MCPRO+ 2.9

Quick Start Guide

Schrödinger Press

Revision A, September 2012

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].

Getting Started

The exercises in this document are designed to provide familiarity with some of the basic uses of MCPRO+. Before you begin, you should complete the steps described below.

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 `mcpro` zip file from the `tutorials` directory of your installation into your working directory.

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:

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

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 MCPRO+ 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.

Minimization

The exercises in this chapter guide you through the minimization of a strained structure in which the amide bond is nonplanar.

2.1 Creating a Model System

The first stage in any MCPRO+ calculation is to create a model system.

1. From the main window, choose Applications > MCPRO+ > Minimization.

   The MCPRO+ Minimization panel opens at the Model System Creation tab and in the Import step.

2. In the Model system section, enter `mini_ms` in the Model system basename text box.

   This name is used to create file names for the job.

3. In the Model system section, select Ligands only.

4. In the Import section, click the Browse button for Ligand structures.

   A file selector opens. The files that you copied to your working directory should be displayed. If not, you must navigate to the directory you copied the files to in Chapter 1.

5. Select the file `strained.maegz` and click Open.

   The file selector closes, the file name is entered in the Ligand structures text box, and the structure is displayed in the Workspace. If it is not centered, you can click the Fit to Workspace toolbar button to center it. (This has no effect on the results.)

   

6. Rotate the molecule to view the geometry around the amide bond. (Use the middle mouse button.)

7. In the MCPRO+ Minimization panel, click Constrain.

   The default is to allow the ligands to be fully flexible, which is what we want for this exercise. You do not need to change any settings in this step.

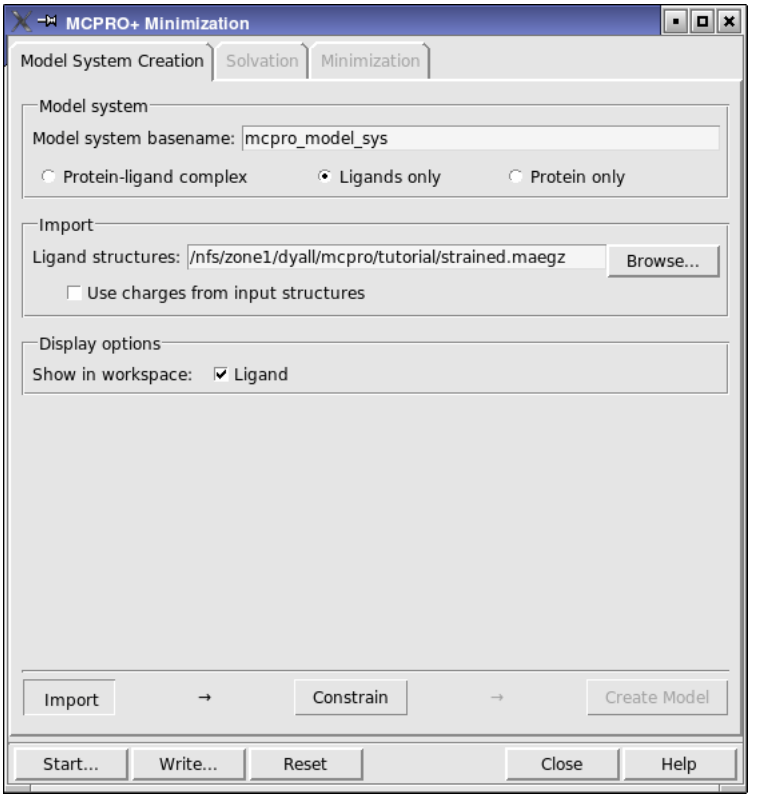

Figure 2.1. The Import step in the MCPRO+ Minimization panel.

8. Click Create Model.

   The job to create the model system is started, and the log file is displayed in the Monitor system creation text area. When it finishes, the message `Model System generated successfully` should appear at the end of the log file.

2.2 Setting Up the Simulation Conditions

In this exercise, you set up the simulation conditions for the minimization. There are only a few options available, so the exercise is short.

