

# MOLECULAR DOCKING CALCULATIONS UTILIZING DISCOVERY STUDIO & PIPELINE PILOT (October 21<sup>st</sup>, 2021)

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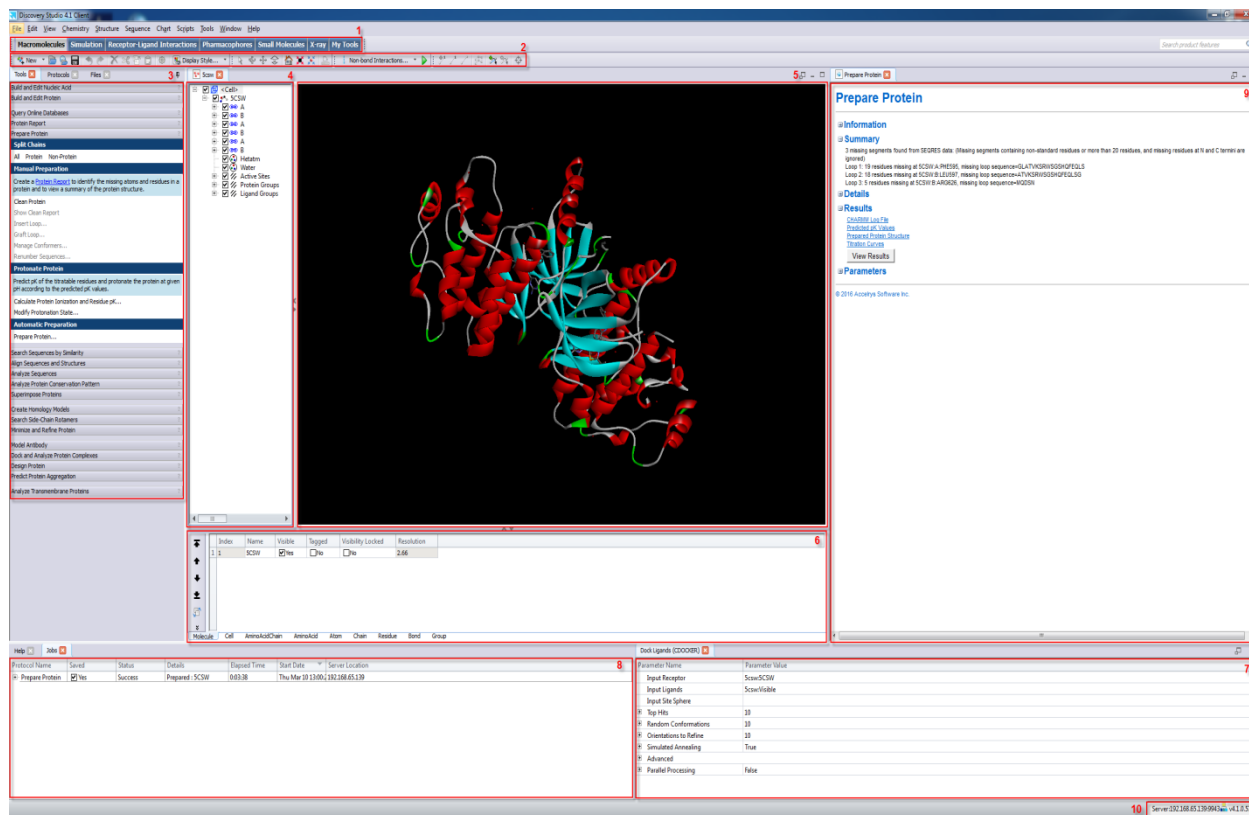
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# A quick introduction to Discovery Studio (DS) user interface



