# CombiGlide 3.7

## Quick Start Guide

Schrödinger Press

May 2015

# Contents

# Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

| Font | Example | Use |
|---|---|---|
| Sans serif | Project Table | Names of GUI features, such as panels, menus, menu items, buttons, and labels |
| Monospace | `$SCHRODINGER/maestro` | File names, directory names, commands, environment variables, command input and output |
| Italic | *filename* | Text that the user must replace with a value |
| Sans serif uppercase | CTRL+H | Keyboard keys |

Links to other locations in the current document or to other PDF documents are colored like this: Document Conventions.

In descriptions of command syntax, the following UNIX conventions are used: braces { } enclose a choice of required items, square brackets [ ] enclose optional items, and the bar symbol | separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

File name, path, and environment variable syntax is generally given with the UNIX conventions. To obtain the Windows conventions, replace the forward slash / with the backslash \ in path or directory names, and replace the $ at the beginning of an environment variable with a % at each end. For example, `$SCHRODINGER/maestro` becomes `%SCHRODINGER%\maestro`.

Keyboard references are given in the Windows convention by default, with Mac equivalents in parentheses, for example CTRL+H (⌘H). Where Mac equivalents are not given, COMMAND should be read in place of CTRL. The convention CTRL-H is not used.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

# Overview

CombiGlide employs combinatorial technology for lead identification and optimization. It presents two distinct workflows:

1. The Virtual Combinatorial Screening workflow—Use our proprietary technology to explore an extremely large combinatorial space in order to find side chains for a core chemical scaffold that will optimize binding to a receptor of interest.
2. The Enumerate and Dock workflow—Enumerate a combinatorial library; dock it, analyze and evaluate the results. This is most useful for relatively small libraries.

These can be used either as a prelude to combinatorial design or as a means of conventional lead discovery and optimization. See the *CombiGlide User Manual* for details.

Chapter 2 provides a tutorial example of the Virtual Combinatorial Screening workflow. The center of the tutorial—the docking step—takes more than an hour on a 2 GHz Pentium processor, so you should plan the resources you need for the tutorial accordingly.

Chapter 3 provides a tutorial example of the analysis of the results of a virtual combinatorial screening run in terms of the distribution of chemical features and the enrichment of actives. This examples uses files taken from a run as input, and does not use much processing time.

## 1.1 Preparing for the Exercises

To run the exercises, you need a working directory in which to store the input and output, and you need to copy the input files from the installation into your working directory. This is done automatically in the Tutorials panel, as described below. To copy the input files manually, just unzip the `combiglide` zip file from the `tutorials` directory of your installation into your working directory.

On Linux, you should first set the `SCHRODINGER` environment variable to the Schrödinger software installation directory, if it is not already set:

**csh/tcsh:** `setenv SCHRODINGER` *installation-path*

**sh/bash/ksh:** `export SCHRODINGER=`*installation-path*

If Maestro is not running, start it as follows:

- **Linux:** Enter the following command:

  ```
  $SCHRODINGER/maestro -profile Maestro &
  ```

- **Windows:** Double-click the Maestro icon on the desktop.

  You can also use Start → All Programs → Schrodinger-2015-2 → Maestro.

- **Mac:** Click the Maestro icon on the dock.

  If it is not on the dock, drag it there from the SchrodingerSuites2015-2 folder in your Applications folder, or start Maestro from that folder.

Now that Maestro is running, you can start the setup.

1. Choose Help → Tutorials.

   The Tutorials panel opens.

2. Ensure that the Show tutorials by option menu is set to Product, and the option menu below is labeled Product and set to All.

3. Select CombiGlide Quick Start Guide in the table.

4. Enter the directory that you want to use for the tutorial in the Copy to text box, or click Browse and navigate to the directory.

   If the directory does not exist, it will be created for you, on confirmation. The default is your current working directory.

5. Click Copy.

   The tutorial files are copied to the specified directory, and a progress dialog box is displayed briefly.

If you used the default directory, the files are now in your current working directory, and you can skip the next two steps. Otherwise, you should set the working directory to the place that your tutorial files were copied to.

6. Choose Project → Change Directory.

7. Navigate to the directory you specified for the tutorial files, and click OK.

You can close the Tutorials panel now, and proceed with the exercises.

## 1.2 Creating a Maestro Project

You should create a new named Maestro project to save your work, in case you want to complete the exercises at a later time. If you are using an existing Maestro session, it is advisable to create a new project to keep the tutorial separate from your other work. When you start Maestro, a scratch project is created, which must be named in order to keep it for later use.

1. Choose Project → New.

   The New Project dialog box is displayed. The Look in option menu should contain the current Maestro working directory.

2. In the File name text box, type `cg_tutorial`.

3. Click Save.

This procedure creates a project named `cg_tutorial`. The work that you do during the exercises that follow is automatically saved in this project for later use.

# Virtual Combinatorial Screening Tutorial

This chapter takes you through the use of CombiGlide for focused library design, including reagent preparation and combinatorial screening. The example used in this tutorial is a pyrazole library, which is designed to generate inhibitors of p38 MAP kinase. The synthetic approach for these compounds is described in Figure 2.1.

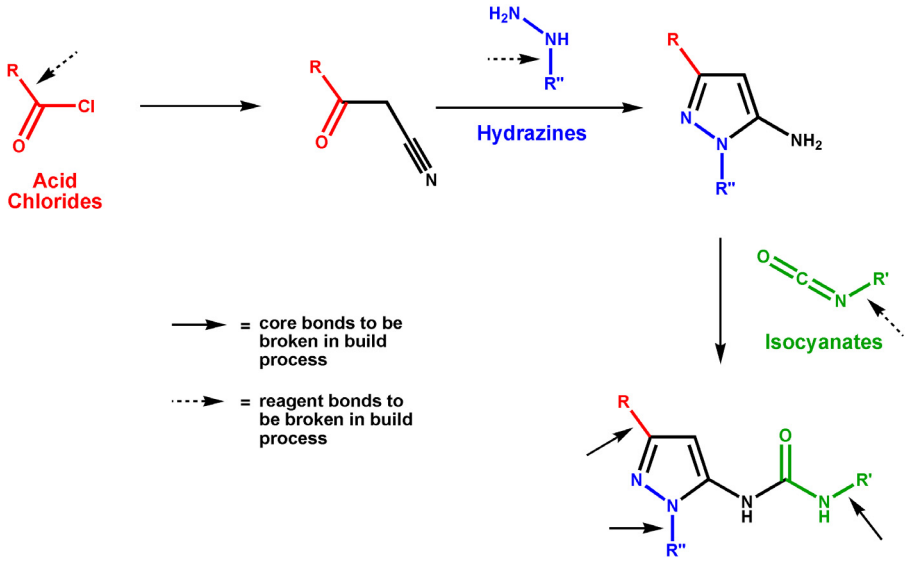



*Figure 2.1. Synthetic route to pyrazole library.*

The *core* is the structural element that is constant throughout the library. In the pyrazole example, the core is the structure given in Figure 2.2 minus the R, R', and R" groups.

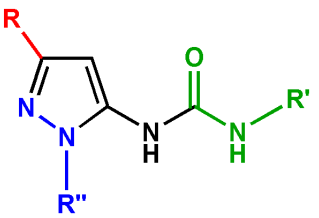



*Figure 2.2. Core structure for pyrazole library design.*

CombiGlide builds library members by adding the R, R', and R" groups from the reagents to the core structure. In the first part of the CombiGlide workflow, you provide a 3D, minimized structure of a molecule that contains this core, define the points at which the R, R', and R" groups are to be attached, and associate a set of reagents with each attachment point. You then select a receptor and set up parameters for docking with Glide. CombiGlide performs a series of docking calculations to determine a reduced set of reagents that is likely to contain the best candidates for the chosen receptor. In the final stage, you can narrow the library down to a small set, using various strategies for selection of the "best" reagents, then generate the library.