1. In the Solvation tab, select Constant dielectric of and ensure that the value in the text box is 78.3.
2. In the Minimization tab, ensure that the Number of optimization cycles is set to 500, and that the Method is set to CONJUG.

2.3 Running the Simulation and Examining the Results

In this exercise, you run the minimization job and examine the results.

1. Click Start.

   The MCPRO+ Start dialog box opens. This job is very quick, so there is no need to run on a remote host, and you can accept the default job name of `mcpro_mini`. This name determines the names of various files.

2. Click Start.

   The job starts, and the Monitor panel opens. The log file is displayed in the File tab. The job finishes almost immediately, and a new structure is displayed in the Workspace.

3. Rotate the molecule to view the geometry around the amide bond.

   Note that the amide bond is now planar.

4. In the Monitor panel, click the Details tab.

5. Select `mcpro_mini.out` in the list of files, and click the File tab.

   The output file is displayed. This is the main text output file, and gives details of the optimization. The energy components are also added to the Maestro output file and displayed as properties in the Project Table.

Creating a Linear Response Model

The exercises in this chapter guide you through the generation of a linear response model from data generated by MCPRO+ simulations. The fitting is done with Strike.

3.1 Creating a Model System

In this exercise, you create a model system that includes both a protein and a set of ligands.

1. From the main window, choose Applications > MCPRO+ > Linear Response.

   The MCPRO+ Linear Response panel opens at the Model System Creation tab and in the Import step.

2. In the Model system section, enter `factorXa_lrm_ms` in the Model system basename text box.

   This name is used to create file names for the job. There is only one choice for the system type, Protein-ligand complex, and it is selected.

3. In the Import section, click the Browse button for Ligand structures.

   A file selector opens. The files that you copied to your working directory should be displayed. If not, you must navigate to the directory you copied the files to in Chapter 1.

4. Select the file `factorXa_lrm_ligands.maegz` and click Open.

   The file selector closes, the file name is entered in the Ligand structures text box, and the first ligand is displayed in the Workspace. If it is not centered, you can click the Fit to Workspace toolbar button to center it. (This has no effect on the results.)

   

5. (Optional) From the Ball & Stick button menu on the Representation toolbar, choose Molecule, and click on the ligand in the Workspace.

   

   The ligand is displayed in Ball & Stick representation. This will help to distinguish the ligand from the protein in a subsequent step.

6. In the Import section of the MCPRO+ Minimization panel, click the Browse button for Protein structure.
7. Select the file `factorXa_1fjs_protein.maegz` and click Open.

   The file selector closes, the file name is entered in the Protein structures text box, and the protein is displayed in the Workspace along with the first ligand. Note that the ligand is already in the frame of reference of the protein.

   You can change what is displayed in the Workspace by selecting or deselecting the options in the Display options section.
8. Click Chop/Cap.

   The Chop/Cap step is displayed in the panel. For speed, the protein is truncated and the cut bonds are capped with H.