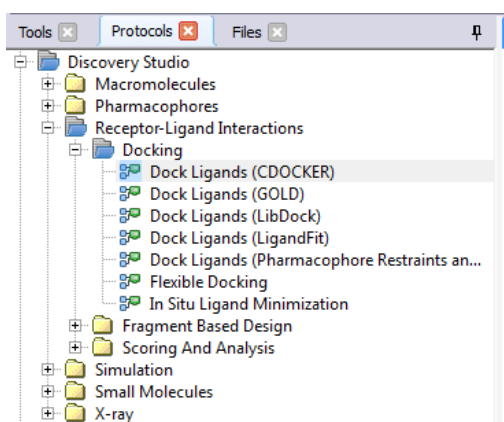
1. Tool panels (Macromolecule, Simulation, Receptor-Ligand Interactions, etc.)
2. Toolbars
3. Tool panel collections
4. Hierarchy tree view
5. Molecule window
6. Molecular detail and navigation panel
7. Protocol parameter window
8. Jobs explorer
9. Results window
10. Server status

## DS protocols for structure-based design (SBD)

Discovery Studio is equipped with six different protocols for structure-based drug design:

1. CDOCKER (a grid-based molecular docking method that employs CHARMM forcefield)
2. GOLD (genetic algorithm for docking flexible ligands into a protein binding site)
3. LibDock (algorithm for docking small molecules into an active receptor site)
4. LigandFit (shape-based docking with Monte Carlo conformational sampling)
5. CDOCKER with structure-based pharmacophore restraints
6. Flexible Docking (CDOCKER-based method allowing protein side-chains flexibility)

These protocols can be accessed under **Protocols tab > Discovery Studio > Receptor-Ligand Interactions > Docking subdirectory**.



**Note:** The Protocols tab (DS collections) might be unavailable in case the DS Client is not connected to the AEP server (see AEP server status in the right-down corner of the DS-GUI) due to several reasons:

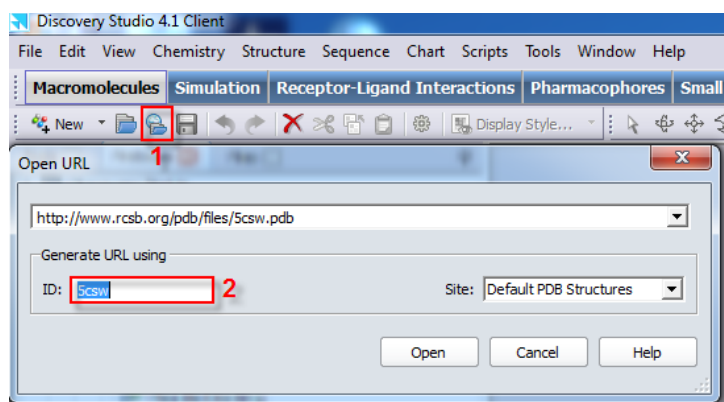
- The client-server connection is down because of technical issues.
- Another user is connected to the AEP server (licensing issues).

In case you are connected to the AEP server and the Protocols tab are not visible, you can enable it manually (**View > Explorers > Protocols**).

## Data accessibility and preparations for structure-based calculations

In order to perform structure-based (molecular docking) calculations in DS, the accessibility to structural data (e.g., a protein, a ligand, or ideally a protein-ligand complex) of the biological system under consideration is necessary (e.g., protein database repository – [www.rcsb.org](http://www.rcsb.org)). This can be done by downloading the X-ray, NMR or CryoEM structure manually from the [www.rcsb.org](http://www.rcsb.org) repository or in an automated fashion directly through the DS interface.

To automatically fetch the protein structure from the PDB repository in the DS environment, follow these two steps (see picture below):

