

# Texas A&M HPRC Short Course Series

## Drug Docking with Schrodinger

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**DIVISION OF RESEARCH**  
TEXAS A & M UNIVERSITY

# Outline

10:00 -10:20 Intro to Molecular Modeling in Drug Discovery

10:20 -11:10 Hands-on Session 1 – Structure Preparation with Maestro

11:10-11:30 Basics of Structural Based Virtual Screening

11:30-12:15 Hand-on Session 2 – Docking with Glide

12:15-12:30 Covalent Docking with Covdock & Wrap-up

# A Tough Road of Drug Discovery

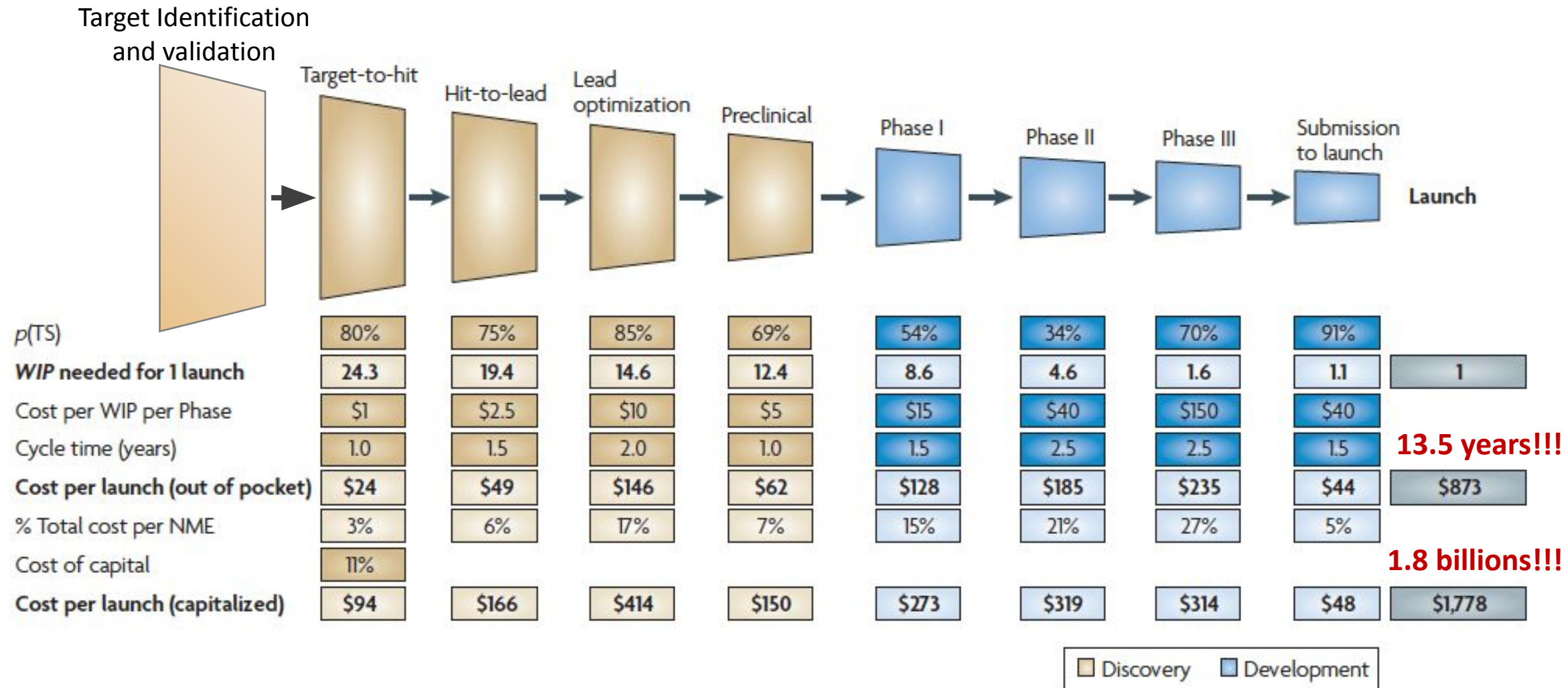
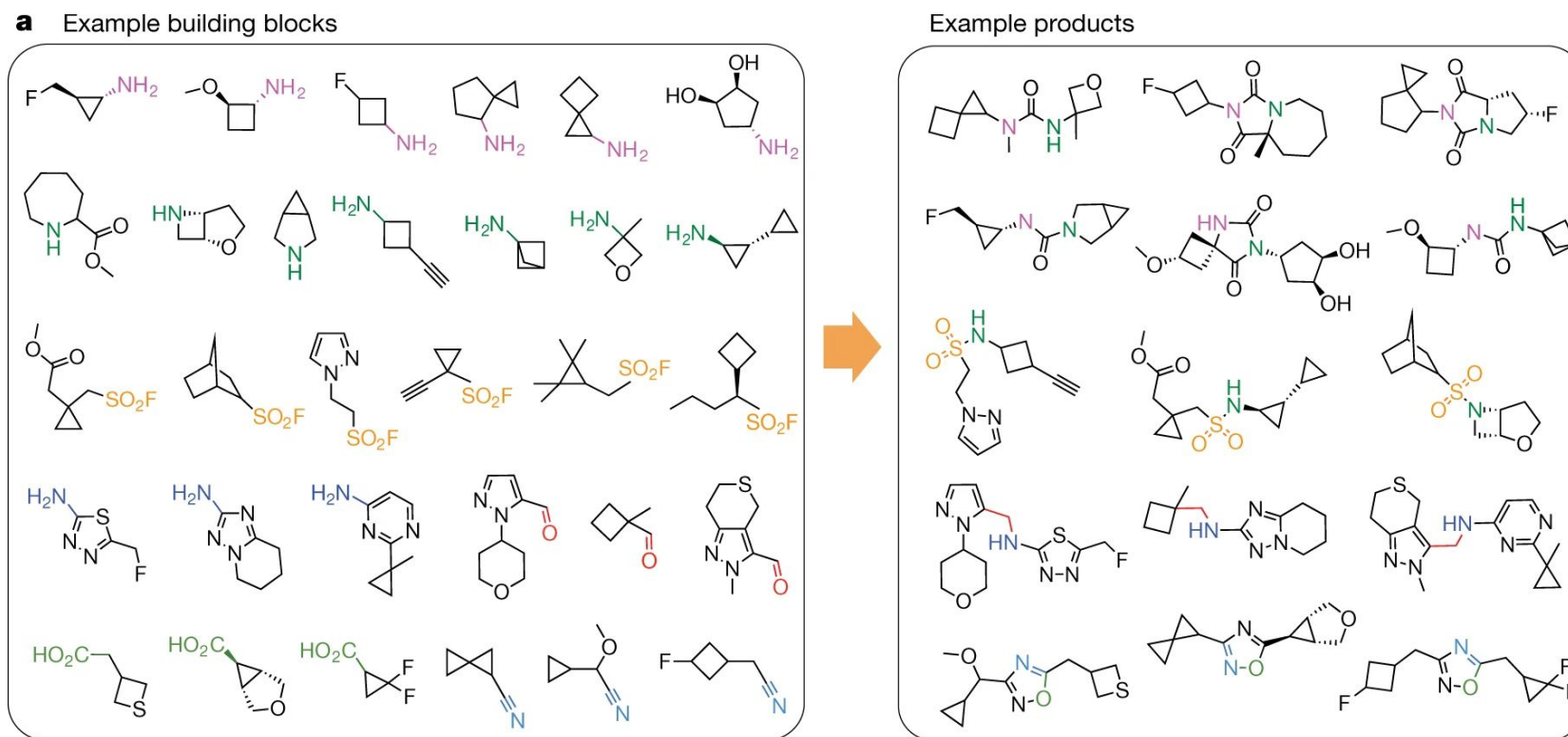


Figure adapted from Paul SM et al., Nat. Rev. Drug Discov., 2010, 9, 203-214

# Search larger and more diverse chemical space



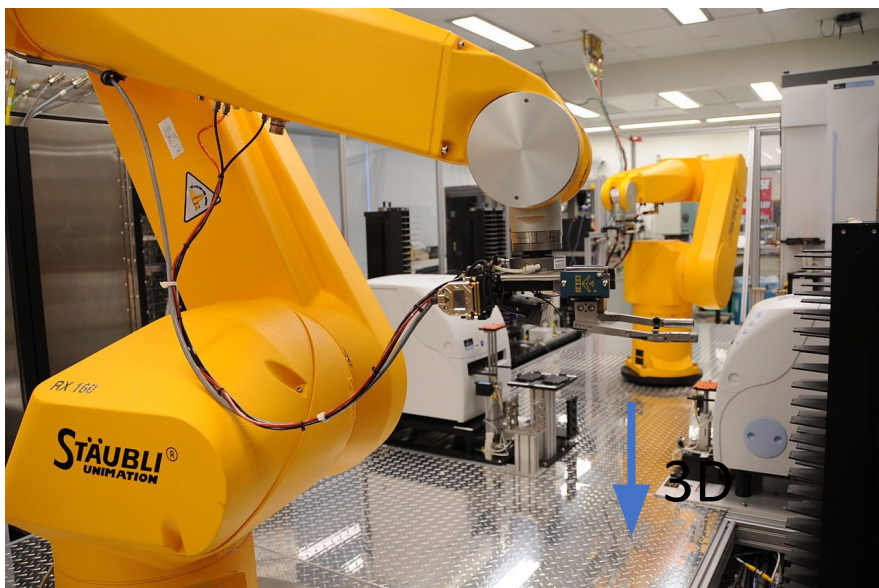
- Chemical diversity (scaffolds) increases with large chemical space searching
- As screening decks expand there will be more tighter binders that could be found

Nature 2019, 566, 224–229

# Methods for Hit Identification

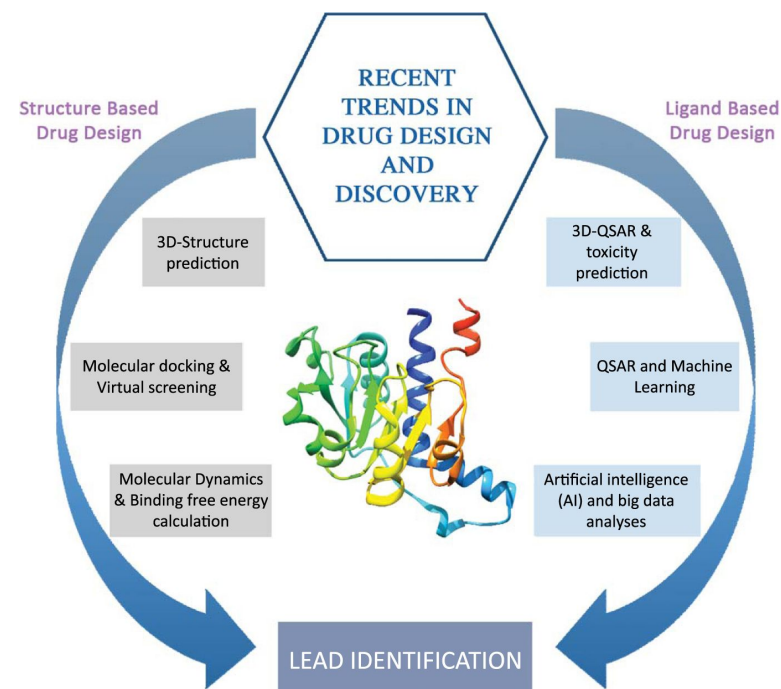
**Hit:** A small molecule that is known to bind to a target in drug discovery.