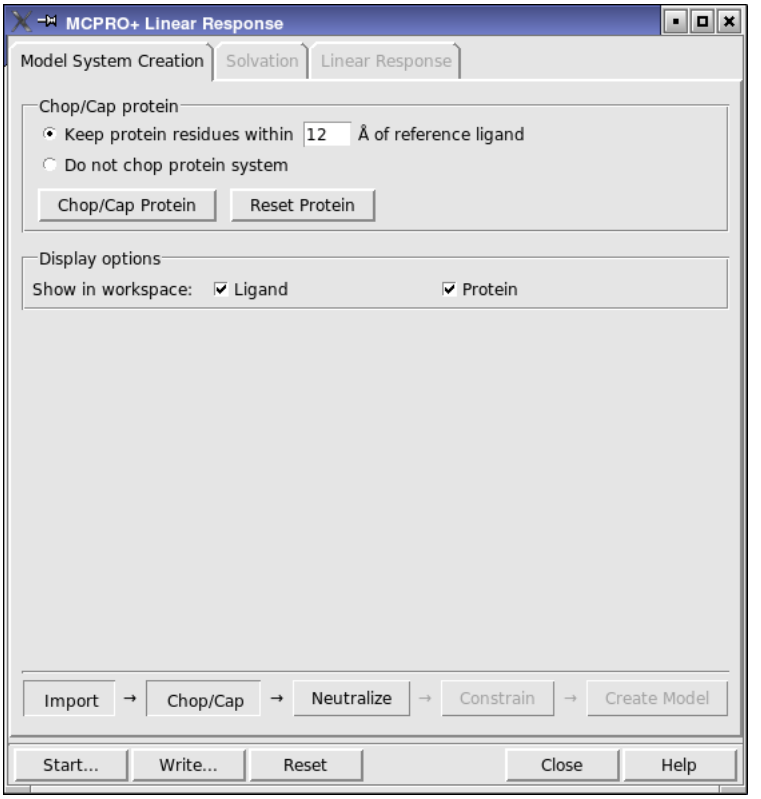

Figure 3.1. The Chop/Cap step in the Model System Creation tab of the MCPRO+ Linear Response panel.

9. Ensure that Keep protein residues within *N* Å of reference ligand is selected, and that the value in the text box is 12.

   These are the default settings, so you should not need to change anything. The protein residues that will be kept are colored yellow in the Workspace, and the residues that will be deleted are colored blue.

10. Click Chop/Cap Protein.

    After a short time, the operation finishes, and the Neutralize button becomes available.

11. Click Neutralize.

    The Neutralize step is displayed. In this step, protons are added or removed to ensure electrical neutrality of the protein-ligand complex. You do not need to change any settings.

12. Click Neutralize Protein.

    After a short time, the operation finishes, and the Constrain button becomes available.

13. Click Constrain.

14. Ensure that, for the protein, Residue sidechains within *N* Å are flexible is selected, and the value in the text box is 8.

15. Ensure that for the cofactors, Fully flexible is selected.

    These are the defaults, so no changes should be needed. The cofactors include the ligand.

16. Click Create Model.

    The job to create the model system is started, and the log file is displayed in the Monitor system creation text area. When it finishes, the message `Model System generated successfully` should appear at the end of the log file.

3.2 Setting Up the Simulation Conditions

In this exercise, you set up the simulation conditions for the Monte Carlo sampling that is used for the ligand binding energy. The simulations are severely shortened so that the results are obtained quickly. This is only done so that the use of the panel can be demonstrated: it is *not* recommended to use such short simulations routinely.

1. In the Solvation tab, ensure that TIP3P is chosen for the solvent (the default) and that the cap radius is 22 (also the default).