## 2.1 Preparing the Reagents

The structures of the reagents that you want to use are often 2D structures. CombiGlide converts these structures to all-atom 3D structures suitable for the docking stage of the process, using LigPrep. The information needed to identify the fragment that will be added to the core is also added during reagent preparation. In this exercise, you will prepare the three reagent files needed to evaluate the pyrazole library.

1. Choose Applications → CombiGlide → Reagent Preparation in the main window.

   The Reagent Preparation panel opens.

2. Click Browse.

   A file selector opens.

3. Select MDL SD from the Files of type option menu.

4. Select `acid_chlorides.sdf` from your working directory, and click Open.

5. Select SD property in the Create reagent titles from section and type `ReagentCode` into the text box.

   The ReagentCode property from the SD file will be used for the reagent title. Reagent titles are used for identification in CombiGlide. If you do not set unique titles, the reagent preparation procedure assigns arbitrary unique titles; however, if you use a descriptive field for the title, it will be easier to understand the output. If the descriptive field occurs multiple times, the procedure adds a suffix such as `-1`, `-2`, and so on.

6. Click the Acid_Chloride_C_C button in the Functional group to identify section.

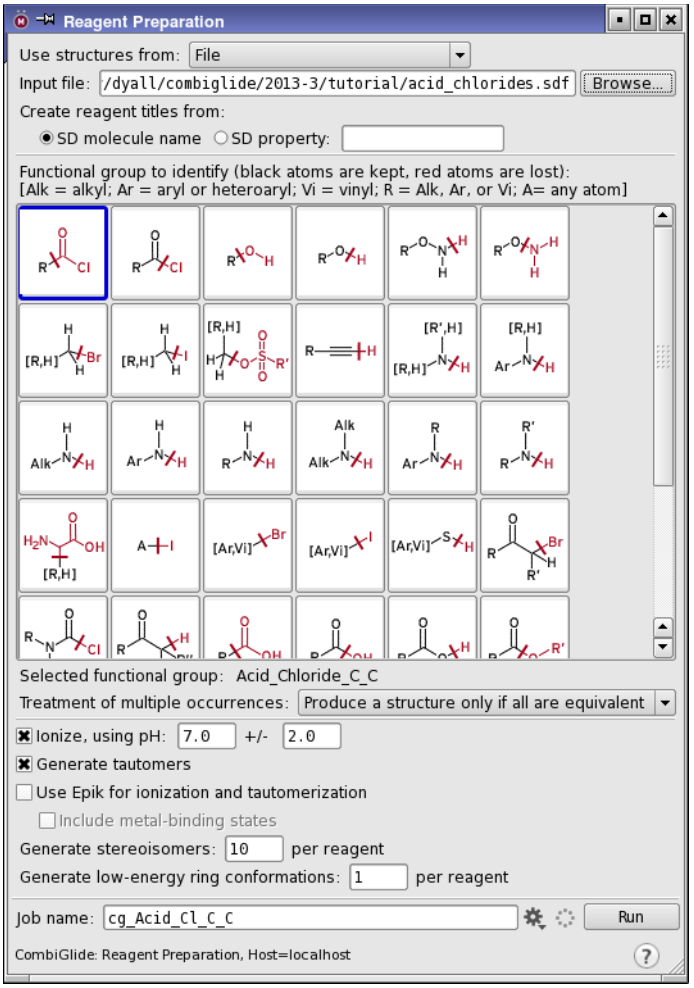



***Figure 2.3. The Reagent Preparation panel.***

Note that there is more than one copy of most functional groups. In each copy, a different bond is replaced during the build process. When you select a functional group, you are also selecting the bond that is replaced.

The name of the button, displayed in the tool tip, encodes the functional group, the fragment to be kept and the fragment to be discarded in the build process. The name of the functional group is Acid_Chloride (acid chloride). The two C's at the end of the name define the atoms on either side of the bond that is replaced in the build process: the first is the atom in the fragment that is kept, and the second is the atom in the fragment that is discarded. In this case, the C atom of the –COCl group is discarded, and the C atom of the

R group is kept. Thus, what is attached to the core is just the R group. For information on the functional group definitions, see Section 4.2.2 of the *CombiGlide User Manual*.

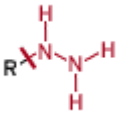
7. Click Run.

   For this exercise, you can use the default job settings. The progress of the reagent preparation process is indicated by the Jobs button in the status bar of the main window.

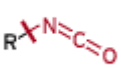
   A number of files, named `cg_acid_chlorides_Acid_Cl_C_C*`, are written to your working directory. The `cg_acid_chlorides_Acid_Cl_C_C.bld` file is the file used by CombiGlide in the build process. Do not delete any of the reagent preparation files since many of them are used later in CombiGlide.

8. Repeat the reagent preparation process (Step 2 – Step 7) for the other two reagent files:

   - With `hydrazines.sdf` use the Hydrazine_C_N functional group.

   - With `isocyanates.sdf`, use the Isocyanate_C_N functional group.

   You do not need to wait for the first reagent preparation job to finish before you start the next job.

9. Close the Reagent Preparation panel.

You have now prepared all of the necessary reagent files. One of the reagents in the isocyanates input file contains an ionizable group and thus four structures are in the output file. The other two files should have three structures each. If you want to examine any of these files, you can import them into Maestro. When you open the Import panel, choose ReagentPrep from the Files of type option menu.

## 2.2 Importing the Core-Containing Molecule

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 has already been built and minimized, and you only need to import it.

1. Click the Import button on the Project toolbar.

   The Import panel opens.

2. Ensure that Common (or Maestro) is chosen from the Files of type option menu.

3. Select `core_tutorial.mae` and click Open.

   The Import panel closes and the 3D, minimized core-containing molecule is imported into the Project Table and displayed in the Workspace.

## 2.3 Defining the Reagent Combinations

Once you have a core-containing molecule and a set of reagents, you can start the combinatorial screening process. First, you must select the core-containing molecule, and determine which bonds in this structure will be replaced in the build process for each of the reagents. These are the *attachment positions*. In the pyrazole library example, the bonds to be replaced are marked in Figure 2.4.

1. Choose Applications → CombiGlide → Combinatorial Screening in the main window.

   The Combinatorial Screening panel opens with the Define Combinations step displayed and Pick Molecule selected.

2. Pick any atom in the core-containing molecule, which is displayed in the Workspace.

   The Core Molecule Title dialog box is displayed.

3. Type in a title and click OK.

The core-containing molecule is now defined. Next, you will define the attachment positions by clicking on the atoms of the bonds to be replaced in the build process. The bonds to be replaced are designated by numbers in Figure 2.4.

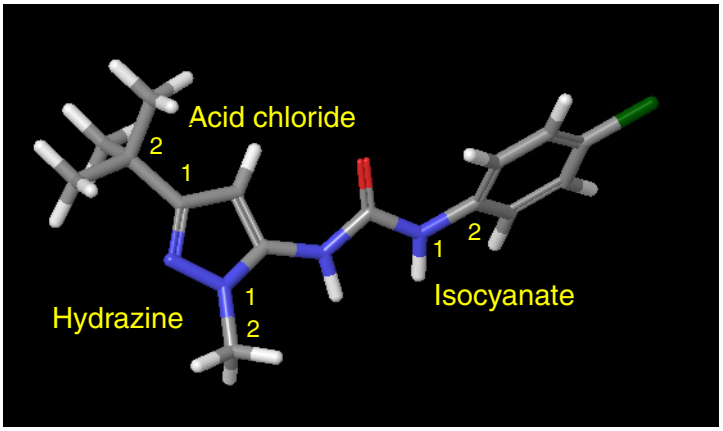



***Figure 2.4. Attachment positions for the three reagents.***

4. For the acid chloride bond, pick atom 1 then pick atom 2.

   A magenta cube appears around atom 1 when you pick it. After picking atom 2, a turquoise arrow pointing from atom 1 to atom 2 is displayed, labeled with the attachment position name, which is a number by default. The Select Reagent File panel opens.

