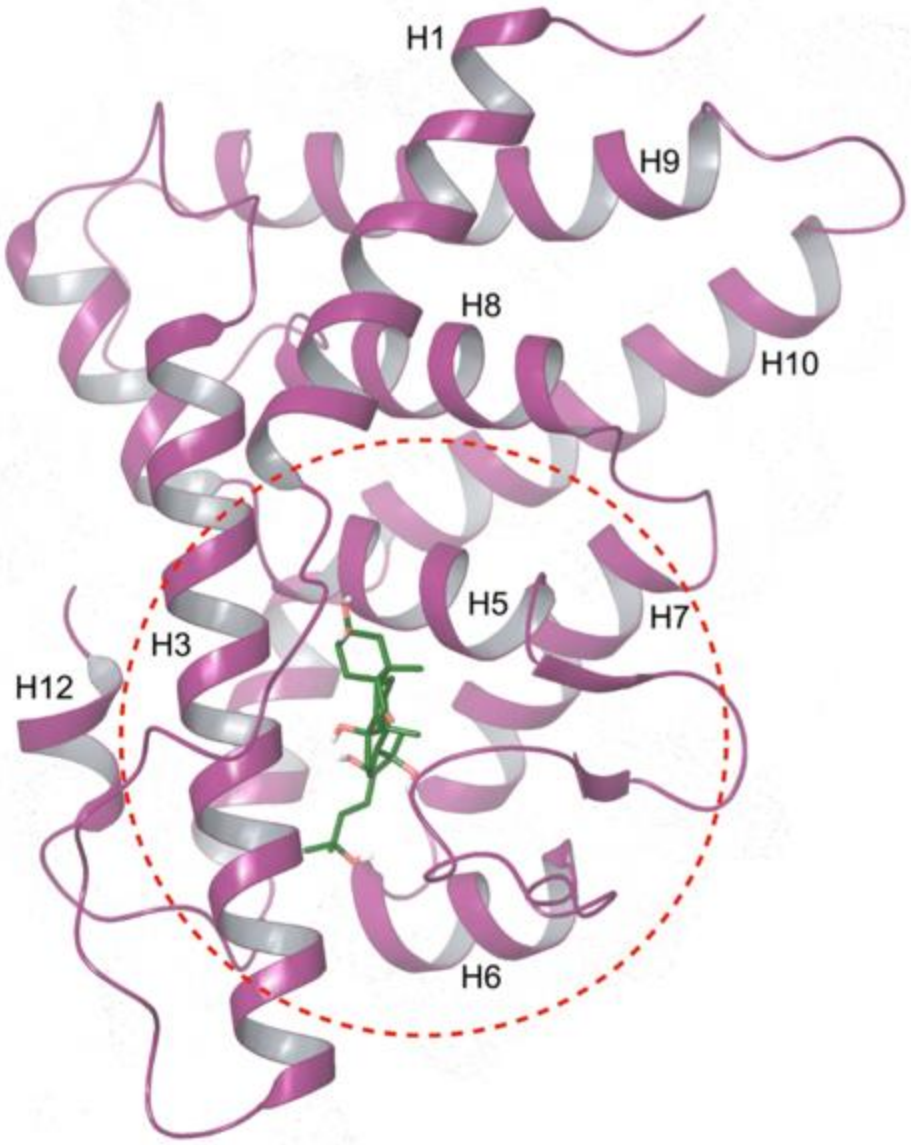
“Hand and glove” model → implies receptor and ligand are both flexible



Thus we need:

Flexible ligand/flexible receptor docking!

Induced Fit Docking (IFD) in Schrödinger:



Initial ligand docking with Glide SP (using reduced vdW radii, can mutate large side-chains to alanine)

↓

Prime (protein structure prediction tool) used for each initial pose to predict multiple receptor conformations

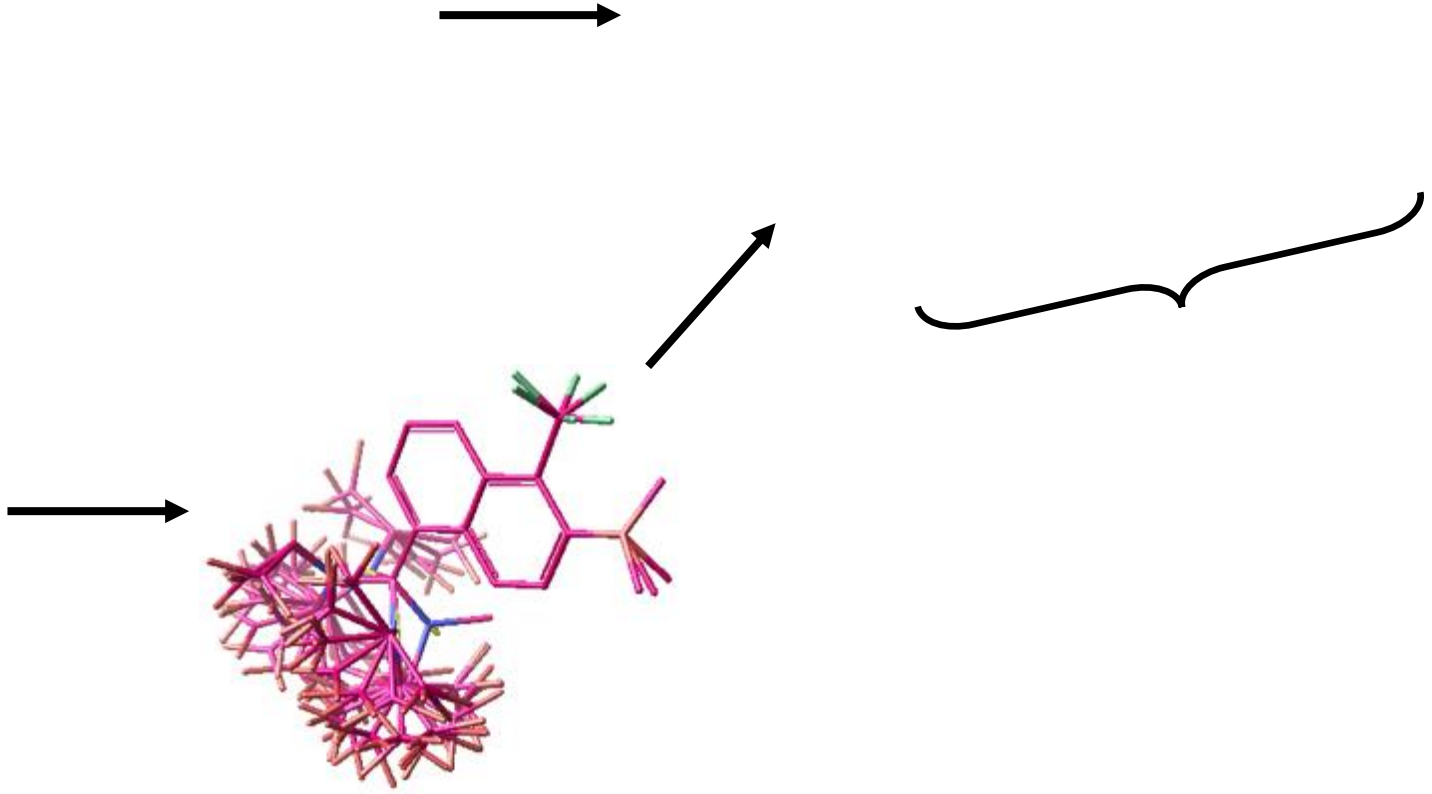
↓

Glide XP “redocking” into different receptor conformers

↓

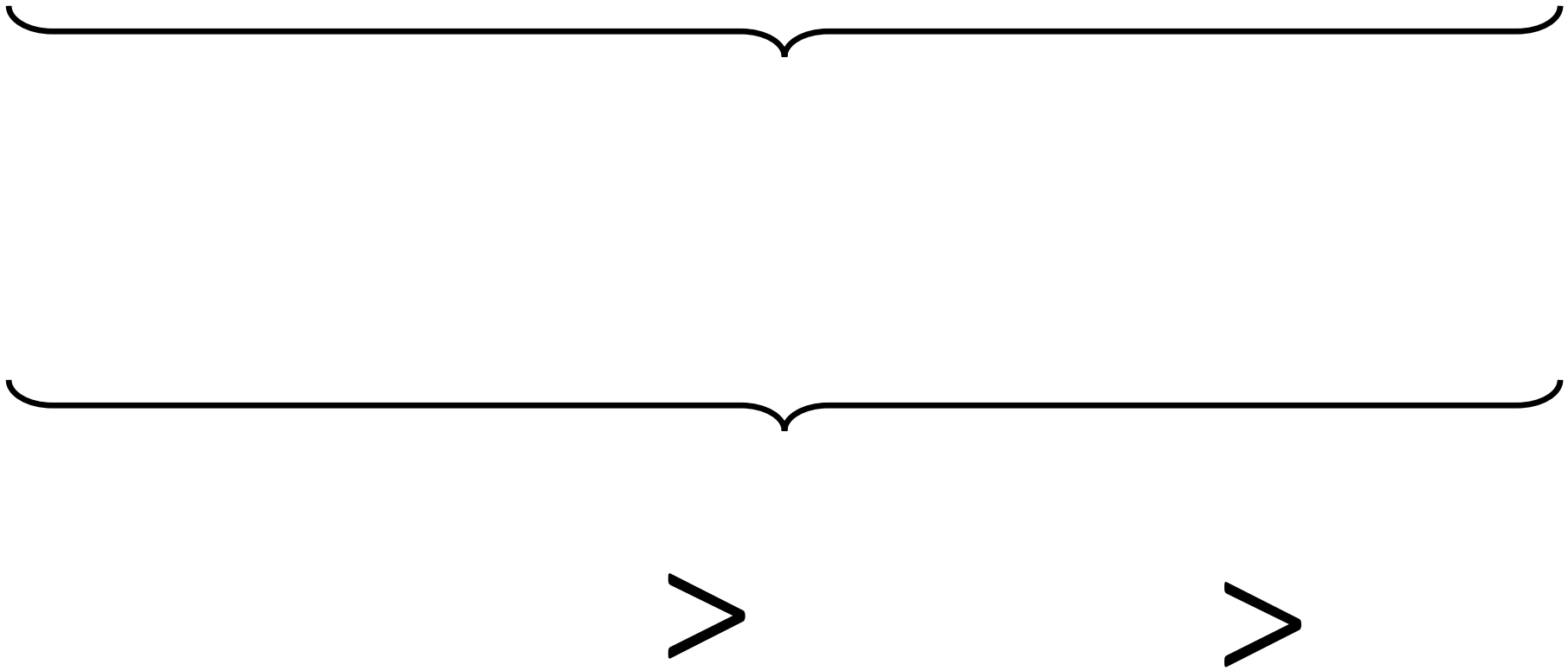
GlideScore calculated and complexes ranked, XP descriptors written

