Tutorial

Basic operation of MolDesk

MolDesk Basic/Screening ver. 1.1.53

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In this tutorial we will learn the basic operations of MolDesk that is necessary to perform docking calculations between a protein and low molecular compounds.

Table of contents

1. Introduction

1.1. Overview

In this tutorial, we will learn the basic operations which are carried out commonly in MolDesk Screening and MolDesk Basic. In this tutorial, the following contents are covered.

- Launch of MolDesk
- Reading a molecular file
- Docking between a protein and a ligand

1.2. About myPresto and MolDesk

myPresto is a molecular simulation software package for the drug development support developed in Japan, supported by the Ministry of Economy, Trade and Industry, NEDO and AMED. myPresto itself can be used for free. It is used by more than 30 companies in Japan. myPresto includes a number of programs such as docking simulation program (sievgene), molecular dynamics simulation program (cosgene). You can download myPresto from the website. The program contained in myPresto is basically executed from the command line except one new GUI program (myPresto Portal).

MolDesk is a graphic user interface (GUI) developed by IMSBIO Co., Ltd. It is possible to run myPresto's program from the GUI. MolDesk is a commercial software. MolDesk has two versions, MolDesk Basic and MolDesk Screening. MolDesk Screening implements many advanced functions that MolDesk Basic cannot execute. For example, MolDesk Screening can perform screening calculations for 2 million compounds on a PC without using an external server.

Fig. 1 Web pages of myPresto and MolDesk

Download page of myPresto: https://www.presto5.jp/

MolDesk (IMSBIO): http://www.moldesk.com

2. Training for basic operations of MolDesk

In this tutorial, human HMG-CoA reductase is used as a target protein. We will execute a docking calculation between the receptor protein and its inhibitor. Here, a PDB file with PDB code 2Q6B is used.

2.1. Launch of MolDesk

If there is an icon on the desktop, click on it to launch MolDesk (Figure 2). If there is no MolDesk icon on the desktop, look for MolDesk Basic or MolDesk Screening from the Windows program list and run it. Since the layout immediately after startup (Fig. 3) becomes the same one as at the time of the last termination, the layout may be different from the Fig. 3.

Fig. 2 Desktop icon of MolDesk

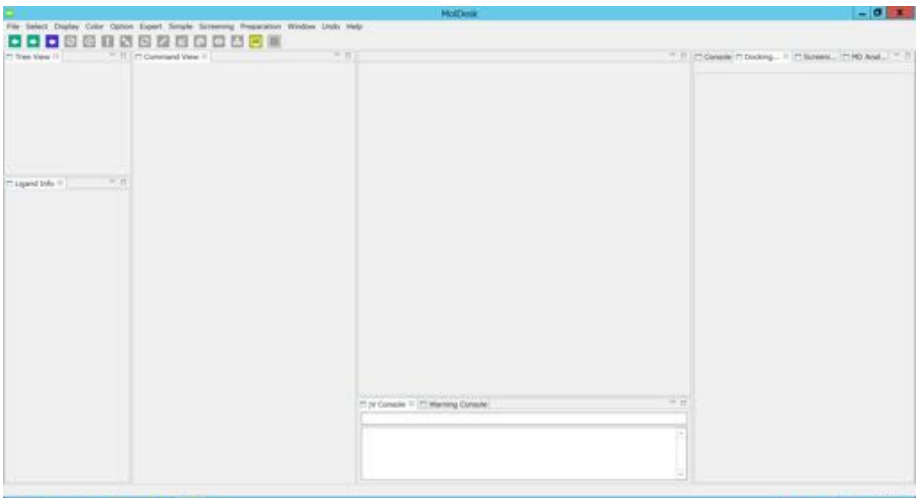

Fig. 3 MolDesk window just started

2.2. Name of parts on the MolDesk Screen.

Figure 4 shows the name of each part on the MolDesk screen.

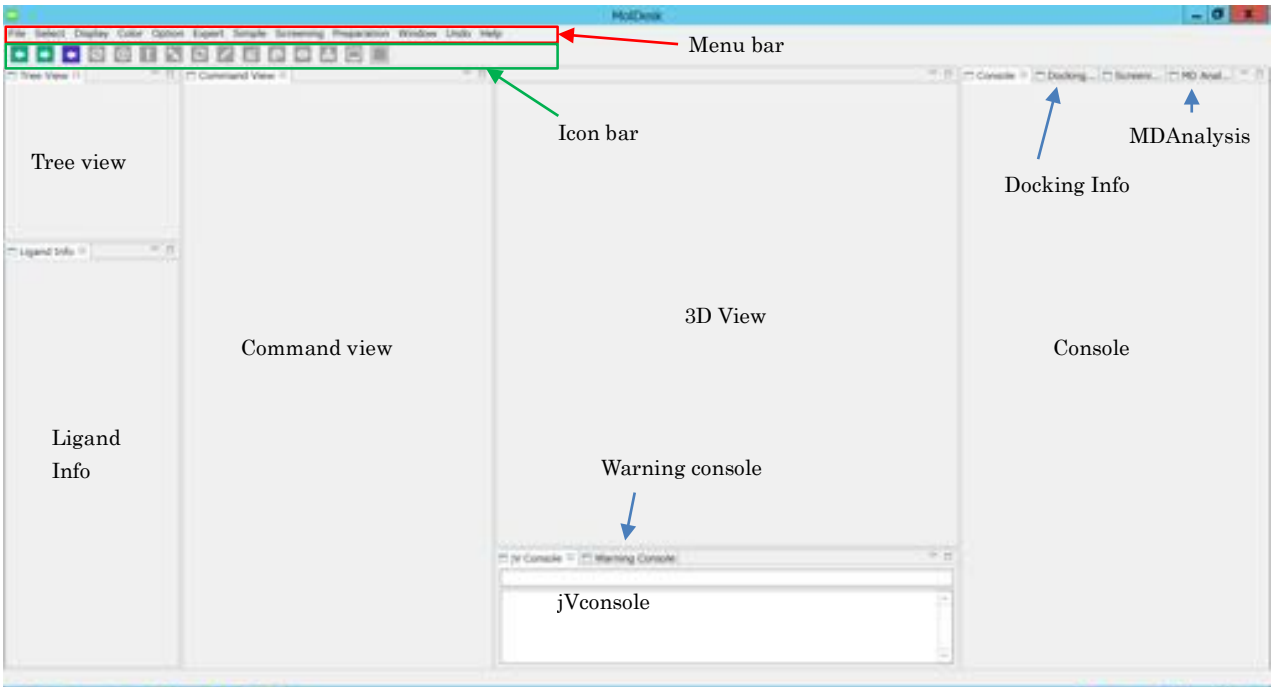

Fig. 4 Names of parts of a MolDesk window

2.3. Opening a molecule file

To open a molecule file, select "File" → "Open Remote PDB" (Figure 5) and enter the PDB ID from the dialog. If you are not connected to the Internet, select "File" → "Open Molecular File" from the file selection dialog box.

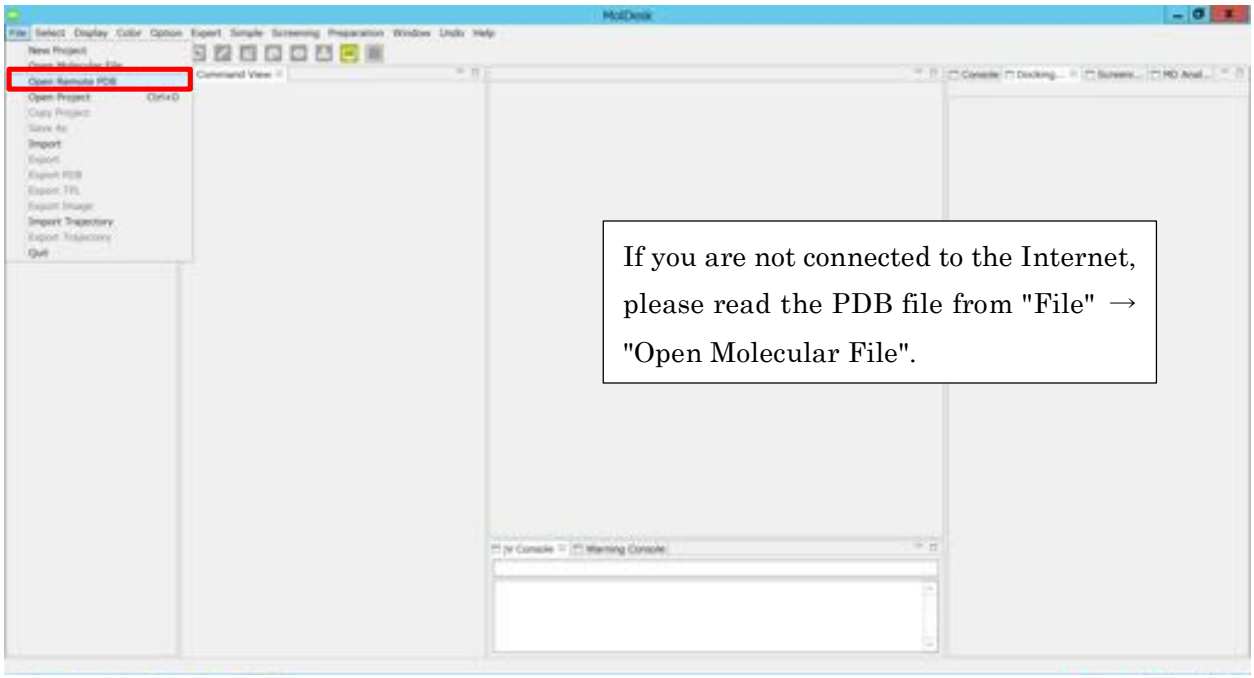

Fig. 5 Reading a molecule 1

Here enter 2Q6B (Figure 6).

Fig. 6 Reading a molecule 2

The contents of the loaded molecule can be confirmed in the tree view (indicated by the red frame in Figure 7). In this case, you can see that the loaded file contains four peptide chains (pro1 to pro4), eight ligands (lig 5 to lig 12), and water molecules. Ligand information is displayed in the Ligand Info.