## High Throughput Screening (HTS)



[https://en.wikipedia.org/wiki/High-throughput\\_screening](https://en.wikipedia.org/wiki/High-throughput_screening)

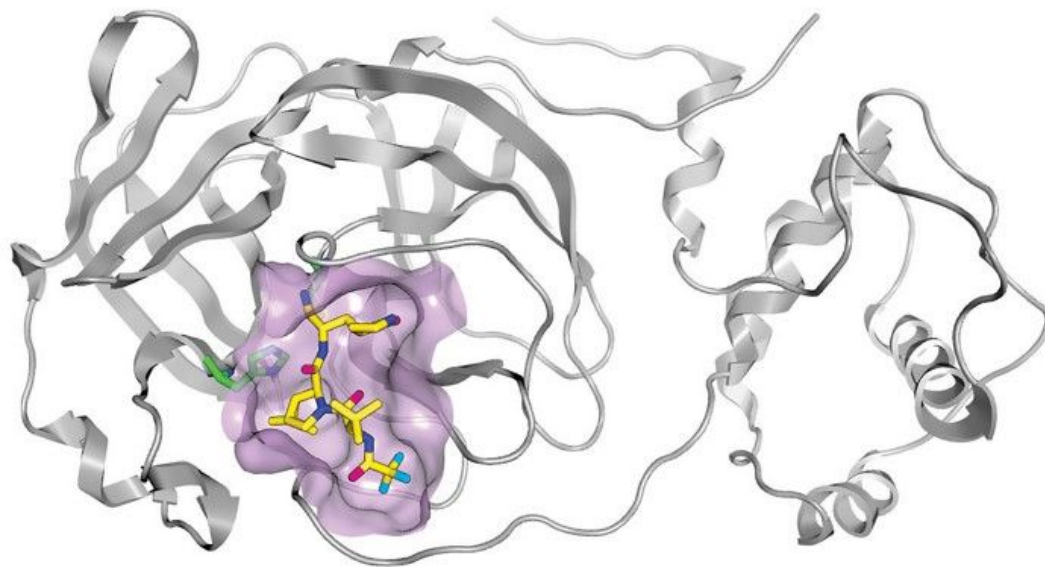
## High Throughput Virtual Screening (HTVS)



*Curr Top Med Chem.* 2020; 20(19): 1761-1770.



# Virtual Screening



Paxlovid

Figure from Joy Yang/Pfizer, *C&EN*, 2022, 100, 3

## Structure-based Drug Design

- known target structure
- known ligand binding site
- (optional) bound ligands/hits

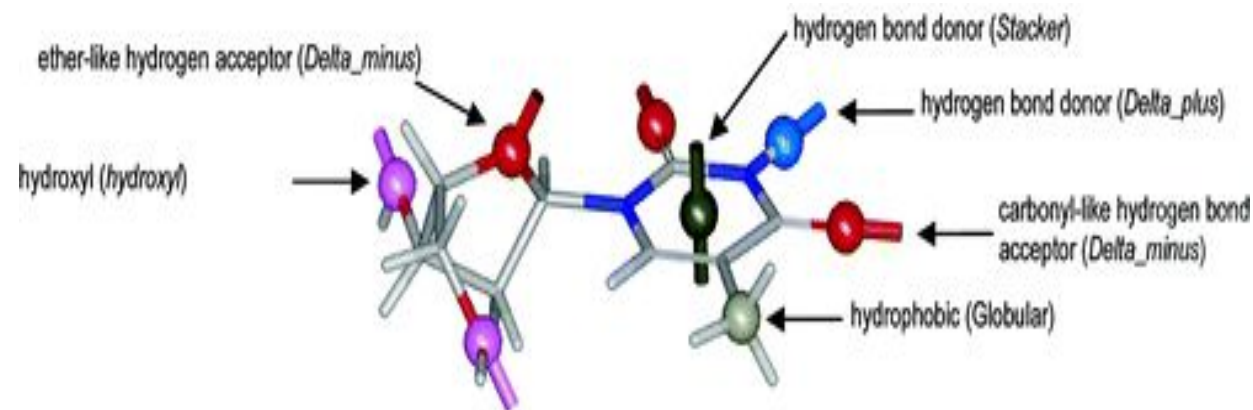


Figure from *J. Chem. Inf. Model.* 2007, 47, 3, 1097–1110

## Ligand-based Drug Design

- known hits
- (optional) active conformation

# Protein Target

- Crystal structure

RCSB Protein Data Bank (PDB)

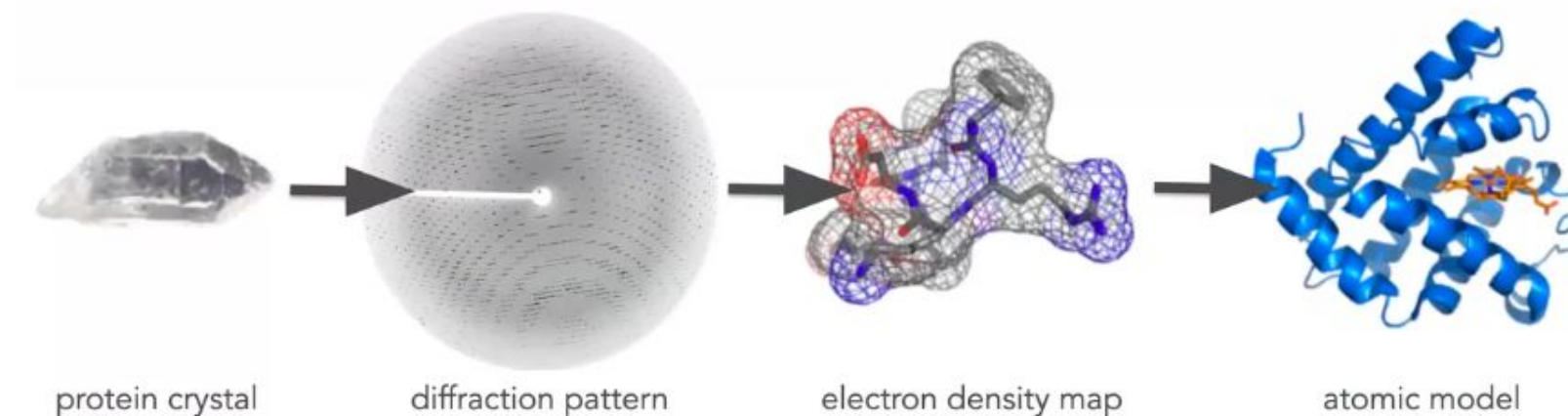
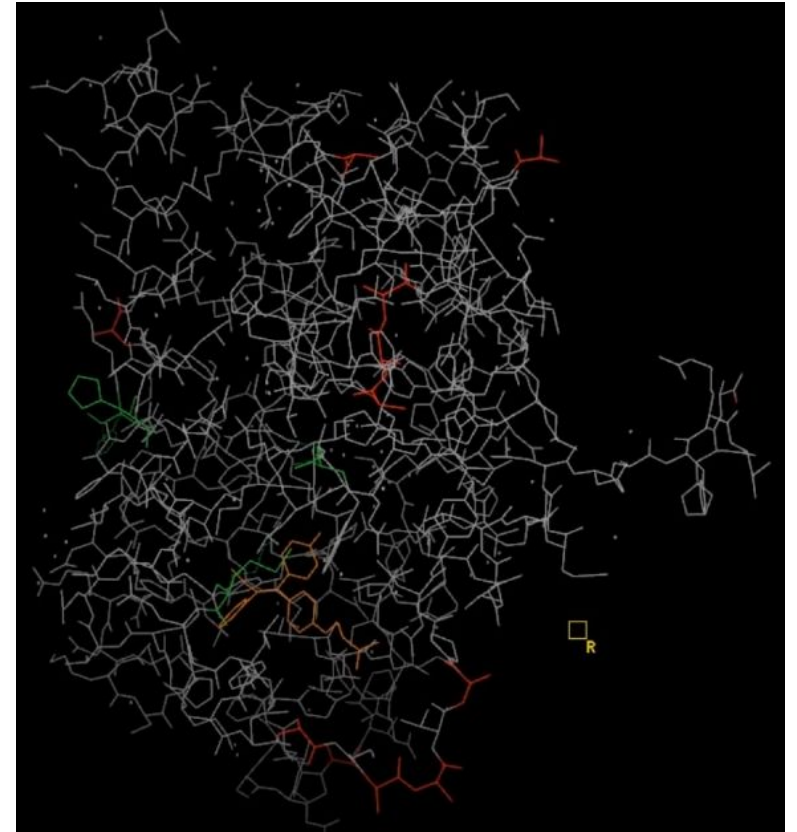


Figure from <https://www.schrodinger.com/webinars/archives/1248/virtual-screening/469153>

- NMR
- Homology Model
- Cryoelectron Microscopy (cryo-EM)

# Protein Preparation

- Typical PDB structure is not suitable for immediate use
  - it typically contains heavy atoms, co-crystallized ligand, water molecules, metal ions, cofactors, ...
  - may be multimeric, need to be reduced to a single unit
  - limited resolution, eg. it's difficult to distinguish carbonyl oxygen and secondary amine nitrogen's of amide
  - may have incorrect bond orders, assignment of charge state, orientation of groups



Color protein with **PDB conversion Status**

Gray: standard residue connect by standard

Red: standard residue with missing atoms

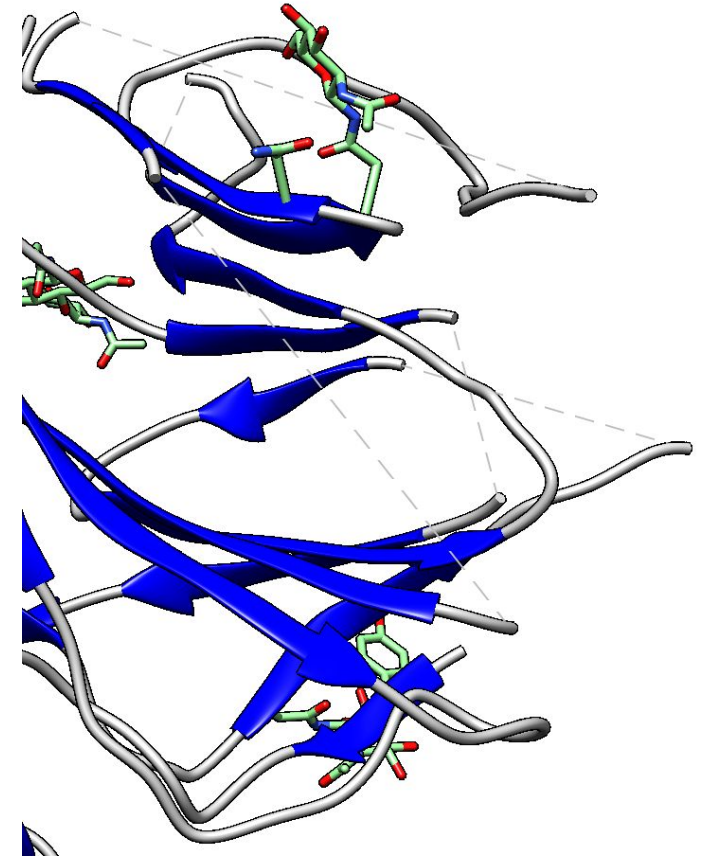
orange: nonstandard residues, HET groups