CHARMM-based Flexible Receptor Docking



O'Boyle, N. M.; Vandermeersch, T.; FlProtein_2acr_contrast_900dpi.pngynn, C. J.; Maguire, A. R.; Hutchison, G. J. Cheminf., 2011, 3, 8-15.
Lee M. S.: Feig, M.; Salsbury, Jr. F. R.; and Brooks III. C. L. J. Comp. Chem., 2003, 24, 1348-1356.
Suárez, M, P. T.; and Alfonso J. Syst. Synth. Biol., 2008, 2.3, 105-113.
Wu, X., Brooks, B.R. J. Chem. Phys., 2011, 135, 204101.

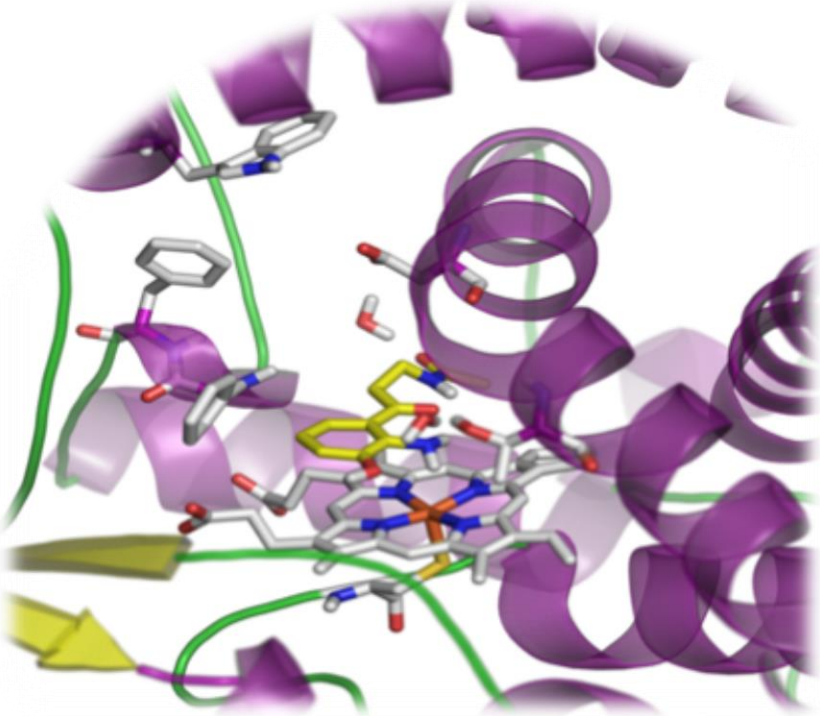
CHARMM-based Flexible Receptor Docking



So is rigid docking useless?

- NO! Use it to identify *false positives* and *false negatives* before further screening!
  - *rigid docking is computationally inexpensive…*
  - *narrow the library before using expensive tools…*

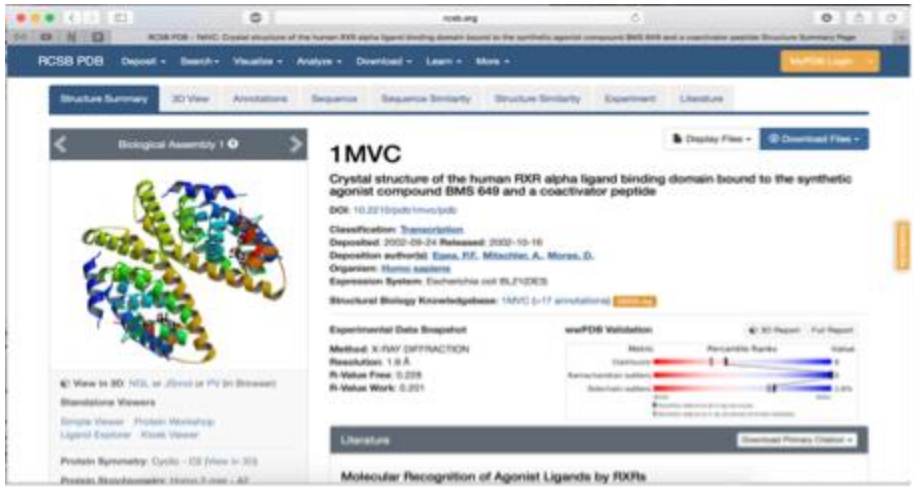
- Use flexible docking to predict binding modes and affinities



Tutorial:
Docking with AutoDock Vina

AutoDock Vina Publication

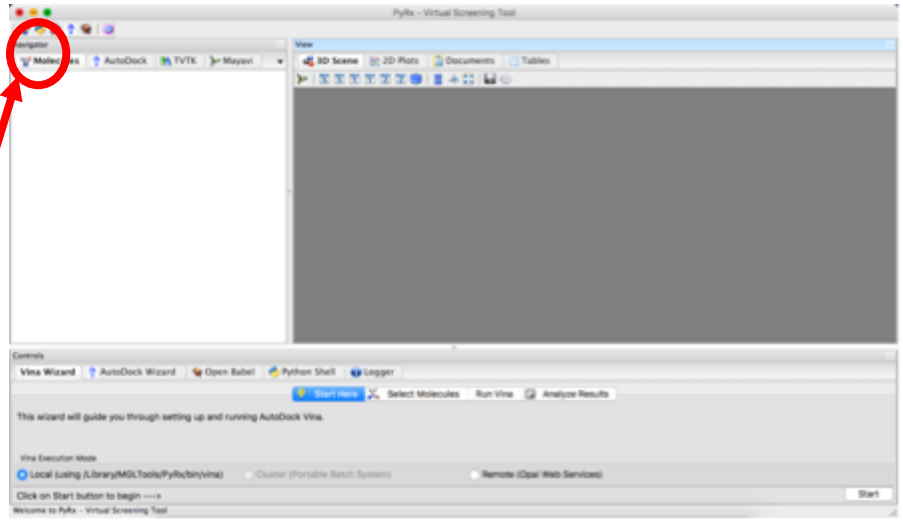
1. Navigate to the PDB website (http://www.rcsb.org/pdb) and search for the PDB ID 1MVC (http://www.rcsb.org/pdb/explore/explore.do?structureId=1MVC)



2. Click “Download Files > PDB Format”, this will download the 1MVC structure (a human RxR) with bound BMS649 agonist.

This is PyRx, a GUI for AutoDock Vina!

The ***Navigator Panel*** is where you can load and organize molecules for jobs. The ***View Panel*** is where you can view molecules, documents, plots and charts! You can also make plots, documents and charts. The ***Controls*** section has a Vina wizard, an AutoDock Wizard, a Babel wizard, and a python shell, as well as an error log.