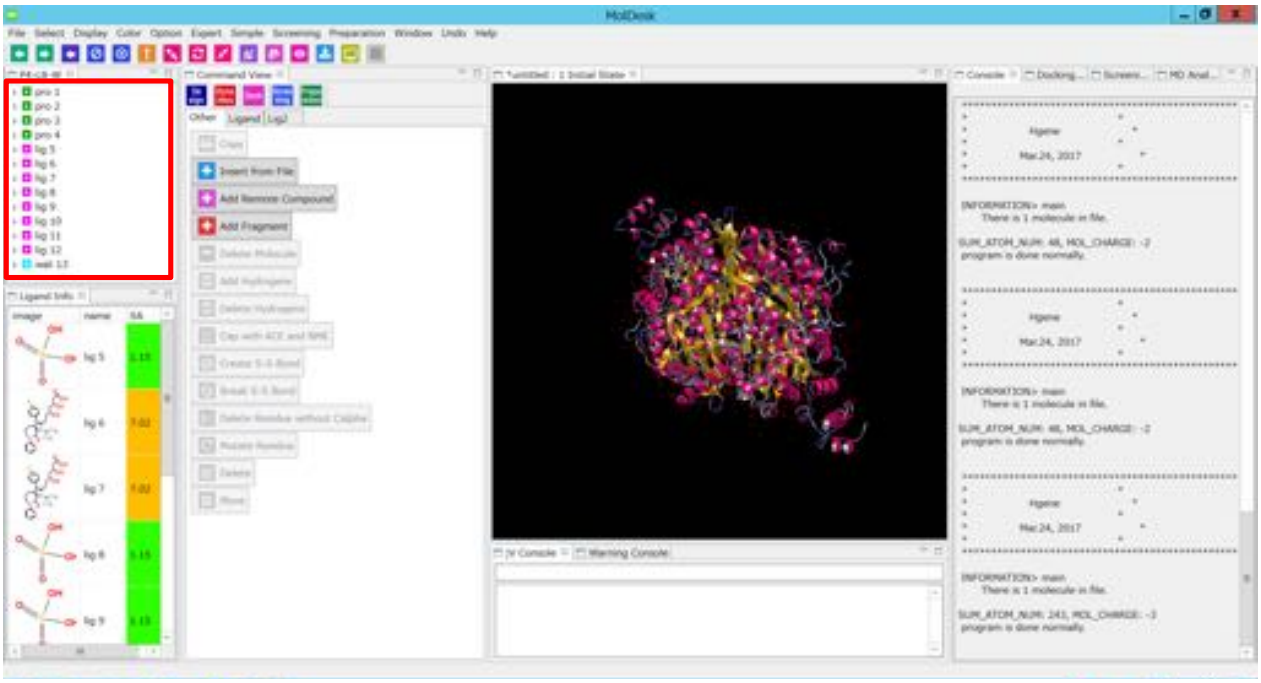

Fig. 7 Screen just after reading molecules

2.4. Deleting molecules not to be used

When you observe the complex structure (2Q6B) of the HMG-CoA reductase and inhibitor, it is found that there are four identical chains, four same inhibitors bind to four pockets, and each pocket locates between two chains. For this case, only one of pockets may be considered as the target site. We will leave only two chains and delete the other two chains. First, delete pro3 and pro4. When selecting multiple molecules, use the Ctrl key or Shift key. Alternatively, click pro3 with the mouse, hold down the Ctrl key on the keyboard, and click pro4 with the mouse. In the tree view, if you select molecules that are sequentially aligned at once, you can select multiple molecules by clicking on the first molecule and holding down the Shift key and clicking on the last molecule.

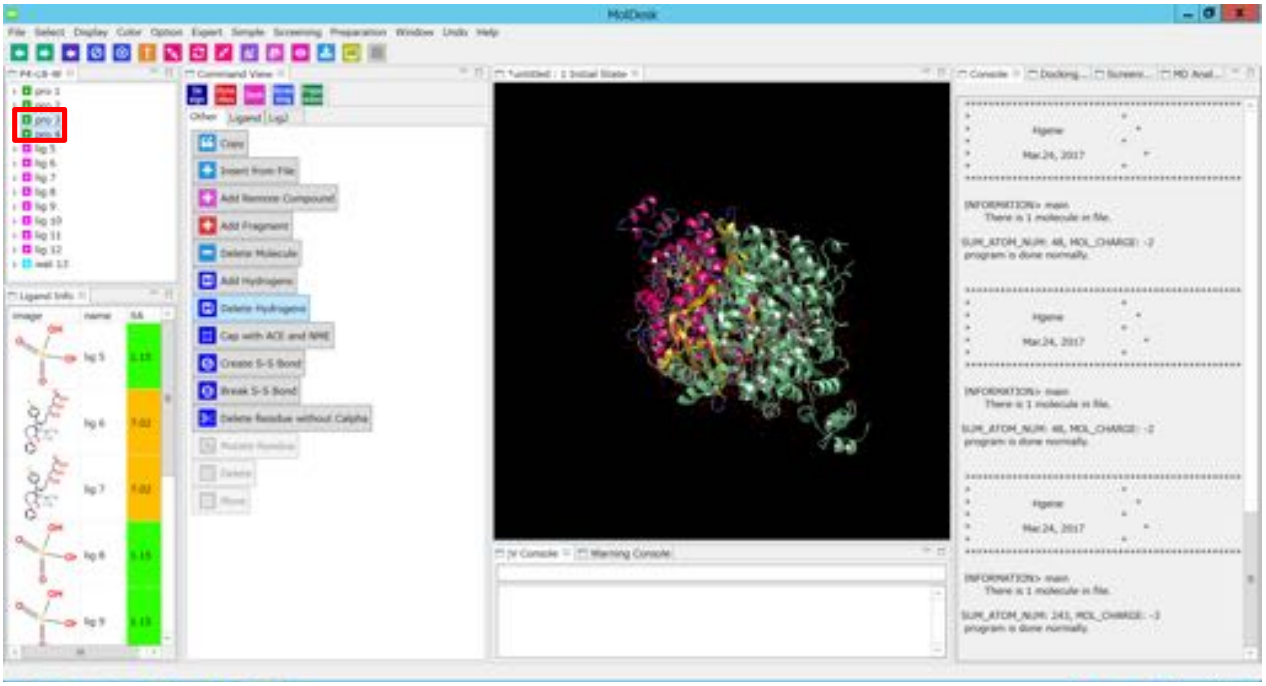

Fig. 8 Selecting pro3 and pro4

After selecting both pro3 and pro4, click the "Delete Molecule" button in the command view, indicated with a red frame in Fig. 9. If there is no "Delete Molecule" button, switch tabs of the Command View.

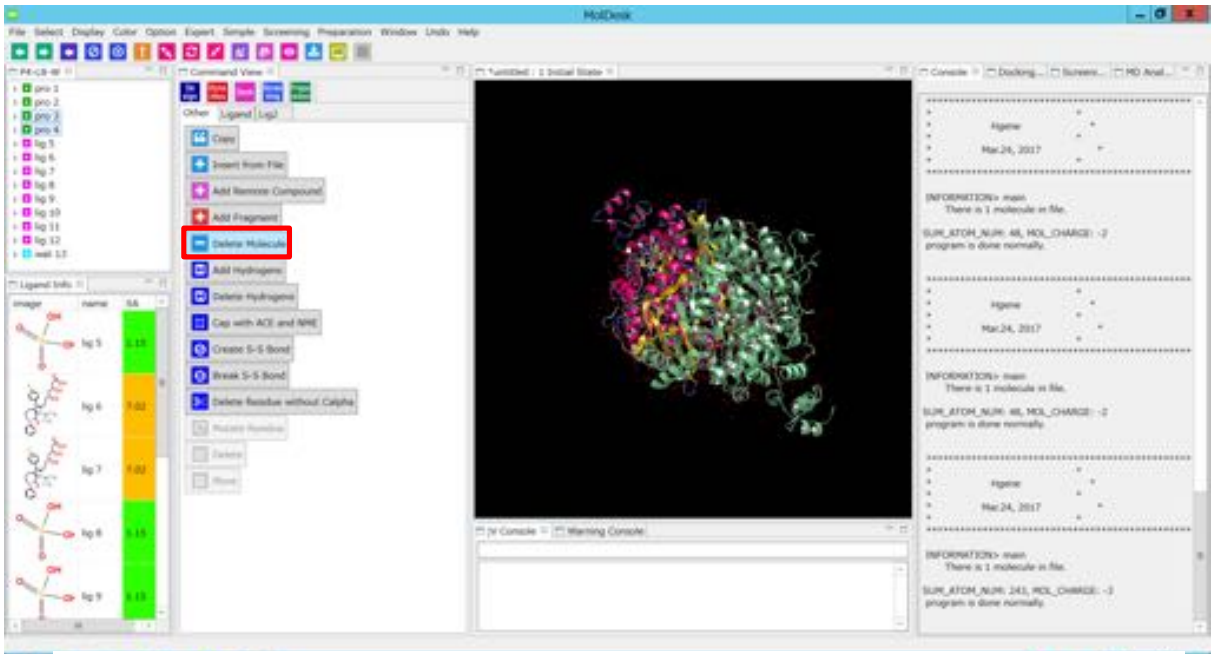

Fig. 9　Deleting selected molecules

Even if pro3 and pro4 are deleted, the right numbers of lig and wat retain the numbers assigned first (Figure 10). At this time lig6 and lig7 are inhibitors. Since both are the same molecule and are considered to be an equal relationship, we will make the site to which lig6 is bound as the target site. Delete ligands and water molecules (lig 5, lig 7 ~ lig 12, wat 13) other than lig 6 bound to the target site by the operation like deleting pro 3 and pro 4.

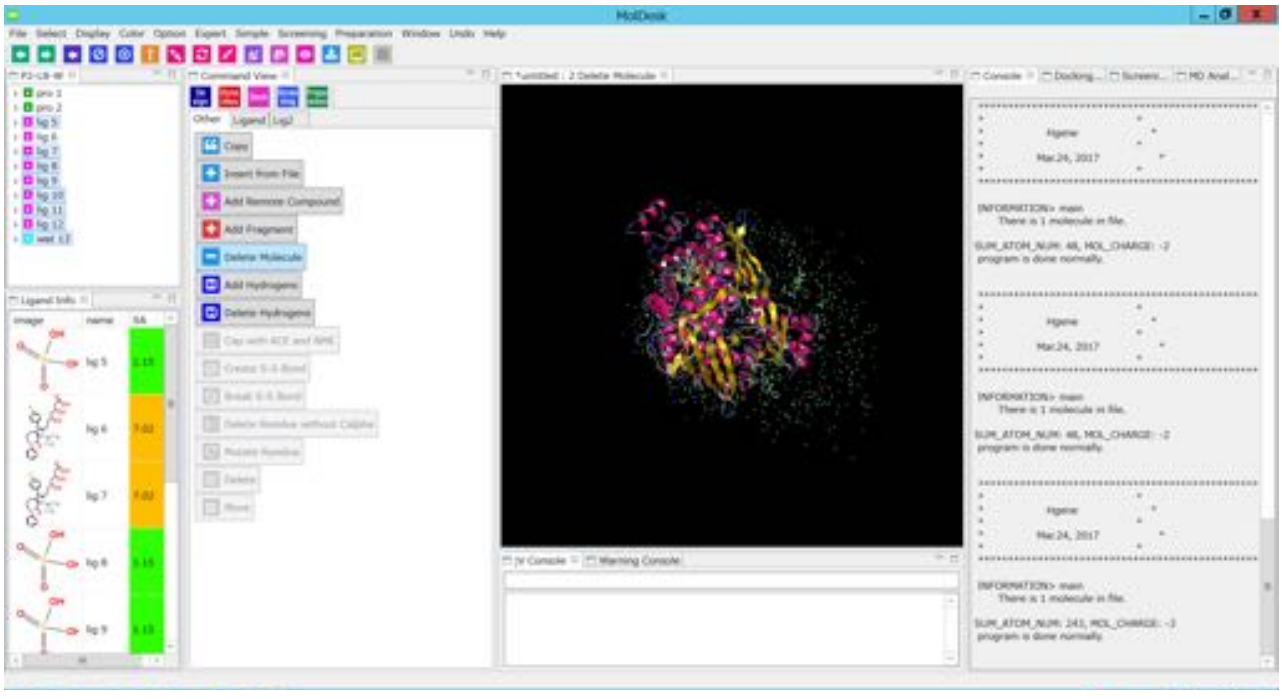

Fig. 10 Screen after deleting pro3 and pro4

Figure 11 shows the screen after deleting the unnecessary molecules.