5. Select the *reagent*`.bld` file to be associated with this attachment position and click Open.

   For the acid chloride position, this file is `cg_acid_chlorides_Acid_Cl_C_C.bld`.

   The attachment position and the reagent file name appear in the Attachments table along with the name of the functional group used to prepare the reagent file and the number of reagents in the file. (If multiple stereoisomers, ionization states, and tautomeric states were generated from the same molecule during reagent preparation, all of them are considered the same reagent and only counted once.)

   The arrow over the bond that will be replaced (the *attachment* bond) changes to a tube connecting to a sphere, colored gold, with the name associated with the position in the Attachments table still displayed. To rename the attachment, you can edit the table cell.

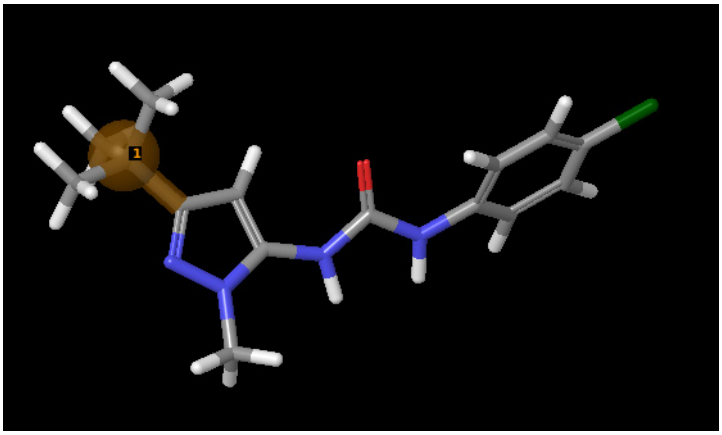



***Figure 2.5. Attachment position for the acid chlorides after adding the reagent file.***

6. Repeat the above process (Step 4 and Step 5) to define the attachments for the hydrazine and isocyanate positions.

   If you make a mistake in the attachment position, select the table row and click Delete Attachment. You can then pick the correct atoms for the attachment position. If you make a mistake in the reagent file selection, select the table row and click Browse. You can then select the correct reagent file. When you select a table row, the attachment position is marked in turquoise in the Workspace.

   The Name cells in the table can be edited. The default names are just consecutive numbers. You can consider naming the positions after the reagent libraries selected, using mnemonics such as AcCl for position 1, Hyd for position 2 and NCO for position 3. The names must be unique.

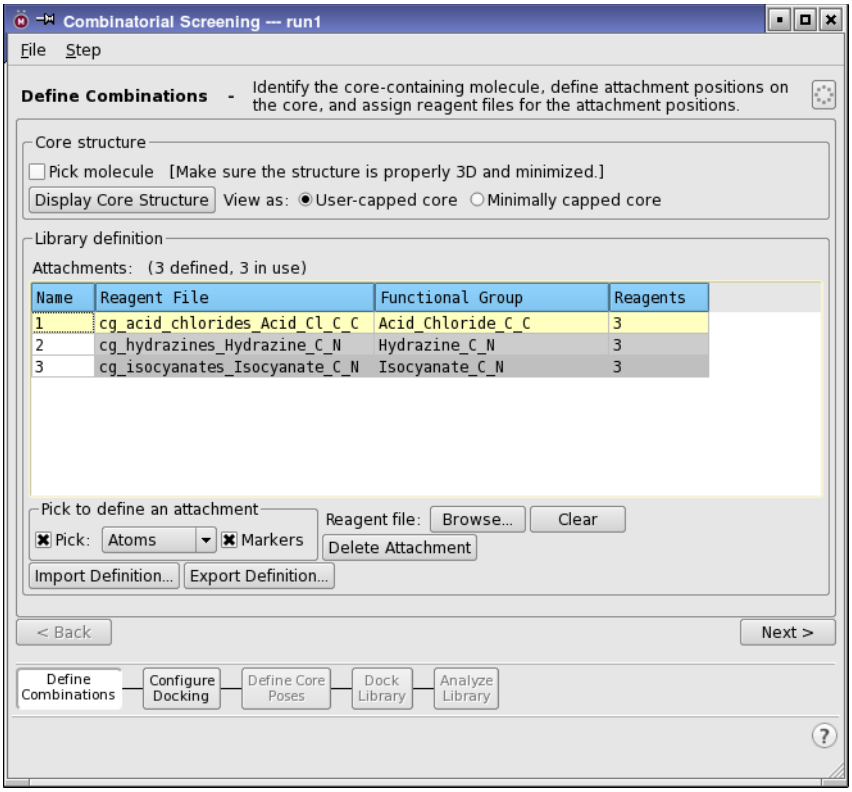



***Figure 2.6. Define Combinations step after defining attachment positions.***

7. Click Next.

   The Configure Docking step is displayed.

## 2.4 Configuring the Glide Docking Calculations

The next step is to configure the CombiGlide docking calculations. In a real application, you would select a receptor and generate the grids before starting the combinatorial screening process. You would then set up the parameters for the docking process in this step. For this tutorial, grids have already been generated.

1. In the Settings tab, click Browse in the Receptor grid section.
2. Select `receptor_grid.zip`, and click Open.

   The path to the grid files is displayed in the Receptor grid base name text box. We will be using the default docking settings in the tutorial, so no further settings need to be made.

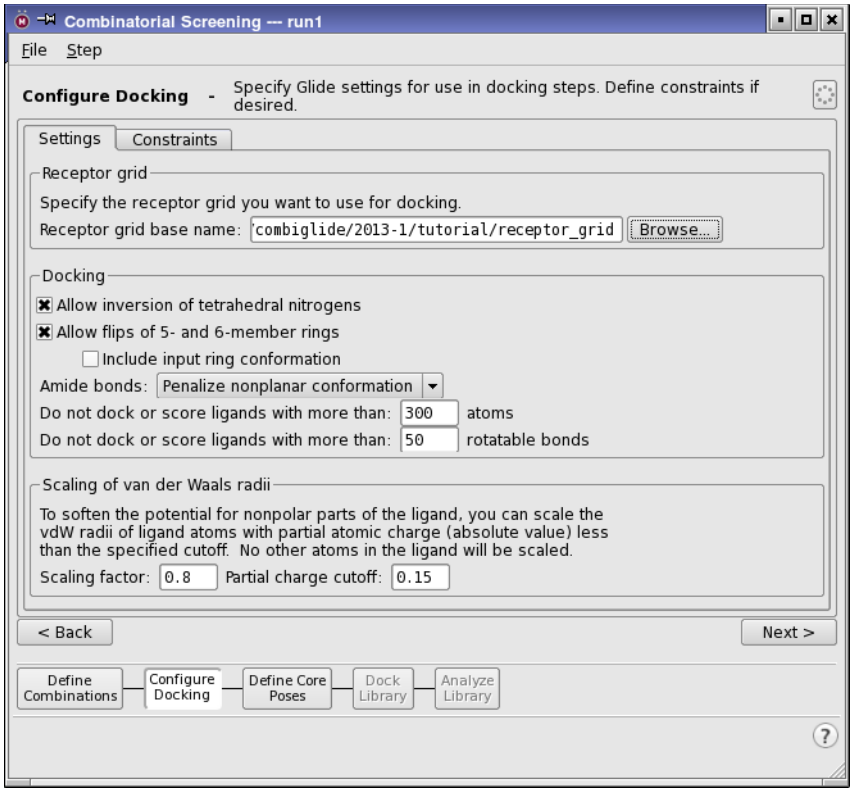



***Figure 2.7. Configure Docking step after selecting the grid file.***

3. Click Next.

   The Define Core Poses step is displayed.

## 2.5 Defining the Core Poses

In this tutorial, you will use the default settings for the docking of the core-containing molecule. The poses of the core-containing molecule are used as initial poses in the library docking.