green: residue with an alternate conformation



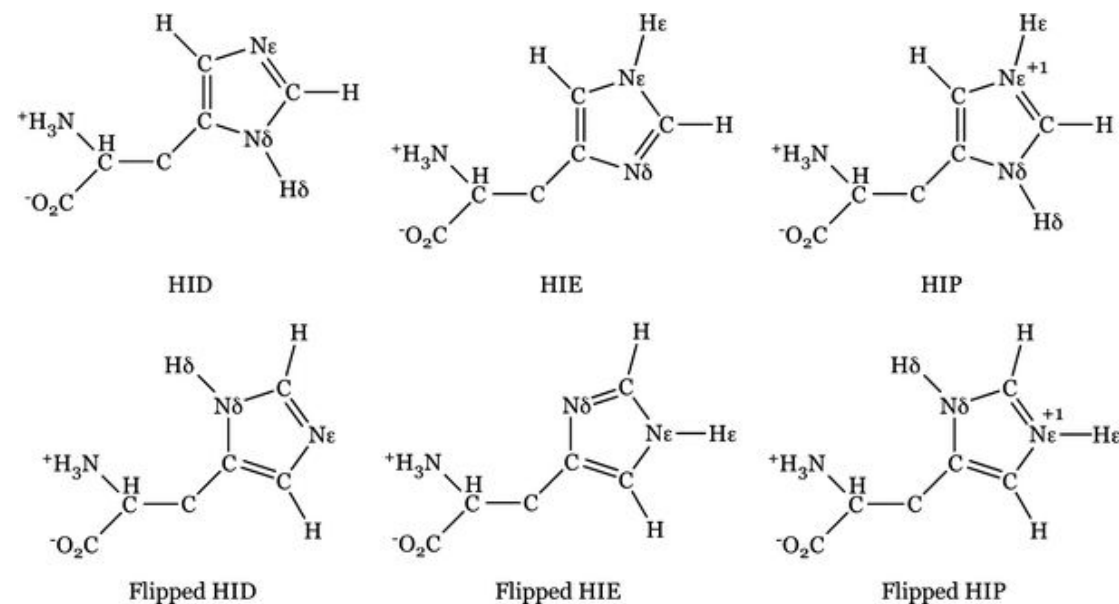
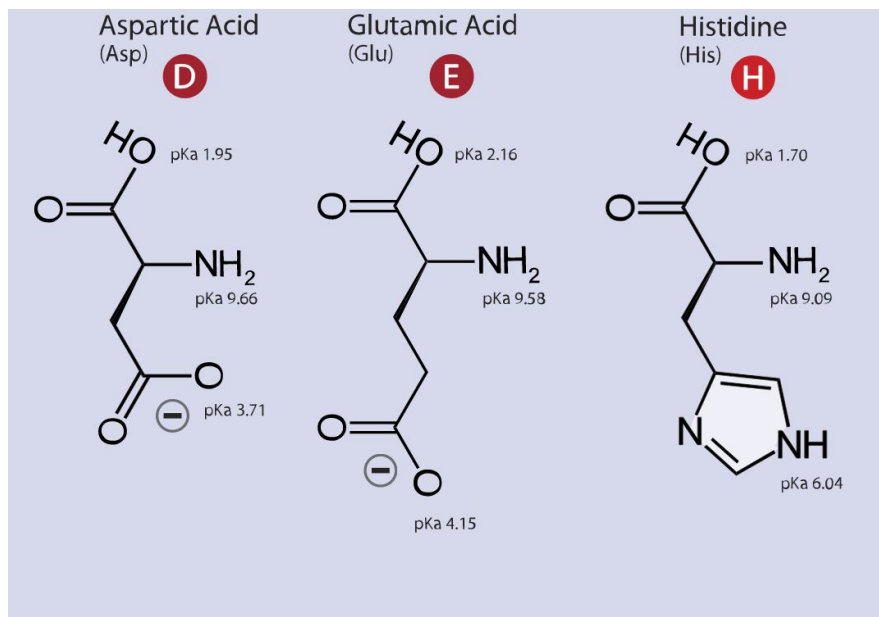
# Protein Preparation – Missing atoms

- Missing atoms
  - Hydrogens are not included
  - Entire side chains may be missing
  - There are a number of utilities to fill in missing atoms/sidechain
- Missing segments
  - More complicated to fix
  - Normally requires homology modeling to obtain reasonable results if more than a few residues are missing



# Protein Preparation – Protonation states

- ASP, GLU and HIS



Adapted from [https://commons.wikimedia.org/wiki/File:Amino\\_Acids.svg](https://commons.wikimedia.org/wiki/File:Amino_Acids.svg)  
Dancojocari / CC BY-SA (<https://creativecommons.org/licenses/by-sa/3.0>)

<https://link.springer.com/article/10.1007/s10822-013-9643-9>

# Protein Preparation Workflow

## Preparation Workflow Tab

- **INTERACTIVE** button: switching between running the workflow interactively or as a batch job

Protein Preparation Workflow (Interactive) - 1FJS

Preparation Workflow | Diagnostics | Substructures

Click a button to run a step. Wait for each process to finish and ensure the correct entry is in the Workspace before requesting the next step. **INTERACTIVE**

**1. Specify Protein**  
Source: **Workspace** Get PDB...  
Entry: 1FJS (1)  
Review Structure Global Settings ▾

**2. Preprocess**  
☐ Cap termini ☒ Fill in missing side chains More Options ▾  
Preprocess Default actions selected (6)

**3. Diagnose and Analyze**  
Run diagnostics and review the structure in the secondary tabs.  
Check Structure

**4. Optimize H-bond Assignments**  
Optimize to address any overlapping hydrogens. Settings ▾  
Optimize - or - Assign with Constraints...

**5. Minimize and Delete Waters**  
Run a restrained minimization, then optionally delete specified waters. Settings ▾  
Clean Up

Workflow group: 2QVH - with-deletions-proteinprep\_1

Protein Preparation Workflow

Preparation Workflow | Diagnostics | Substructures

Toggle steps on to include them in the job. **INTERACTIVE**

**Specify Protein**  
Use structures from: **Workspace (included entry)** Get PDB...  
Entry: 1FJS (1)  
Review Structure Global Settings ▾

☒ **Preprocess**  
☐ Cap termini ☒ Fill in missing side chains More Options ▾  
Default actions selected (6)

☒ **Optimize H-bond Assignments**  
If checked, automatic optimization will be performed to address any overlapping hydrogens. Settings ▾

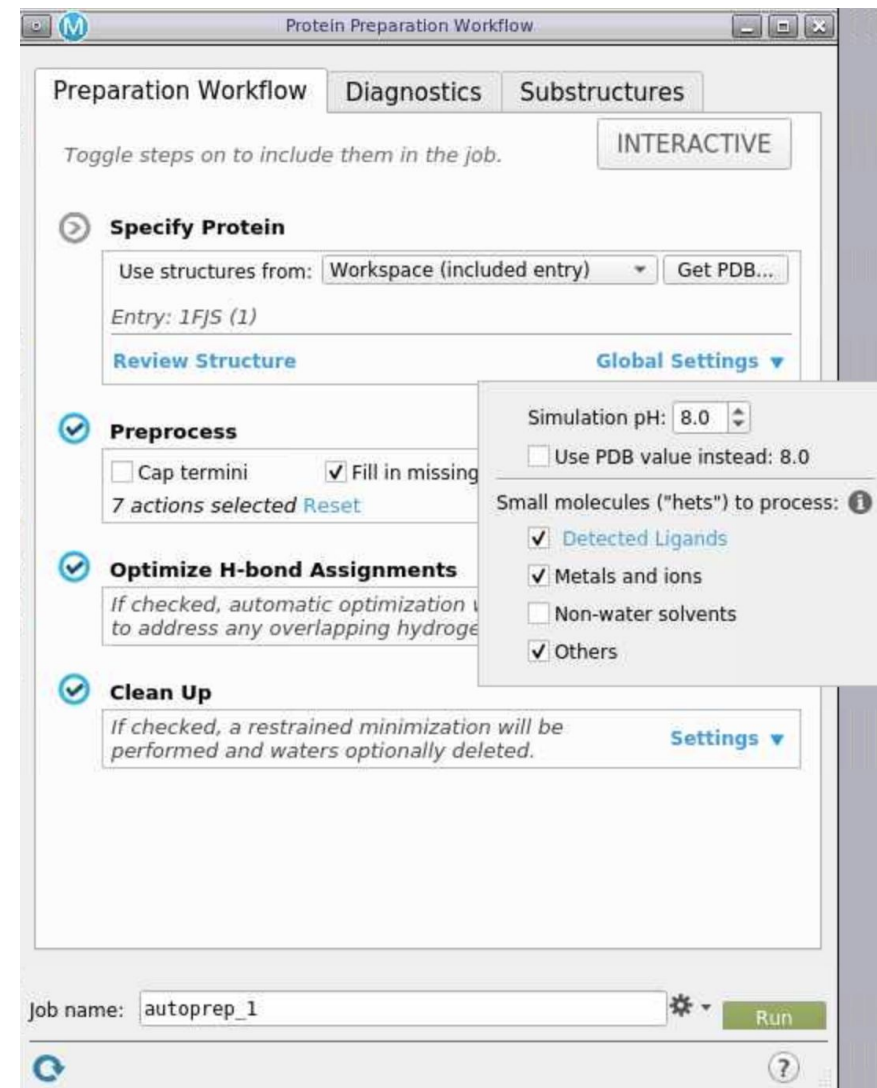
☒ **Clean Up**  
If checked, a restrained minimization will be performed and waters optionally deleted. Settings ▾

Job name: autoprep\_1 ⚙️ Run

# Protein Preparation Workflow

## Preparation Workflow Tab

- **Specify Protein step**
  - from local files
  - get PDB from RCSB website (need web access)
- **Review Structure link**
  - Links to the Substructures Tab
- **Global Settings link**
  - pH
  - small molecules to be included in the generation of ionization states (ligands, metal and ions, non-water solvents, other...)



# Protein Preparation Workflow

## Preparation Workflow Tab

- **Preprocess step:** fix structural defects and add necessary information
  - Cap protein termini with ACE and NMA residues
  - Align one protein to another protein
  - Assign bond order, replace hydrogens, and correct metal ionization states to ensure proper formal charge and force field treatment
  - Add sulfur bond between sulfur atoms that are within 3.2 Å of each other
  - Convert selenomethionines to methionine
  - Protein refinement with Prime
  - Remove water molecules at the user's discretion
  - generate ionization and tautomeric states for hets

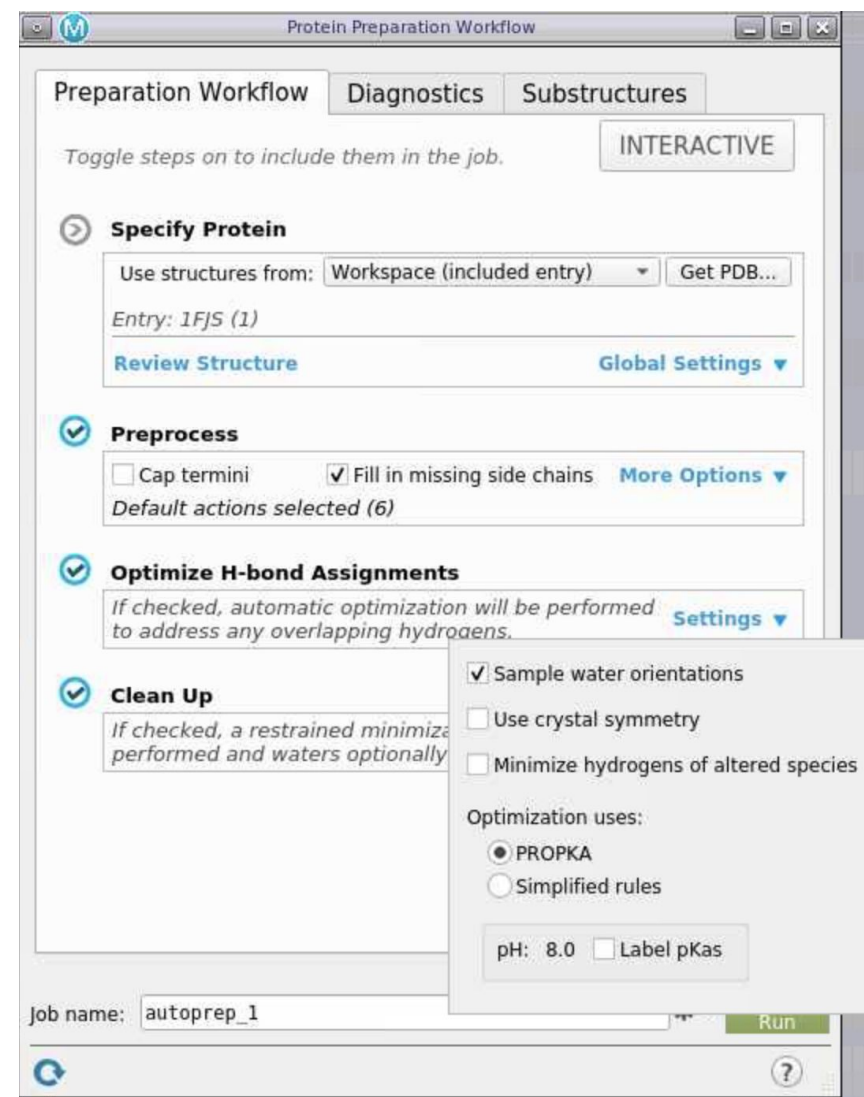
The screenshot shows the 'Protein Preparation Workflow' window with the 'Preparation Workflow' tab selected. The 'INTERACTIVE' button is highlighted. The 'Specify Protein' section shows 'Use structures from: Workspace (included entry)' and 'Entry: 1FJS (1)'. The 'Preprocess' section has checkboxes for 'Cap termini' (unchecked) and 'Fill in missing side chains' (checked). The 'Optimize H-bond Assignment' section has a checkbox for 'If checked, automatic optimization to address any overlapping' (checked). The 'Clean Up' section has a checkbox for 'If checked, a restrained minimization is performed and waters optimized' (checked). A 'More Options' dropdown is open, showing settings for 'Align to: Selected entry', 'Assign bond orders: Using CCD database', 'Replace hydrogens', 'Create: Zero-order bonds to metals, Disulfide bonds', 'Antibody annotation scheme: Kabat', 'Convert selenomethionines to methionines', 'Delete waters beyond hets: 5.00 Å', 'Fill in missing loops (using Prime)', 'Generate het states (with Epik): pH: 8.0 +/- 2.0', and 'Max states to process automatically: 1'. The 'job name' field is 'autoprep\_1' and the 'Run' button is green.