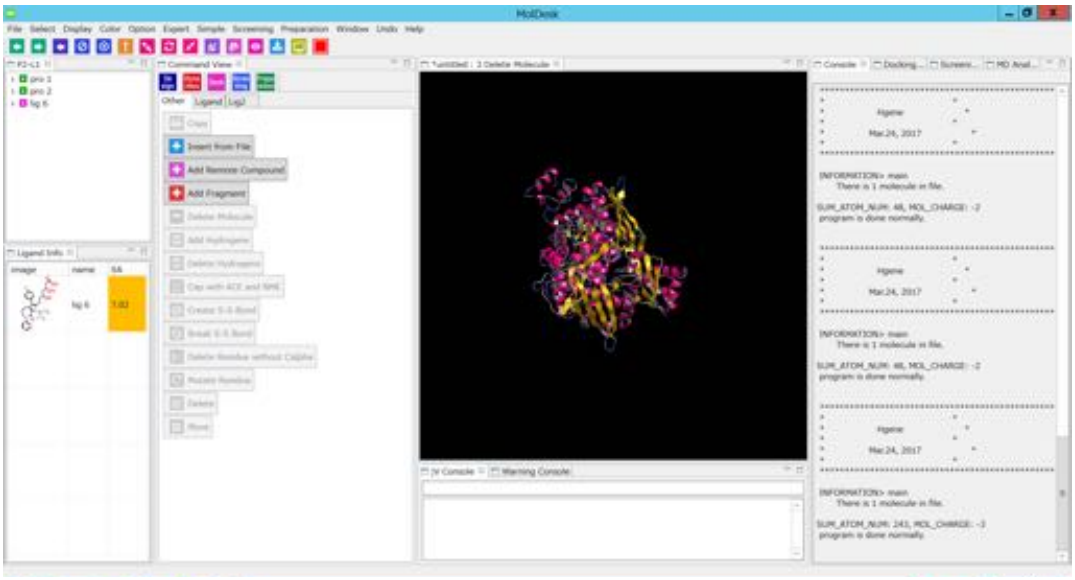

Fig. 11 Screen after deleting the unnecessary molecules

When molecules are difficult to see, space filling display makes it easier to see. Figure 12 shows the screen with the space filling indication of the inhibitor (select lig6 → "Display" → "Space Filling" → "Only").

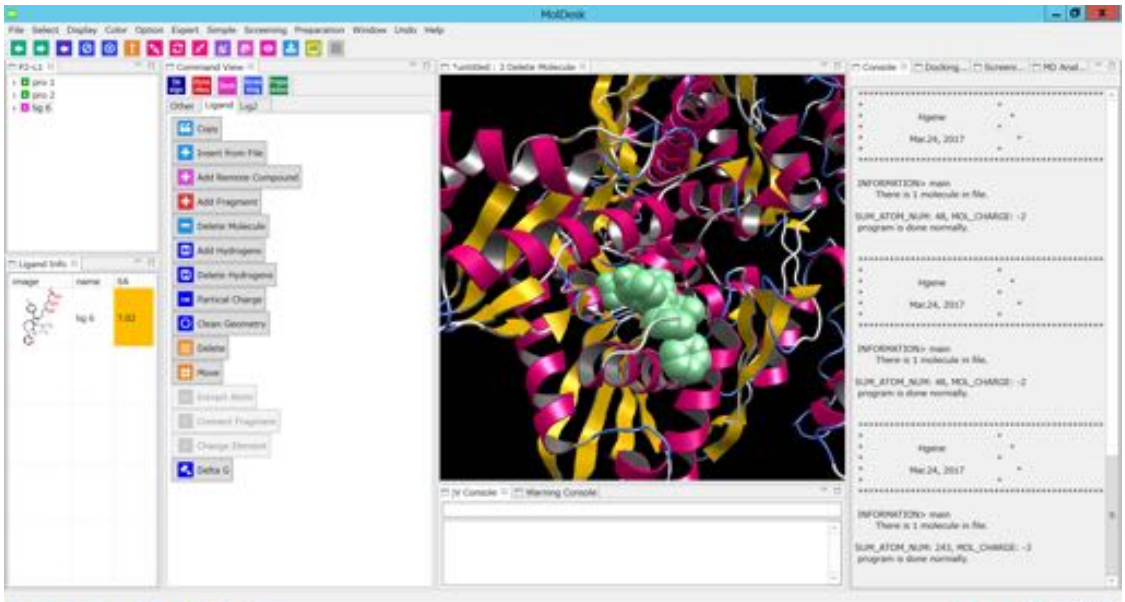

Fig. 12　Screenshot where a ligand is drawn with space filling

2.5. Creating probe points for docking calculations

This section describes performing the test docking before the screening calculation. In order to perform docking calculation, it is necessary to first create probe points to specify the target site. To create probe points, we here use coordinates of existing molecules as probe points. In the tree view, select molecules that use coordinates as probe points. In this case, click lig6. Then click "Make Pocket".

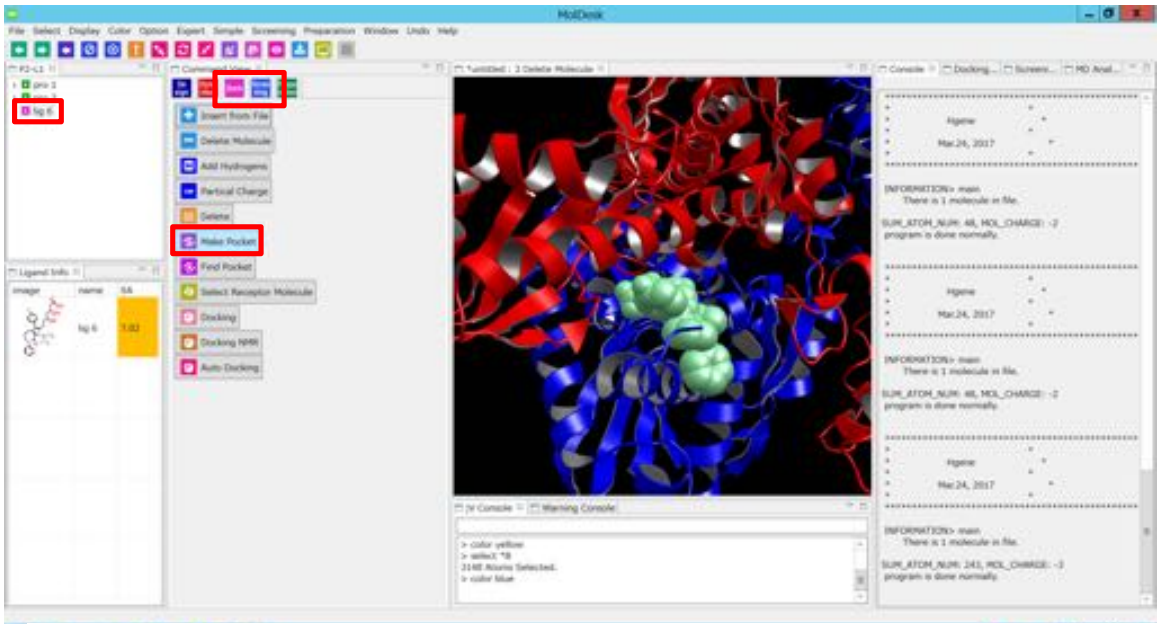

Fig.13 Creating probe points for docking

point7 newly appeared in the tree view after executing "Make Pocket" (Figure 14).

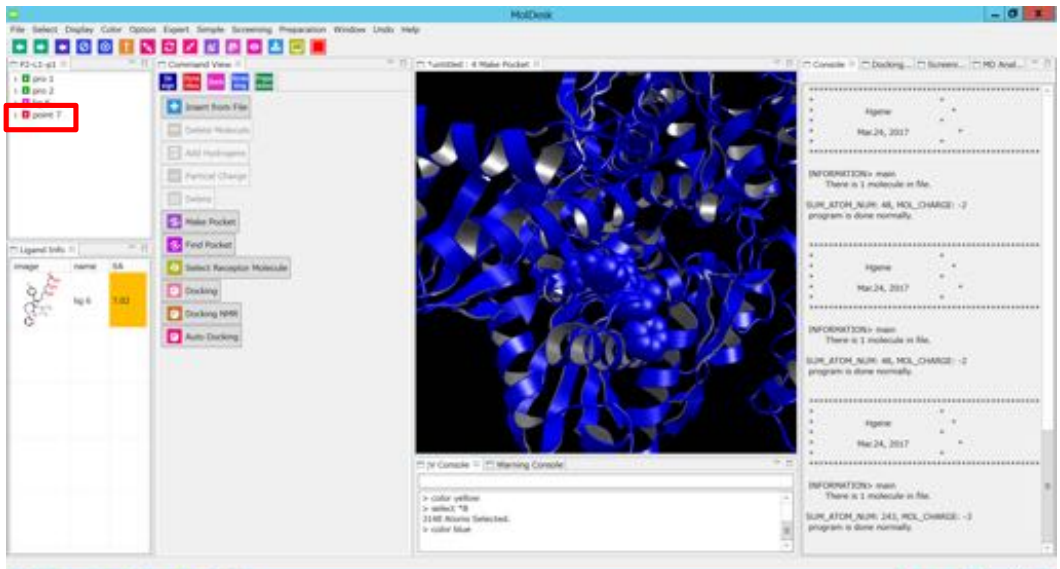

Fig. 14 Snapshot after creating the probe points

Let's hide lig6 to see the created probe points. Select "Hide Atom" from the pulldown menu that appears by right-clicking lig6 in the tree view.