1. From the top toolbar in PyRx, click the “Load Molecule” icon.

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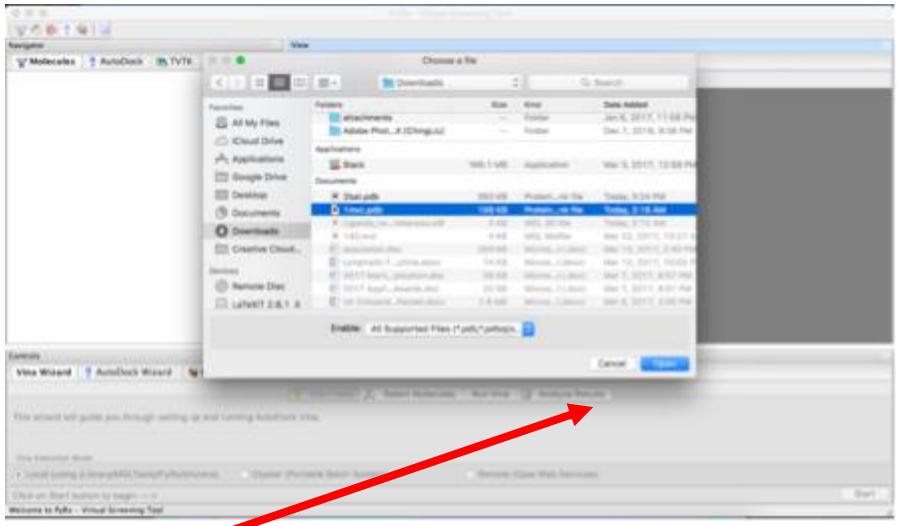
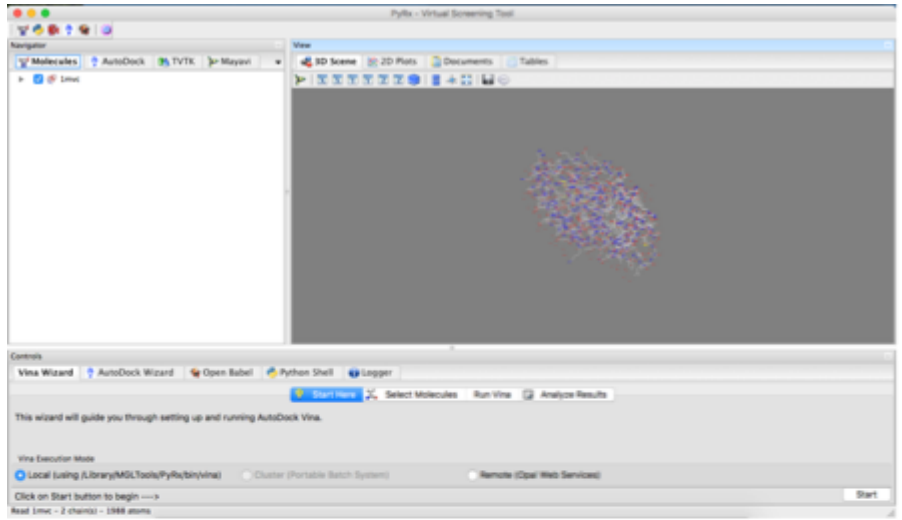


1. From the top toolbar in PyRx, click the “Load Molecule” icon.

2. A ‘Finder’ window (or windows equivalent) will open. Navigate to the downloads folder, select “1mvc.pdb” to open.

This is PyRx, a GUI for AutoDock Vina!

The ***Navigator Panel*** is where you can load and organize molecules for jobs. The ***View Panel*** is where you can view molecules, documents, plots and charts! You can also make plots, documents and charts. The ***Controls*** section has a Vina wizard, an AutoDock Wizard, a Babel wizard, and a python shell, as well as an error log.



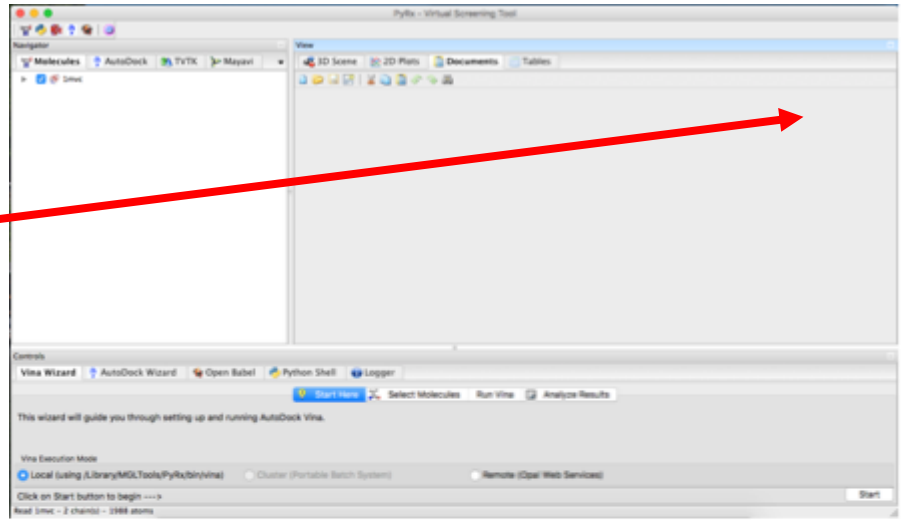
1. From the top toolbar in PyRx, click the “Load Molecule” icon.

2. A ‘Finder’ window (or windows equivalent) will open. Navigate to the downloads folder, select “1mvc.pdb” to open.

3. The macromolecule is now loaded in the 3D Scene!

Now we need to modify the 1mvc.pdb file so that we can have the macromolecule (1mvc) and the ligand (bms649) in separate pdb files.

1. In the “View” Panel, select the “Documents” Tab.



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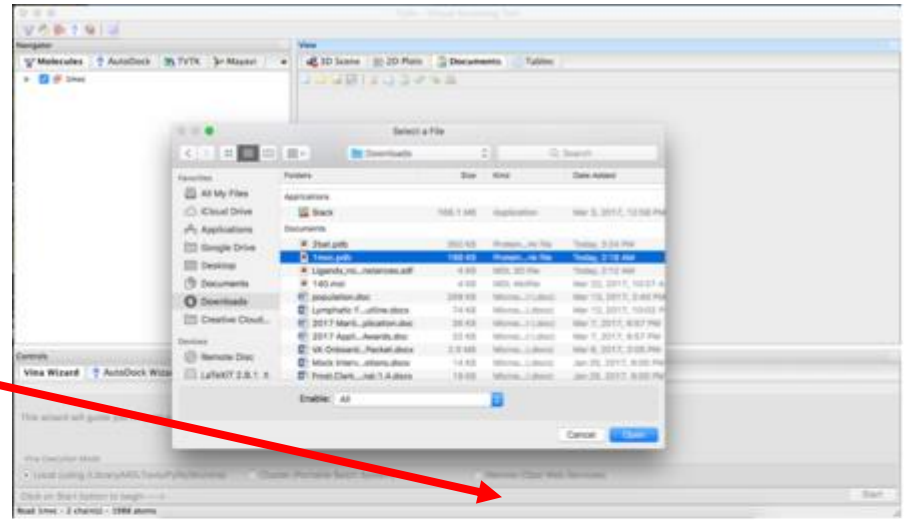

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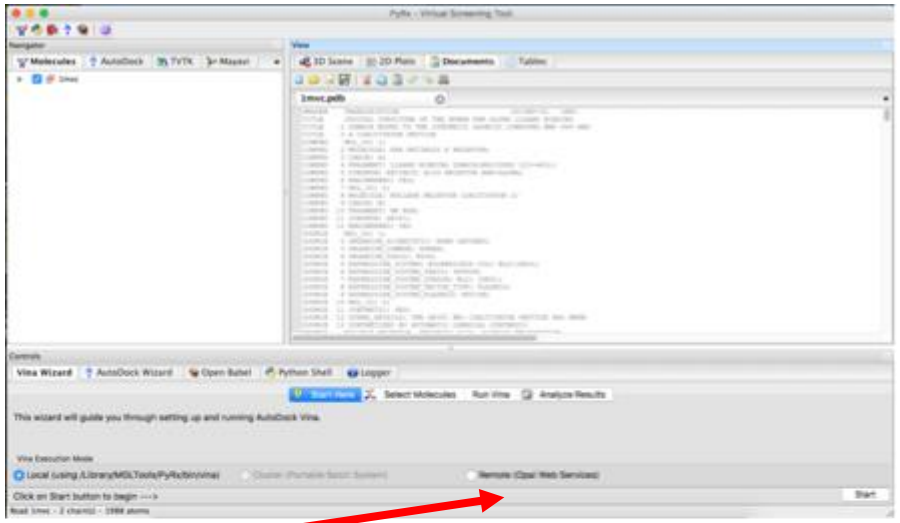
2. Click the “Open” icon (a Folder), again a “Finder” window will open, select “1mvc.pdb”.

3. This is what it should look like after opening the 1mvc.pdf file in documents!



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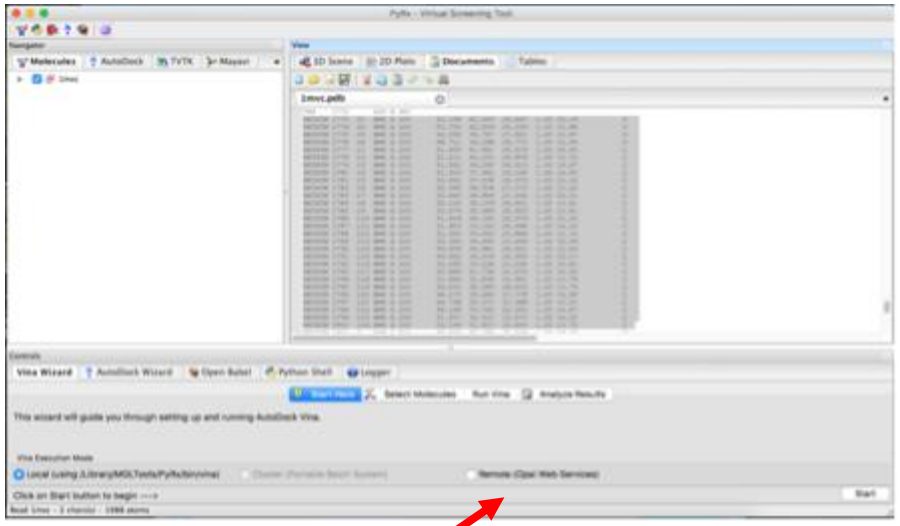

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3. This is what it should look like after opening the 1mvc.pdf file in documents!