The structure to be used in the core pose determination is the *user-capped core*, which should appear automatically in the Core structures table. The user-capped core is the core-containing molecule that you imported, with the original group at each attachment position. The molecule provided for the user-capped core in this tutorial has been docked into the frame of reference of the receptor. This is necessary when constraining to the position of the user-supplied core-containing molecule during the docking stage. For other choices, CombiGlide docks the core-containing molecule first.

An alternative is to use a minimally capped core, in which a minimal capping group is placed at each position. The minimal capping group is defined on page 40 of the *CombiGlide User Manual*. You can view the user-capped core by clicking in the In column for this molecule in the Core structures table.

1. Click Next.

   The Dock Library step is displayed.

## 2.6 Docking the Structures

You are now ready to start the docking phase of CombiGlide. In this phase, all possible structures generated by a single substitution at each attachment position are docked first ("single-position docking"), then a selection process is run on the results of this docking run to screen out poor poses, and finally a set of fully substituted structures is built and docked.

1. Click Dock.

   The Dock dialog box opens.

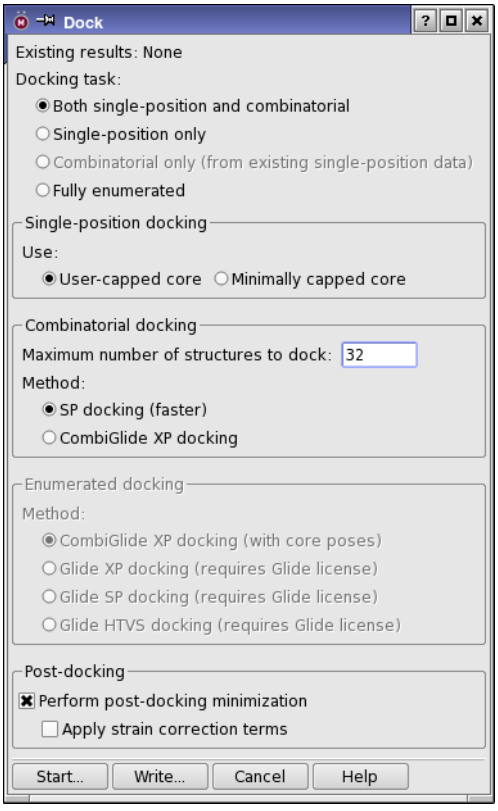



***Figure 2.8. The Dock dialog box.***

2. Under Docking task, ensure that Both single-position and combinatorial is selected.

   This is the default. This choice runs the entire docking process: single-position docking, selection, and all-position docking. If you wish to view the results of the single-position docking runs before proceeding to docking the fully substituted structures, select Single

position only. Once the single-position results are returned, you can perform the all-position docking by selecting Combinatorial only.

3. In the Single-position docking section, ensure that User-capped core is selected.
4. In the Combinatorial docking section, enter 32 in the Maximum number of structures to dock text box, and ensure that SP docking is selected.

   In the final stage of docking, CombiGlide builds and docks the structures that the selection algorithm considers to be the best, up to a maximum of 32 structures. The total number of structures that can be generated from the 3x3x3 library is 3x3x4 = 36 as one of the reagent files contained an ionizable group and therefore now contains four structures.
5. Click Start.

   The Start dialog box opens.
6. Select the host you wish to run the docking jobs on and distribute them as you see fit.

   For the tutorial, it is not necessary to separate the docking into subjobs, as the library is small. The overall docking process could take 30 minutes on a 2 GHz processor.
7. Click Start.

   The jobs start and the job status button starts spinning. You can open the Monitor panel to monitor the docking jobs during the CombiGlide run by clicking the button.

   When all the jobs finish, the Single and Comb columns are populated in the Reagent retention table, and the total number of final docked structures is reported in the Number of final structures text box in the Combinatorial results section. Single is the number of reagents at the given position in the structures that were successfully docked in the single-position docking stage. Comb is the number of reagents at the given position in the structures that were successfully docked in the all-position docking stage. There should be 3 reagents in each column for each position.

   You can view the single-position results by selecting the row for the attachment position you wish to view in the Reagent retention table, then clicking Add to Project Table in the Single position results section of the panel. You can then view the structures using the Project Table. Note that more than one pose is saved for each reagent.

   To view the combinatorial results, click Add to Project Table in the Combinatorial results section. You can then view the structures using the Project Table.

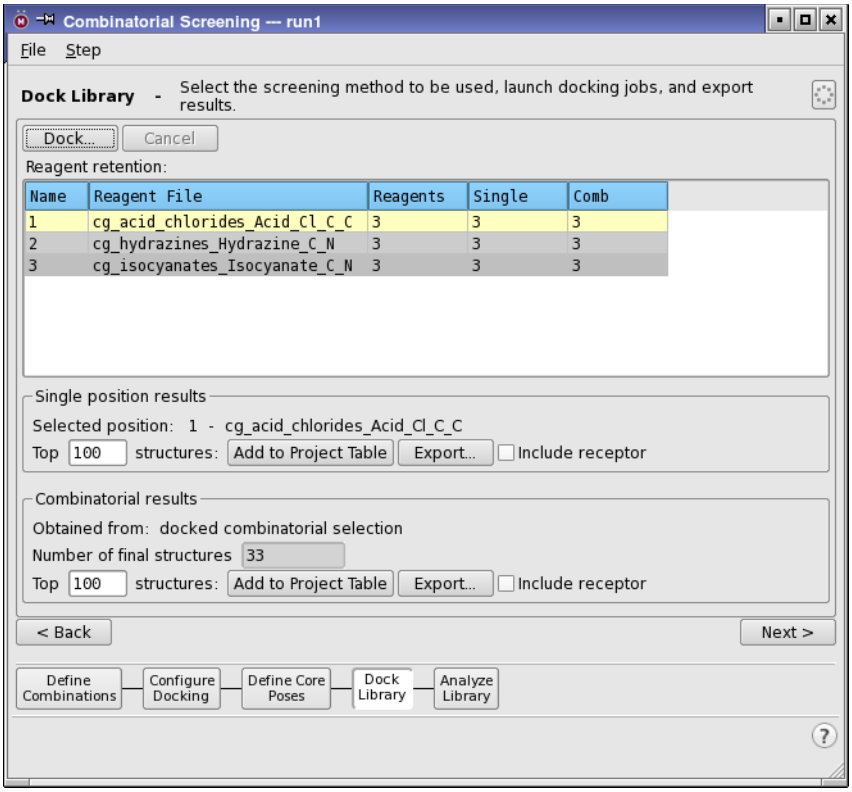



***Figure 2.9. The Dock Library step after docking.***

8. Click Next.

   The Analyze Library step is displayed.

## 2.7 Analyzing the Library

When the docking jobs are finished, you can proceed to design the optimal focused combinatorial library based on the all-position docking results.

1. Click Filter and Select.

   The Filter and Select dialog box opens.

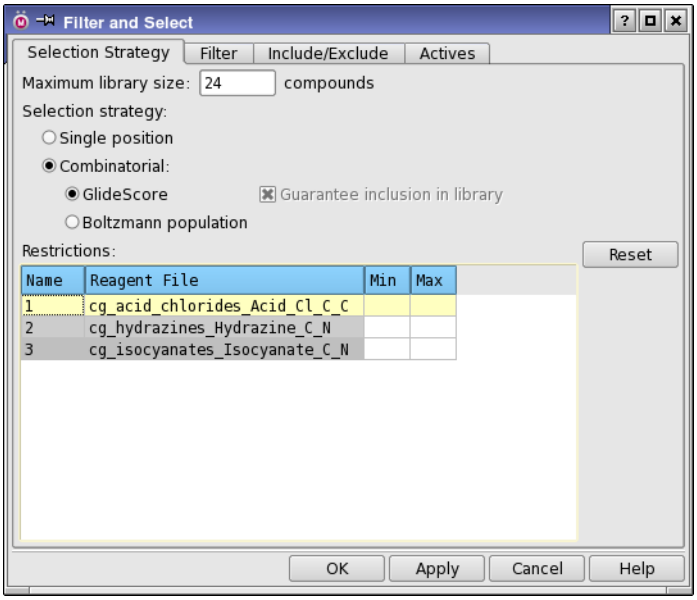



***Figure 2.10. The Selection Strategy tab of the Filter and Select dialog box.***

2. In the Selection Strategy tab, select Combinatorial and GlideScore.
3. Enter 24 into the Maximum library size text box.
4. Click OK.

