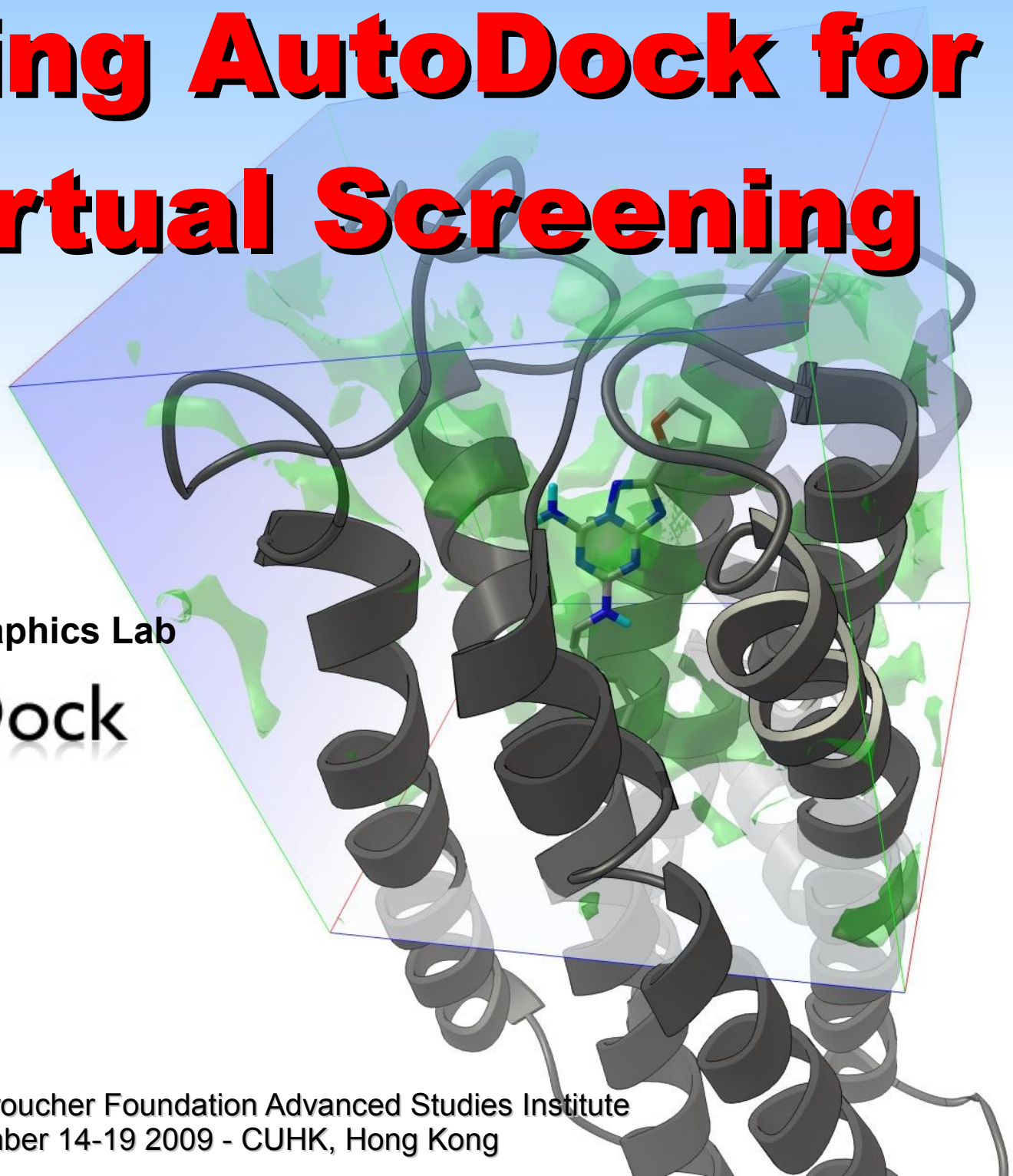
Using AutoDock for Virtual Screening



Stefano Forli
Ruth Huey
Garrett M. Morris
William Lindstrom

The Molecular Graphics Lab

AutoDock

The Scripps Research Institute®

The Croucher Foundation Advanced Studies Institute
December 14-19 2009 - CUHK, Hong Kong

Virtual Screening Session

Outline

Introduction to Virtual Screening

- Definition
- The goal of a vs
- Preparing the inputs

Hands-on Tutorials

- Raccoon

Introduction to Virtual Screening

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Screening and Virtual Screening

The ultimate tool for identifying active compounds is the biological test:

High-Throughput Screening

- Expensive (both money and time)
- Can be automated but it still needs a lot of human intervention
- Not all assays can be automated

Screening and Virtual Screening

Compounds can be pre-screened *in silico* enriching the ligand set

Virtual

High-Throughput Screening

- Cheap (both money and time)
- Can be easily automated
- Dramatic reduction of the number of:
  - compounds to be tested
  - false negative

Virtual Screening

Definition

"Search for compounds with a defined biological activity using a computational model"

It's a *knowledge-based* method

Ligand based

(pharmacophores,QSAR...)

Structure based

(docking)

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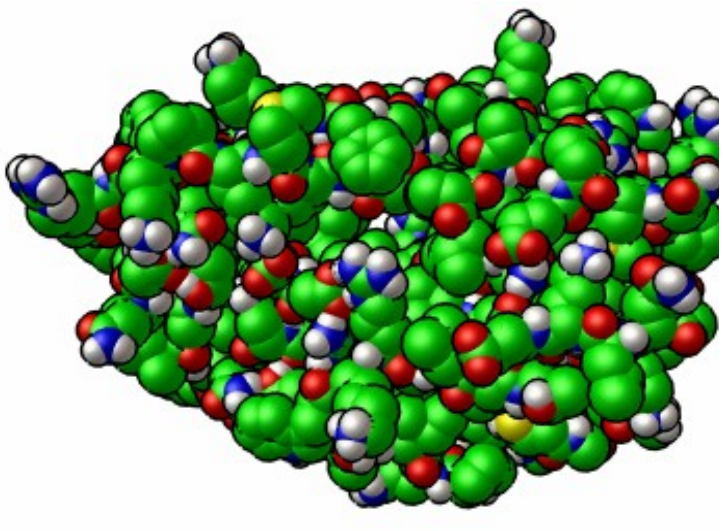
Horvat, D., "A virtual screening approach applied to the search for trypanothione reductase inhibitors", **1997**, *Journal of Medicinal Chemistry* (40), 2412-2423

The Goal

Identify a molecule able to bind to a target providing a biological function

K_i / Energy



RECEPTOR

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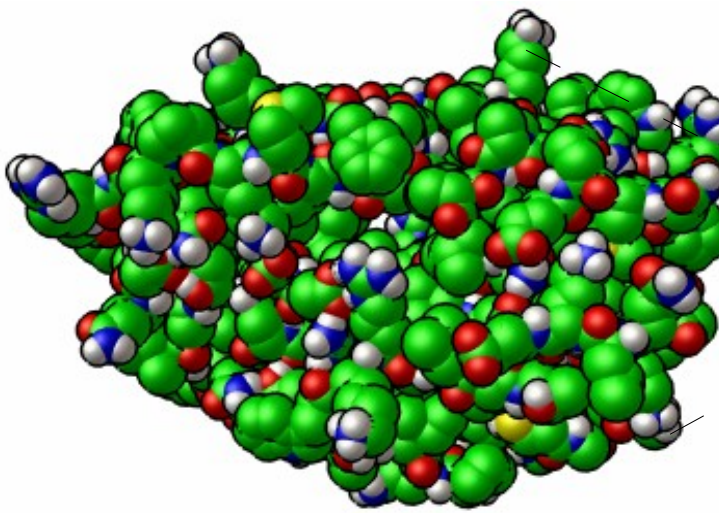
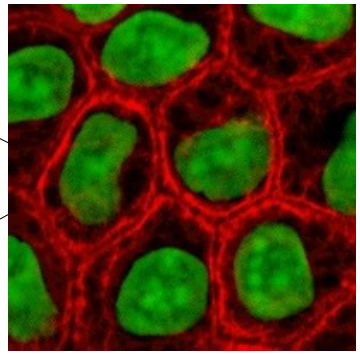
The Goal

Identify a molecule able to bind to a target providing a biological function

K_i / Energy

Unusual elements (Pt, Ru, U…)
Reactive chemical groups
Over/Under-functionalized cpds
Partition coefficient