4. Scroll to nearly the bottom of 1mvc.pdb, looking for lines that start with the word “HETATM”

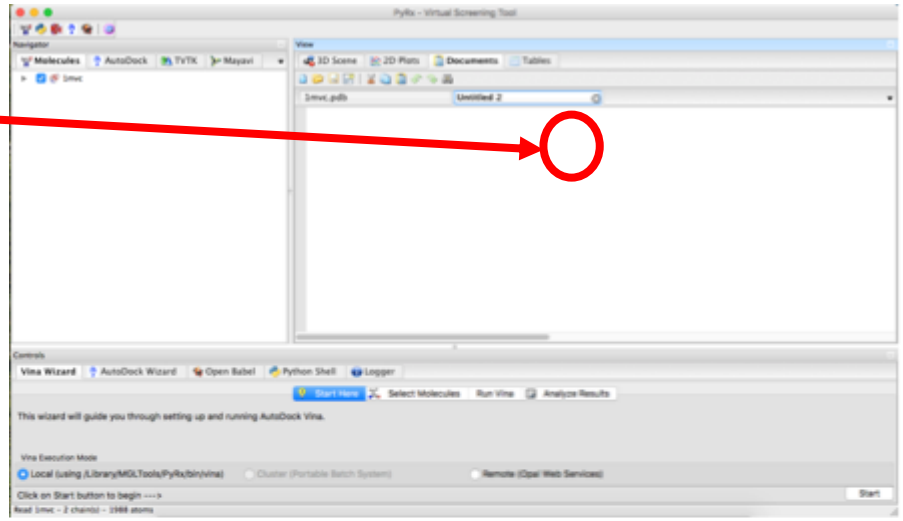
   The lines of interest are:

   HETATM 1773 O1 BM6 A …
   ……
   HETATM 1800 C24 BM6 A …

   Ctrl + C (copy) these lines of the pdb file!

Modifying 1mvc.pdb (cont.)

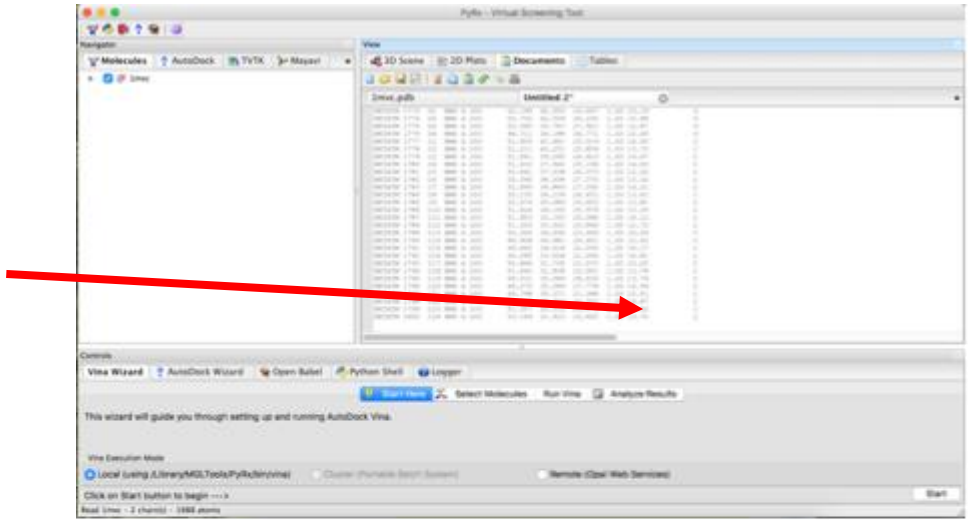
5. Make a new document, this will be the BMS649 ligand file, by clicking the “New” Icon (looks like a piece of paper).



Modifying 1mvc.pdb (cont.)

5. Make a new document, this will be the BMS649 ligand file, by clicking the “New” Icon (looks like a piece of paper).

6. Paste the copied BM6 lines into this new untitled document.

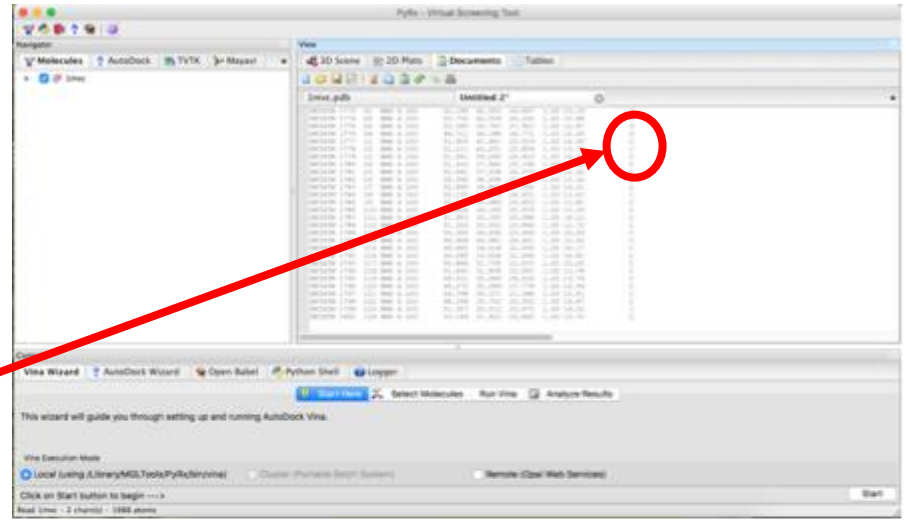


Modifying 1mvc.pdb (cont.)

5. Make a new document, this will be the BMS649 ligand file, by clicking the “New” Icon (looks like a piece of paper).

6. Paste the copied BM6 lines into this new untitled document.

7. Click the yellow floppy disk icon to save the new document.



Modifying 1mvc.pdb (cont.)

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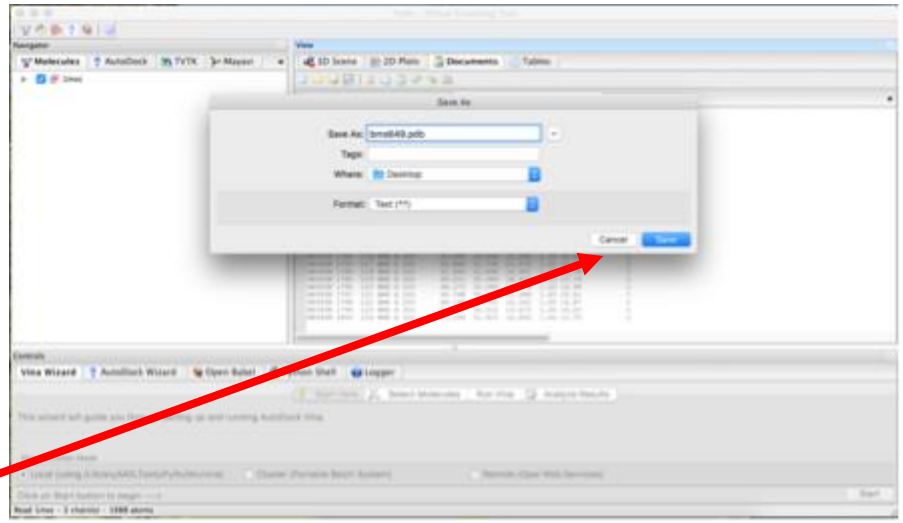
8. Save this new document as ‘bms649.pdb’.



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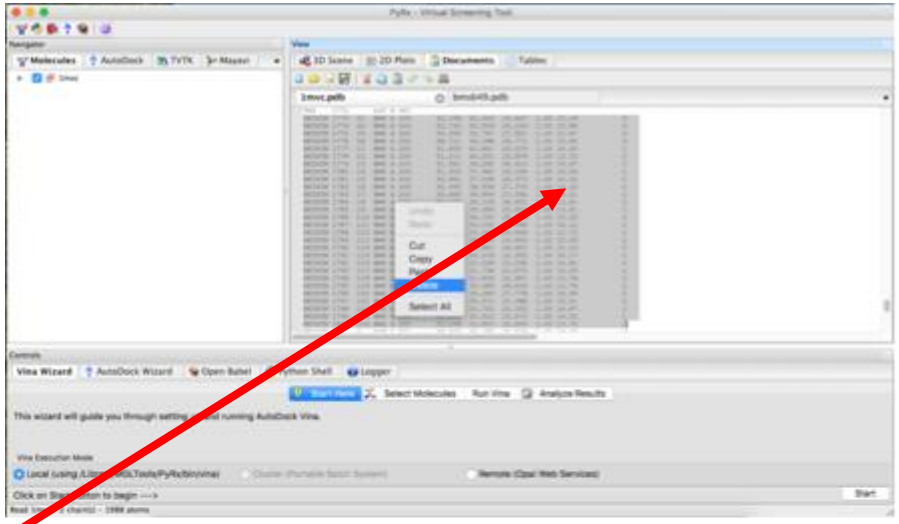
9. Return to the ‘1mvc.pdb’ file, find the BM6 lines again, and delete them, we are making a macromolecular file without the ligand in it.