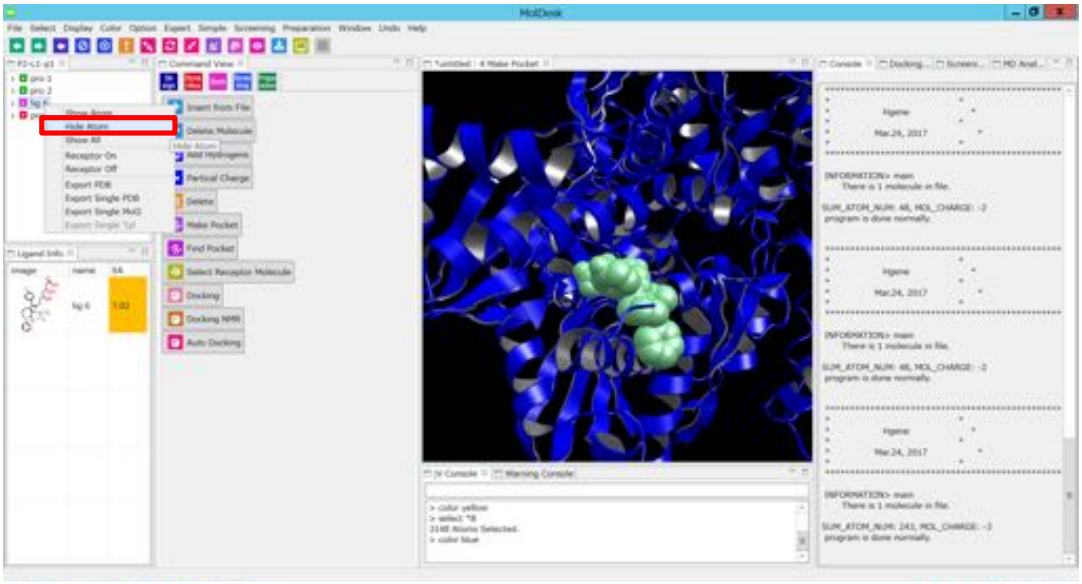

Fig. 15 Hiding a molecule

Probe points can be confirmed by hiding lig6 (Figure 16).

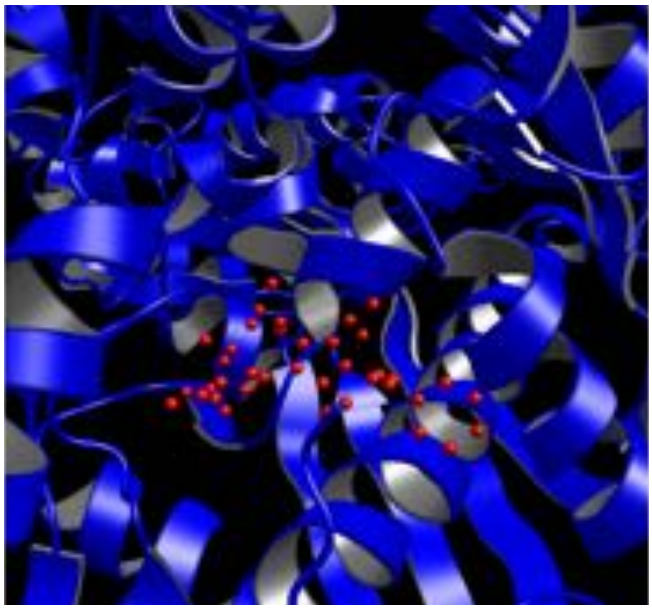

Fig. 16 Probe points created

2.6. Selection of a receptor protein

We will designate the receptor protein. Here we use both pro1 and pro2 as receptor proteins. After selecting pro1 and pro2 (shift key / press ctrl key to select), select "Select Receptor Molecule" in command view.

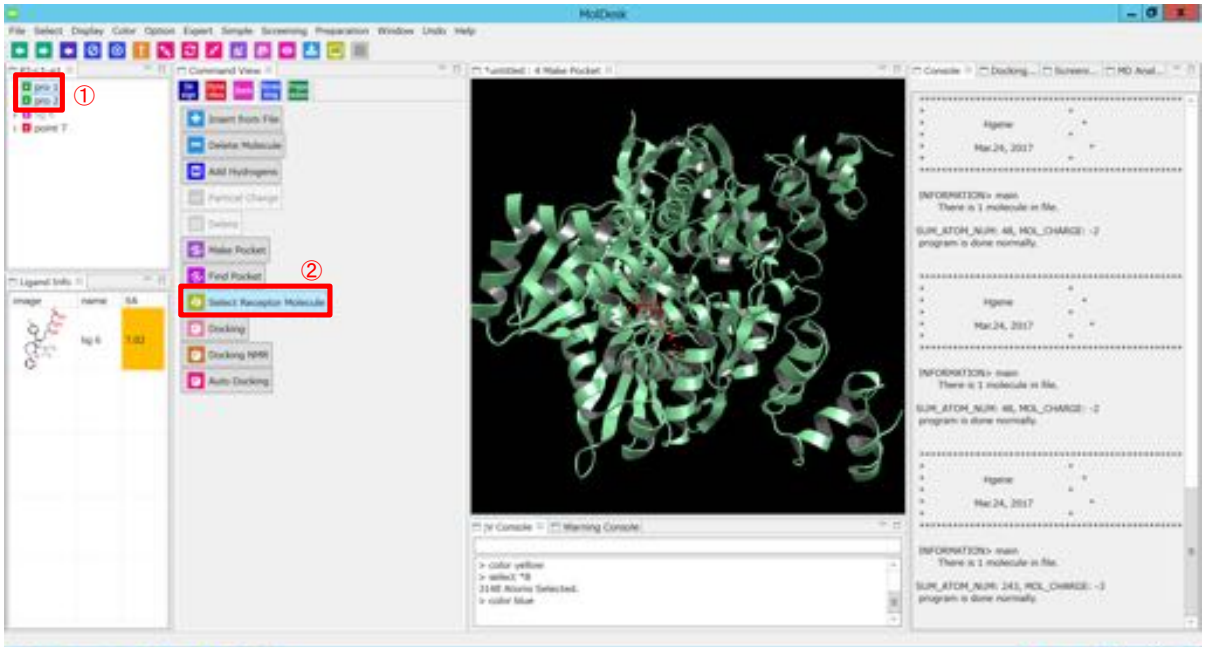

Fig. 17 Screenshot just after selecting receptor proteins

2.7. Preparation of a ligand for docking

Next, we will prepare a ligand for docking. Ligands used for docking must have (1) hydrogen atoms, (2) partial charge information, and (3) 3D structure coordinates. Here we use a ligand contained in the X-ray crystal structure, so (3) is unnecessary.

Right click on lig6 in the Tree View → "Show Atom" to redisplay hidden lig6. To observe the state of hydrogen addition, stick display should be better than space filling display. Select lig 6 in the Tree View and select Display in the menu bar → Stick → Only.

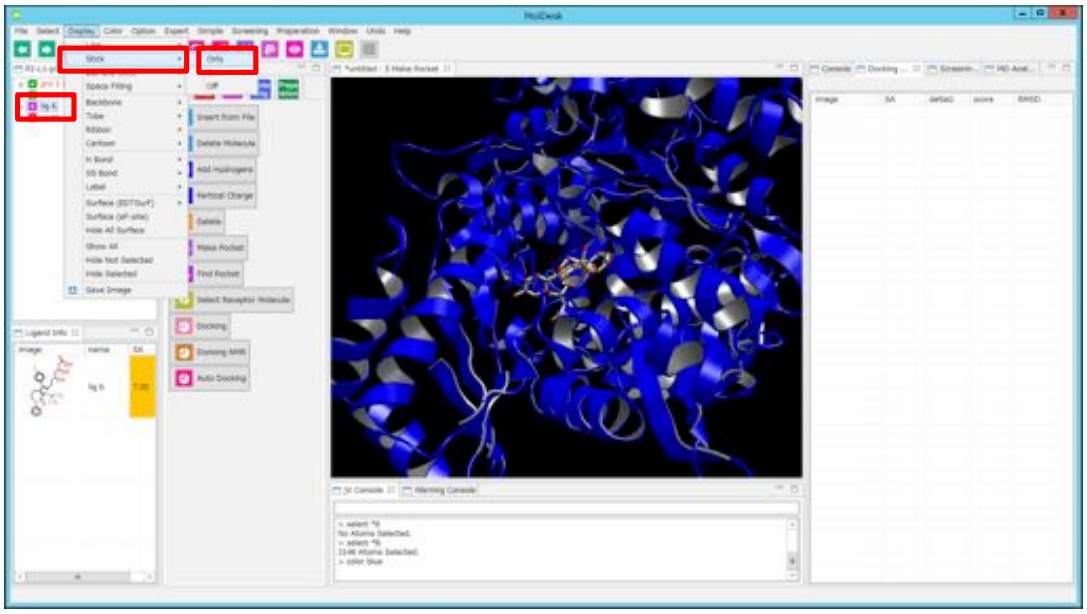

Fig. 18 Screenshot where a ligand drawn with stick

To add hydrogen atoms, select lig6 in Tree View and click "Add Hydrogens" in Command View.

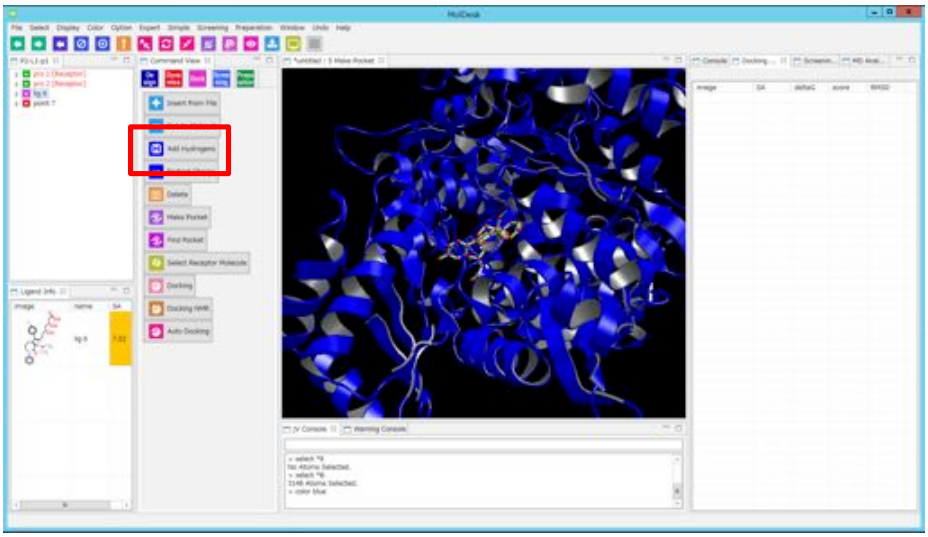

Fig. 19 Add Hydrogens

Running "Add hydrogens" may change the color of the ligand. Let's change the color of lig6 for easy viewing. After selecting lig6, select the "Color" in the menu bar -> "Atoms" -> "Cpk".