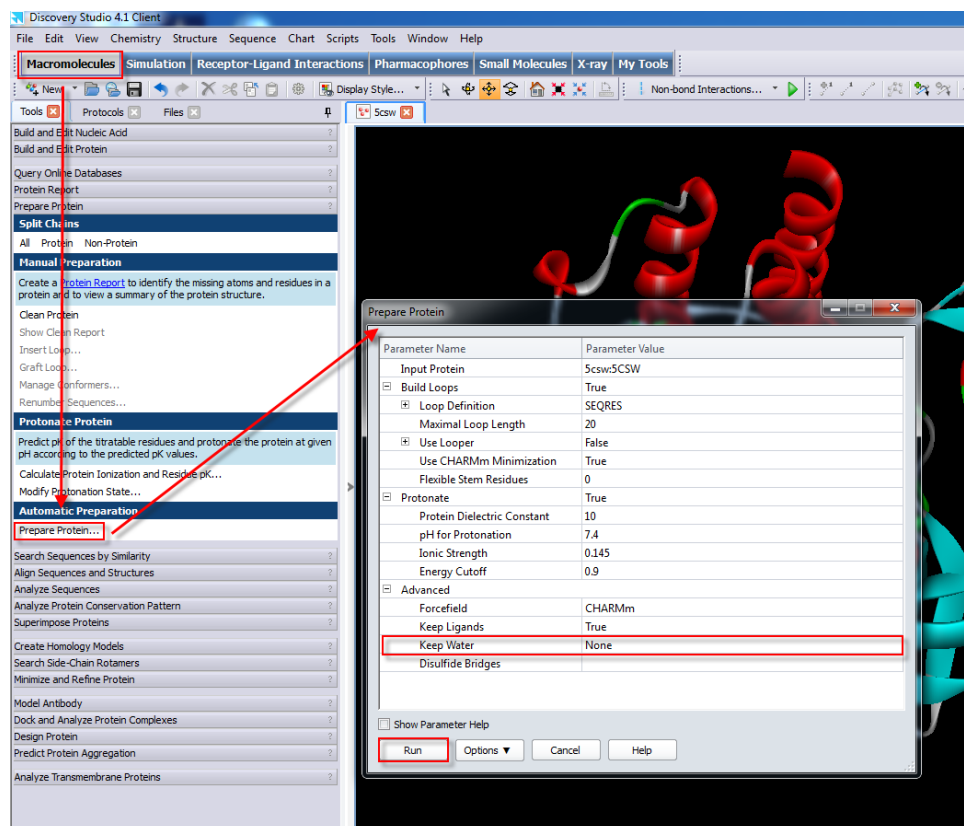


1. Click on the **Open URL** button on the toolbar.
2. Write-down the PDB **ID** of the needed structure and click on the **Open** button.

In this way, the downloaded structure will be automatically displayed in the **Molecule window** as **solid-ribbon** (see picture below).



In the next step, the downloaded protein structure should be prepared for structure-based calculations. To do this, click on the **Macromolecule tool panel** and open the **Prepare Protein** tools collection. Under the **Automatic Preparation** section click on **Prepare Protein** button. This will open the **Prepare Protein** parameter dialog (see picture below).