   CombiGlide calculates the optimal combinatorial library using the GlideScore to determine the best reagents, with a maximum library size of 24. As can be seen in the Library column of the uppermost table in the panel, a 3x3x2 library (18 members) was generated.

5. Click on the row for the attachment position associated with the isocyanate reagent file (Reagent Title: cg_isocyanates_Isocyanate_C_N).

   The data for this attachment position appear in the Reagents table. The rank 1 reagent is the reagent at that position for the best scoring structure from the all-position docking. The row for the rank 3 reagent is colored blue to indicate that the reagent was not selected

for the library but was the reagent from the next best scoring structure from the all-position docking. This feature allows you to see the reagents that were close to being included in the focused library, and thus can help you to refine the library.

To view the docked pose of the best-scoring structure containing a particular side chain, click on the square to the left of the reagent in the Reagents table.

6. Save the results of this library selection strategy by clicking Save and giving it the name `original`.

Next, you will filter the library using a set of properties, to further refine the library.

7. Click Filter and Select.
8. The Filter and Select dialog box opens.

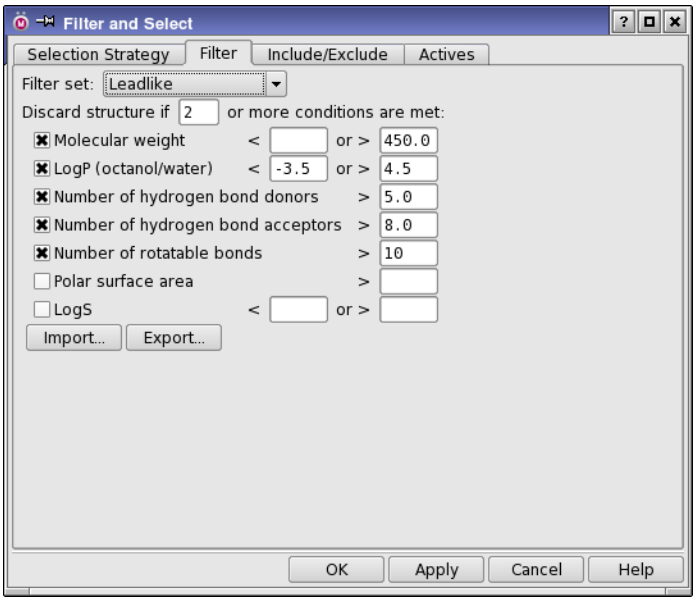



***Figure 2.11. The Filter tab of the Filter and Select dialog box.***

9. In the Filter tab, select Leadlike from the Filter set option menu.
10. Click OK.

    This strategy adds a filter to the previous strategy, and returns a 3x3x2 library.

11. Save the results of this library selection strategy by clicking Save and giving it the name `leadlikefilter`.

To compare results from different strategies:

12. Click Compare in the Results section.

    The Compare Results dialog box opens.

13. Select original and leadlikefilter from the Select results to compare list.

14. Select 3 from the Position option menu.

    The reagents selected with both strategies appear in the panel for comparison. In this case there is no difference, because all reagents pass the leadlike filter. The GlideScore values that you obtain may differ a little from those in Figure 2.12.

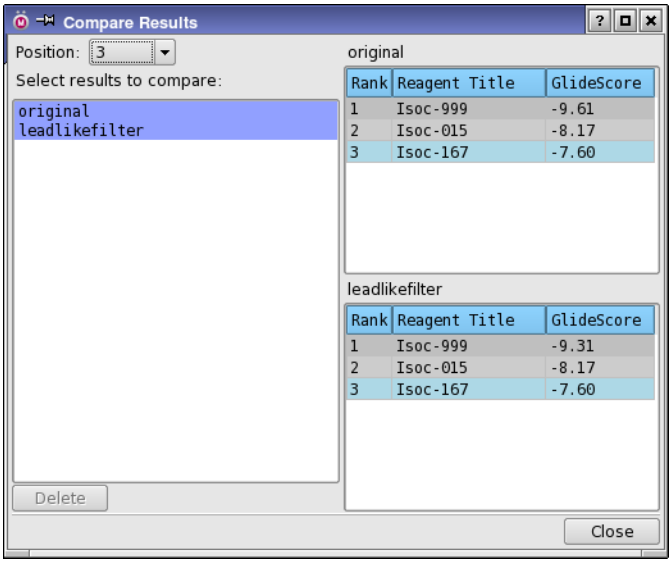



***Figure 2.12. The Compare Results dialog box.***

To generate a text file summarizing the results of the current strategy, click Write Text File in the Results section of the Analyze Library step. The file contains the settings used in the strategy, the GlideScore ranges, and the list of reagents selected for each attachment position.

Once you select your final focused library, you can enumerate the entire library that can be prepared from the reagents chosen by your selection strategy, by clicking Create Library. By default, the structures in the library are untangled and minimized.

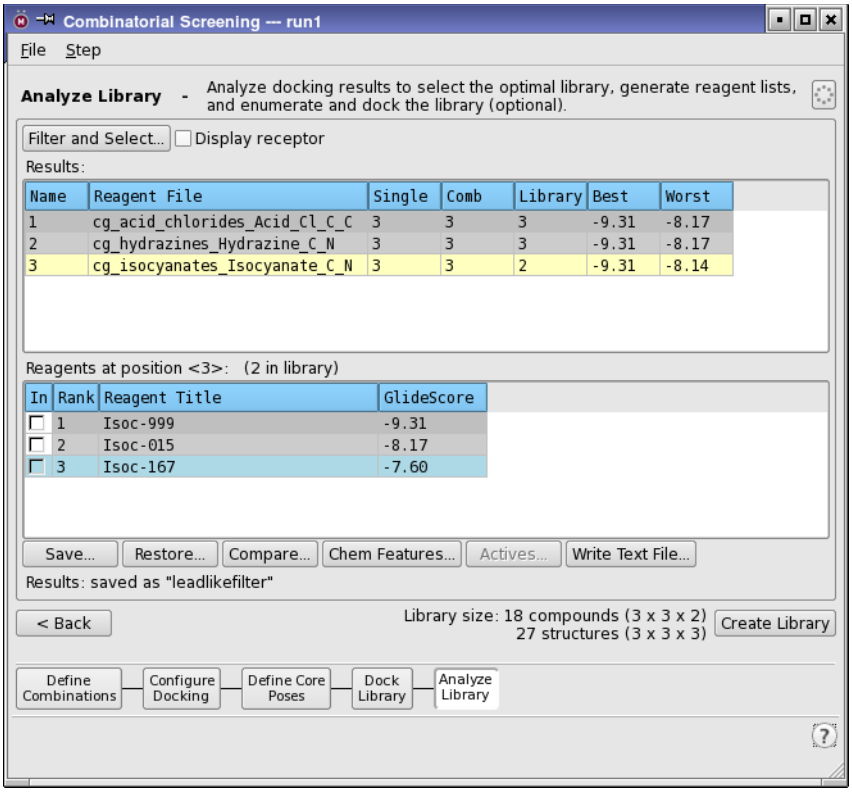



*Figure 2.13. The Analyze Library step after analysis.*

## 2.8 Changing Settings and Rerunning

There are occasions on which you may want to change some settings and rerun the calculations. You do not need to start from the beginning, but you can simply go back to the point where the settings need to be changed, and start from there. This section shows how to start from a point in the workflow. In this exercise, you will change the settings for the core poses.