RECEPTOR

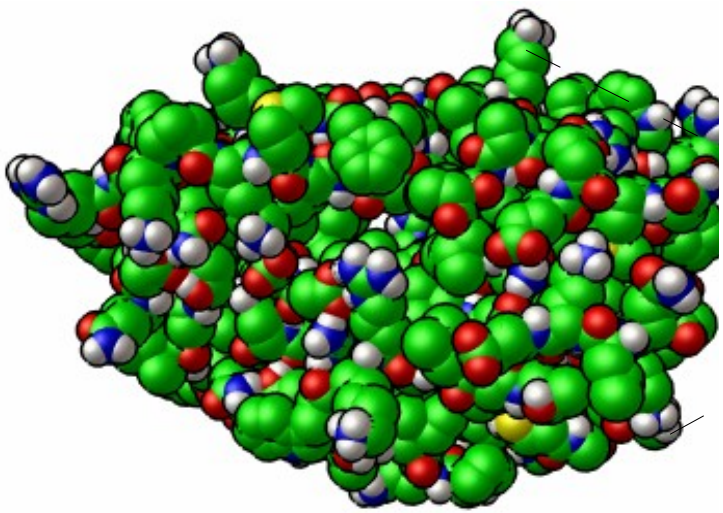
CELL

The Scripps Research Institute®

The Goal

Identify a molecule able to bind to a target providing a biological function

K_i / Energy



RECEPTOR

Unusual elements (Pt, Ru, U…)
Reactive chemical groups
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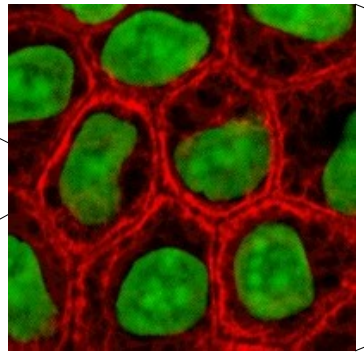
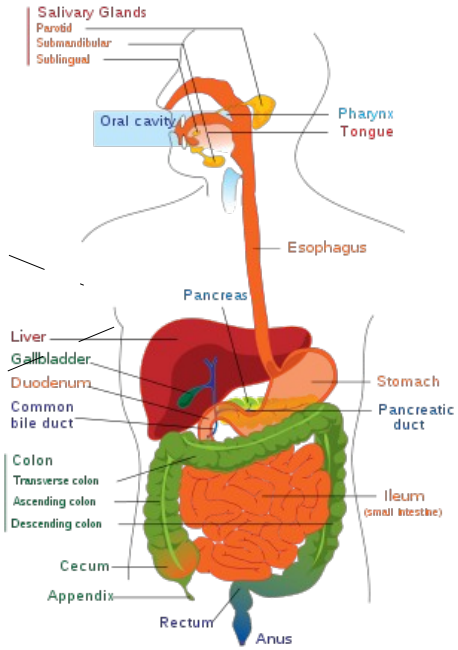
Partition coefficient



CELL

Absorption
Distribution + **Tox**
Metabolism
Excretion



BODY

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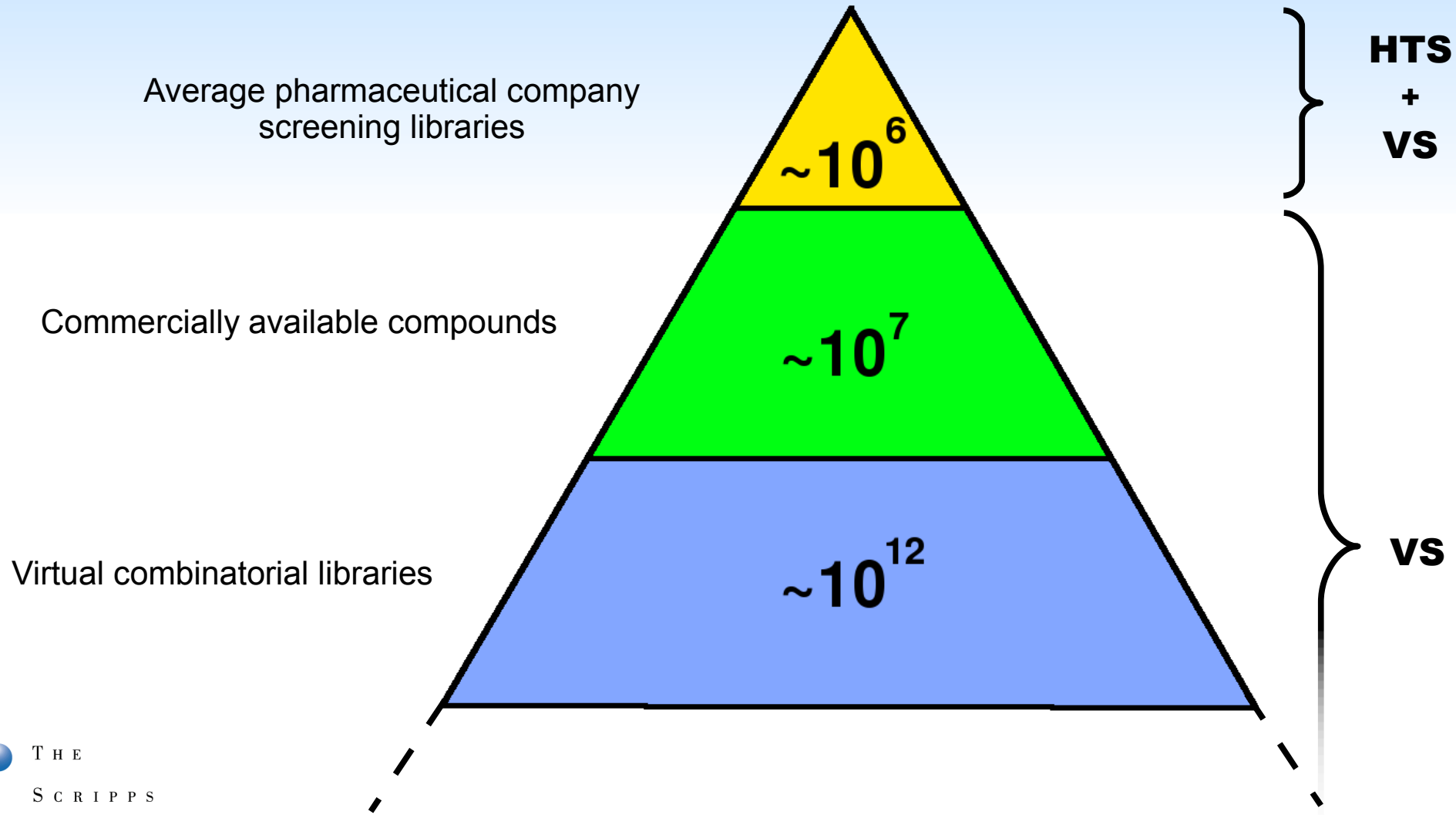
Where to look for: The Chemical Space



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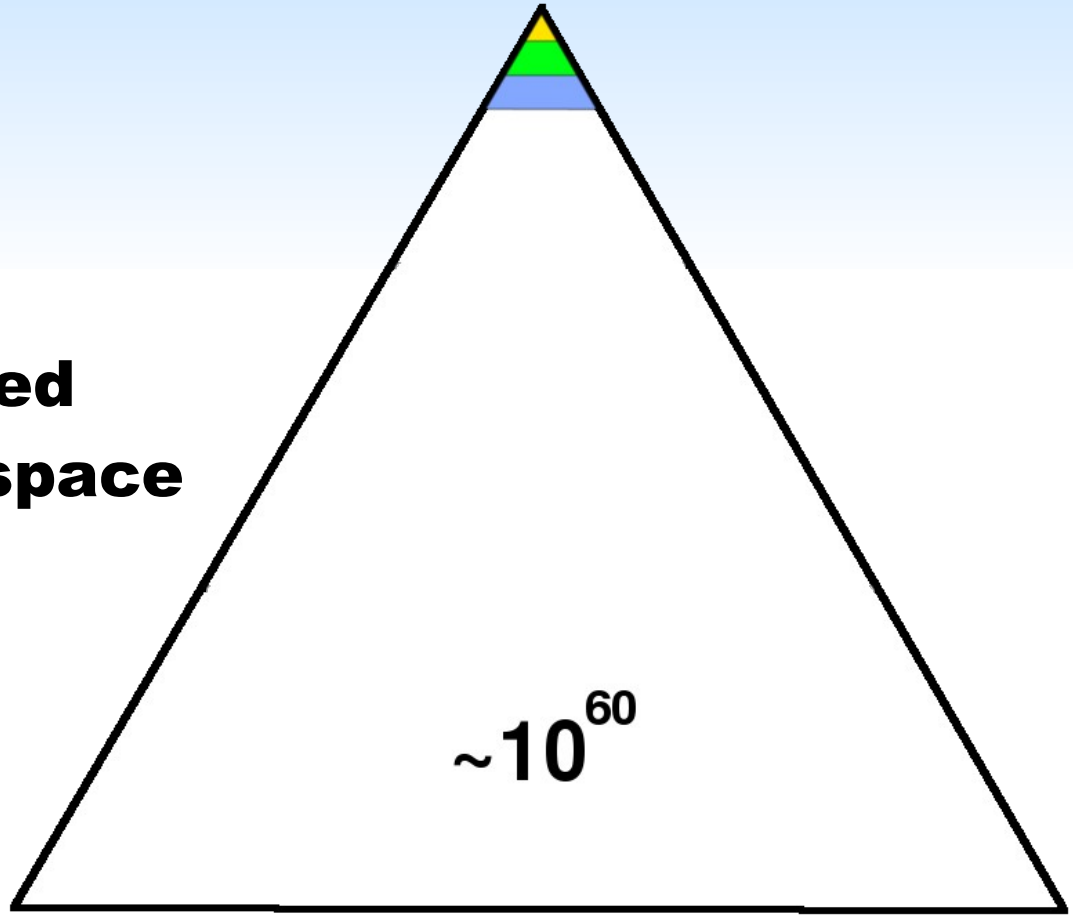
Where to look for: The Chemical Space