# Protein Preparation Workflow

## Preparation Workflow Tab

- **Optimize H-bond Assignment step:** to optimize H-bonding network, to improve charge-charge interaction and hydrogen bonding
  - reorienting hydroxyl and thiol groups
  - flip terminal amide groups and histidines ring
  - predict protonation states of histadine, ASP and Glu
  - predict tautomeric states of histadine
  - iterative process, pass over all groups multiple times
- Sample water orientation
  - ensure water molecules are optimally placed
  - Delete unwanted water molecule before sampling

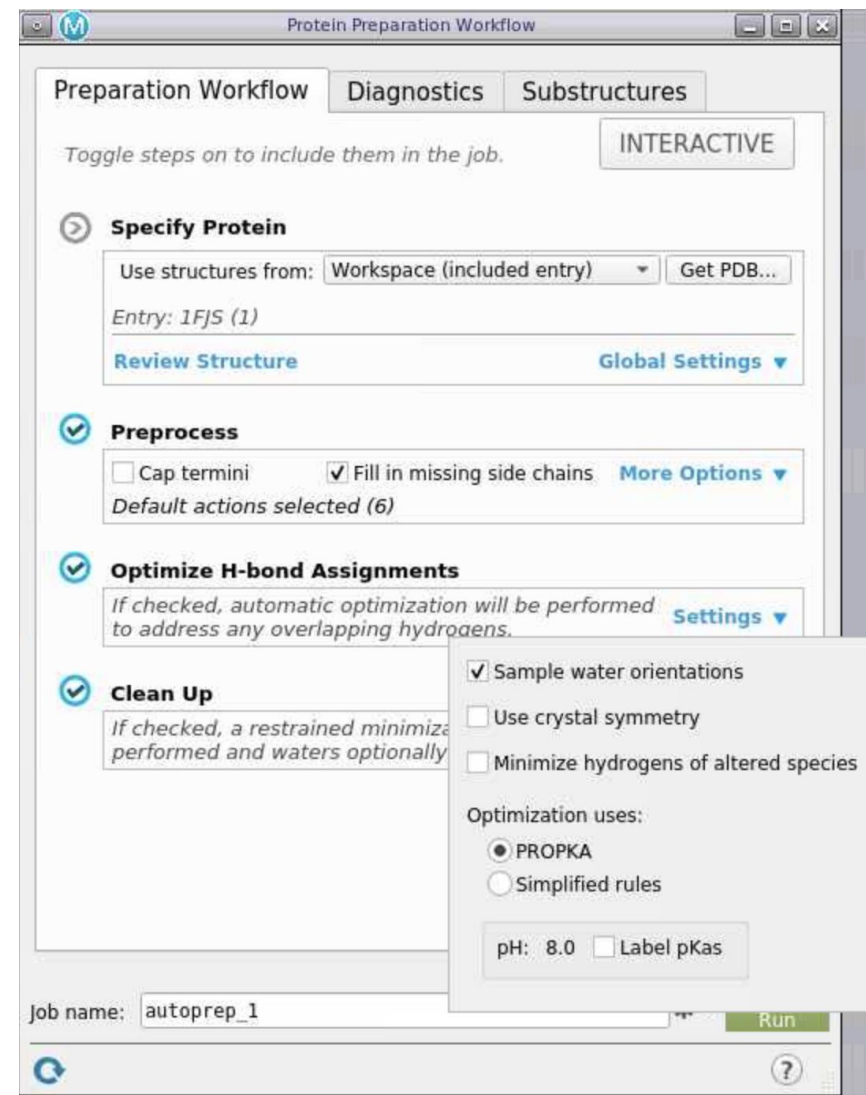


# Protein Preparation Workflow

## Preparation Workflow Tab

### Optimize H-bond Assignment step:

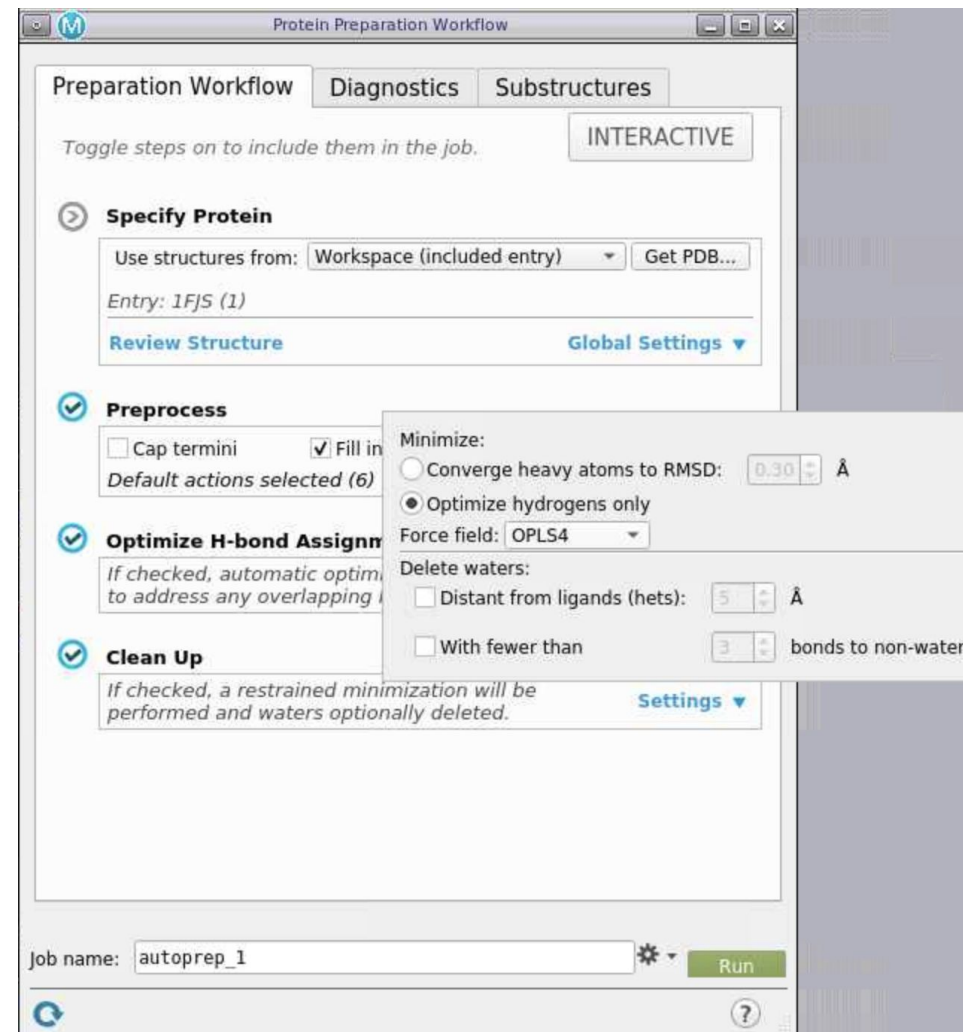
- Use crystal symmetry: important when part of structure is present in the asymmetric unit
- Minimize hydrogens of altered species (only)
- Two options for pH
  - PROPKA
  - simplified rules
- very low: protonate ASU, GLU, HIS
- low: protonate HIS
- neutral: normal biological state
- high: deprotonate cystines



# Protein Preparation Workflow

## Preparation Workflow Tab

- **Clean Up step:** Perform a restrained minimization on the structure and delete classes of water molecules. By default, all atoms are minimized, and only the waters near het groups are kept.
- **Minimize:** to relieve any strain and fine-tune the placement of various groups
  - optimize hydrogens only: allows some movement of the heavy atoms and will result in some deviation from the input structure
- **Forcefield:**
  - OPLS4: latest forcefield since 2021-1 release
- **Delete waters:** For applications such as docking, where retaining the volume of the binding site can be important, you might want to remove waters after performing the restrained minimization, rather than before, as the minimization without waters can cause the binding site to shrink, and therefore not allow larger ligands to dock.



# Protein Preparation Workflow

**Substructures Tab:** allow users to select, examine, and delete ligands, metals, waters and chains

- Table of **het groups**

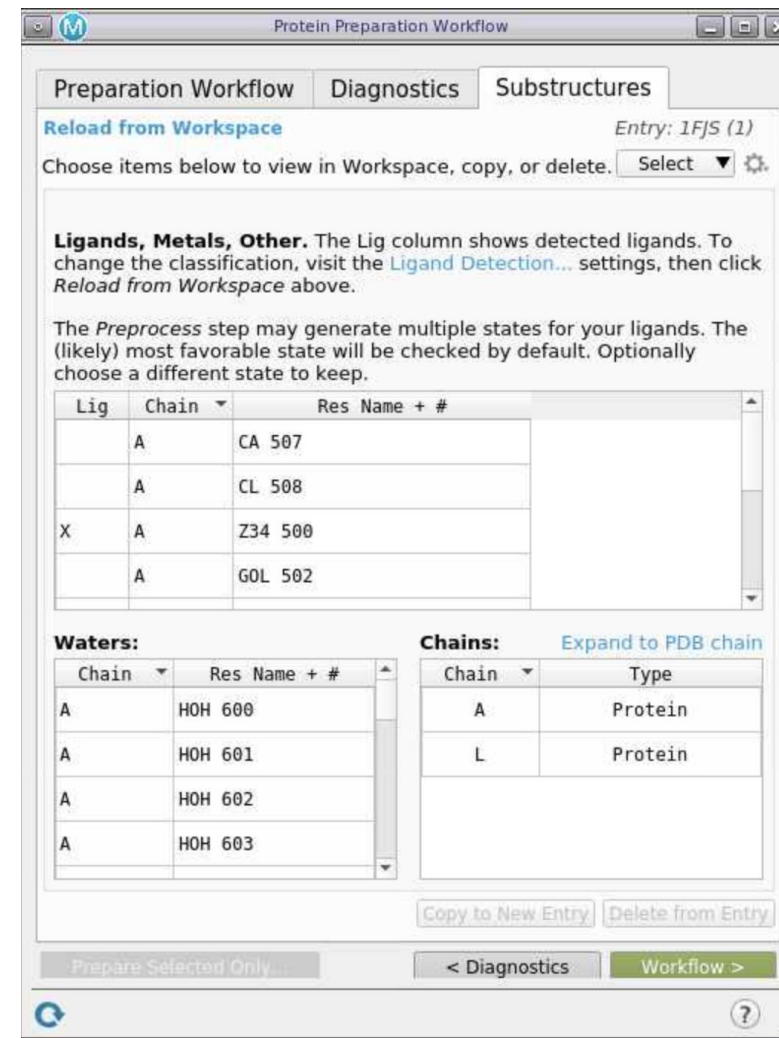
Het groups are everything that is not a water or a protein residue, and include ligands, metal ions, and cofactors.

- Table of **water molecules**

- Table of **chains**

Chains are defined by the chain label, and can include waters and het groups.