2. In the Linear Response tab, set the value in all text boxes in the Bound Monte Carlo sampling section to 250.

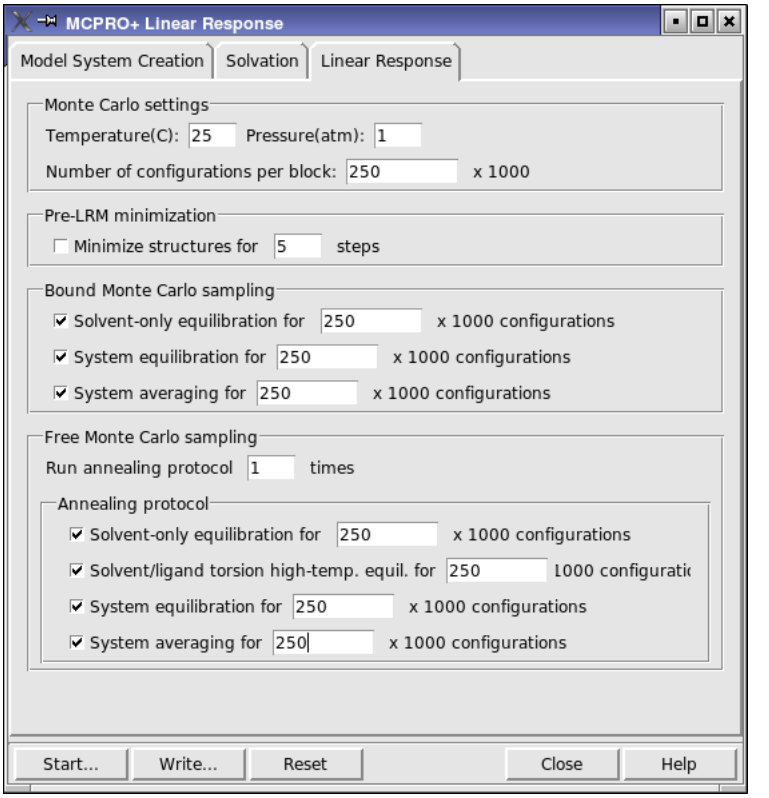

Figure 3.2. The Linear Response tab of the MCPRO+ Linear Response panel.

3. In the Free Monte Carlo sampling section, set the value in the Run annealing protocol N times text box to 1.
4. In the Free Monte Carlo sampling section, in the Annealing protocol subsection, set the value in all text boxes to 250.

3.3 Running the Simulations

In this exercise, you run the simulations. For each of the five ligands, a bound and a free simulation is run, making a total of 10 simulations. A subdirectory is created for each ligand, labeled *jobname_n*, where n is 1 through 5.

1. Click Start.

   The MCPRO+ Start dialog box opens.

2. In the Job section, change the Name to `factorXa_lrm`.

   This name determines the names of various files and the subdirectories that are created for each ligand.

3. Choose a host from the Host option menu.

   The simulations each take about 20 minutes if you run them serially on a 2GHz workstation. If you choose a multiprocessor host, the simulations for each of the ligands can be run simultaneously.

4. Click Start.

   The job starts, and the Monitor panel opens. The log file is displayed in the File tab.

3.4 Creating an Extended Linear Response Model

In this exercise, you create an extended linear response model from the results of the simulation in the previous exercise, using Strike. The structures and associated data were incorporated as an entry group in the Project Table, but the binding free energies need to be imported.

1. Click the Table button on the Project toolbar.

   

2. In the Project Table, choose Table > Import > Spreadsheet.

   The Import Spreadsheet panel opens.

3. Select the file `factorXa_lrm_dG.txt` and click Open.

   The Choose Import Key dialog box opens.

4. Select title in the File key list.

5. Select Title in the Match to property in Project Table list.

6. Click OK.

   Two new properties should appear in the Project Table, Binding Free Energy (kcal/mol) and Ki(nM), and these properties should have values for the five ligands used in the simulation.