1. Click the Define Core Poses button in the Guide.

   The Define Core Poses step is displayed.

2. Select Apply Glide core constraints.

   A warning dialog box is displayed, which allows you to choose whether to save the current results and create a new run, to proceed in the current run and delete the results that depend on this setting, or to cancel the change.

3. Select Save a copy before proceeding, and click OK.

   The default name for the new run is accepted (which should be `run2`). The old run is preserved, and the changes are made in the new run, which is now the current run. You can also save a run explicitly, by choosing Save As from the File menu.

4. Proceed to the Dock Library step, by clicking the button in the Guide or Next.

You can now continue the tutorial from Section 2.6 on page 15. You might want to compare the results from run1 to those from run2, to examine the effect of core constraints.

# Library Analysis

This chapter provides instruction on performing analysis of the chemical features in the library and of the enrichment of known actives. For a useful analysis, both of these tasks require a CombiGlide run that includes many more reagents for each attachment than we have used in the focused library design tutorial. Running the docking jobs to obtain the results is therefore impractical for the purposes of a tutorial. Instead, we provide results that you can analyze by running scripts from the command line. These scripts operate on the same files as are generated in a CombiGlide run, and display the same panels as are displayed from Maestro.

A detailed description of the interpretation of the features is given in Chapter 10 of the *CombiGlide User Manual*. Links to the manual material are provided so that you can read more on the interpretation of the panel displays.

If you have not already created a working directory and copied the tutorial files into it, do so now, using the instructions in Section 1.1 on page 1. If you are running on a Windows machine, open a Schrödinger Command Prompt window from the Start menu, and type `sh`. You can then use the Unix commands given in this chapter to complete the exercises.

## 3.1 Chemical Features

The analysis of the chemical features in a library is done in Maestro with the Chemical Features panel. This panel can also be opened from the command line, which you will do in this tutorial. The system for which the data are provided is the same as for the virtual combinatorial screening tutorial, but with an expanded reagent set.

1. Change to your working directory:

   `cd` *workdir*

2. Run the following command to open the Chemical Features panel.

   ```
   $SCHRODINGER/utilities/cg_chem_features chem_features-rgnt.txt &
   ```

   This utility opens the file `chem_features-rgnt.txt` and uses it to generate the graphical data that are displayed in the panel. The file is generated by the program `libselector`. When you use the Filter & Select panel to run this program from Maestro, the file is stored inside the project.

   To open this panel from Maestro, you can click Chem Features in the Analyze Library step after performing a library selection in the Filter & Select panel.

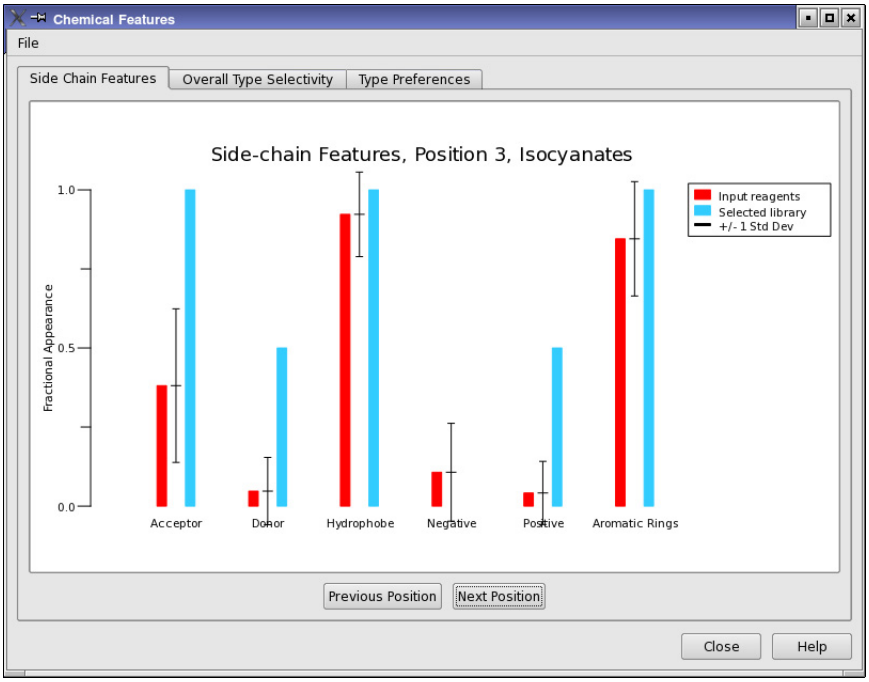



***Figure 3.1. Chemical Features panel, showing Side Chain Features chart.***

When you first open the panel, you will see a display headed Side-chain Features, Position 1, Acid_Chlorides. This heading refers to the type of display, which is selected by using the options at the top of the panel, and the attachment position, for which the position number and user-assigned name are both given. Below the chart are two buttons, which can be used to display the chart for other attachment positions.

The main purpose of the side-chain features chart is to examine the enrichment or depletion of chemical features in the selected library as compared to the full library (defined by the input reagent collection). The height of the blue bars relative to the red bars shows how much the feature is enriched (or depleted) in the selected library.

For the first position, there are significantly fewer acceptors in the selected library than in the input reagent collection. Donors and positive features have been eliminated, but the depletion is within the standard deviation, and is not statistically significant. To test whether this position selects against these features, you would have to supplement the reagent collection with compounds that contain these features.

Reagents without a hydrophobe have also been eliminated.

3. Click Next Position.

   This chart shows that there is no significant enrichment of any of the chemical feature types for the hydrazine reagent. However, reagents without an aromatic ring have been eliminated.

4. Click Next Position again.

   The third chart shows significant enrichment of acceptors, donors, and positive features at the isocyanate position. The core-containing structure in this case is the 1kv1 lead compound. In the more strongly binding 1kv2 ligand, BIRB796, the p-chlorophenyl substituent is replaced with one that contains donors, acceptors and positive centers as well as an aromatic ring. Thus, the chemical-feature information inferred by CombiGlide is consistent with the observed stronger binding of BIRB796. Note also that reagents that lack acceptors, aromatic rings, or hydrophobes have been eliminated: 100% of the reagents at this position in the selected library contain all these features.

The second kind of chart displays type selectivity. For background information, see Section 10.1.2.2 of the *CombiGlide User Manual*.

5. Select Overall Type Selectivity.

   The overall selectivity chart is displayed. It consists of vertical bars for each position that indicate how selective each position is for side-chain types. (A "type" is defined by a combination of features, so there are many more than 6 possible types. See Section 10.1.1 of the *CombiGlide User Manual* for more information.)