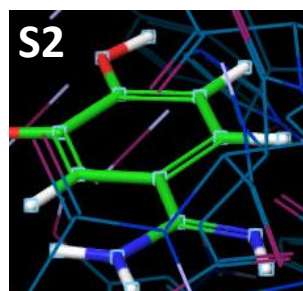
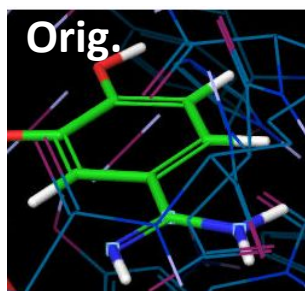
- Before inspecting the structure, it is advisable to delete unwanted parts of the structure. If the protein is a multimer and you want to simplify it, you should delete the chains for the duplicate structural units. When you delete the chains, the waters and het groups that are labeled with that chain label are also deleted.



# Protein Preparation Workflow

## Substructures Tab:

- Delete waters (bulk water, water away from binding site, ...)
- Correct the ionization and tautomeric states of listed HET groups
  - Generate States: run an epic job at the target pH range



- Display state penalty

Protein Preparation Workflow (Interactive) - 1FJS - 2-preprocessed

Preparation Workflow | Diagnostics | **Substructures**

[Reload from Workspace](#) Entry: 1FJS - 2-preprocessed (4)

Choose items below to view in Workspace, copy, or delete. [Select](#) [Settings](#)

**Ligands, Metals, Other.** The Lig column shows detected ligands. To change the classification, visit the [Ligand Detection...](#) settings, then click [Reload from Workspace](#) above.

The Preprocess step may generate multiple states for your ligands. The (likely) most favorable state will be checked by default. Optionally choose a different state to keep.

Lig	Chain	Res Name + #	S1	S2	S3	S4
	A	CL 508	<input checked="" type="checkbox"/>			
X	A	Z34 500	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	A	CA 507	<input checked="" type="checkbox"/>			
	A	GOL 502				

**Waters:**

Chain	Res Name + #
A	HOH 612
A	HOH 613
A	HOH 614
A	HOH 615

**Chains:** [Expand to PDB chain](#)

Chain	Type
A	Protein

1 item selected [Clear](#) [Copy to New Entry](#) [Delete from Entry](#)

[Prepare Selected Only...](#) [< Diagnostics](#) [Workflow >](#)

State penalty: 1.50 kcal/mol; H-Bond count: 0; Q: 0



# Protein Preparation Workflow

**Diagnostic Tab:** lists errors or issues found in the Workspace structure

- **Valences:**  
This tab lists atoms that have valence violations, such as missing hydrogens or the incorrect number of bonds.
- **Missing**  
This tab lists residues for which atoms are missing.
- **Overlapping**  
This tab lists pairs of atoms that are too close (bad contacts).
- **Alternates**  
This tab lists residues that have alternate positions in the input structure. Although these positions are legitimate, the protein preparation can only be done on a structure with a single set of coordinates, so you must choose one of the alternate positions for each residue.
- **Reports**

The screenshot shows the 'Protein Preparation Workflow' window with the 'Diagnostics' tab selected. The 'Check Workspace Entry' section indicates 'Entry: 1FJS (1)' and 'One issue was found. See Reports for more information about the protein.' The 'Valences' tab is active, displaying a table of steric clashes. The table has columns for 'Atoms', 'Distance', 'Min Allowed', and 'De'. The data is as follows:

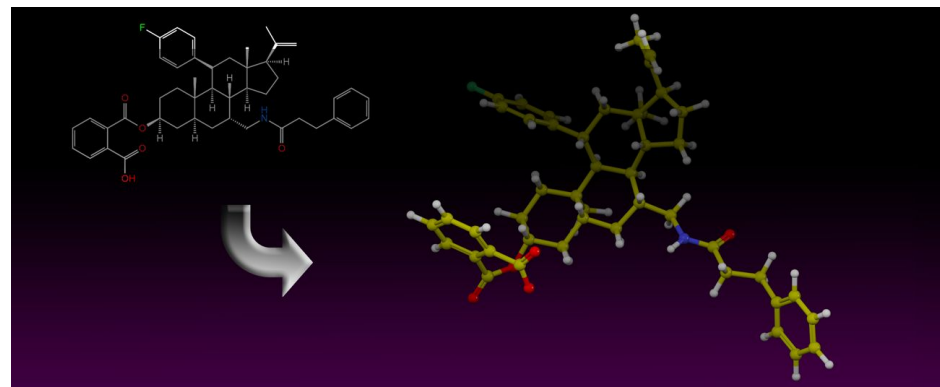
Atoms	Distance	Min Allowed	De
A:GLY 18: O - A:LYS 156: NZ	2.647	3.3	0.65
A:GLN 20: N - A:GLN 20: CD	2.823	3.42	0.59
A:CYS 22: O - A:ARG 71: NH1	2.477	3.25	0.77
A:LYS 23: CE - L:ASP 95: O *	2.772	3.4	0.62
A:LYS 23: NZ - L:ASP 97: OD1 *	2.749	3.3	0.55
A:GLY 25: N - A:ASN 117: OD1	2.526	3.2	0.67
A:CYS 27: N - A:PRO 28: CD	3.059	3.6	0.54
A:GLN 30: NE2 - A:SER 139: OG	2.626	3.35	0.72
A:ILE 34: CD1 - A:ASN 38: ND2	3.113	3.75	0.63
A:GLU 36: N - A:GLU 36: OE1	2.681	3.2	0.51
A:GLY 43: N - A:SER 195: O	2.715	3.2	0.48
A:THR 45: OG1 - A:PRO 198: CB	2.914	3.5	0.58

At the bottom of the window, there is an 'Export...' button, a checkbox for 'All reports', and a 'Structure average: N/A' label. Navigation buttons '< Workflow' and 'Substructures >' are also present.

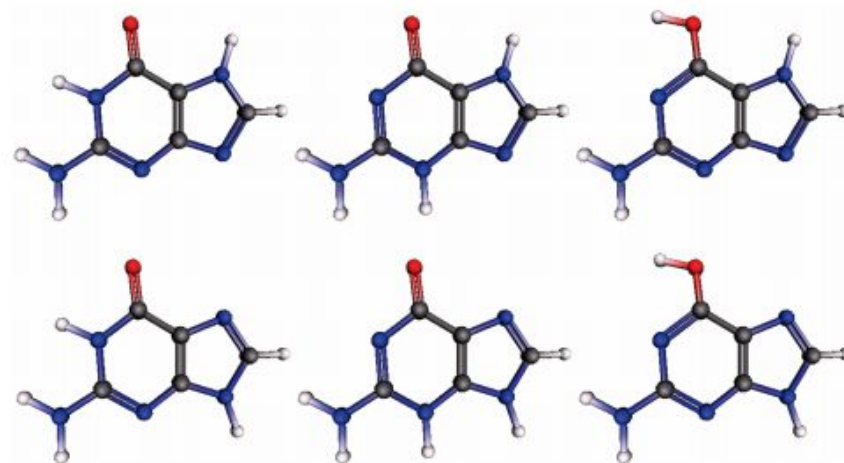
# Ligand Preparation

- Take 2D or 3D structures and produce low energy 3D structures
- Generate reasonable atomic coordinates for a ligand dataset

- tautomeric states
- ionization states
- ring conformations
- stereoisomers
- conformers



<https://www.schrodinger.com/ligprep>



Generation of multiple tautomeric forms  
of the ring system in a guanine ligand

*J. Chem. Inf. Model.* 2009, 49, 6, 1535–1546

# Ligand Preparation with LigPrep

- **Import structures:** from project, SD, SMILES format ....
- **Filter criteria:**
  - properties
  - general attributes: MW, number of atoms, ...
  - functional group counts
- **Force field**
- **Generate ionization states:**
  - Ionizer
  - Epik (recommended)
- **Desalt:** removes extra water molecule or counter ions that are present in ligand files that originate from some structure databases
- **Generate tautomers:** keto-enol, sulfur/nitrogen, histidine, DNA base tautomerization
- **Stereoisomers**

LigPrep takes about 1-2 seconds on average to process a ligand.

Result in difference in Epik State penalty (kcal/mol)

The screenshot shows the LigPrep application window. At the top, it says 'Use structures from: Workspace (1 included entry)'. Below this are fields for 'Filter criteria file' with 'Create...' and 'Browse...' buttons. The 'Force field' is set to 'OPLS3e'. Under 'Ionization', the 'Generate possible states at target pH' option is selected, with a target pH of 7.0 and a range of +/- 2.0. There are also checkboxes for 'Add metal binding states' and 'Include original state'. The 'Using' section has 'Ionizer' and 'Epik' options, with 'Epik' selected. Below this are checkboxes for 'Desalt' (checked) and 'Generate tautomers' (checked). The 'Stereoisomers' section has a 'Computation' area with three radio buttons: 'Retain specified chiralities (vary other chiral centers)' (selected), 'Determine chiralities from 3D structure', and 'Generate all combinations'. There is a 'Generate at most' field set to 32 per ligand, and a checkbox for 'For SD V2000 input, generate enantiomers if the chiral flag is 0'. The 'Output format' has 'Maestro' (selected) and 'SDF' options. At the bottom, there is a 'Job name' field set to 'ligprep\_1', a 'Run' button, and a status bar showing 'Host=ada-cpu-48, Incorporate=Append new entries as a new group'.

# Hands-on Session 1

## Structure Visualization and Preparation with Maestro

1. Creating Projects and Importing Structures
2. Preparing Protein Structures (**Protein Preparation Workflow**)
3. Preparing Ligand Structures (**LigPrep**)
4. Visualizing Protein-Ligand Complexes (configuration bar, Ligand Interaction Diagram)

Download tutorial from /scratch/training/glide\_docking/ on Grace

# Steps of structure based virtual screening

explore poses of  
ligand in the  
binding site

**Docking**

- Rigid receptor docking
- Induced fit docking
- Covalent docking
- ...

quantify the poses  
with a function

**Scoring**

- Docking Score
- Glide Score
- Emodel
- ...

improve poses  
and select  
compounds

**Refining**

- RMSD
- Enrichment
- Receiver operator characteristic plots
- ...

<https://www.schrodinger.com/webinars/archives/1248/virtual-screening/469153>

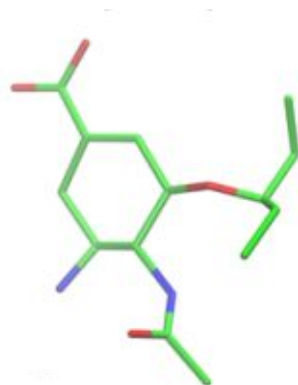
<https://www.schrodinger.com/>



# Docking fits ligands to a rigid receptor in a pose

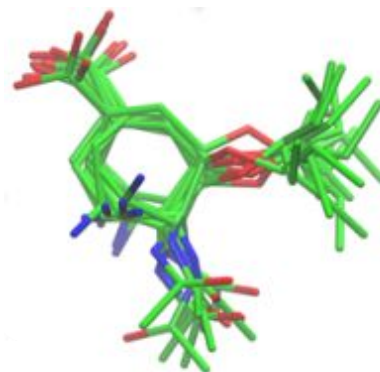
## Docking

Search for the best-scoring binding pose for a given ligand  
Rigid receptor docking with Glide HTVS, SP, XP  
Receptor is rigid  
Ligand is flexible



