

P38 Example for Docking and Combinatorial  
Library generation  
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**SCHRÖDINGER**

## Overview



All data for this tutorial is located on your machine in the directory **schrodinger**. The following targets will be used as illustrative examples:

- P38 MAP kinase (1kv1) for Protein preparation and virtual combinatorial screening.
- Chemical feature analysis of CombiGlide library
- HIV Reverse transcriptase for Core Hopping (no hands on)
- ITK for Shape based screening
- Factor Xa to use the *XP Visualizer* for detailed docking pose analysis

## Protein Preparation

Our Applications are using the OPLS all atom force field. Therefore it is very important to prepare proteins and ligands, so that atoms and bonds are chemically meaningful<sup>1</sup>. For complexes this is done with the *Protein Preparation Wizard*:


1. In a terminal open *Maestro* with the command  
  

```
maestro &
```
2. If you are not already in the **schrodinger** directory, go there using the main menu *Maestro > Change Directory...*
3. Import (, CNTRL-i) the P38 structure **1kv1.pdb**: In the Import panel you have to choose *Format: PDB* to be able to see the file in the *Files* field.
4. To save your project click the toolbar icon  and enter e.g. P38
5. Prepare the PDB structure with the protein preparation wizard: In the *Workflows* menu in the main window, go to *Protein Preparation Wizard*.
6. To assign bond orders, add hydrogens and delete waters click *Setup*
7. Generate protonation states for the ligand: Click the *Generate states* button. Epik (Hammett and Taft method) will be used to generate protonation states. After the calculation is done you can display the different states using the switches below the S1, S2 column. Choose the state

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<sup>1</sup>A detailed tutorial is available via *Help > Manuals...* A pdf document opens and there click in the **General** section on *Protein Preparation Guide*

which fits better to the receptor environment and which has the lower state penalty<sup>2</sup>. Choose the S1 state here.

8. Optimise the hydrogen bond network: Click *Optimize...* The green job submission panel appears: Start the job by clicking *Start*. After a moment, the Monitor panel is displayed. The job starts.
9. Finally to relax the hydrogens you should do a OPLS force field minimization using the *Minimize...* button, but to save time we just import (, CNTRL-i) the prepared P38 complex **1kv1-prep.mae**
10. Zoom into the structure (press middle and right mouse button): The ligand is displayed in tubes.


## Virtual Combinatorial Screening

To run CombiGlide, you must supply a molecule that contains the core structure. This molecule must be an all-atom, 3D structure that has a reasonable representation of the experimental geometry of the core structure. Ordinarily you would have to build or obtain this structure and minimize it using MacroModel or LigPrep, for example. For this tutorial, the core, which is the ligand from our previous P38 example has already been built and minimized, and you only need to import it.

1. Import (, CNTRL-i) the file **core.tutorial.mae**
2. In the main menu open the CombiGlide Quick Start Guide using *Help > Manuals...* and do section *2.4 Defining the Reagent Combinations*.

We skip to combinatorial dock the prepared core, because takes much more time to run.


## Chemical Feature Analysis

1. The project **Tutorial.prj** contains the CombiGlide results from the previous setup. Open it with the Project import button(, CNTRL-o)
2. Open the Combinatorial Screening wizzard with *Applications > CombiGlide > Combinatorial Screening...* and in the panel go to the last step *Analyze Library* Choosing *Chemical Features...* the panel for chemical feature analysis opens. You can now compare chemical features on the input reagents with the generated library. A detailed explanation of the tools you will find at p 22 in section *3.1 Chemical Features* in the *CombiGlide Quick Start Guide*.

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<sup>2</sup>The state penalty is based on the Boltzmann factors of the populations - see the Epik User Manual, section 4.2 for details

## Shape based screening

1. We will screen here a Phase database of ligands for the shape of an ITK inhibitor. Import (, CNTRL-i) the ITK inhibitor `itk.mae`
2. In the main menu go to *Scripts > Shape-based Screening...* and check that *Use template/shape from: Workspace* is choosen.
3. At *Screen file or Phase DB* browse to `PHASE/PhaseDB/phaseDB_phasedb`
4. This pregenerated Database already contains conformers. So you should switch off the button *Generate conformers*.
5. Start the job by clicking *Start*.
6. In the green start panel choose *Incorporate: Append new entries*
7. When the job is completed you could use the ePlayer in the Project table to display the compounds aligned to the ITK ligand.

## Build a pharmacophore

This is an optional exercise.

1. Include and select the ITK ligand in the workspace, by clicking on the *In* checkbox on the entry which contains the previously imported ligand.
2. In the main menu go to *Applications > Phase > Hypothesis Table...*
3. In the Table click *New...* and choose in the pop up window the the offered row of the selected entry.
4. The New Hypothesis panel opens, select the Ligand Sites you would like to use for a pharmacophore and confirm with *OK*.

## Search your pharmacophore in a Phase database

1. In the main menu go to *Applications > Phase > Manage 3D Database...* Click on Open Existing Database and browse to  
  
`PHASE/PhaseDB/phaseDB_phasedb`
2. Go to *Applications > Phase > Find Matches to Hypothesis...* In the Find Matches to Hypothesis panel use conformers which are already in the database by switch on the *Use existing conformers* switch.

## Glide XP Visualizer

You can use the Glide XP Visualizer to examine the contributions of various terms to the XP scoring function. The terms are given a spatial representation that you can display together with the ligand and the receptor.

1. From *Applications > Glide > XP Visualizer...* the XP Visualizer panel opens
2. Open `refine_xp.xpdes` in the file selector. Further details you will find in the *Glide Quick Start Guide: 4.5 Visualizing Glide XP Descriptors*