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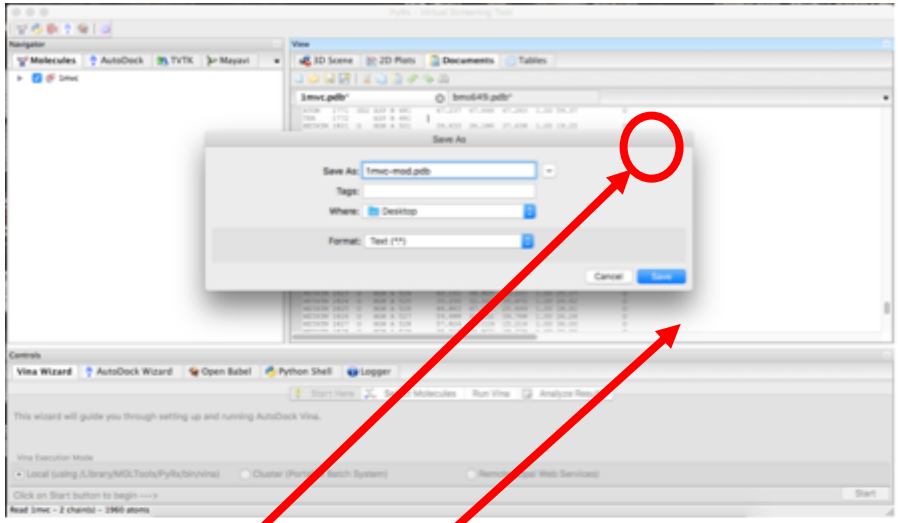
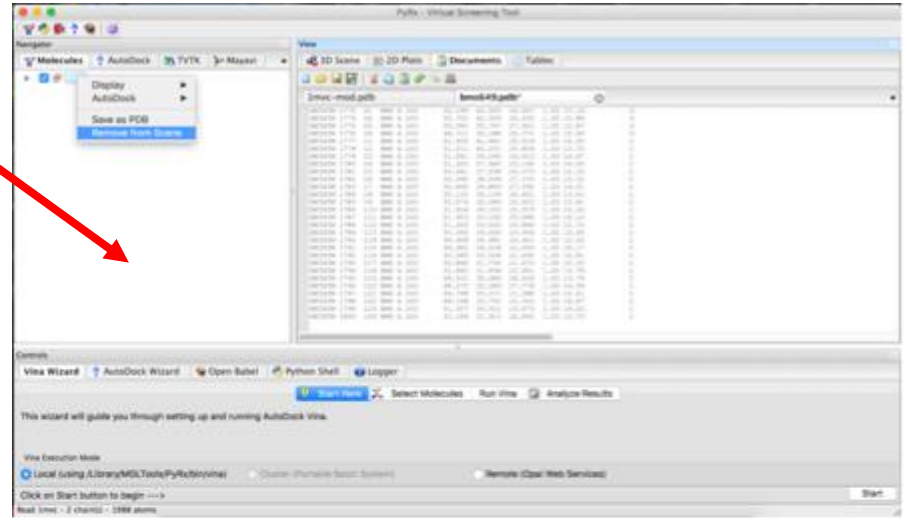
10. Click “Save As” (blue floppy-disk) icon, and while saving, rename the file to “1mvc-mod.pdb” just to distinguish it from the original file downloaded from the PDB



Modifying 1mvc.pdb (cont. 2)

11. Now, we need to remove the original 1mvc.pdb from the Navigation Pane, so that we can instead include the separate macromolecule and ligand files.



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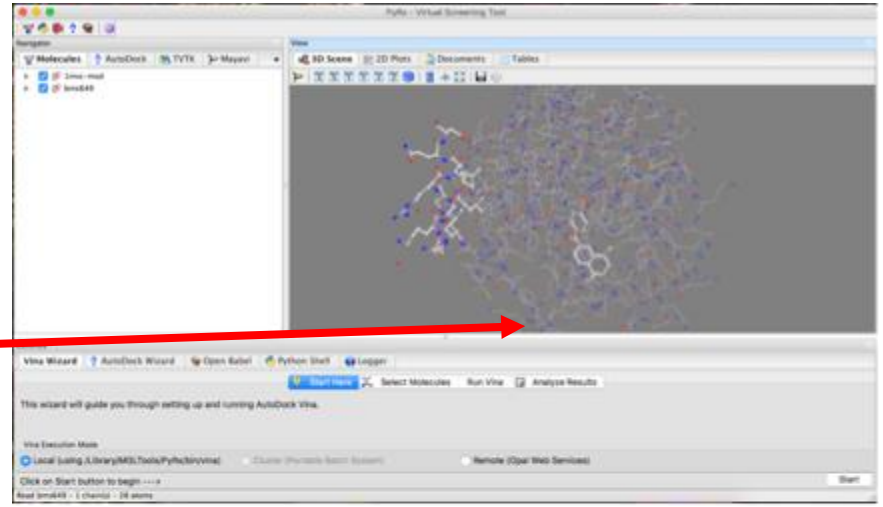
12. With a newly cleared Navigation Pane, load 1mvc-mod.pdb and bms649.pdb into PyRx (as done in steps 1-2). You can see, ligands (as well as some elements of the macromolecular structure) will be represented in “ball-and-stick:, while the protein is represented in “lines”. If you toggled between structures in the Navigation Pane (by checking and unchecking boxes) you can verify that the ligand and protein are in fact in separate files.



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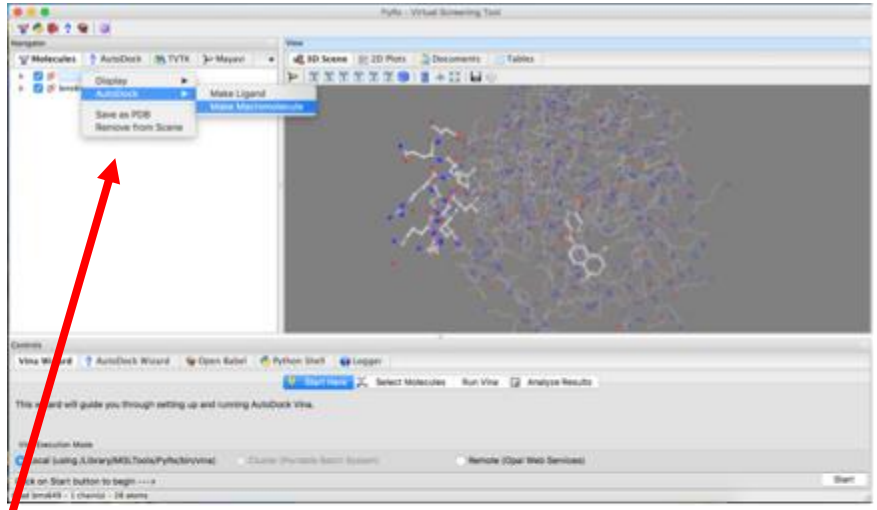
13. Right click on “1mvc-mod.pdb” in the Navigation Pane. Select “AutoDock > Make Make Macromolecule”



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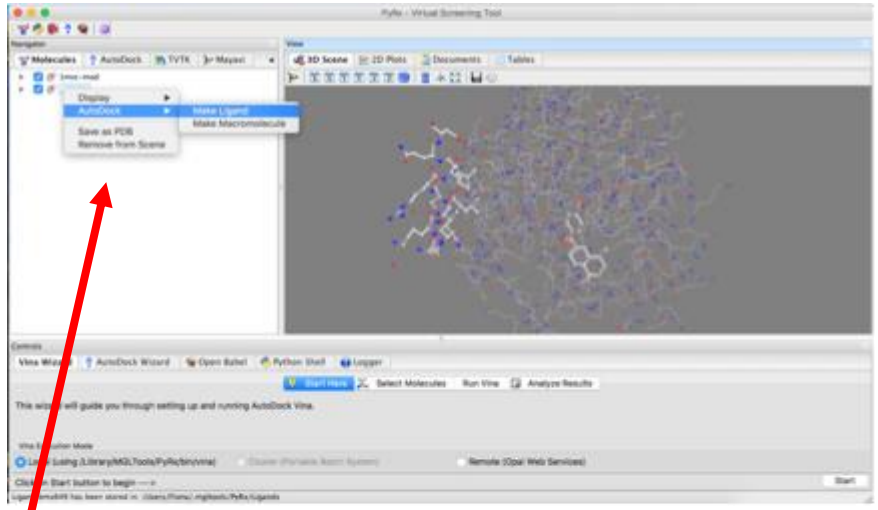
14. Right click on it in the navigation pane, select “AutoDock > Make Ligand”



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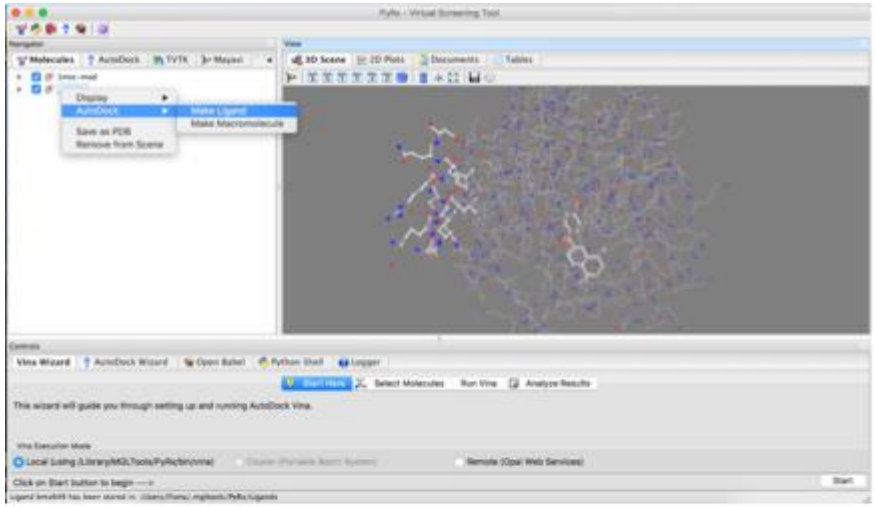

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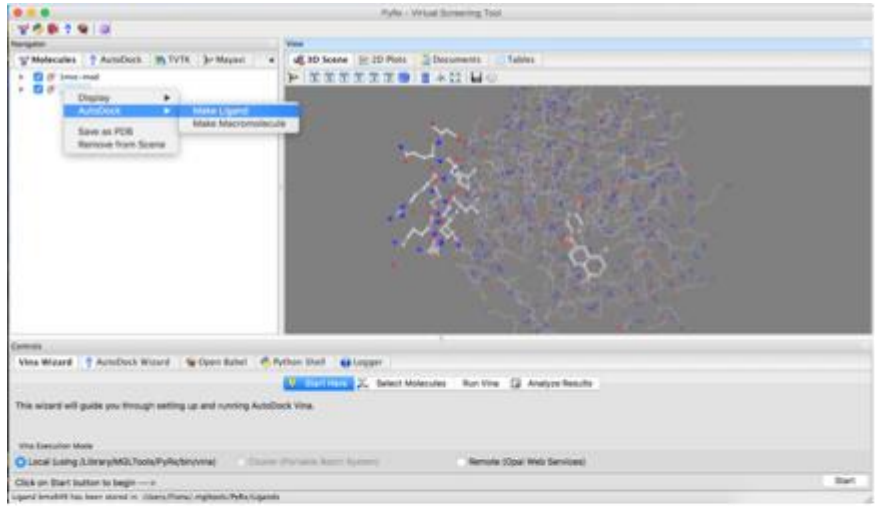
14. Right click on it in the navigation pane, select “AutoDock > Make Ligand”

15. Now everything is ready for re-docking with AutoDock Vina!

Re-docking with AutoDock Vina!