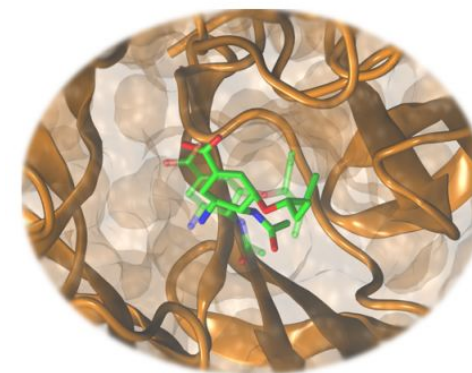
prepared  
ligand

Ligand sampling



collection of ligand  
conformations

docking



ensemble of  
receptor-ligand poses

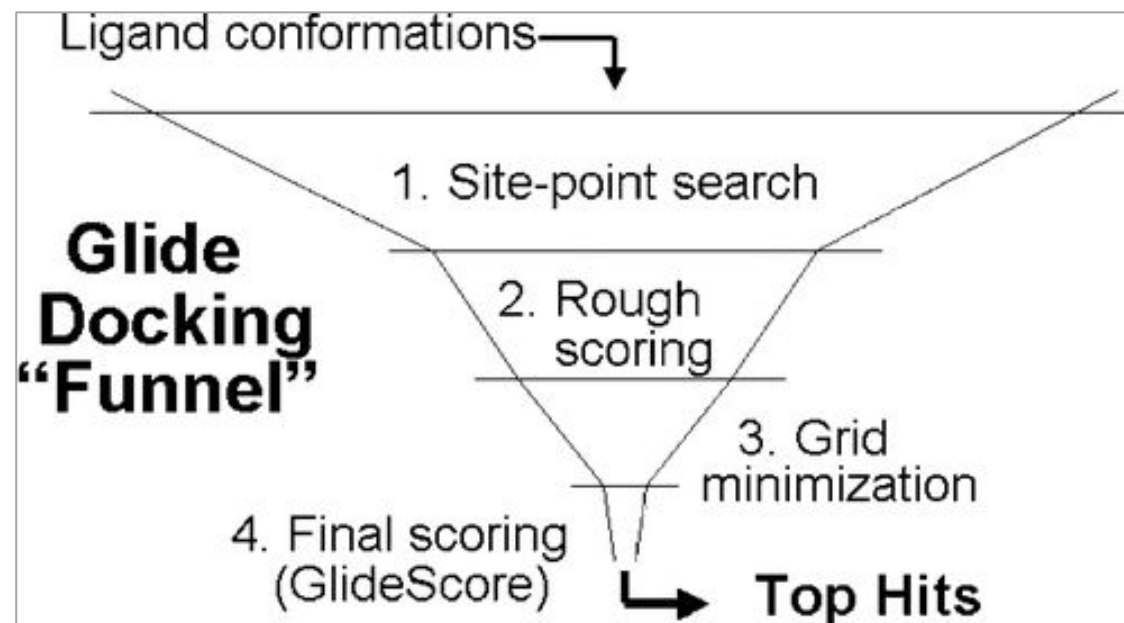
Figures from *J. Chem. Inf. Model.* 2013, 53, 11, 3097–3112

<https://www.schrodinger.com/>

# Ligand Docking

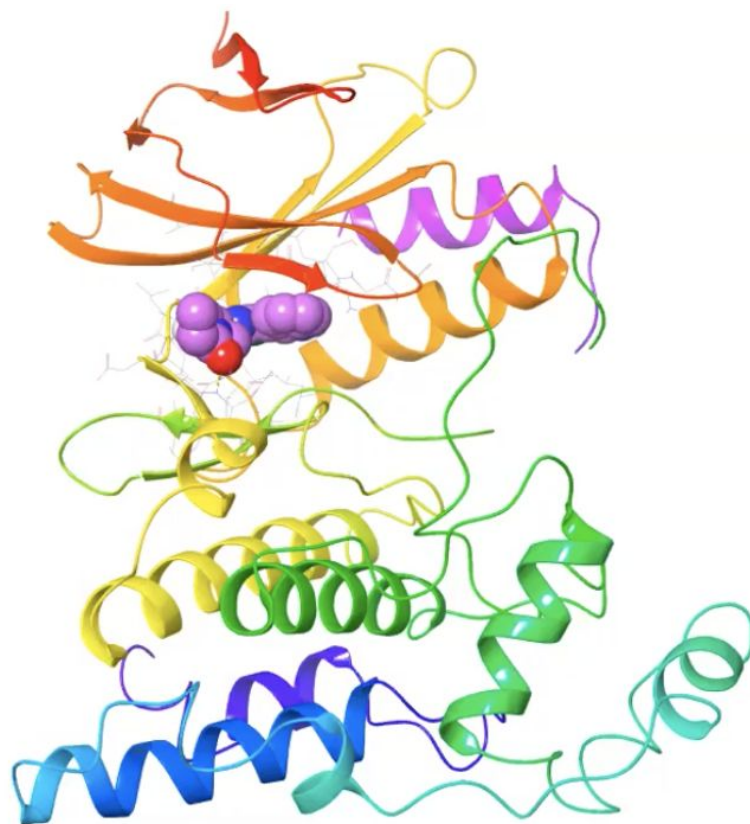
- Procedure
  - Prepare the protein
    - Missing atoms/side chains
    - Protonation state
    - Flexible side chains
  - Prepare the ligand
    - Protonation state
  - Create a docking grid
    - Specify where to dock the ligand
  - Dock the ligand(s)
  - Scoring
  - Refinement

- Glide docking hierarchy

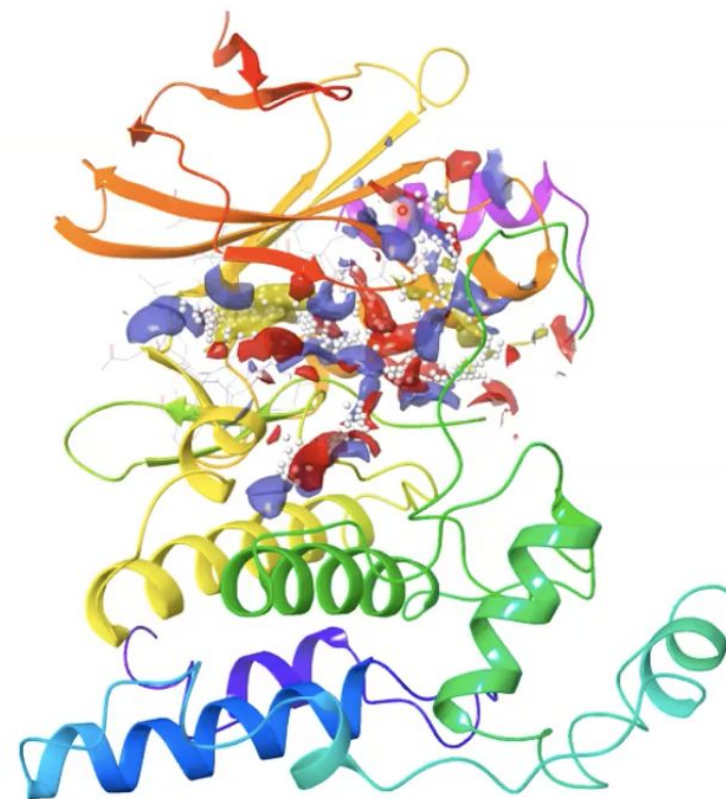


Glide docking "funnel", showing the Glide docking hierarchy.

# Binding Site



Crystallized Ligand



SiteMap

Figure from <https://www.schrodinger.com>

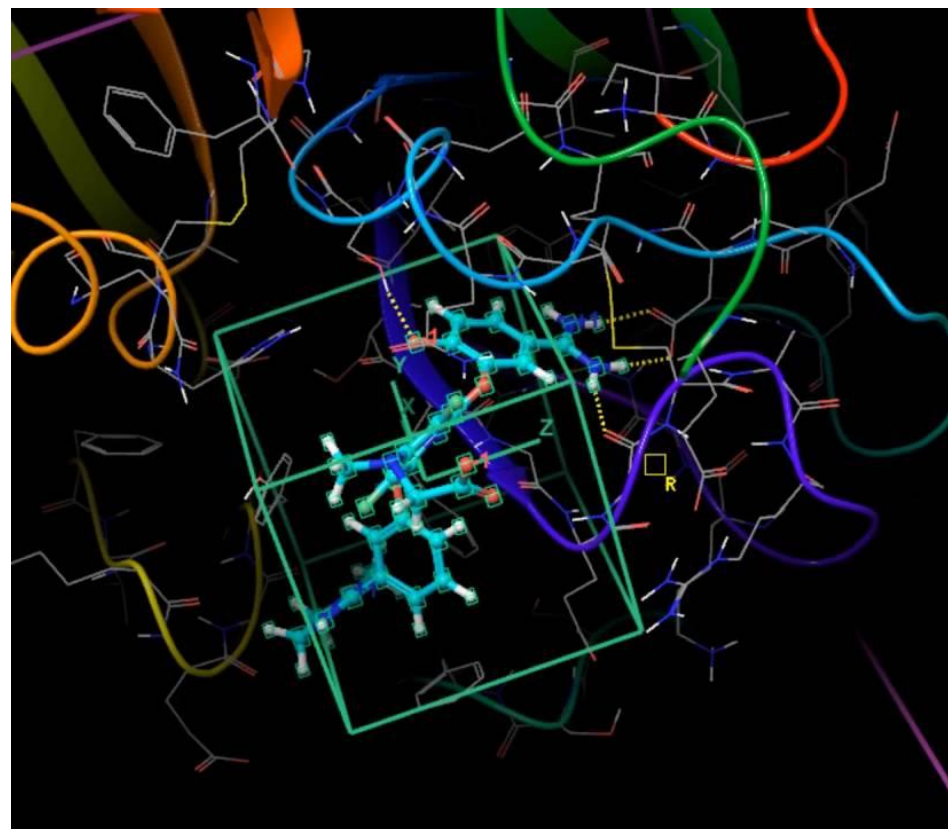
# Binding Pocket – Grid Generation

- Binding Pocket Grid

- Bounding box where docking is performed
- Too small
  - ligands won't dock
  - miss good ligands
- Too big
  - increase computational cost substantially
  - miss good binding poses

- Is the binding pocket rigid or flexible?

- Molecular dynamics simulations can be used to investigate the stability of the binding pocket



# Steps of structure based virtual screening



A scoring function very **roughly** approximates the **binding affinity** of a ligand to a protein given a binding pose.

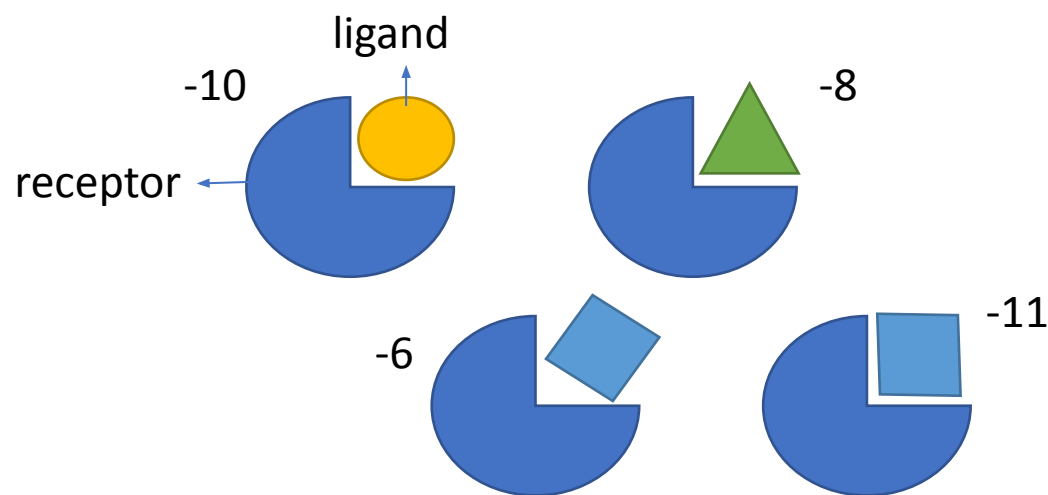


Illustration of binding pose ensembles

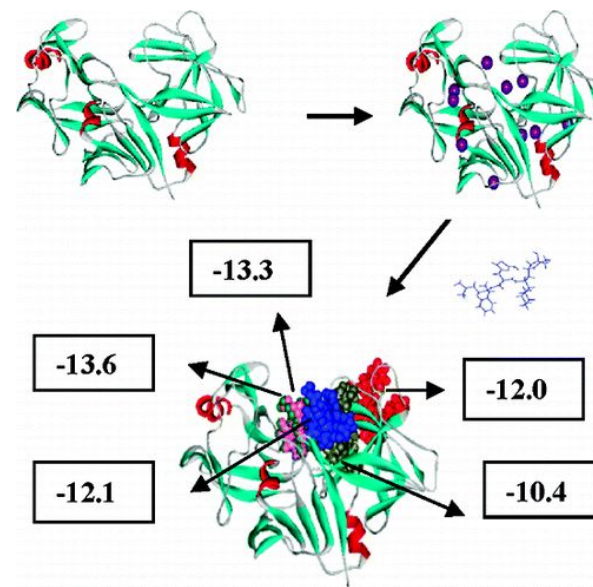


Figure from *J. Chem. Inf. Model.* 2011, 51, 10, 2515–2527



# Scoring evaluates the ligand pose



- Do not correlate with  $IC_{50}$ ,  $K_d$ ,  $EC_{50}$ , etc
- More negative the score, the better
- Are optimized to give good enrichment
  - Separate good from bad ligands
  - Limit the number of ligands that need to be investigated further