Estimated chemical space



100,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000

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What we are looking for

Hit low/medium target affinity

Lead sub-optimal target binding affinity

To be chosen for further development a **lead** compound should have the following properties:

- relatively simple chemical features (suitable for combinatorial/med-chem optimization, no/few chiral centers)
- belong to a well-established SAR series (similar compounds and or similar chemical groups should present similar activity)
- good ADME properties
- favorable patent situation

What we are looking for

Filtering '*rules*'

Drugs 'Rule of Five' (Lipinski rule)

Hydrogen bond donors <= 5
Hydrogen bond acceptors <= 10
Molecular weight <= 500 dalton
Log$P_{w/o}$ < 5

← Approved drugs

Hit Fragments 'Rule of Three'

Molecular weight <= 300 dalton
HB donor/Acceptors <= 3
C*log*P <= 300
Nrot <= 3

← ASTEX frag hits

HTS efforts by using Lipinski-filtered libraries led to few micromolar hits

LEADS are not DRUGS

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"Rules" are good in principle, but they require to sample a huge chemical space to give really effective molecules.

What we are looking for

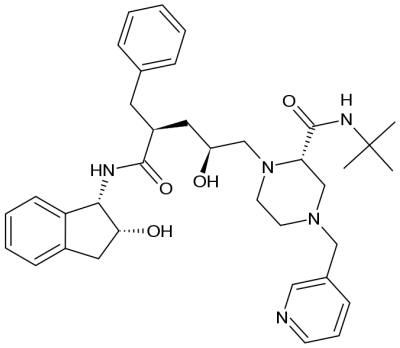
Rules 'Exceptions'

The nature and location of the target must be take into account for properties profile:

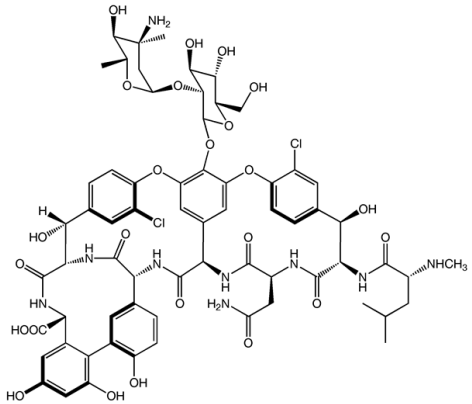
CNS molecule
(lipofilic blood-brain-barrier)

gastro-intestinal antibiotic
(highly soluble)

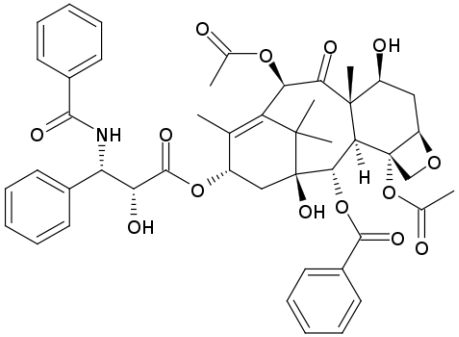
Natural compounds & Pre-drugs and “last resort” compounds (i.e. nitrogen mustards, cisplatin...)



Indinavir



Vancomycin



Paclitaxel

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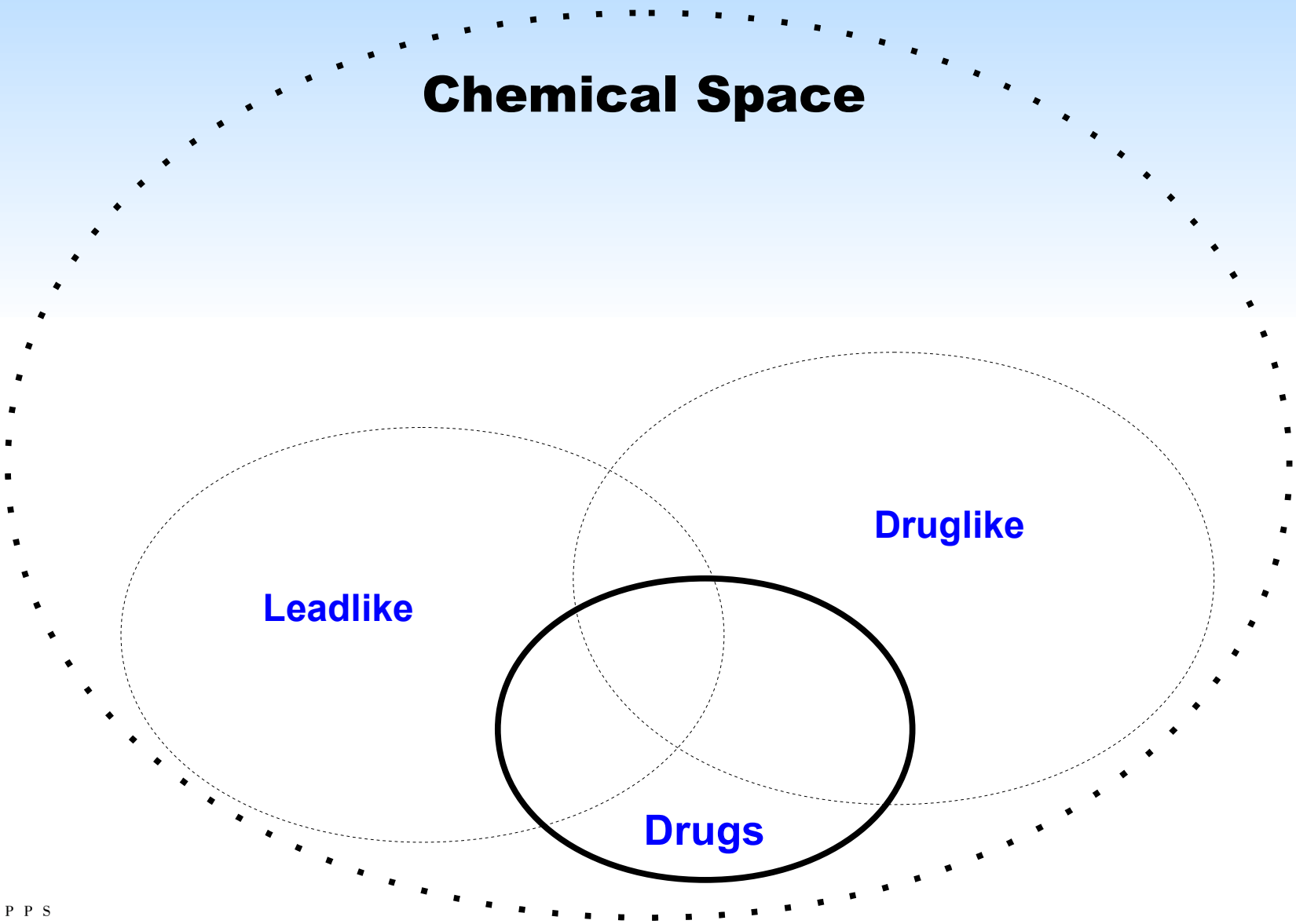
The ultimate tool for identifying hits is the High-throughput screening

What we are looking for



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Virtual Screening

Advantages

- Relatively cheap filter
  (save both time and money)
- Enrichment factor of libraries
- Given the rise of structural genomics
  and crystallography
- It allows to test *in silico* the “druggability”
  of new targets

Virtual Screening

Advantages

- Relatively cheap filter
  (save both time and money)
- Enrichment factor of libraries
- Given the rise of structural genomics and crystallography
- It allows to test *in silico* the “druggability” of new targets

Disadvantages

- Often inaccurate
- Scoring-function dependent
- There is no method that's better than others
- Strongly dependent on:
  - target
  - search method
  - chemical space sampled
- always provides an answer
  (McMaster competition 2005)

Virtual Screening Hints

- **Prepare both target and ligand libraries with care**
  Filter unusual atom types (AutoDock atom types)
  Reliable 3D geometries
  Protonation states and tautomers

- **Reduce the space of your search**
  diversity sets
  generic filtering
  target specific filtering (lipofilic binding site v.s. hydrophobic binding site)

- **Use all available information to select results**
  mutagenesis, SAR...