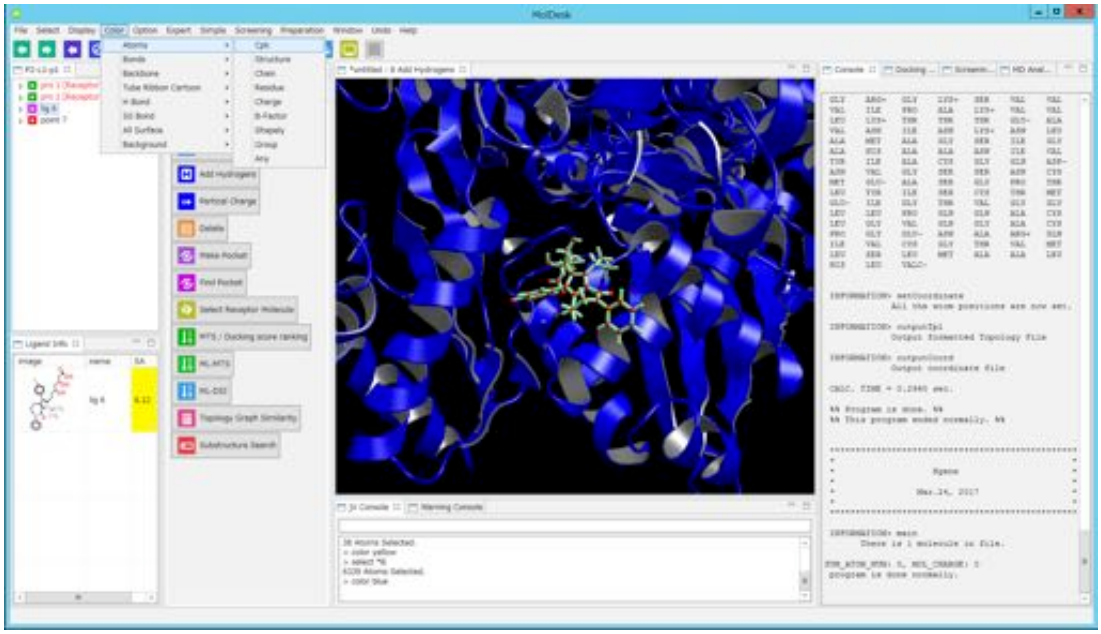

Fig. 20 Changing the color of a ligand

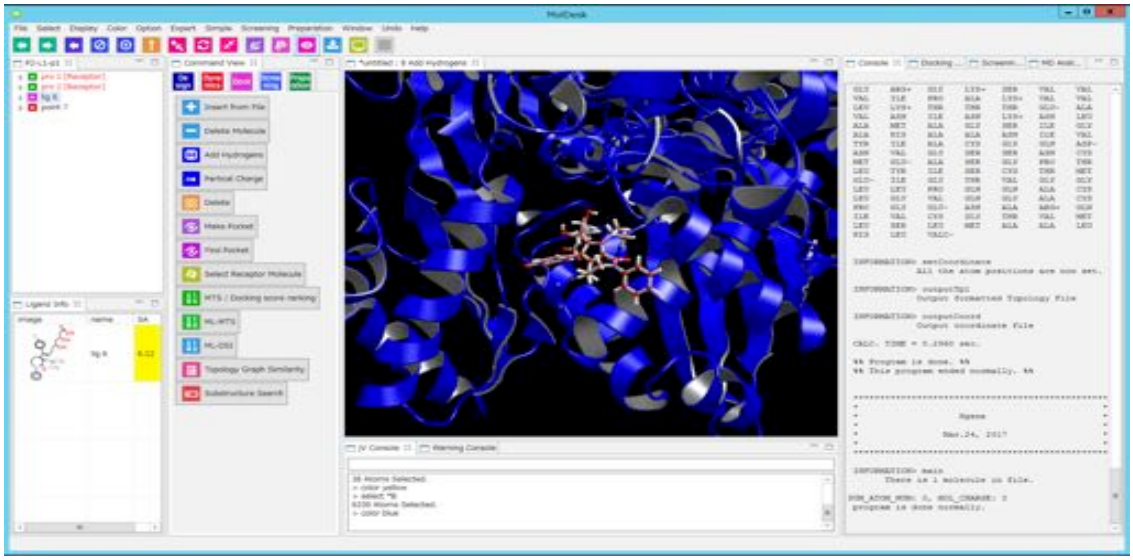

Fig. 21 Screenshot after changing the color of a ligand

Next, partial charge information will be added to lig6. Select lig6 in Tree View and click "Partial Charge". In the dialog that come out, select "MOPAC7 AM1 BCC" and then click OK.

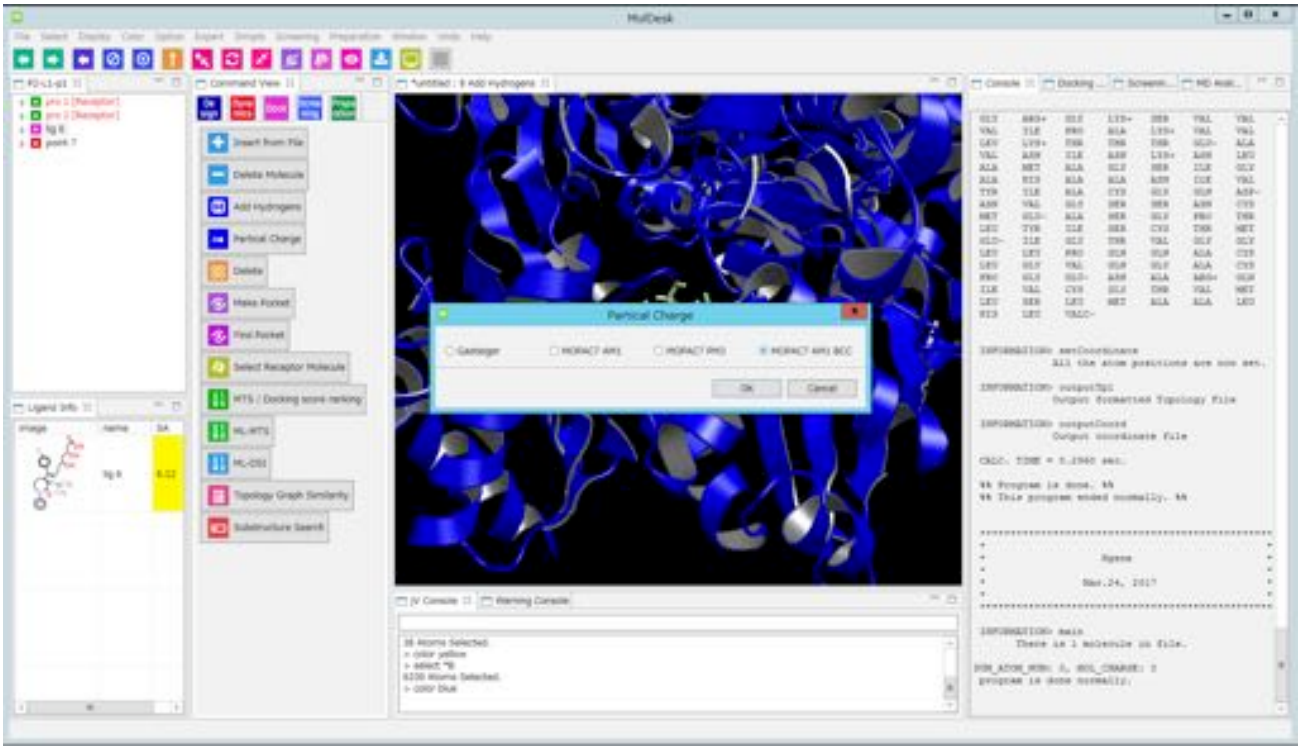

Fig. 22 Screenshot after setting receptor proteins

2.8. Execution of docking

When preparation of the compound is completed, click "Docking" button to start docking. Clicking "Docking" will bring up a dialog box to select the ligand to be docked.

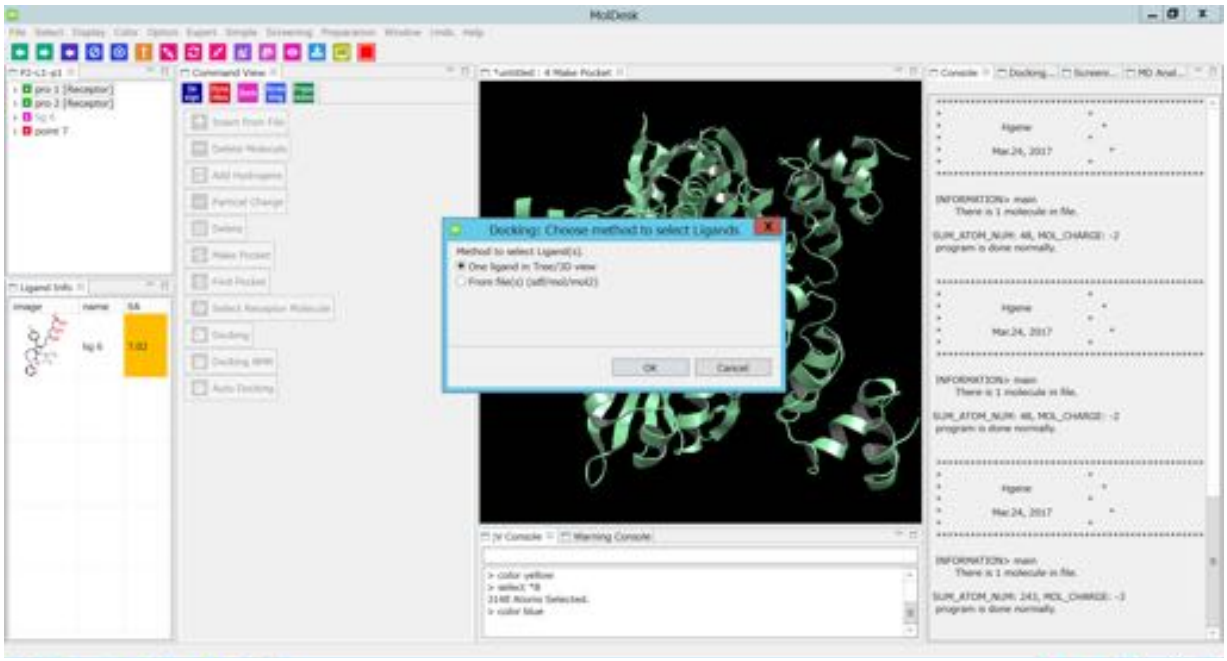

Fig. 23 Dialog for choosing method to select ligand(s)

In this case, select the "One ligand in Tree / 3D view" radio button and press the OK button. Furthermore, the dialog box of "Docking: Select Ligand" appears, so after selecting lig6, press the OK button.