Re-docking is a technique in which a ligand with an already known binding mode in a binding site (such as from successful co-crystalization or other structural methods) is docked into the binding site to verify that the docking process can replicate the known binding mode.

1. Click on the “Vina Wizard” in the “Controls” section below, and press the “Start” button in the lower right corner.



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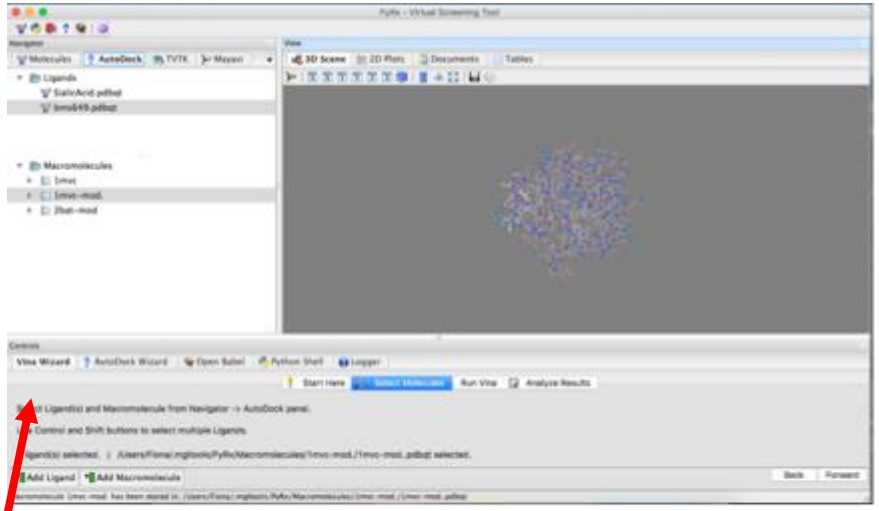


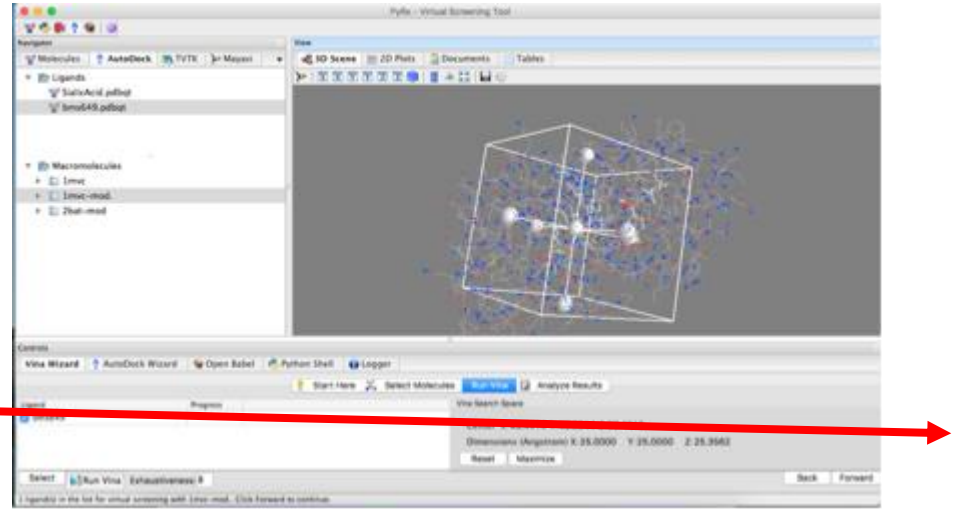
1. Click on the “Vina Wizard” in the “Controls” section below, and press the “Start” button in the lower right corner.

2. AutoDock Vina will now prompt you to select a macromolecule and a ligand. Use the “+ Add Ligand” and “+ Add Macromolecule” buttons on the bottom left, make sure that bms649.pdbqt is loaded under the “Ligands” tab, and “1mvc-mod” is loaded under the macromolecule tab. Select them by clicking on them. After making sure the macromolecule and ligands are selected properly, click “Forward” in the bottom right corner.

Re-docking with AutoDock Vina! (cont.)

3. The next step is generating a grid for flexible ligand docking. In the 3D Scene you should now see a cube as well as a 3D axis definition.

Click and hold the white spheres that border the 3D axes to extend the size of the grid. For redocking, make sure that the grid encompasses the volume in which bms649 is known to bind.



Re-docking with AutoDock Vina! (cont.)

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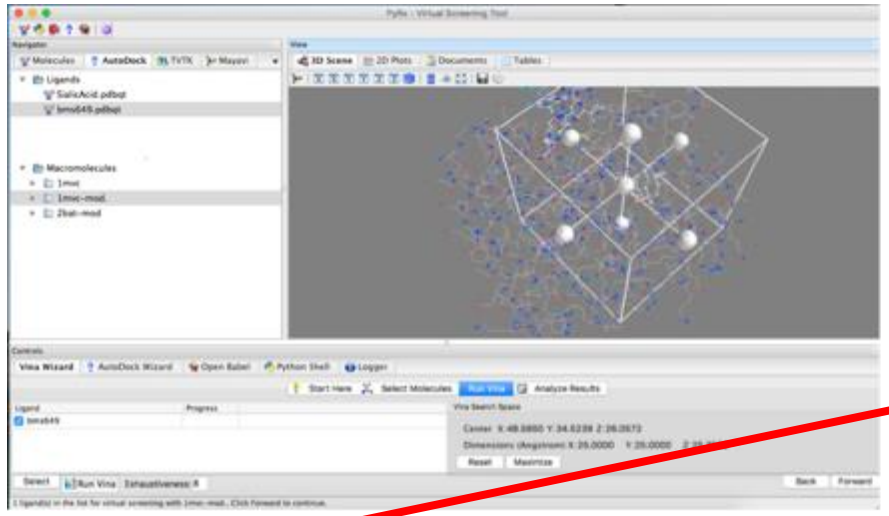
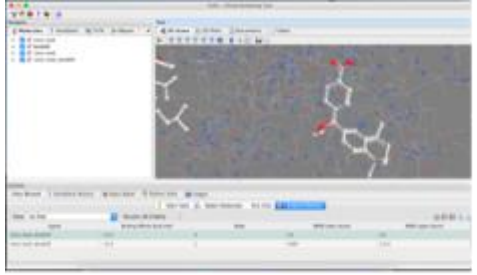
Click and hold the white spheres that border the 3D axes to extend the size of the grid. For redocking, make sure that the grid encompasses the volume in which bms649 is known to bind.

4. The center of the receptor grid can also be moved by click, holding, and dragging the center sphere on the 3d axes. Move the center of the receptor grid to the center of bms649. Click “Forward” in the bottom right corner once you have the grid appropriately placed.



Re-docking with AutoDock Vina! (cont. 2)

5. Clicking “Forward” in the prior step will start the docking procedure! Output from the docking procedure will be displayed in the “3D Scene” window until the job is complete! You should have two resulting predicted binding modes! One that nearly matches the crystal structure alignment, and one that has some rotation.



Docking with CHARMMing!

https://www.charmming.org/charmming/

ProBiS: Protein Binding Site Comparison

- Compare your protein (3D) structure to all other known 3D protein structures in the PDB!

- ProBiS Ligands allows you to collect ligands that bind in other similar binding sites!