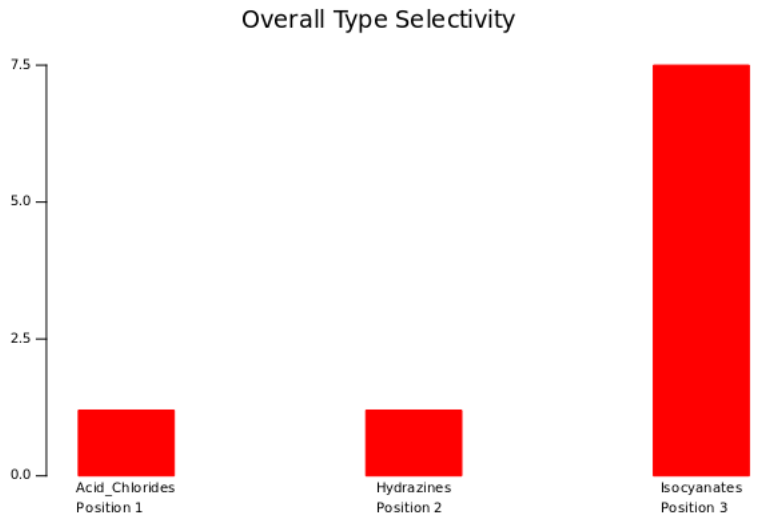



***Figure 3.2. Overall type selectivity chart.***

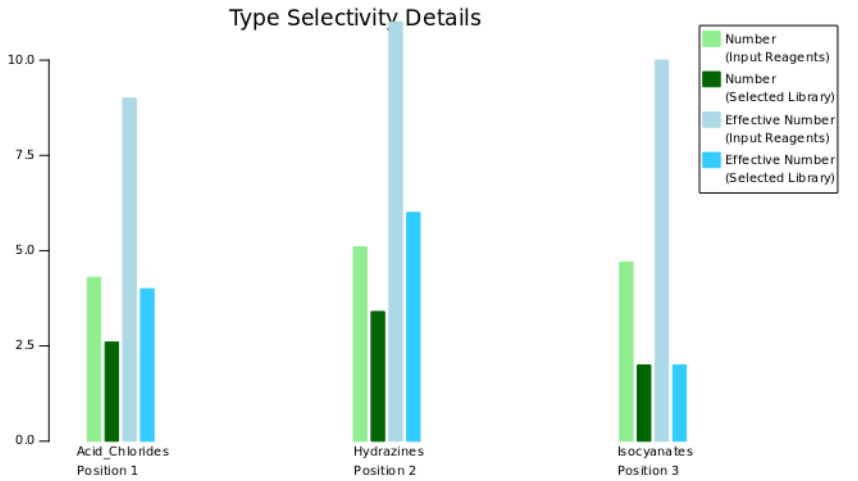



***Figure 3.3. Type selectivity details chart.***

The large value of 7 at position 3 indicates high selectivity, whereas the values of 1 at the other positions indicate low selectivity. Since selectivity is relative to the diversity of the reagent set, it is important to determine whether the low selectivities of positions 1 and 2 are due to lower diversity in their input reagent sets or to greater discrimination at position 3. This can be done by examining the type selectivity details.

6. Click Show Type Details.

   The Type Selectivity Details chart is displayed. The pale blue bars show the number of types in the input collection at each position. The numbers do not differ significantly between the positions, so on this basis the selectivity is not due to lower diversity at positions 1 and 2. The green bars show a diversity measure that takes into account the non-uniform distribution of types at a position. Again, there is not a significant variation in diversity between the three positions. The conclusion is that position 3 strongly discriminates between chemical types, but positions 1 and 2 do not.

   For more information on this display, see Section 10.1.2.2 of the *CombiGlide User Manual*.

Information on which types are enriched can be examined in the third chart type.

7. Select Type Preferences.

   The Type Preferences chart for position 3 is displayed. This was the last position displayed earlier. If for some reason this position is not displayed, click Next Position or Previous Position until it is.

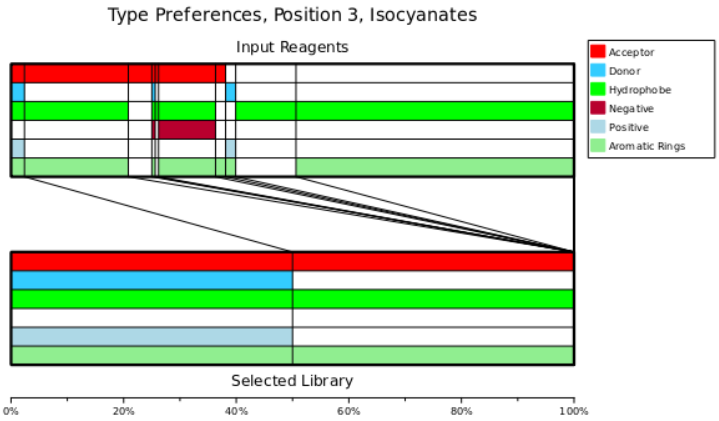



***Figure 3.4. Type preferences plot.***

Only two types (out of the ten that appear in the input collection) appear in the output, and these two types had rather low frequencies in the input collection. Both of these facts contribute to the high overall type selectivity exhibited by this position. The types that remain at this position all include an acceptor, a hydrophobe, and an aromatic ring, and lack a negative feature. The reagents that appear in the final collection each contain some of the features that exhibited significant enhancement in the Side Chain Features display.

8. Examine the chart for the other two positions, by clicking Previous Position or Next Position.

   Neither of these positions shows the same amount of selectivity, but both show the elimination of certain features.

Based on the results of this study, several possible directions for designing a better library might be pursued:

- Focus the reagent set at position 3 on the types that survived in the selected library. When this is done, the analysis will no longer show selectivity because the reagent set is no longer diverse. However, you will be able to explore reagents that are preselected to contain the features discriminated for and will therefore have a good chance of finding stronger binders.
- Check whether a hydrophobe is required at position 1 and an aromatic ring at position 2 by decreasing the proportion of reagents containing these features. The current statistics might be too small to judge whether the elimination of types containing these features is significant.

## 3.2 Enrichment of Actives

The analysis of the chemical features in a library is done in Maestro with the Actives panel. This panel can also be opened from the command line, which you will do in this tutorial.

1. Change to your working directory:

   `cd` *workdir*

2. Run the following command to open the Actives panel.

   ```
   $SCHRODINGER/utilities/cg_active_plot -r actives-rgnt.txt
   ```

   The Active Plot panel is displayed, with the data from the `actives-rgnt.txt` file plotted. This is the same panel as is displayed when you click Plot Enrichment Factors in the Actives panel, which in turn is opened by clicking Actives in the Analyze Library step of the Combinatorial Screening panel.

3. If Log/Log Plot is not selected, select it.

   The display is updated, and the plot should appear as shown in Figure 3.5.

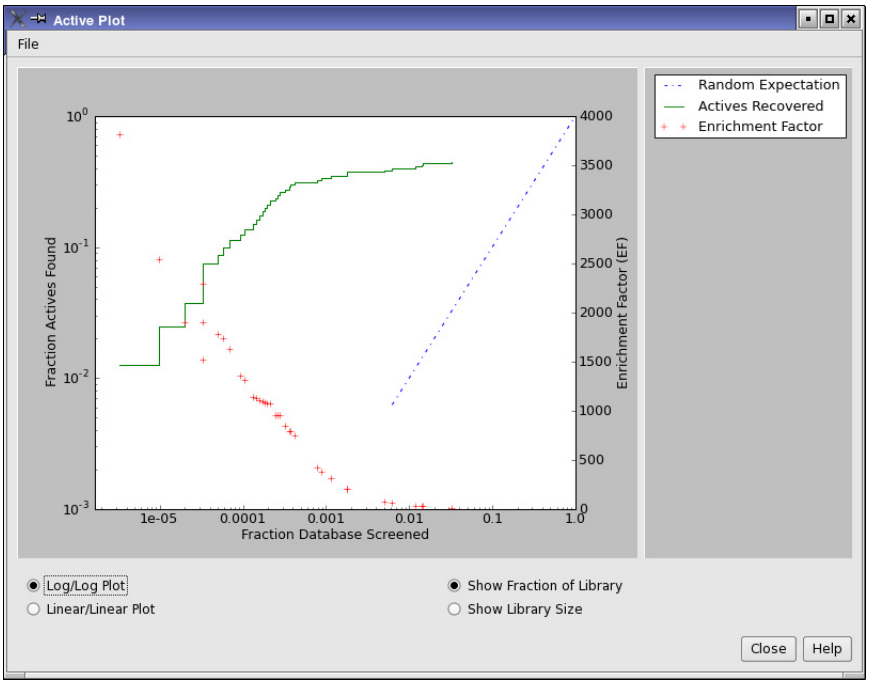



***Figure 3.5. Enrichment factor plot.***

The green stepped line displays a standard enrichment curve of the fraction of actives found against the fraction of the database screened. The axes for this curve are displayed on the left and the bottom of the plot area. The fact that all points on this curve appear above the dashed line displaying the random expectation shows that the enrichment factor is everywhere greater than unity.