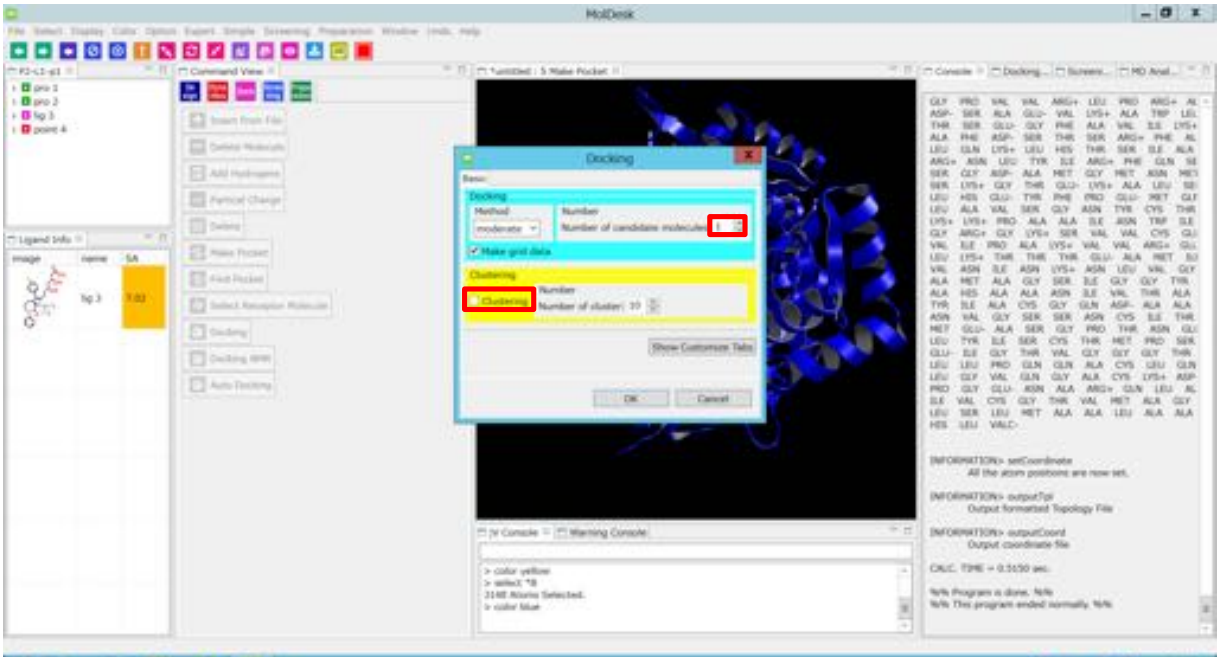

Fig. 24 Dialog box of the docking parameters setting

In this example, change "Number of candidate molecule" to 1, change Clustering to OFF, and press OK. Start docking. (At this point, lig6, point7 becomes lig3, point4.)

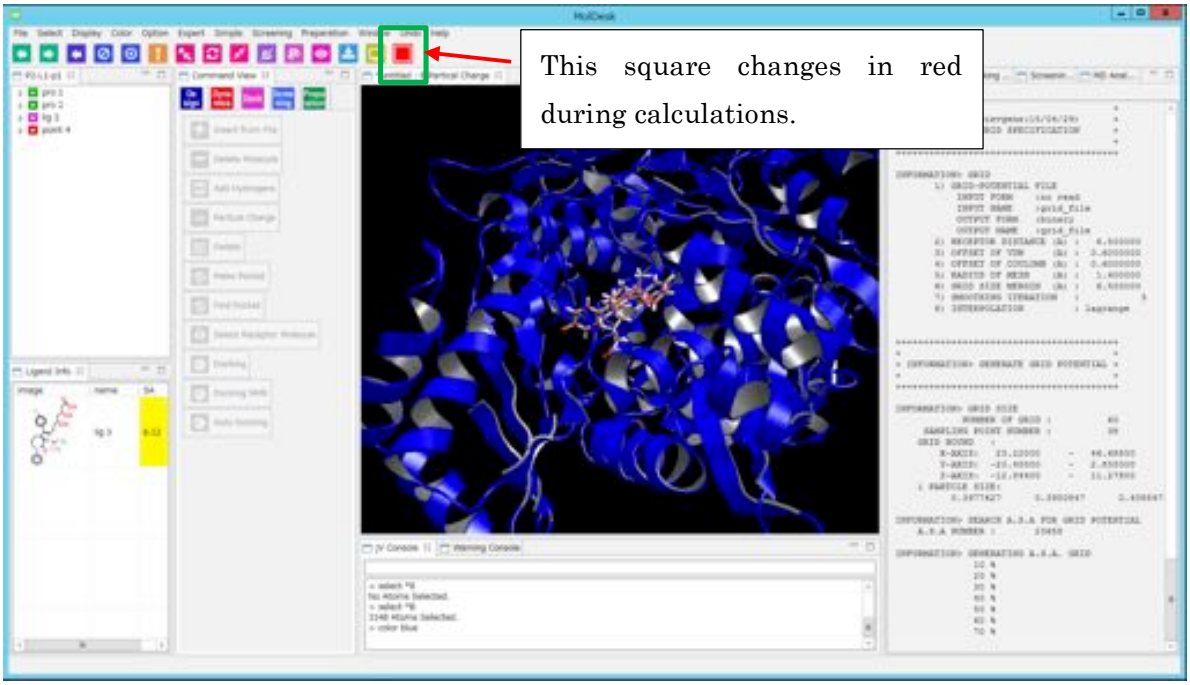

Fig. 25 Screenshot during a docking calculation

During docking calculation, the square mark icon in the icon bar turns red. You can also check the progress of calculation from the console screen. (If not shown, Window → console) When the docking calculation is completed, the red icon will be grayed out and the docking pose will appear in the docking info. The 3D structure is displayed on the screen by right clicking on the docking pose in the Docking Info and clicking "Add Selected Docking Result". At that time, lig5 is added to the left window

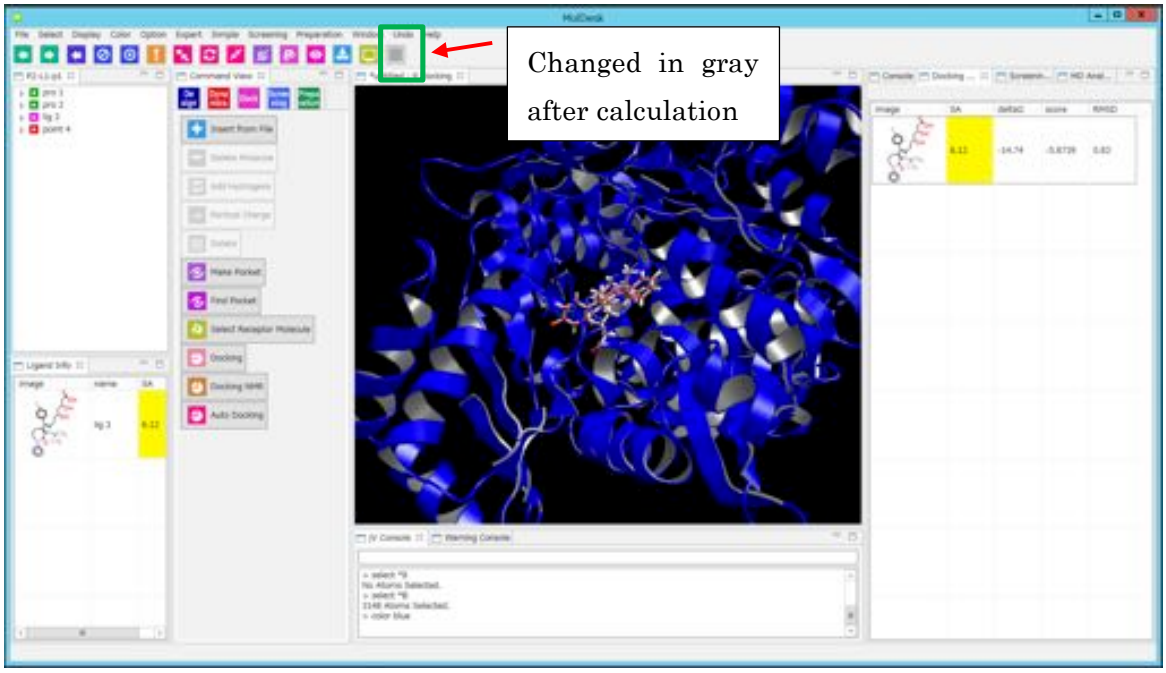

Fig. 26 Screenshot after completing a docking calculation

Here, in order to make the result of docking easier to see, try to hide the proteins. Select pro1 and pro2, right click and select "Hide Atom" from the menu that appears.

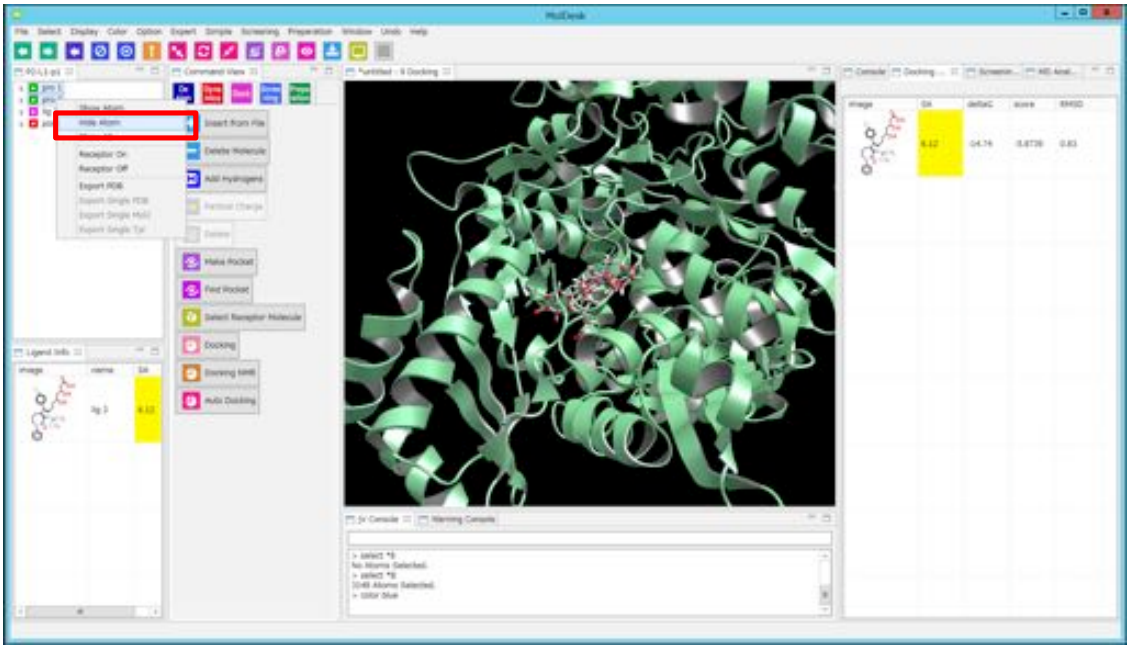

Fig. 27 Hiding a protein

Let's hide the probe point in the same way. Right click point 4 in Tree View and select "Hide Atom".