7. In the Project Table, ensure that the five entries in the `factorXa_lrm_out` entry group are selected.

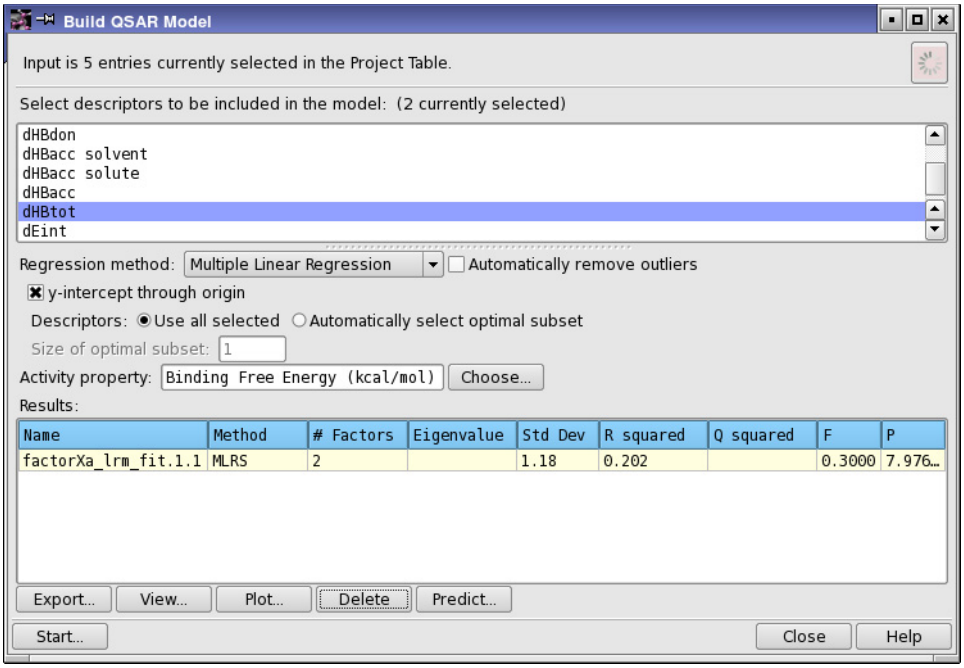

Figure 3.3. The Build QSAR Model panel.

8. In the main window, choose Applications > Strike > Build QSAR Model.

   The Build QSAR Model panel opens.

9. From the Select descriptors to be included in the model list, select EXX-LJ and dHBtot.

   Use control-click to make the selection. These two descriptors will be the independent descriptors.

10. From the Regression method option menu, choose Multiple Linear Regression.

11. Select y-intercept through origin.

12. Click the Choose button for the Activity property.

    The Choose Activity Property dialog box opens. This dialog box presents a list of Maestro properties, from which you can choose one property.

13. Select Binding Free Energy (kcal/mol) and click OK.

    This descriptor is the dependent descriptor.

14. Click Start.

    The Start dialog box opens.

15. Name the job `factorXa_lrm_fit`, and click Start.

When the job finishes, the results are returned to the Results table of the Build QSAR Model panel. This model is based on a very short simulation, whose results are likely to be noisy and show poor statistics. In general good models should show

- a small standard deviation
- a large R^2
- a large F value
- $P < 0.05$
- good leave-n-out cross-validation results
- physically meaningful descriptors
- a low R^2 from randomization tests

Instead of using Strike, fitting can be done in a spreadsheet program, by exporting the data as a CSV file, which you can do from the Table menu in the Project Table panel.

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/, particularly the Support Center, http://www.schrodinger.com/supportcenter, and the Knowledge Base, http://www.schrodinger.com/kb.

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 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 your browser.
- Choose Help → Online Help or press CTRL+H (⌘H) to open the default help topic in your browser.
- When help is displayed in your browser, use the navigation links or search the help in the side bar.
- Choose Help → Manuals Index, to open a PDF file that has links to all the PDF 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*.
- Software updates: choose Maestro → Check for Updates.
- New software features: choose Help → New Features.
- Scripts available for download: choose Scripts → Update.
- 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.

E-mail: help@schrodinger.com
USPS: Schrödinger, 101 SW Main Street, Suite 1300, Portland, OR 97204
Phone: (503) 299-1150
Fax: (503) 299-4532
WWW: http://www.schrodinger.com
FTP: ftp://ftp.schrodinger.com

Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information:

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

Gathering Information for Technical Support

This section describes how to gather the required machine, licensing, and installation information, and any other job-related or failure-related information, to send to technical support.

For general enquiries or problems:

1. Open the Diagnostics panel.
   - **Maestro:** Help → 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. Attach the file specified in the dialog box to your e-mail message.

If your job failed:

1. Open the Monitor panel in Maestro.

   Use Applications → Monitor Jobs or Tasks → Monitor Jobs.
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 in your working directory, and an information dialog box with the name of the file opens. You can highlight and copy the name of the file.
5. Attach the file specified in the dialog box to your e-mail message.
6. Copy and paste any log messages from the window used to start Maestro (or the job) into the email message,or attach them as a file.

If Maestro failed:

1. Open the Diagnostics panel.
   - `$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. Attach the file specified in the dialog box to your e-mail message.
4. Attach the file `maestro_error.txt` to your e-mail message.

   This file should be in the following location:

   - Maestro's working directory specified in the dialog box (the location is given in the terminal window).

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
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3rd Main Road, 3rd Stage
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Basaveshwaranagar
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