- **Try to sample different conformations of the protein**
  reduce false negative

- **Use reference compounds whenever available**
  Useful for comparing results with ligands with known activity

Target preparation

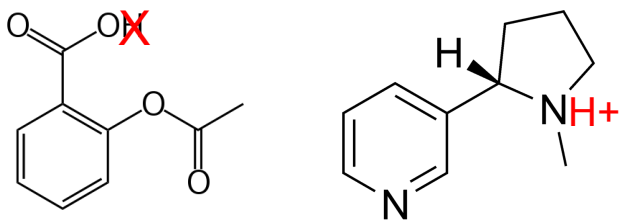
- **Inspect the protein structure**
  Check the quality of the target structure, missing residues...
- **Protonation states**
  Inspect the protonation states
- **Check side chains alternate conformations**
  Select the most suitable conformation when alternate choices are available
  Take into account the use of flexible residues, if necessary
- **Waters and cofactors**
  Some waters (or co-factors) can be essential for the binding... or not...

Compound libraries preparation

Pre-processing of ligand libraries can affect dramatically the quality of results

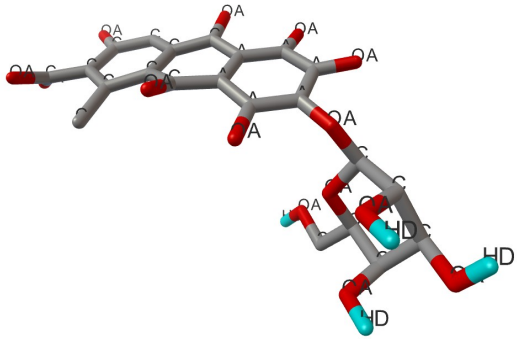
Aspirin (SMILES) : OC(=O)C1=C(C=CC=C1)OC(=O)C

- protonation states
- geometry optimization
- tautomer generation
- custom partial charges



Aspirin **Nicotine**

PROTONATION STATE



OPTIMIZED GEOMETRY

Common file formats:

1D: SMI (multistructure)

2/3D: MOL2 (multistructure)
SDF (multistructure)
PDB

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Ligand libraries

Prepare your molecules 2D->3D

Manually

Avogadro [OPEN SOURCE]
http://avogadro.openmolecules.net/wiki/Main_Page

Automatically

Corina [COMMERCIAL, DEMO AVAILABLE]
http://www.molecular-networks.com/online_demos/corina_demo.html

ProDRG2 server [FREE BUT LIMITED]
http://davapc1.bioch.dundee.ac.uk/prodrg/index.html

ChemAxon Marvin [FREE FOR ACADEMICS]
http://www.chemaxon.com/product/marvin_land.html

OpenBabel [OPEN SOURCE]
http://openbabel.org/wiki/Main_Page

Ligand libraries

PubChem

http://pubchem.ncbi.nlm.nih.gov/

Search unique chemical structures using names, synonyms or keywords, SMILES, schetched. Links to available biological property information are provided for each compound

All biological data related to a compound

2D structures

ZINC

http://zinc.docking.org/

A free database of commercially available compounds for virtual screening

109 commercial compound suppliers+FDA approved drugs,metabolites...

$30x10^6$ compounds (non-unique)

- different tautomers/protonation states
- reliable 3D structures
- pre-filtered for not allowed chemical groups and too complex structures

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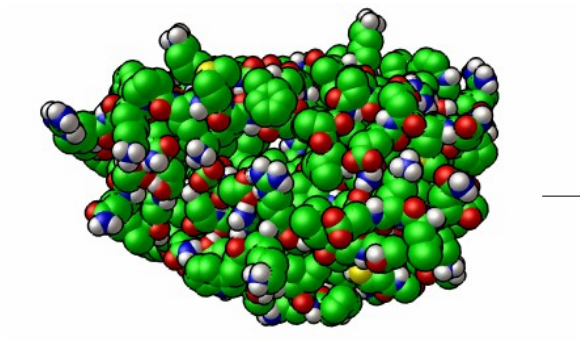
Irwin and Shoichet (2005) *J. Chem. Inf. Model.* **45**(1), 177-82

AutoDock Single Docking

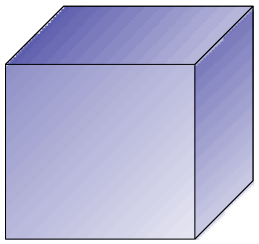
Input
(PDB, Mol2)

PDBQT
(partial
charges,torsions...)

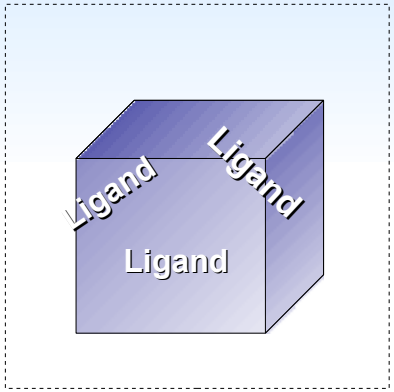


PDBQT
(protonation states,
waters, cofactors...)

Maps



GPF



DPF

DOCKING

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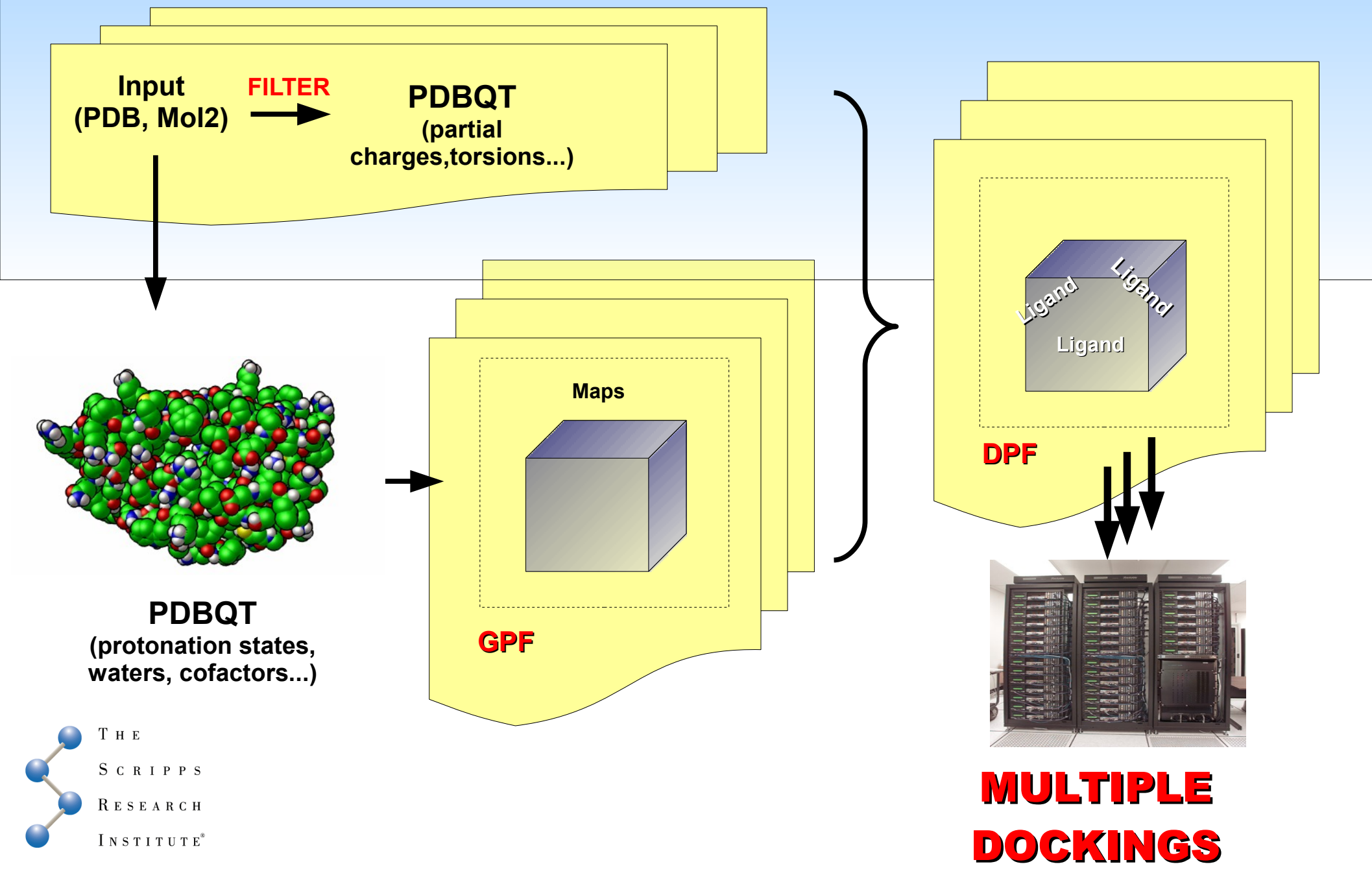
AutoDock VS