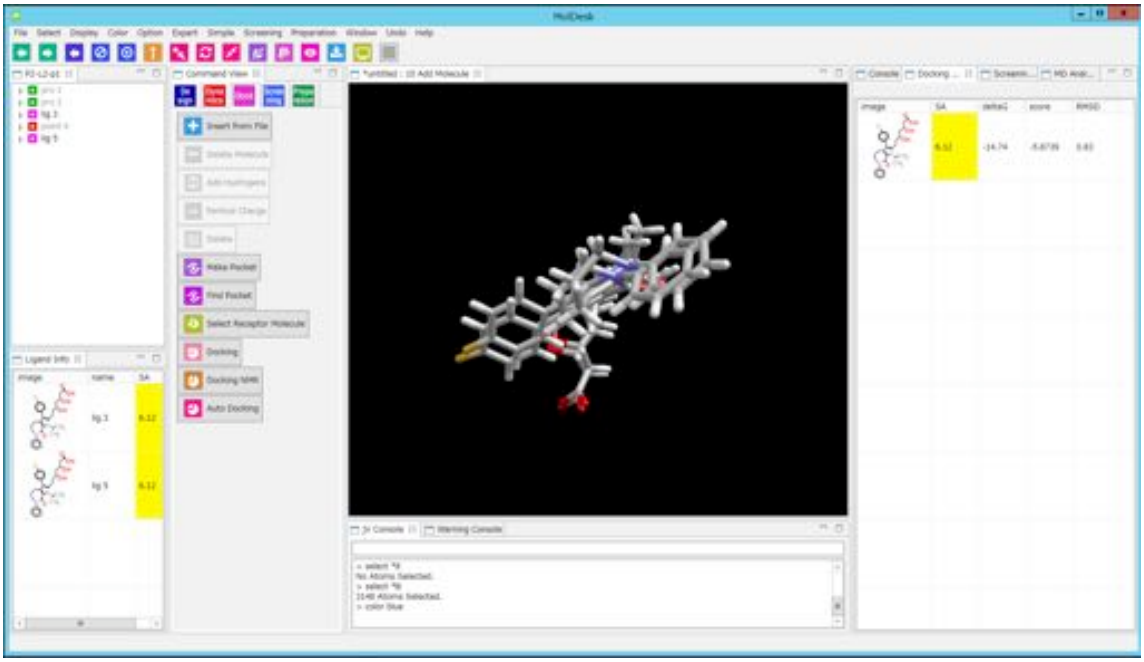

Fig. 28 Comparison between a pose of X-ray crystal structure and a re-docking pose

3. Auto docking

3.1. Preparation

Here we will execute the docking with easier method using "Auto Docking" in the Docking tab. In the following, we will use the same 2q6b as above and delete unnecessary molecules (delete pro3, pro4, lig5, lig7-lig12, wat13).

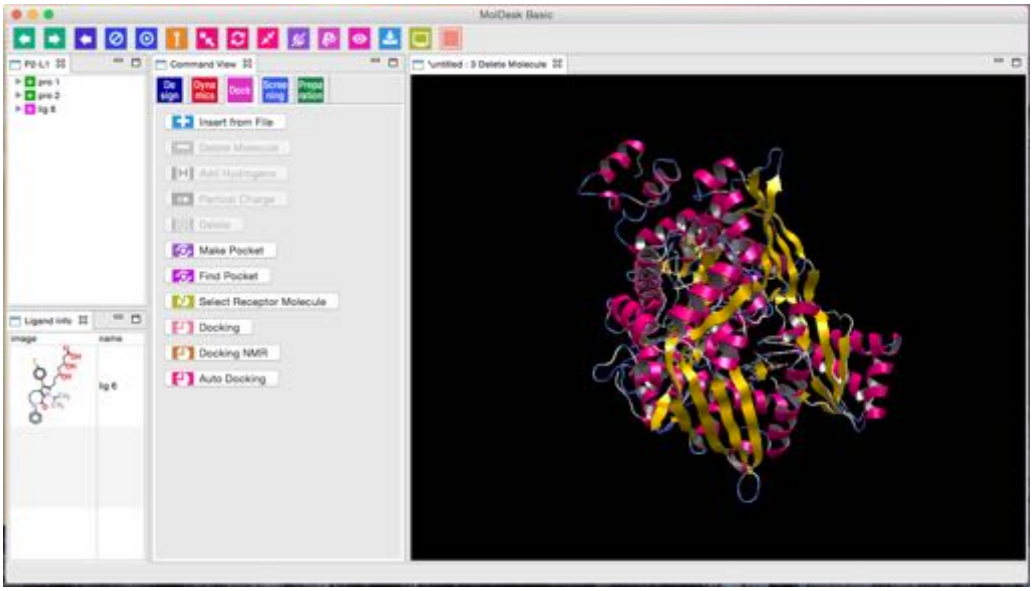

Fig. 29 Screenshot after deleting molecules which are not used for calculations

3.2. Starting auto docking

After deleting unnecessary molecules, click "Auto Docking" in the Docking tab.

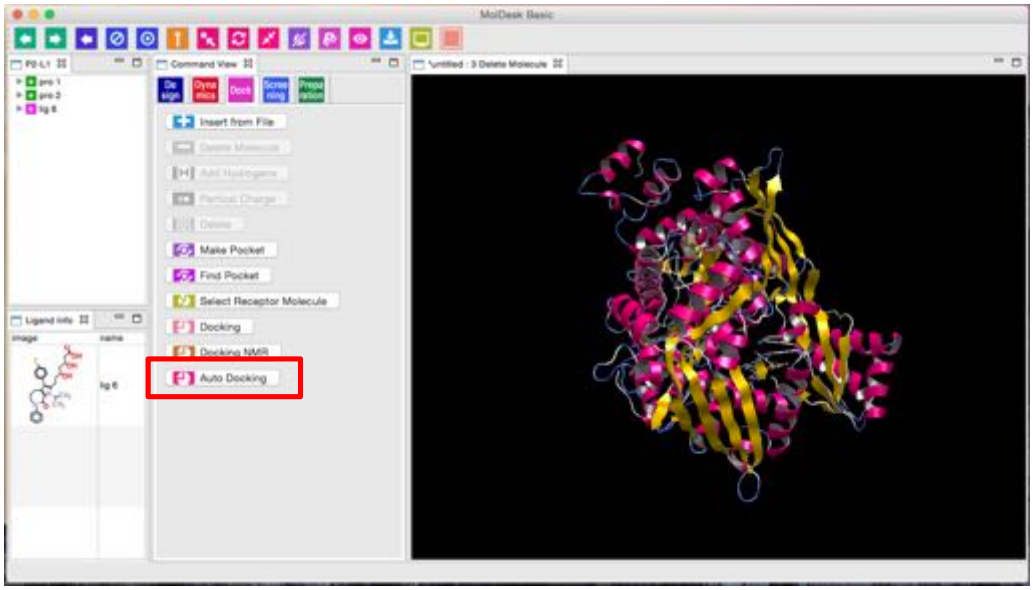

Fig. 30 Starting "Auto Docking"

3.3. Selection of receptor protein

After you click the "Auto Docking" button, first you are asked to select the receptor protein to be used for docking, so select the receptor protein and then click the "OK" button in the dialog. Here we designate both pro1 and pro2 as receptor proteins.

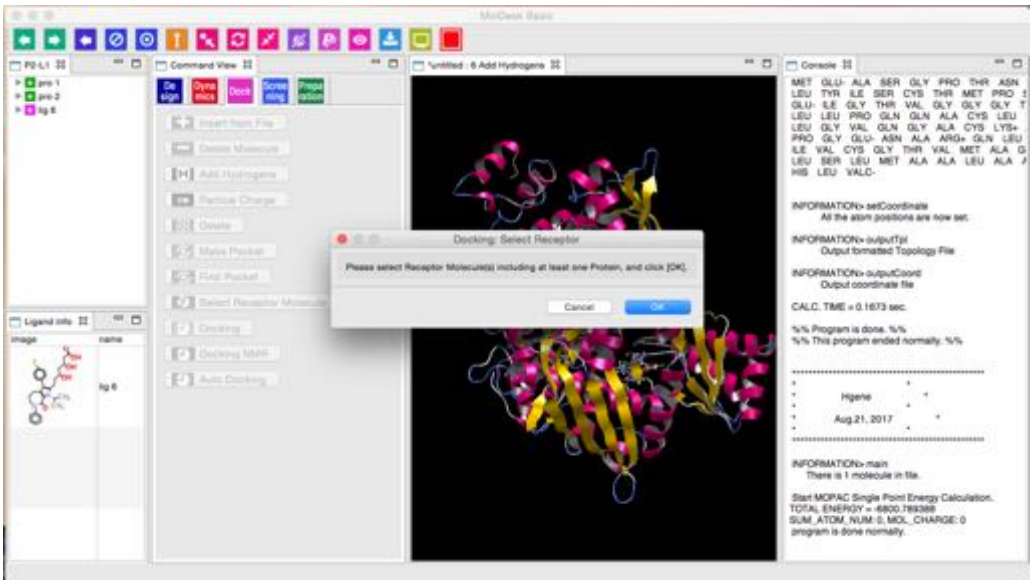

Fig. 31 Selection of receptor molecules

If you press OK here, [Receptor] appears next to pro1 and pro2 in the Tree View.