<https://www.schrodinger.com/webinars/archives/1248/virtual-screening/469153>

# GlideScore and Emodel

- Glidescore

rank-order compounds to separate compounds that bind strongly (actives) from those that don't (inactives)

Scoring Function	Computing Time	When to Use
SP	5 – 20 sec/molecule	<u>First pass</u> virtual screening on large databases/hit generation
XP	3-5 min/molecule	<u>Refinement</u> of a smaller dataset for lead optimization

- SP seeks to minimize false negatives while XP seeks to minimize false positives
- The XP scoring function includes more stringent terms for modeling desolvation, hydrophobic effects, and charged interactions

- Emodel

- primarily defined by protein-ligand coulomb-vdW energy with a small contribution from GlideScore
- Choose the best-docked structure for each ligand

J. Med. Chem. 2004, 47, 1739-49.

# Glide Docking SP

$$\text{GScore} = 0.05 * \text{vdW} + 0.15 * \text{Coul} + \text{Lipo} + \text{Hbond} + \text{Metal} + \text{Rewards} + \text{RotB} + \text{Site}$$

Components	Description
VdW	Van der Waals energy. This term is calculated with reduced net ionic charges on groups with formal charges, such as metals, carboxylates, and guanidiniums.
Coul	Coulomb energy. This term is calculated with reduced net ionic charges on groups with formal charges, such as metals, carboxylates, and guanidiniums.
Lipo	Lipophilic term, which is a pairwise term in SP but is derived from the hydrophobic grid potential for XP. Rewards favorable hydrophobic interactions.
HBond	Hydrogen-bonding term. This term is separated into differently weighted components that depend on whether the donor and acceptor are neutral, one is neutral and the other is charged, or both are charged.
Metal	Metal-binding term. Only the interactions with anionic or highly polar acceptor atoms are included. If the net metal charge in the apo protein is positive, the preference for anionic or polar ligands is included; if the net charge is zero, the preference is suppressed.
Rewards	Rewards and penalties for various features, such as buried polar groups, hydrophobic enclosure, correlated hydrogen bonds, amide twists, and so on. This category covers all terms other than those explicitly mentioned.
RotB	Penalty for freezing rotatable bonds.
Site	Polar interactions in the active site. Polar but non-hydrogen-bonding atoms in a hydrophobic region are rewarded.

# Glide Docking XP (Extra Precision)

- Increase computational cost
- Glide SP with additional Extra Precision terms
- Locate regions where water molecules have unfavorable chemical potentials and occupy these regions with suitable ligand groups that provide exceptional gains in potency with a relatively small number of atoms
- Anchor fragments of the docked ligand, typically rings, are chosen from the set of SP poses and the molecule is re-grown bond by bond from these anchor positions
- Includes improvements to the scoring of hydrogen bonds as well as detection of buried polar groups, and detection of pi-cation and pi-pi stacking interactions

# Glide Docking XP

XP Visualizer

Open... File: user/karen890/maestro/factorXa\_xp\_refine\_pv.maegz Receptor: xp\_rcpt\_frag\_1fjs\_prep\_recep\_45135

Fit to Ligand Display: ☒ Selected ligands ☐ XP Waters ☐ Hydrophobic/philic map ☒ Similarities ☐ Relative Scores

Ligands: ( 10 total, 10 shown, 1 selected ) ☒ Narrow columns Set Column Order... ☒ Conditional coloring Edit...

Name	GScor	DockS	Lipoph	PhobE	PhobE	PhobE	HBond	Electr	Sitema	$\pi$ Cat	ClBr	LowM	Penalt	HBPer	Expos	RotPe	EpikSt	Zpotr	Similar	Activity
16088	-11.9	-11.9	-5.5	-0.9	0.0	0.0	-2.9	-2.3	-0.3	0.0	0.0	-0.2	0.0	0.0	0.0	0.2	0.0	--	1.0	-11.9
15650	-11.1	-11.1	-7.0	-1.0	0.0	0.0	-0.9	-2.1	-0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	--	0.1	-11.1
1167	-10.2	-10.2	-4.8	-0.2	0.0	0.0	-2.5	-2.3	-0.3	0.0	0.0	-0.2	0.0	0.0	0.0	0.2	0.0	--	0.5	-10.2
15722	-10.0	-10.0	-5.4	-0.7	0.0	0.0	-1.8	-2.3	-0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.0	--	0.4	-10.0
689972	-9.9	-9.9	-5.2	-0.4	0.0	0.0	-2.4	-1.0	0.0	-1.9	0.0	0.0	0.0	0.0	0.7	0.3	0.0	--	0.1	-9.9
612278	-7.1	-7.1	-5.3	-0.2	0.0	0.0	-1.0	-0.4	-0.1	0.0	0.0	-0.3	0.0	0.0	0.1	0.1	0.0	--	0.1	-7.1
494088	-6.5	-6.5	-3.3	-0.8	0.0	0.0	-1.3	-0.5	-0.4	0.0	0.0	-0.5	0.0	0.0	0.0	0.3	0.0	--	0.1	-6.5
334669	-6.1	-6.1	-4.8	0.0	0.0	0.0	-0.6	-0.3	-0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	--	0.1	-6.1
620317	-5.5	-5.5	-4.6	0.0	0.0	0.0	-0.4	-0.2	0.0	0.0	0.0	-0.5	0.0	0.0	0.1	0.2	0.0	--	0.1	-5.5
151943	-5.1	-5.1	-4.6	0.0	0.0	0.0	-0.7	-0.3	0.0	0.0	0.0	-0.4	0.0	0.0	0.6	0.2	0.0	--	0.1	-5.1

Show: All Selected Only Export Data... Export Structures...

Reset Panel...



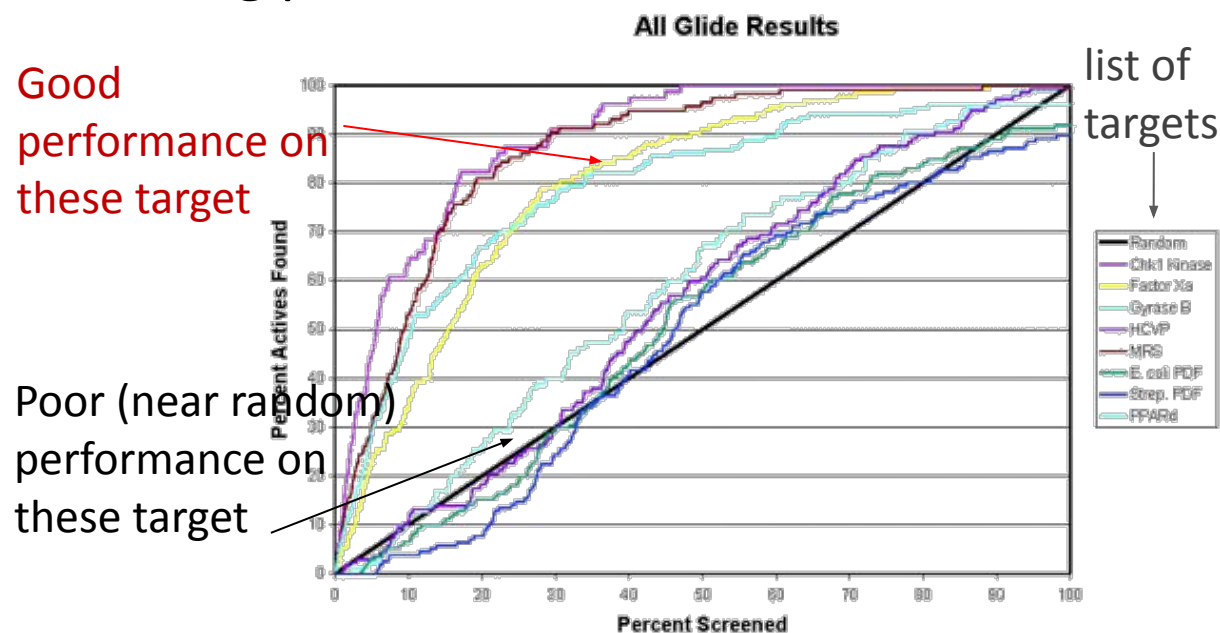
# Filtering refines the ligand evaluation

Docking

Scoring

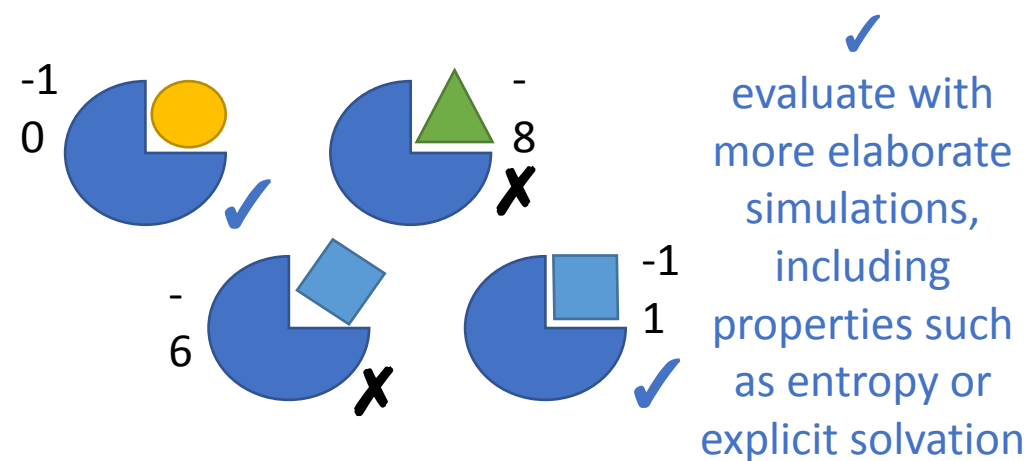
Refining

- Docking performance



J. Med. Chem. 2006, 49, 20, 5912–5931

- Screening compounds for further evaluation



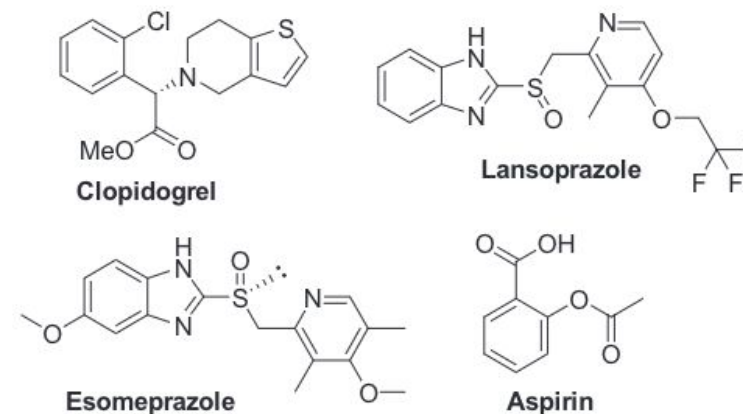
# Hands-on Session 2

## Structure-Based Virtual Screening Using Glide

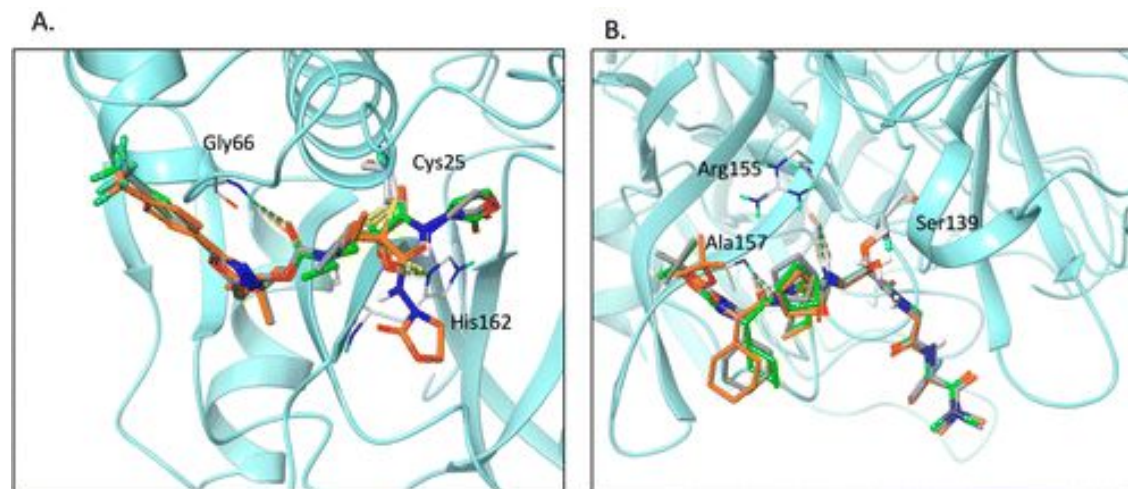
1. Virtual Screening Prerequisites
2. Importing Structures
3. Generating a Receptor Grid
4. Docking the Cognate Ligand and Screening Compounds
5. Analyzing Results and Binding-Site Characterization

# Covalent Docking

- Nearly 30% of the marketed drugs targeting enzymes known to act by covalent inhibition
- The inhibition can be either reversible or irreversible
- Covalent inhibitors derive their activity not only from the formation of a covalent bond between the target and the ligand but also from stabilizing non-covalent forces in the binding pocket



Examples of drug act through covalent mechanisms.