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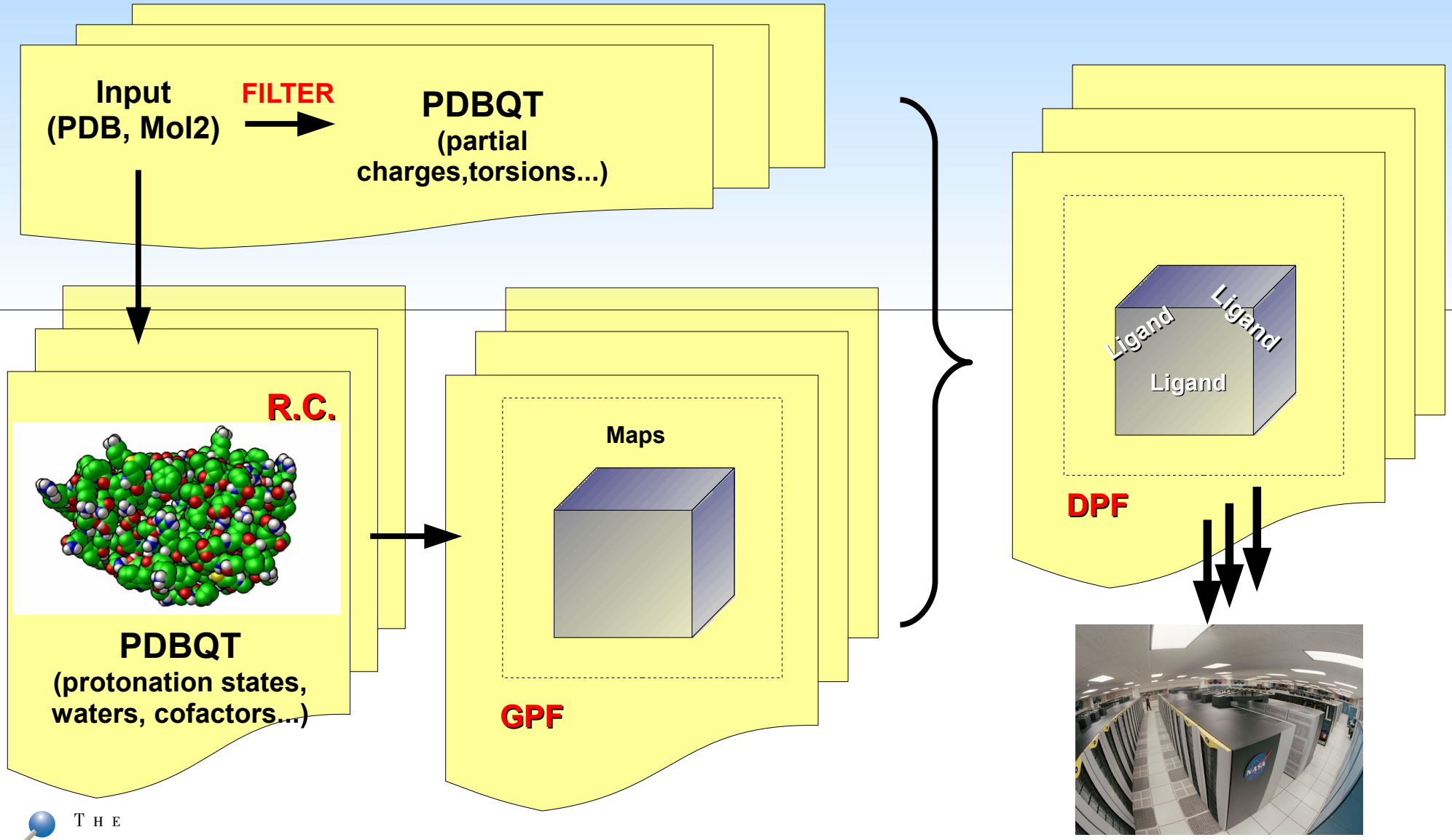
AutoDock VS



MULTIPLE DOCKINGS

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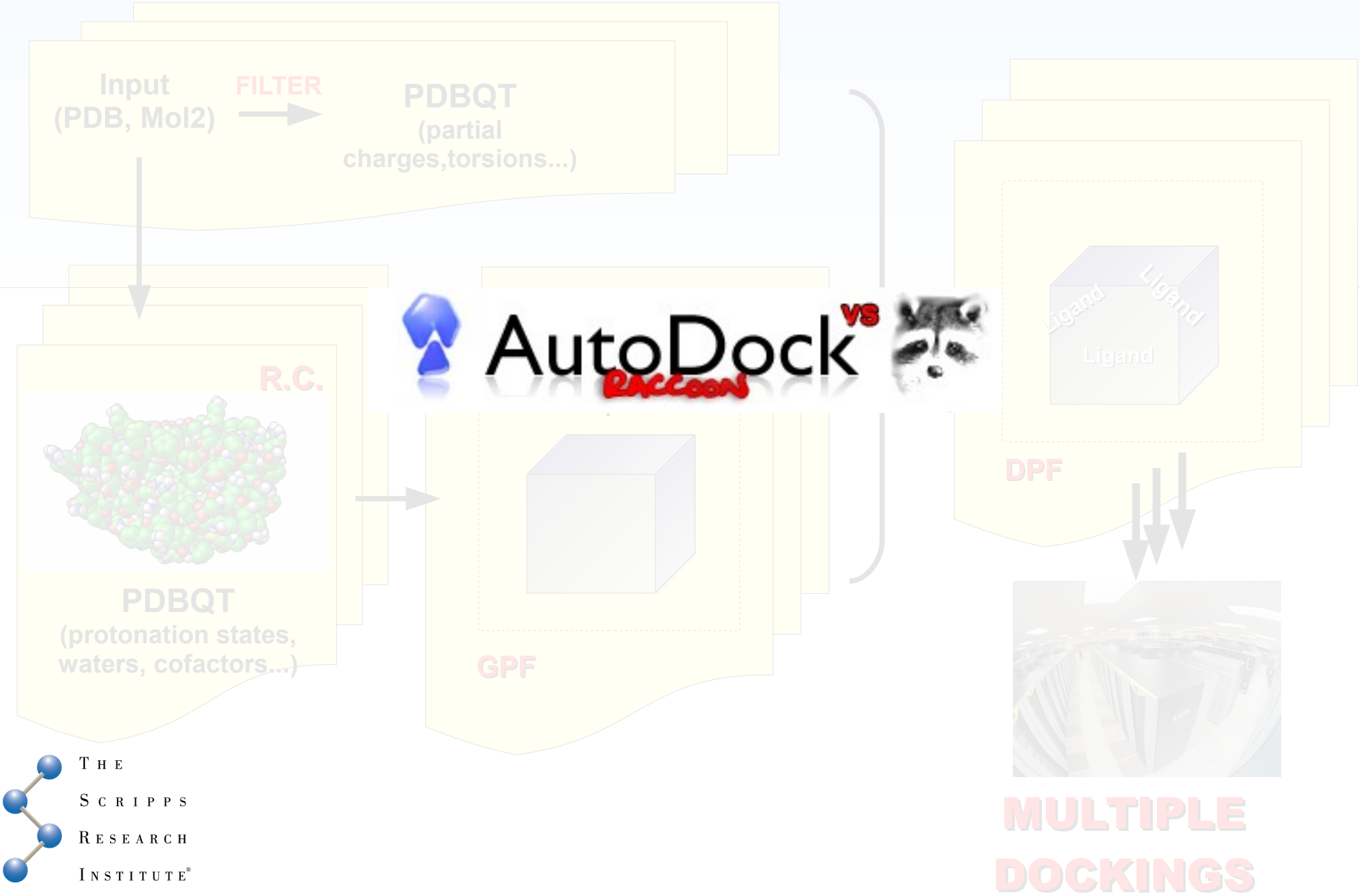
AutoDock VS



AutoDock VS RACCOON

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Run the software

Double-click on the Raccoon link on your desktop

Workflow

Select the inputs for the VS

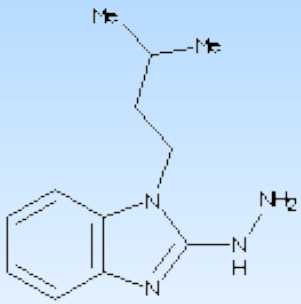
- Define the ligands
- Define the receptor(s)
- Define the grid box
- Define the docking parameters