ProBiS: a web server for detection of structurally similar protein binding sites

Janez Konc[†] and Dušanka Janežič[†,‡,*]

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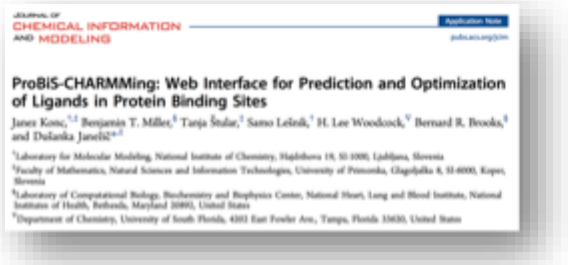
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Application Note

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ProBiS-CHARMMing: Web Interface for Prediction and Optimization of Ligands in Protein Binding Sites

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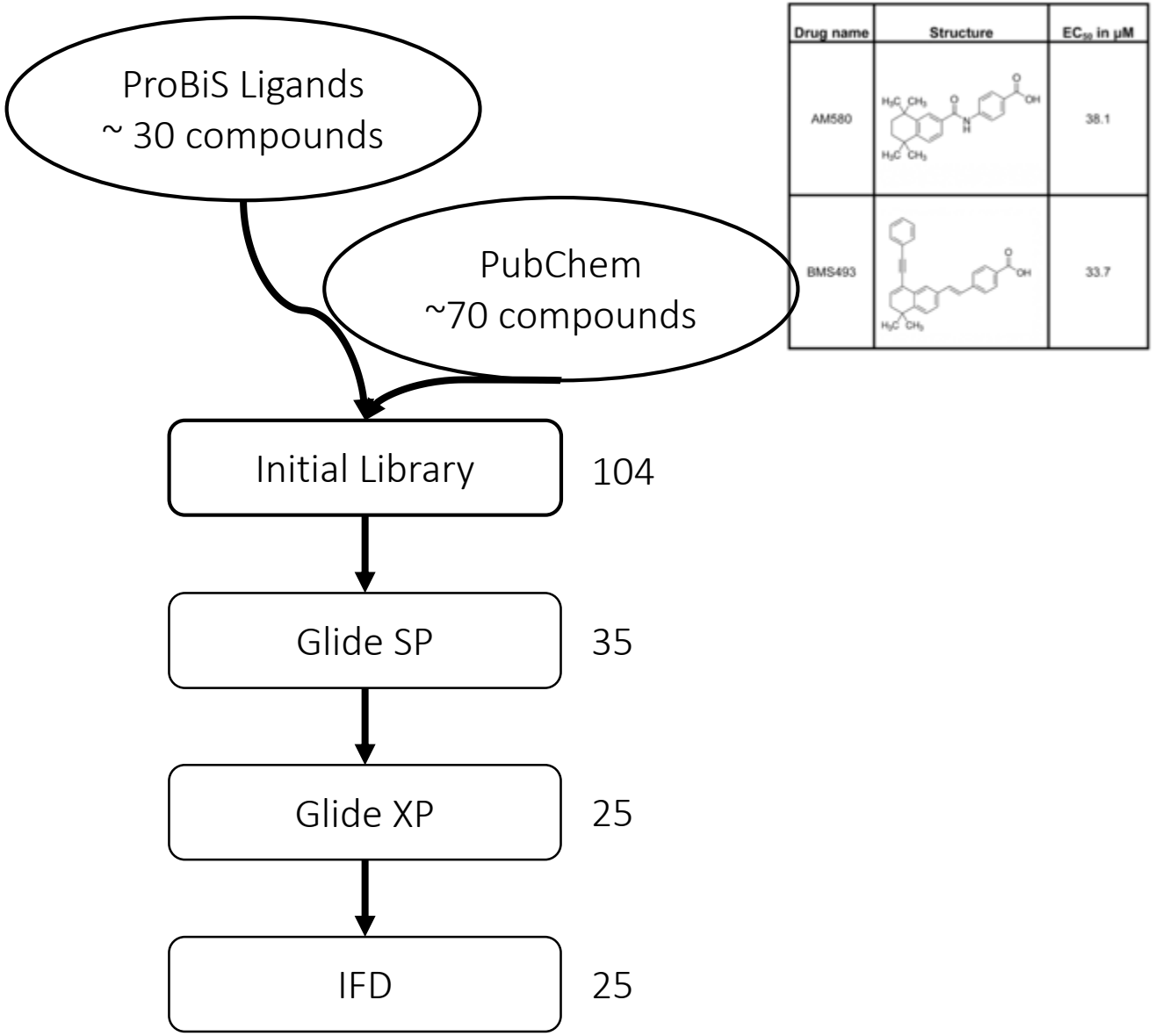
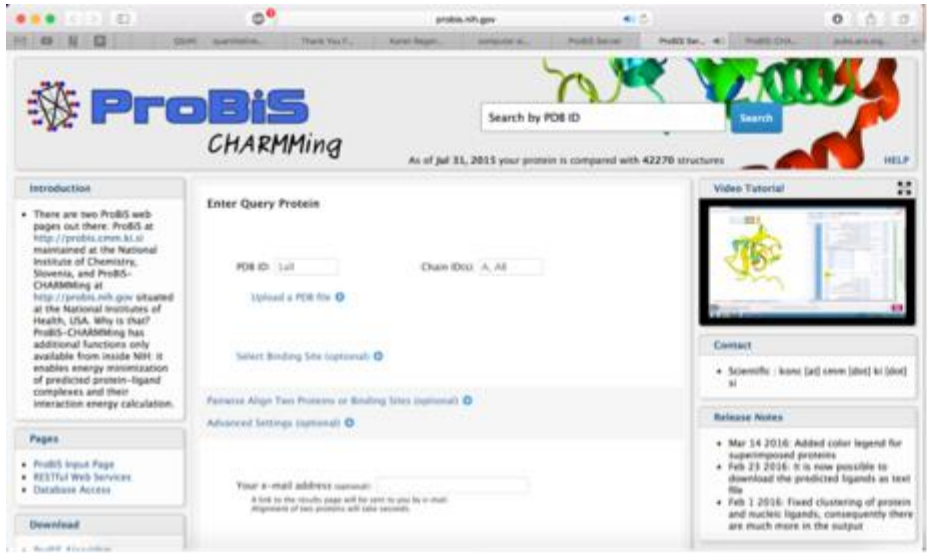
What can you do with ProBiS?? Virtually search for ligands!



Drug name	Structure	EC_{50} in μM
AM580		38.1
BMS493		33.7

Number of Compound	Ligand PubChem ID Number	Docking Score (kcal/mol)
1	5287509	-14.70727
2	49837867	-13.31776
3	56603803	-12.93604
4	16214849	-12.65447
5	445460	-12.346
6	25166350	-12.34432
7	9909190	-12.2792
8	10436120	-12.08685
9	6398761 (Maxacalcitol)	-11.69114
10	ChemSpider ID: 146693	-11.60698
11	11352536	-11.49709
12	5289548	-11.38218
13	9935197	-11.37474
14	4469124	-11.35766
15	5289501	-11.05898
16	5288670 (Lexacalcitol)	-11.0335
17	44192388	-10.9312
18	44141919	-10.80572
19	46901277	-10.75546
20	2126	-10.68504
21	2418	-10.49947
22	56844264	-10.07298
23	49817357	-9.211291
24	44141920	-8.99854
25	10180805	-7.881713

Navigate to http://probis.nih.gov. The website should look like the image on the right.



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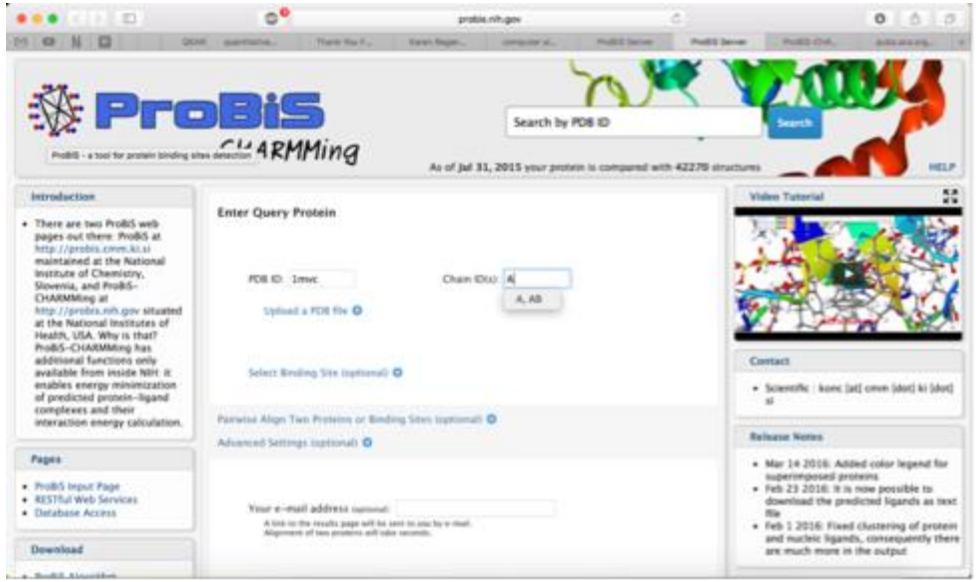
1. Enter a PDB code (or you can upload a PDB file) into the PDB ID box, and select a chain of interest (select A for now). Scroll down and hit “Search”.



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2. While searching you will get updates about progress!

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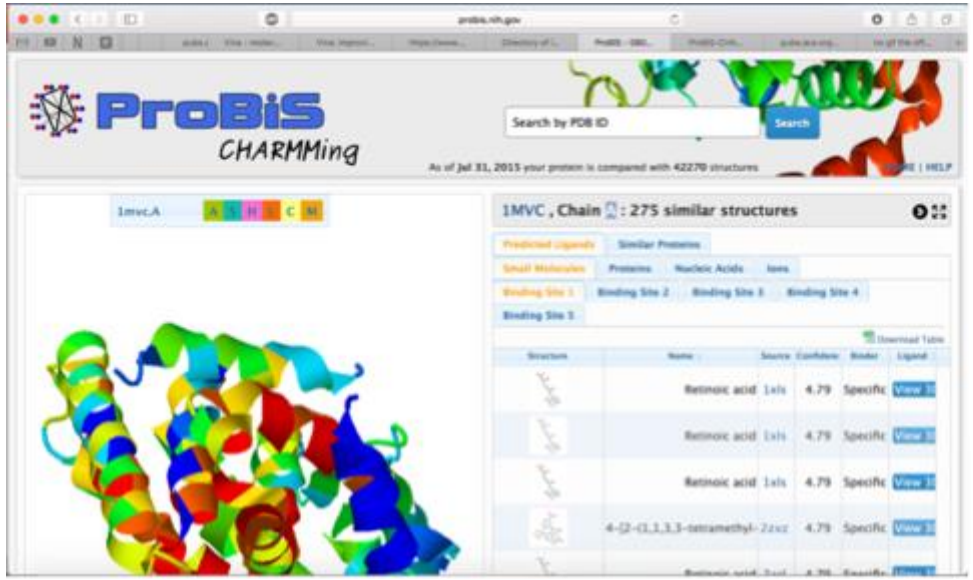

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3. Once done you will get results organized as on the right here!