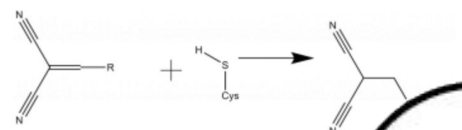
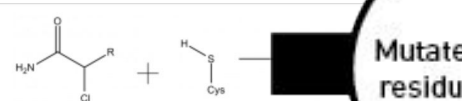
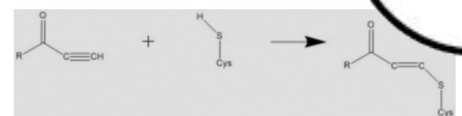
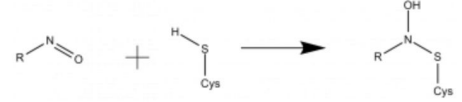
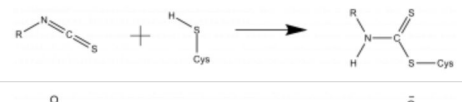
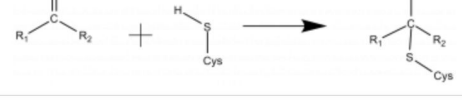
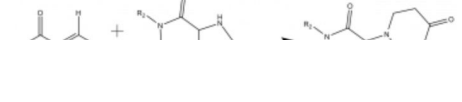


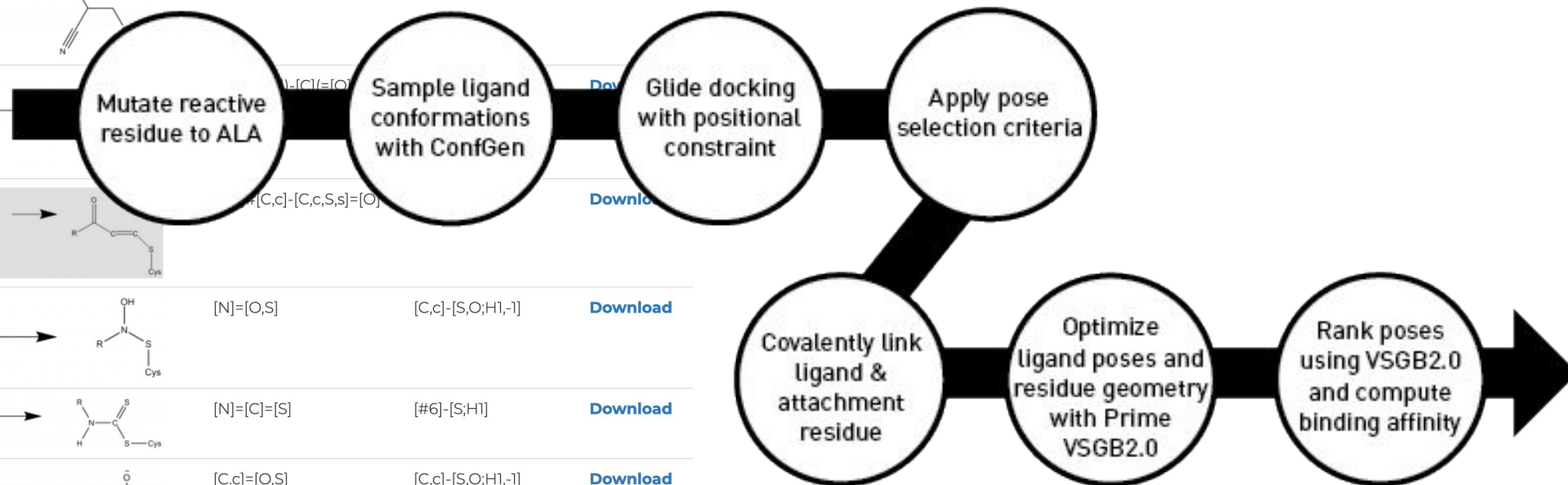
Examples of covalent complexes. A) Cathepsin K structure (PDB ID 1YT7) with the cocrystal ligand, B) HCV NS3 protease structure (PDB ID 2F9U) with the cocrystal ligand.

*Eur. J. Med. Chem.* **138**, 96–114 (2017).  
*J. Chem. Inf. Model.* 2014, 54, 1941–1950

# Covalent Docking

Custom Covalent Reactions

Index	Reaction	Ligand SMARTS	Receptor SMARTS	CDOCK File
1		<chem>[C,c]=[C,c]-[C,c]#[N,n]</chem>	<chem>[C]-[S,O;H1,-1]</chem>	<a href="#">Download</a>
2		<chem>[C,c]=[O]</chem>	<chem>[C,c]-[S,O;H1,-1]</chem>	<a href="#">Download</a>
3		<chem>[C,c]-[C,c,S,s]=[O]</chem>	<chem>[C,c]-[S,O;H1,-1]</chem>	<a href="#">Download</a>
4		<chem>[N]=[O,S]</chem>	<chem>[C,c]-[S,O;H1,-1]</chem>	<a href="#">Download</a>
5		<chem>[N]=[C]=[S]</chem>	<chem>[#6]-[S;H1]</chem>	<a href="#">Download</a>
6		<chem>[C,c]=[O,S]</chem>	<chem>[C,c]-[S,O;H1,-1]</chem>	<a href="#">Download</a>
7		<chem>[C]=[C]-[C]=[O]</chem>	<chem>[C](=[O])-[C]-[C]</chem>	<a href="#">Download</a>



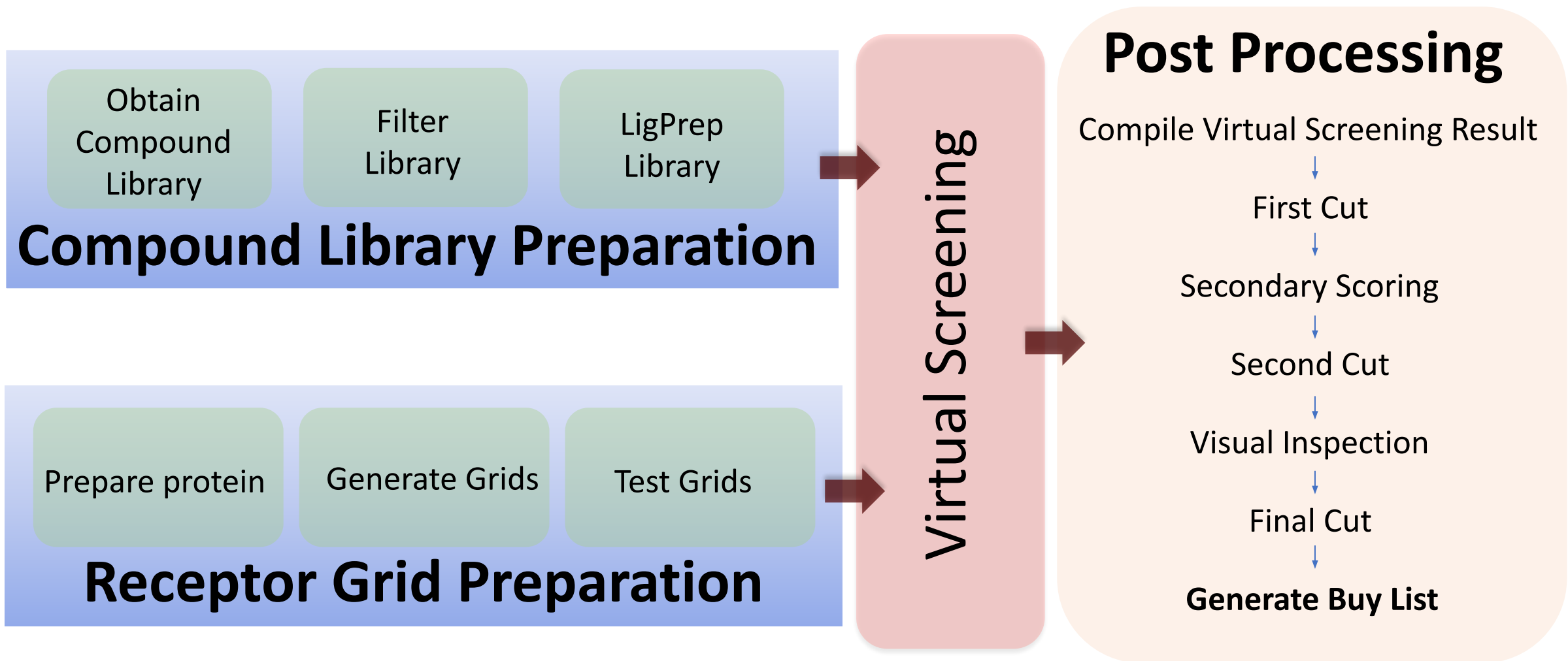
<https://www.schrodinger.com/newsletters/introducing-covdock-covalent-docking>

# CovDock Uses Glide & Prime

- Main steps
  - Conventional non-covalent docking of pre-reactive species (**Glide**)
  - Formation of covalent attachment (via a number of different mechanisms)
  - Structural refinement of the covalent complex (**Prime**)
- Output: **cdock affinity, prime energy, ligand reaction site**
- Speed
  - Pose selection (default) protocol: 1~2 hour per ligand
  - Virtual screening protocol: 10x faster than default protocol
- Challenges for covalent docking
  - Bond formation, bond cleavage and bond rearrangements all require an explicit treatment of electronic degrees of freedom and, hence, a quantum mechanics (QM) approach.



# Drug Docking with Schrodinger: wrap-up



# Running Schrodinger on HPRC

## Schrödinger is a restricted software.

Usage of this software is restricted to subscribers of the [Laboratory for Molecular Simulation \(LMS\)](#).

Running Schrodinger on Grace and Terra, please refer to: <https://hprc.tamu.edu/wiki/SW:Schrodinger>.

More about the Schrodinger: [documentation](#), [training](#)

## The LMS also holds license for:

- Discovery Studio
- MOE
- Amber
- Material Studio
- Gaussian
- ADF
- Molpro
- Chemissian
- NBO
- AIMALL Professional

# Need Help? Contact the HPRC Helpdesk

Website: [hprc.tamu.edu](https://hprc.tamu.edu)

Email: [help@hprc.tamu.edu](mailto:help@hprc.tamu.edu)

Telephone: (979) 845-0219

## Help us, help you -- we need more info

- Which Cluster (Terra, Grace)
- NetID (NOT your UIN)
- Job id(s) if any
- Location of your jobfile, input/output files
- Application used if any
- Module(s) loaded if any
- Error messages
- Steps you have taken, so we can reproduce the problem