Generate the VS jobs

Run the VS jobs

Analyze results

Ligand library



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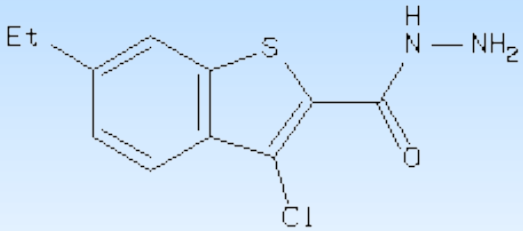

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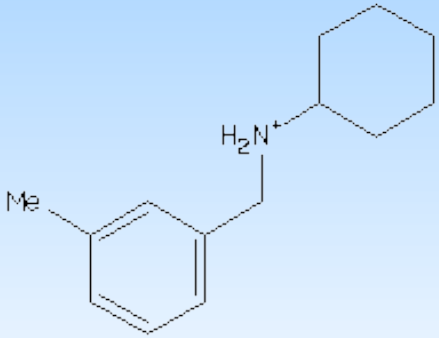

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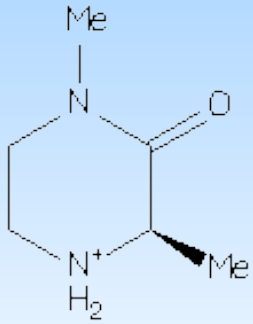

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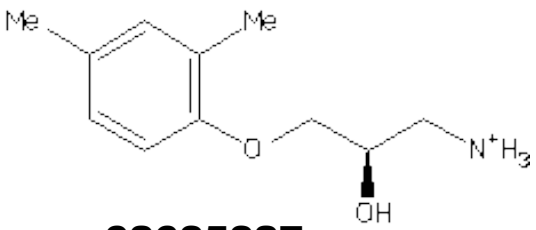

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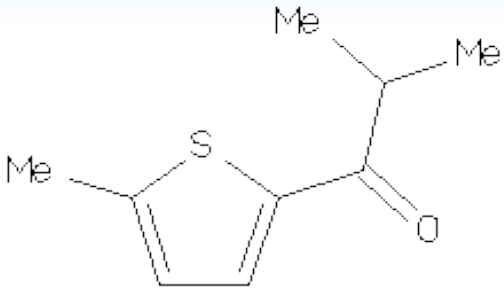

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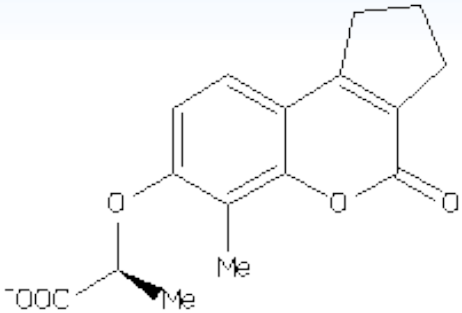

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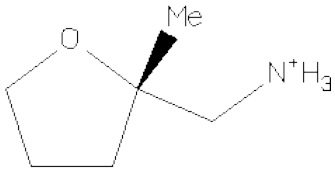

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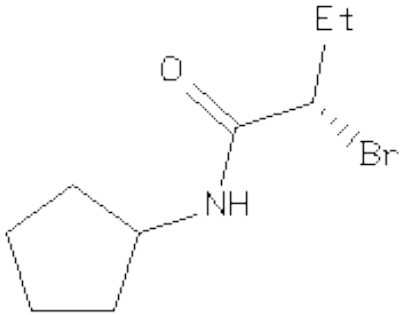

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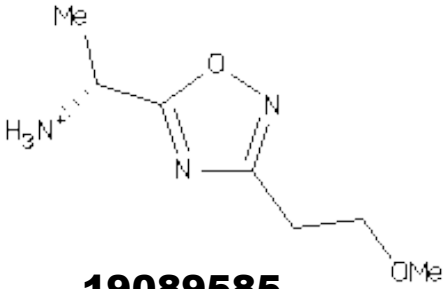
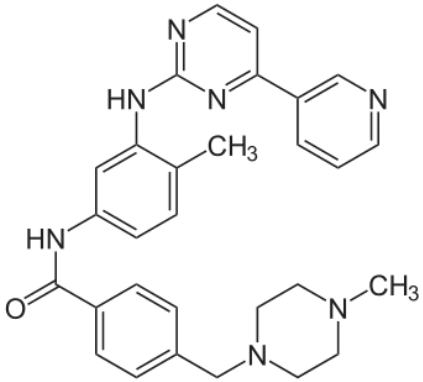


19089585



Imatinib

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Analyze results

```
Number of distinct conformational clusters found = 2,  out of 87 runs,
Using an rmsd-tolerance of 2.0 A

        CLUSTERING HISTOGRAM
        ____________________

_____________________________________________________________________
     |            |     |            |     |
Clus | Lowest     | Run | Mean       | Num | Histogram
-ter | Binding    |     | Binding    | in  |
Rank | Energy     |     | Energy     | Clus|    5    10   15   20   25   30   35
_____|____________|_____|____________|_____|___:____|____:____|____:____|____:___
   1 |      -7.52 |  14 |      -7.52 |   7 |#######
   2 |      -7.39 |  60 |      -7.39 |  80 |##########################################...
_____|____________|_____|____________|_____|_____________________________________

Number of multi-member conformational clusters found = 2, out of 87 runs.
```

BEST ENERGY?

MOST POPULATED CLUSTER?