For each active found, the enrichment factor is denoted by the red crosses and read off the vertical axis on the right. Overall, this plot shows that early enrichments are in the thousands and that enrichment factor decreases, as expected, as more of the library is screened.

The horizontal axis shows the fraction of the database screened. This plot shows that the selected 1000-compound combinatorial library exhibits an enrichment factor of about 500, meaning that it contains 500 times more active compounds than a random selection of 1000 compounds is expected to have. You can change the horizontal axis to show the library size instead.

# Getting Help

Information about Schrödinger software is available in two main places:

- The `docs` folder (directory) of your software installation, which contains HTML and PDF documentation. Index pages are available in this folder.
- The Schrödinger web site, http://www.schrodinger.com/, In particular, you can use the Knowledge Base, http://www.schrodinger.com/kb, to find current information on a range of topics, and the Known Issues page, http://www.schrodinger.com/knownissues, to find information on software issues.

## Finding Information in Maestro

Maestro provides access to nearly all the information available on Schrödinger software.

**To get information:**

- Pause the pointer over a GUI feature (button, menu item, menu, ...). In the main window, information is displayed in the Auto-Help text box, which is located at the foot of the main window, or in a tooltip. In other panels, information is displayed in a tooltip.

  If the tooltip does not appear within a second, check that Show tooltips is selected under General → Appearance in the Preferences panel, which you can open with CTRL+, (⌘,). Not all features have tooltips.

- Click the Help button in the lower right corner of a panel or press F1, for information about a panel or the tab that is displayed in a panel. The help topic is displayed in the Help panel. The button may have text or an icon:

- Choose Help → Online Help or press CTRL+H (⌘H) to open the default help topic.
- When help is displayed in the Help panel, use the navigation links in the help topic or search the help.
- Choose Help → Documentation Index, to open a page that has links to all the documents. Click a link to open the document.
- Choose Help → Search Manuals to search the manuals. The search tab in Adobe Reader

opens, and you can search across all the PDF documents. You must have Adobe Reader installed to use this feature.

**For information on:**

- Problems and solutions: choose Help → Knowledge Base or Help → Known Issues → *product*.
- New software features: choose Help → New Features.
- Python scripting: choose Help → Python Module Overview.
- Utility programs: choose Help → About Utilities.
- Keyboard shortcuts: choose Help → Keyboard Shortcuts.
- Installation and licensing: see the *Installation Guide*.
- Running and managing jobs: see the *Job Control Guide*.
- Using Maestro: see the *Maestro User Manual*.
- Maestro commands: see the *Maestro Command Reference Manual*.

## Contacting Technical Support

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.

| | |
|---|---|
| Web: | http://www.schrodinger.com/supportcenter |
| E-mail: | help@schrodinger.com |
| Mail: | Schrödinger, 101 SW Main Street, Suite 1300, Portland, OR 97204 |
| Phone: | +1 888 891-4701 (USA, 8am – 8pm Eastern Time) |
| | +49 621 438-55173 (Europe, 9am – 5pm Central European Time) |
| Fax: | +1 503 299-4532 (USA, Portland office) |
| FTP: | ftp://ftp.schrodinger.com |

Generally, using the web form is best because you can add machine output and upload files, if necessary. You will need to include the following information:

- All relevant user input and machine output
- CombiGlide purchaser (company, research institution, or individual)
- Primary CombiGlide user
- Installation, licensing, and machine information as described below.

## Gathering Information for Technical Support

The instructions below describe how to gather the required machine, licensing, and installation information, and any other job-related or failure-related information, to send to technical support. Where the instructions depend on the profile used for Maestro, the profile is indicated.

**For general enquiries or problems:**

1. Open the Diagnostics panel.
   - **Maestro:** Help → Diagnostics
   - **Windows:** Start → All Programs → Schrodinger-2015-2 → Diagnostics
   - **Mac:** Applications → Schrodinger2015-2 → Diagnostics
   - **Command line:** `$SCHRODINGER/diagnostics`
2. When the diagnostics have run, click Technical Support.

   A dialog box opens, with instructions. You can highlight and copy the name of the file.
3. Upload the file specified in the dialog box to the support web form.

   If you have already submitted a support request, use the upload link in the email response from Schrödinger to upload the file. If you need to submit a new request, you can upload the file when you fill in the form.

**If your job failed:**

1. Open the Monitor panel, using the instructions for your profile as given below:
   - **Maestro/Jaguar/Elements:** Tasks → Monitor Jobs
   - **BioLuminate/MaterialsScience:** Tasks → Job Monitor
2. Select the failed job in the table, and click Postmortem.

   The Postmortem panel opens.
3. If your data is not sensitive and you can send it, select Include structures and deselect Automatically obfuscate path names.
4. Click Create.

   An archive file is created, and an information dialog box with the name and location of the file opens. You can highlight and copy the name of the file.
5. Upload the file specified in the dialog box to the support web form.

   If you have already submitted a support request, use the upload link in the email response from Schrödinger to upload the file. If you need to submit a new request, you can upload the file when you fill in the form.

6. Copy and paste any log messages from the window used to start the interface or the job into the web form (or an e-mail message), or attach them as a file.
   - **Windows:** Right-click in the window and choose Select All, then press ENTER to copy the text.
   - **Mac:** Start the Console application (Applications → Utilities), filter on the application that you used to start the job (Maestro, BioLuminate, Elements), copy the text.

**If Maestro failed:**

1. Open the Diagnostics panel.
   - **Windows:** Start → All Programs → Schrodinger-2015-2 → Diagnostics
   - **Mac:** Applications → SchrodingerSuite2015-2 → Diagnostics
   - **Linux/command line:** `$SCHRODINGER/diagnostics`
2. When the diagnostics have run, click Technical Support.

   A dialog box opens, with instructions. You can highlight and copy the name of the file.
3. Upload the file specified in the dialog box to the support web form.

   If you have already submitted a support request, use the upload link in the email response from Schrödinger to upload the file. If you need to submit a new request, you can upload the file when you fill in the form.
4. Upload the error files to the support web form.

   The files should be in the following location:

- **Windows:** `%LOCALAPPDATA%\Schrodinger\appcrash`
  (Choose Start → Run and paste this location into the Open text box.)
  Attach `maestro_error_`*`pid`*`.txt` and `maestro.exe_`*`pid_timestamp`*`.dmp`.
- **Mac:** `$HOME/Library/Logs/CrashReporter`
  (Go → Home → Library → Logs → CrashReporter)
  Attach `maestro_error_`*`pid`*`.txt` and `maestro_`*`timestamp_machinename`*`.crash`.
- **Linux:** `$HOME/.schrodinger/appcrash`
  Attach `maestro_error_`*`pid`*`.txt` and `crash_report_`*`timestamp_pid`*`.txt`.

**If a Maestro panel failed to open:**

1. Copy the text in the dialog box that opens.
2. Paste the text into the support web form.

120 West 45th Street
17th Floor
New York, NY 10036

101 SW Main Street
Suite 1300
Portland, OR 97204

245 First Street
Riverview II, 18th Floor
Cambridge, MA 02142

8910 University Center Lane
Suite 270
San Diego, CA 92122

155 Gibbs St
Suite 430
Rockville, MD 20850-0353

Dynamostraße 13
D-68165 Mannheim
Germany

Zeppelinstraße 73
D-81669 München
Germany

Potsdamer Platz 11
D-10785 Berlin
Germany

Quatro House
Frimley Road
Camberley GU16 7ER
United Kingdom

8F Pacific Century Place
1-11-1 Marunouchi
Chiyoda-ku, Tokyo 100-6208
Japan

No. 102, 4th Block
3rd Main Road, 3rd Stage
Sharada Colony
Basaveshwaranagar
Bangalore 560079, India

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