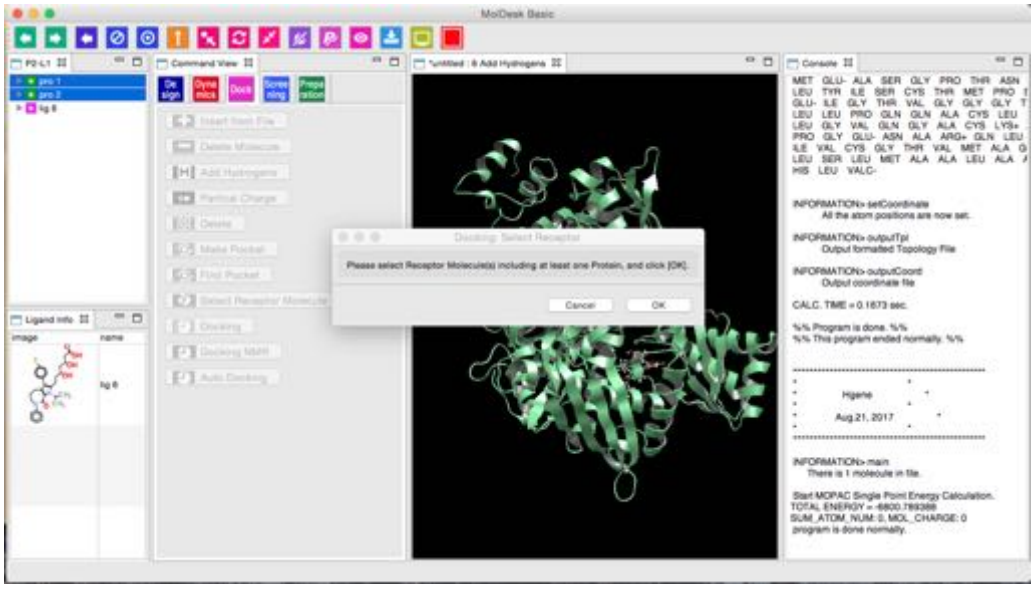

Fig. 32 Screenshot of the dialog box for selecting receptor proteins

3.4. Creating probe points for docking

Create probe points that specifies the docking. There are several ways to create probe points, but here we use the coordinates of the ligand molecules of the X-ray crystal structure as probe points. From the dialog box that came out, select the "Coordinates of the ligand" and press OK.

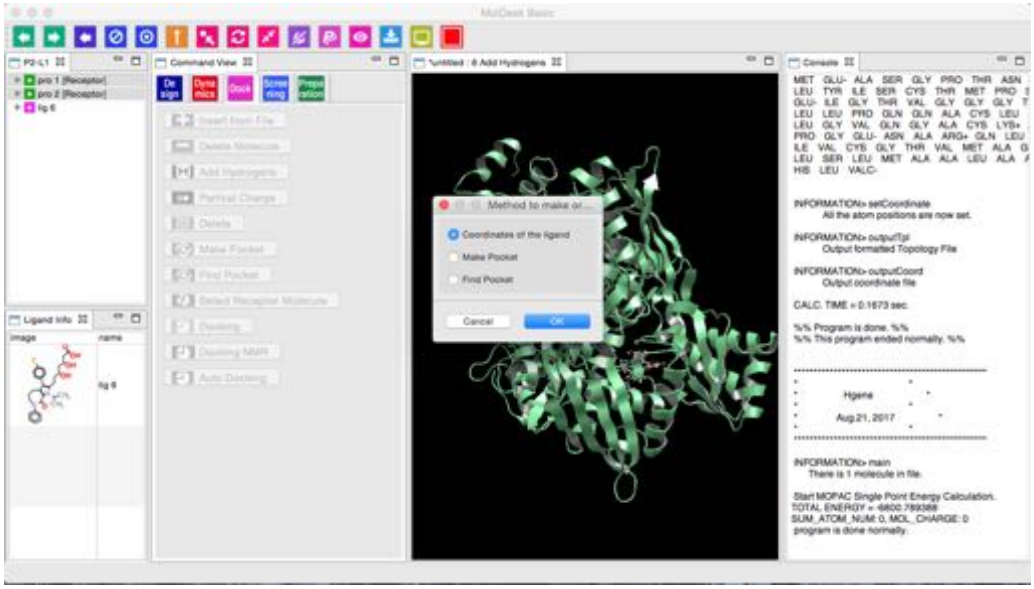

Fig. 33 Selecting method to create probe points

Now select a molecule for using its atomic coordinates as probe points and press OK. Here we select lig6. After clicking OK, point7 will appear in the Tree View.

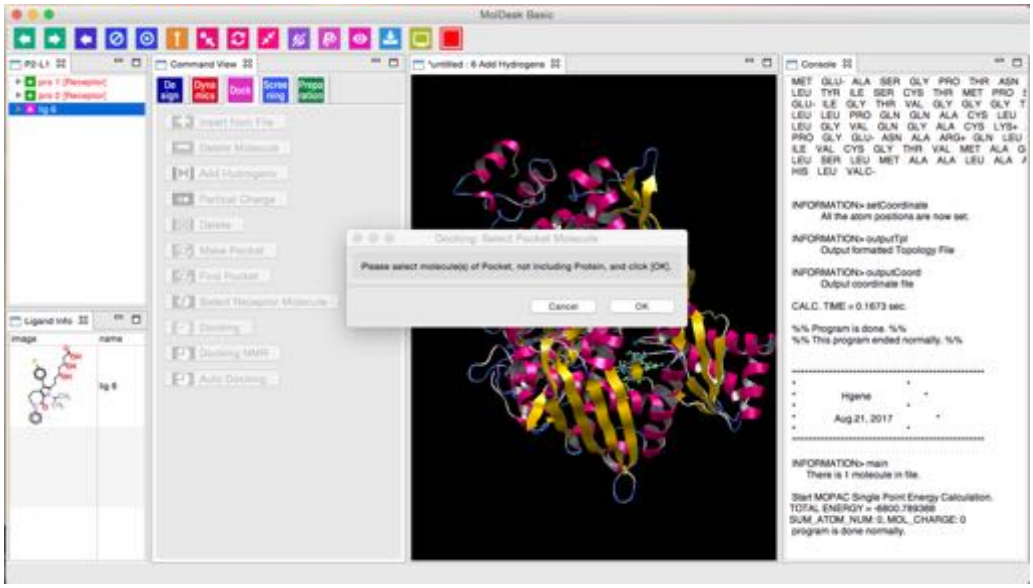

Fig. 34 Screenshot of the dialog box of Select Pocket Molecule

3.5. Selection of a ligand to be docked

Next, specify a low molecular compound to be docked. In this case, select lig6 and press OK.

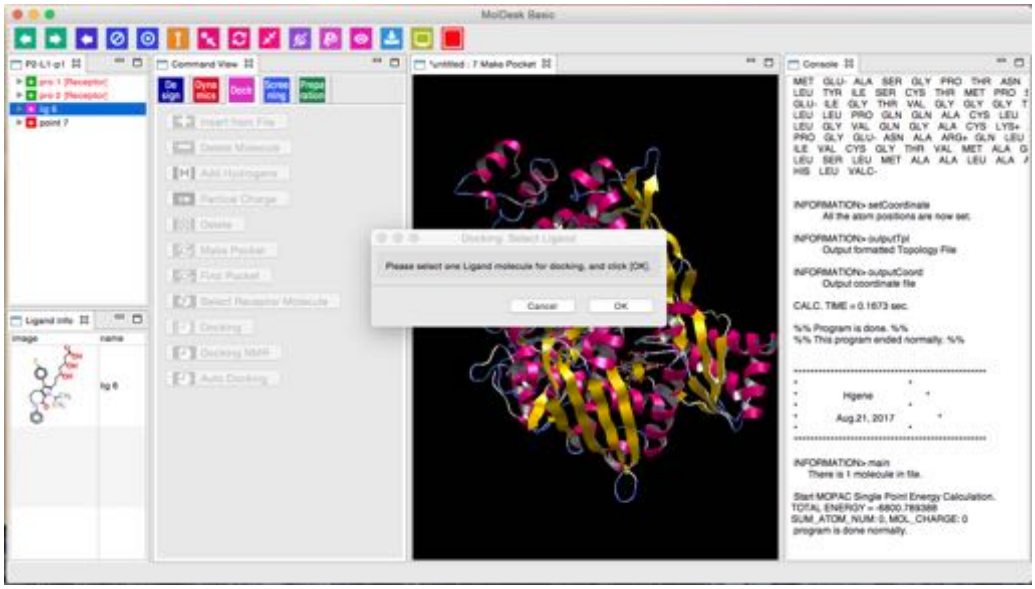

Fig. 35 Choosing a molecule

3.6. Setting of docking conditions

Finally, enter the docking conditions and click OK to start docking calculation. In this case, we set Number of candidate molecules to 1 and tick off the Clustering check box.

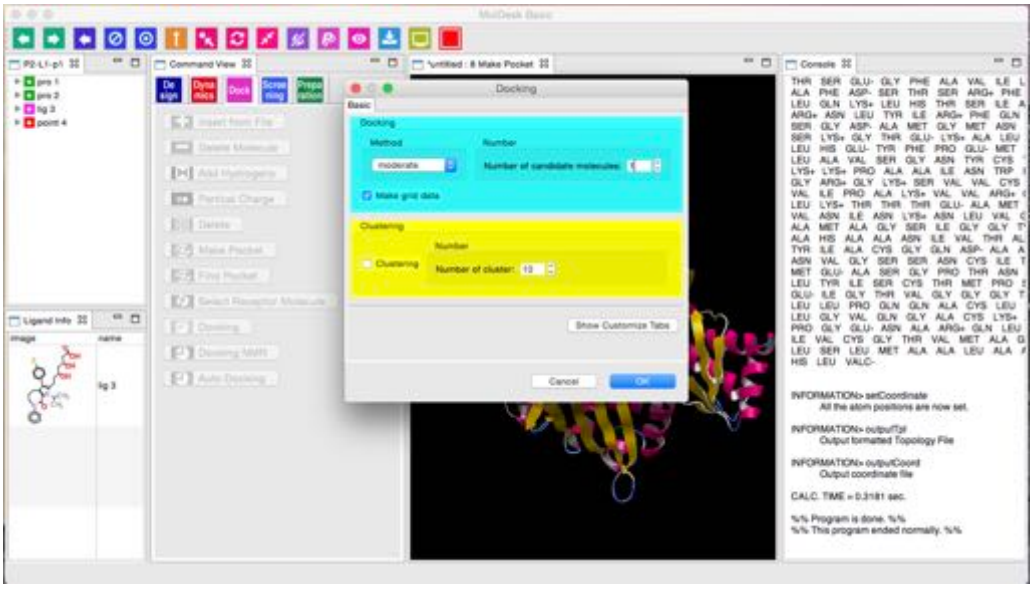

Fig. 36 Setting of docking parameters