Analyze results

```
Virtual screening summarization from user entropia on atara [Thu Dec 10 18:01:37 PST 2009]
==============================================================================

        Summarize results in    :       /disk2/work/hongkong/raccoon/results/1iep_receptor
 Results sorted based on the lowest energy conformation in the
 largest cluster to find your best docking.
-----------------------------------------------------
 largestCl_dlgfn    #runs #cl #LC    LE_LC     rmsd_LC #ats #tors
-----------------------------------------------------
 imatinib_1iep_receptor/imatinib_1iep_receptor, 10,  2,  9,-15.4100, 38.6005,  40, 6
 ZINC04387707_1iep_receptor/ZINC04387707_1iep_receptor, 10,  5,  4, -9.1000, 59.2051,  21, 3
 ZINC02387687_1iep_receptor/ZINC02387687_1iep_receptor, 10,  4,  7, -8.3300, 61.9815,  19, 3
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Ligand Efficiency

$$\Delta g = \frac{-RT \log K_d}{N_{\text{non-hydrogen atoms}}}$$

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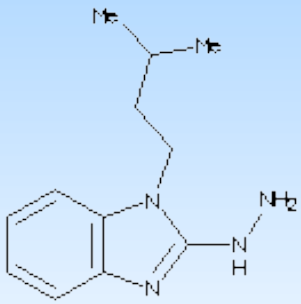
Ligand library



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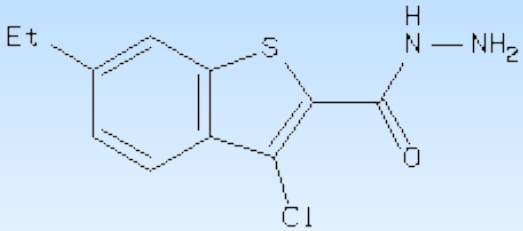

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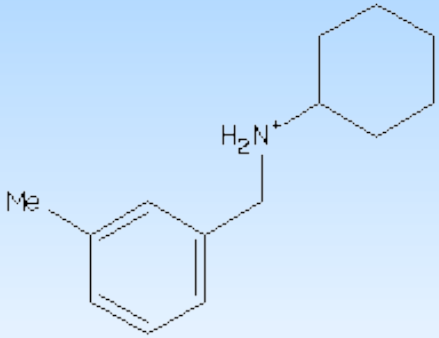
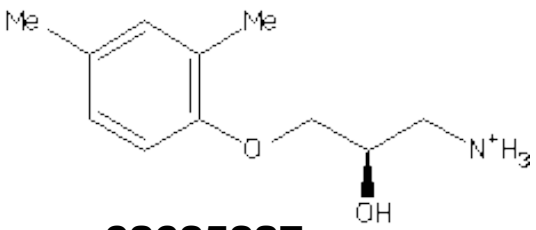


02390501

15015303



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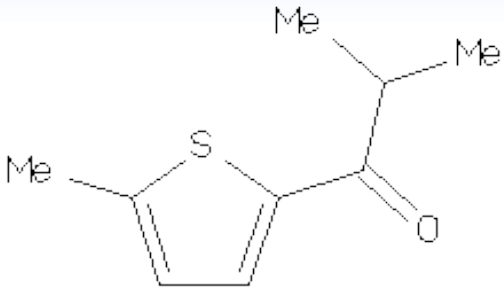

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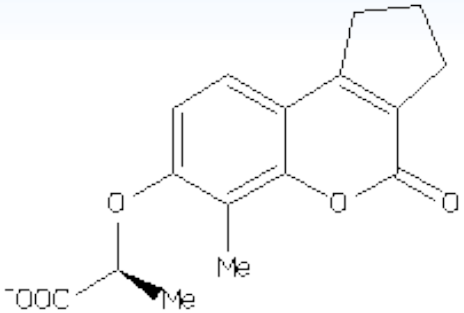

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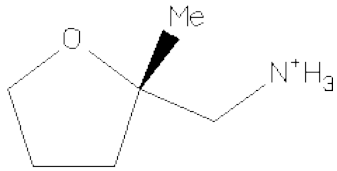
VIRTUAL HIT



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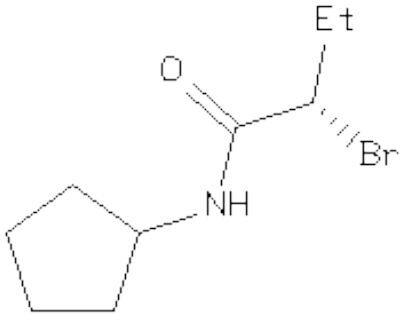

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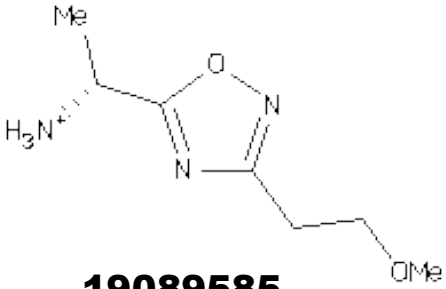

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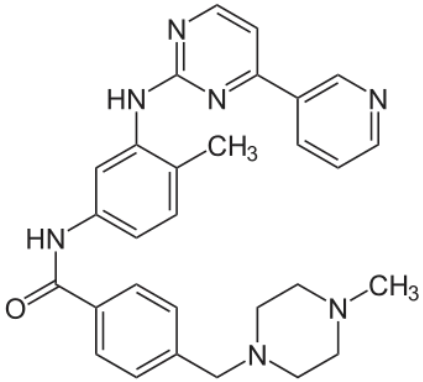

Imatinib

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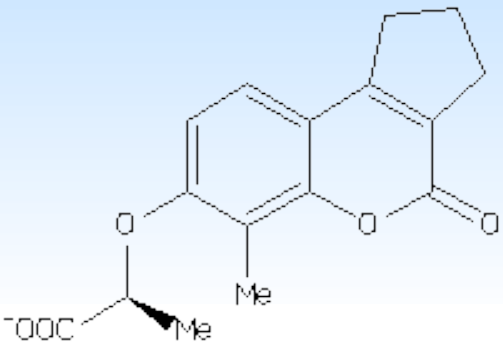
Ligand library



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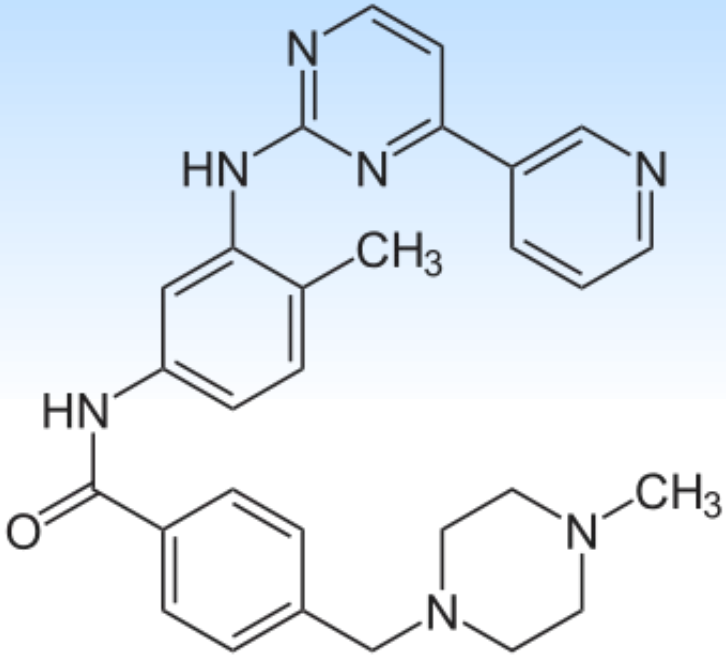

imatinib_xray.pdb

COMPARE THE CONTACTS

- where the interaction is similar
- where the interaction is <u>different</u>
- biological assay to evaluate the activity