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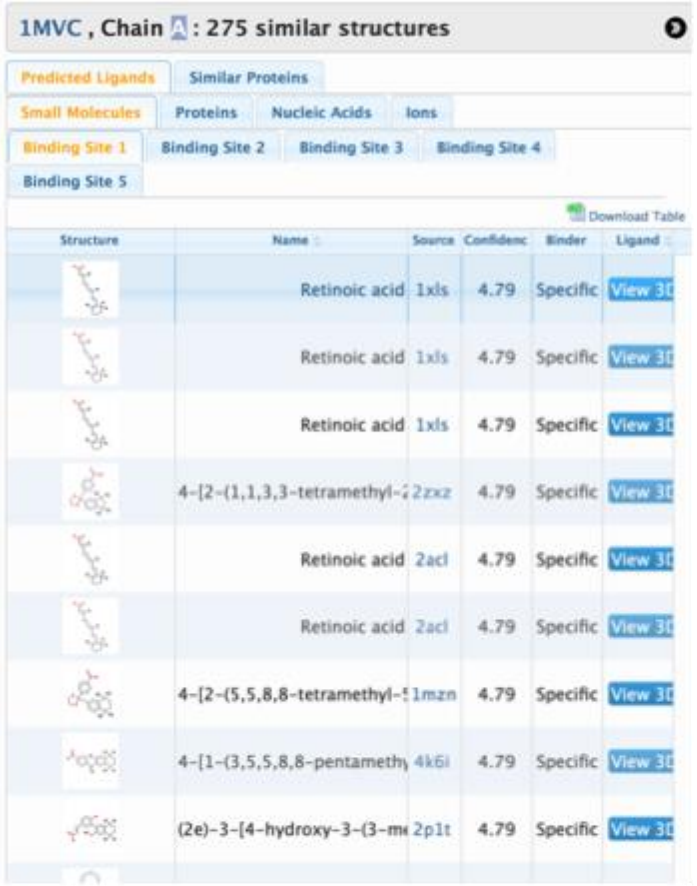
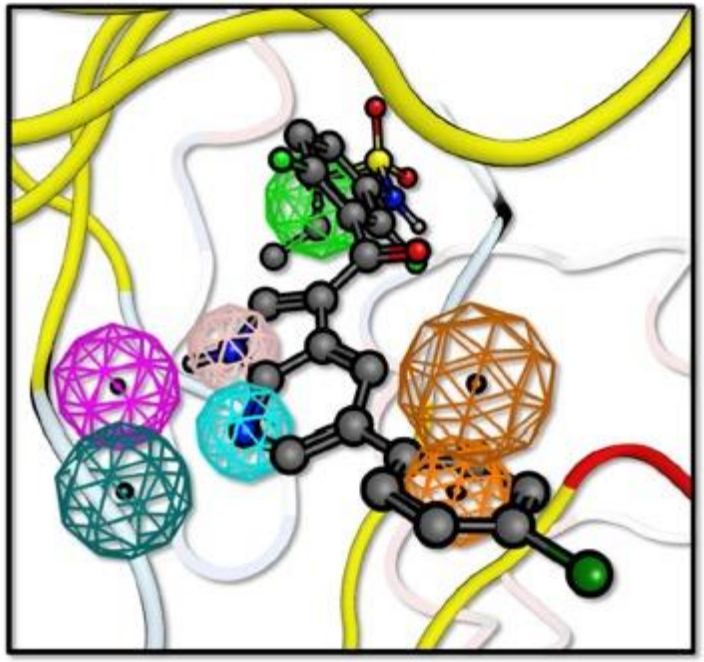
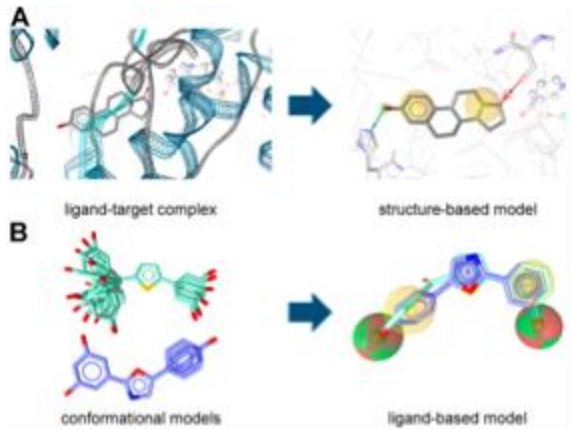
4. Take a look at the Predicted Ligands! ProBiS searches and finds ligands that are likely to bind for you!!



Pharmacophore Modeling Basics:

- Ligand Based vs. Structure Based Pharmacophore Models
- Pharmacophore model = simplified representation of interaction types
- screen ligands by comparing predicted pharmacophore models (very fast)
- Software: Pharmer, MedChem Studio, Phase ($$)

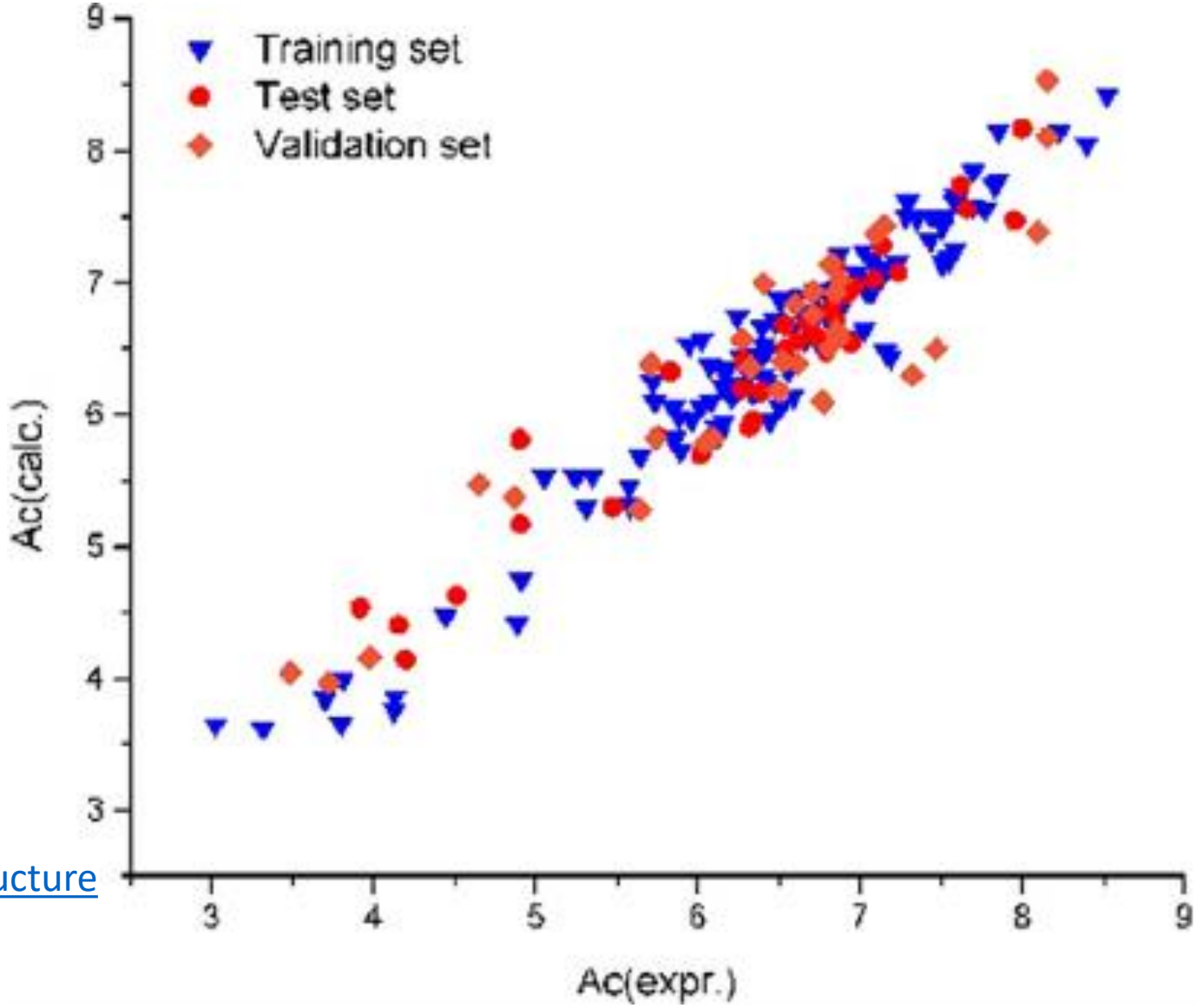




https://en.wikipedia.org/wiki/Pharmacophore
http://www.sciencedirect.com/science/article/pii/S135964461000111X

Quantitative Structure Activity Relationship (QSAR) Basics:

- Regression models: predictor X leads to response Y
- In chemical modeling the predictor X might be some structural element (side chains, physiochemical properties, etc.) and response might be predicted experimental values (binding affinity, biological activity)
- using the regression model allows you to quickly predict values of interest without simulation, just by correlation



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