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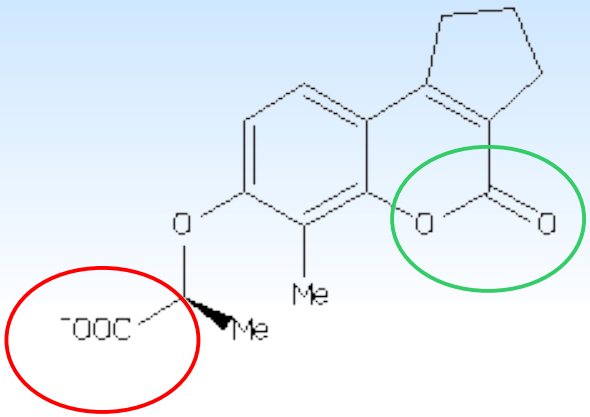
Ligand library



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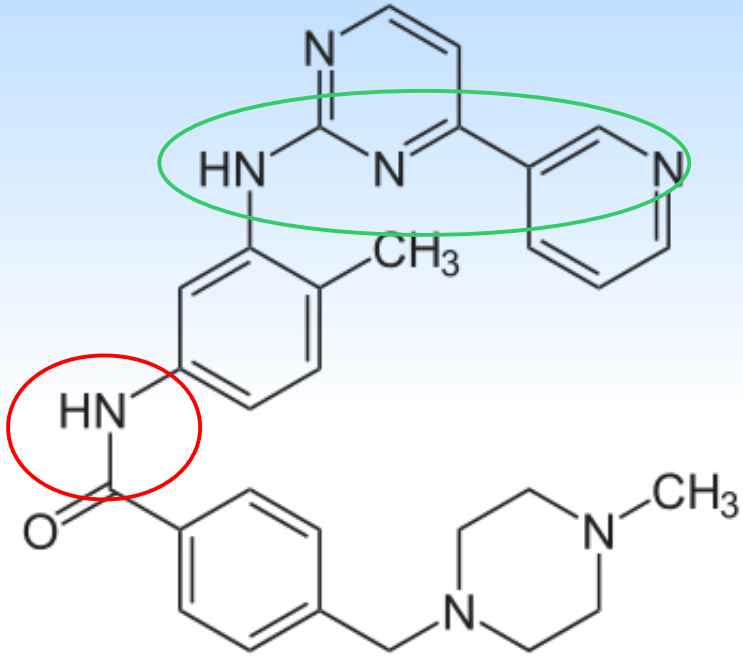

imatinib_xray.pdb

COMPARE THE CONTACTS

- where the interaction is similar **(Met318,Thr315)**
- where the interaction is <u>different</u> **(Lys271)**
- biological assay to evaluate the activity

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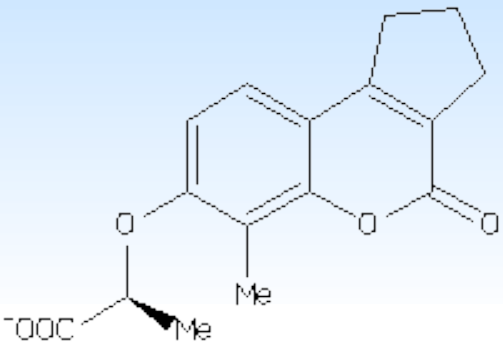
Ligand library



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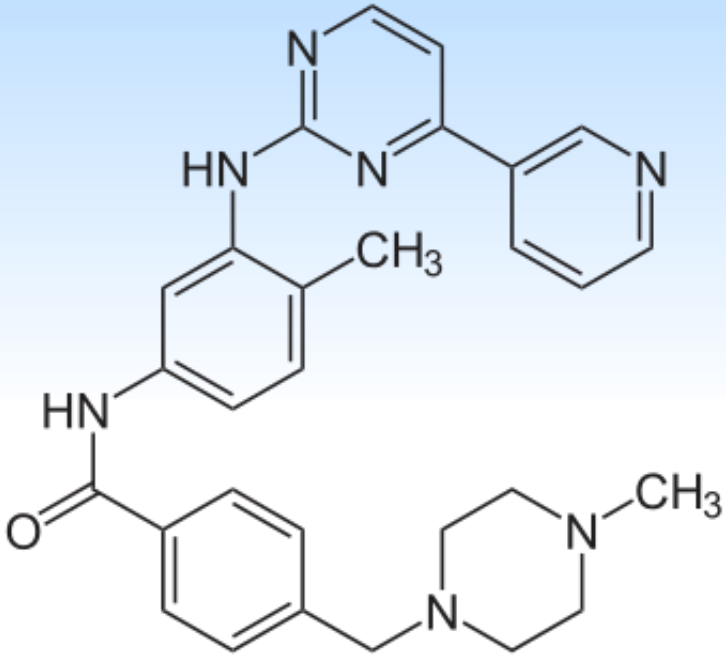
CONFIRMED HIT



imatinib_xray.pdb

HIT-TO-LEAD

- visualize grid interaction maps (*ADT tutorial, exercise 9*)
- identify where to grow the hit-molecule
- similarity search, focused libraries

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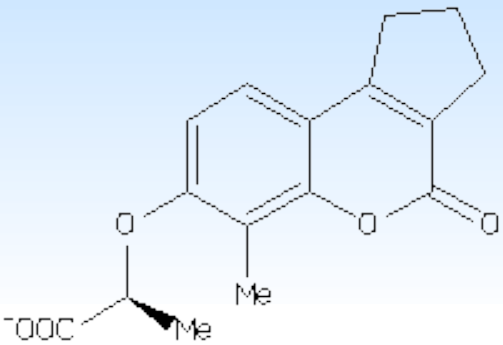
Ligand library



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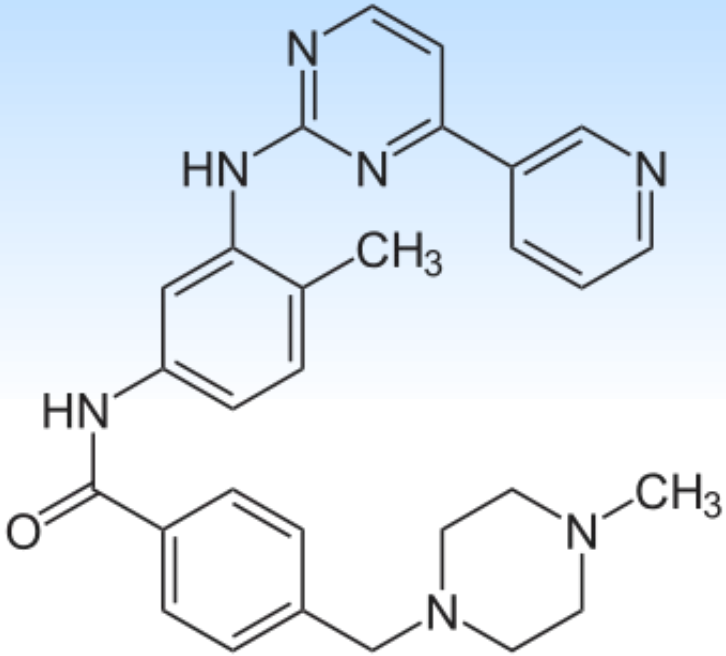
CONFIRMED HIT



imatinib_xray.pdb

HIT-TO-LEAD

- visualize grid interaction maps
- identify where to grow the hit-molecule
- similarity search, focused libraries
- **PATENT IT**!

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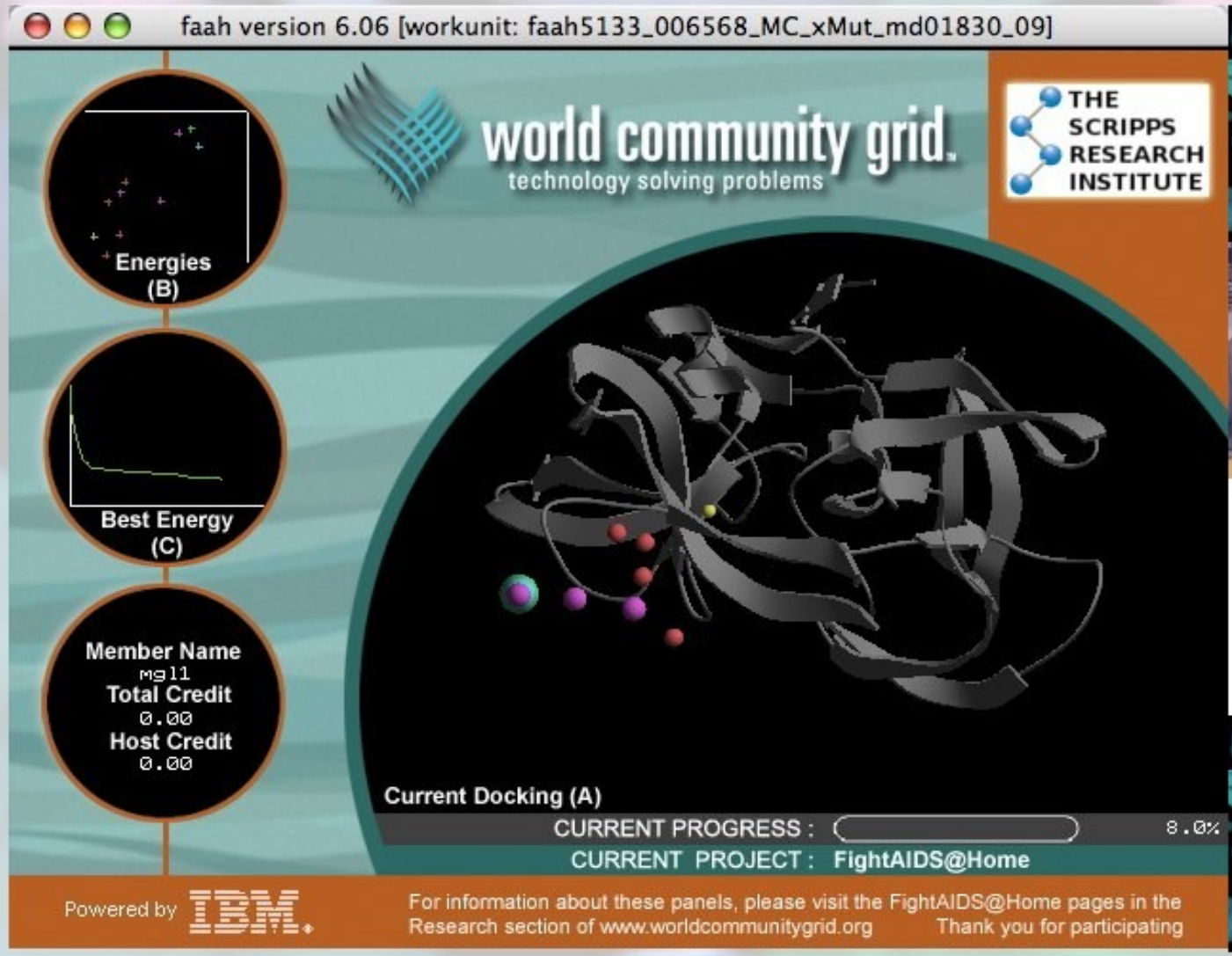
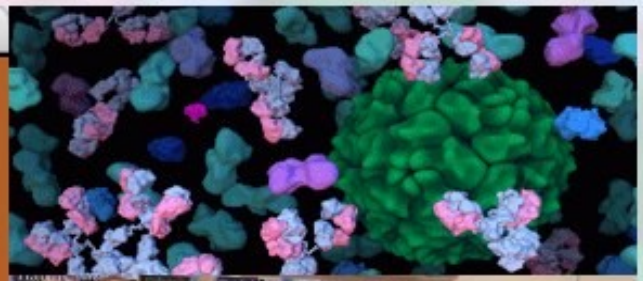
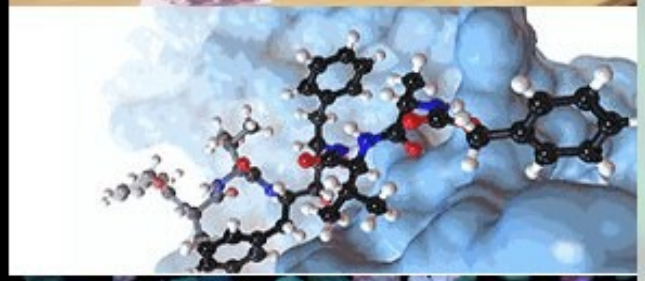
FightAIDS@Home







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http://fightaidsathome.scripps.edu/

Recommended readings

“Is there a difference between leads and drugs? A historical perspective”
Oprea, T., I., Davis, A., M., Teague, S .,J., Leeson, P., D.J.Chem. Inf. Comput.Sci. 2001, 41, 1308-1315

“A 'rule of three' for fragment based lead discovery?”
Congreve, M., Carr, R., Murray, C., Jhoti, H. 2001, Drug Discov. Today, 2003, v8, n19, p876

“Virtual screening - what does it give us?”
Köppen H. Curr Opin Drug Discov Devel. 2009 May;12(3):397-407

”Ligand efficiency: a useful metric for lead selection”
Hopkins AL, Groom CR, Alex A. Drug Discov Today. 2004 May 15;9(10):430-1.

"Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings"
C.A. Lipinski; F. Lombardo; B.W. Dominy and P.J. Feeney (1997). . Adv Drug Del Rev 23: 3–25

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