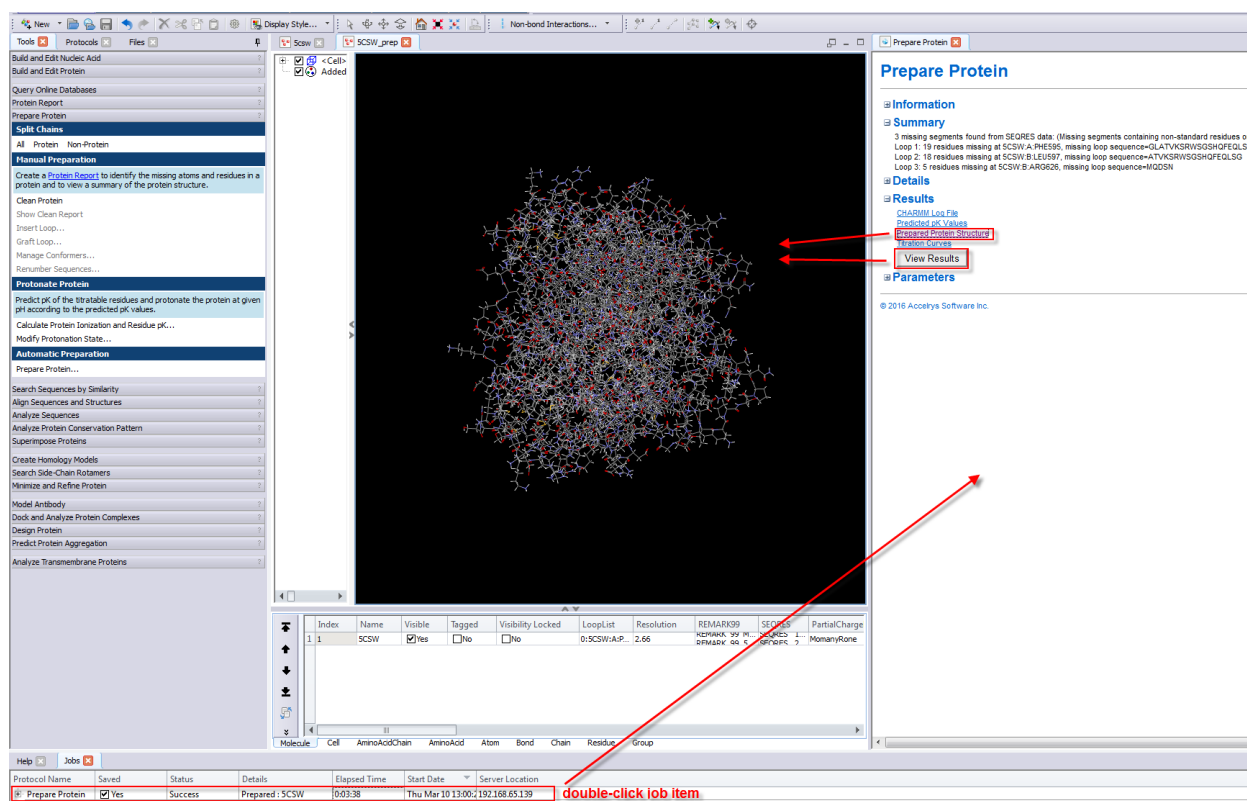


The default **Prepare Protein** settings usually give good results (e.g., missing loops will be added and minimized, crystal waters will be removed, the entire protein structure will be protonated, etc.).

As demonstrated on the picture above, **Keep Water** parameter is set to **None** by default that is good for most of the molecular docking calculations. Optionally, this parameter can be changed only in cases where some water molecules (usually surrounding the ligand in the binding pocket) are necessary for establishing ligand-protein interaction.

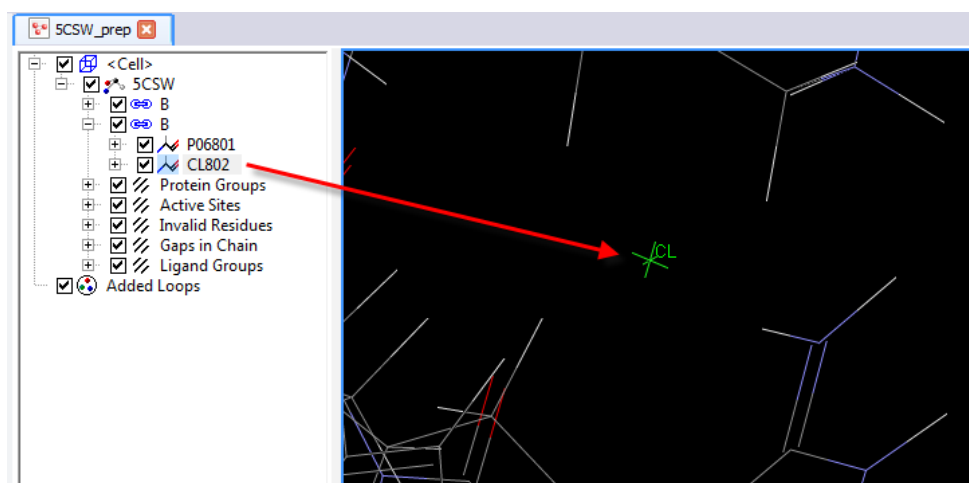
When all parameters are defined, just click on the **Run** button and check when Prepare Protein job is done (check the **job status** in **Jobs explorer**).

When Prepare Protein job is finished, double click the item in the Jobs explorer. This will open the **Results window** containing the job results. To visualize the prepared protein, click on the **Prepare Protein Structure** link or **View Results** button. The prepared protein structure will be opened in a **new Molecule window** (see next picture).



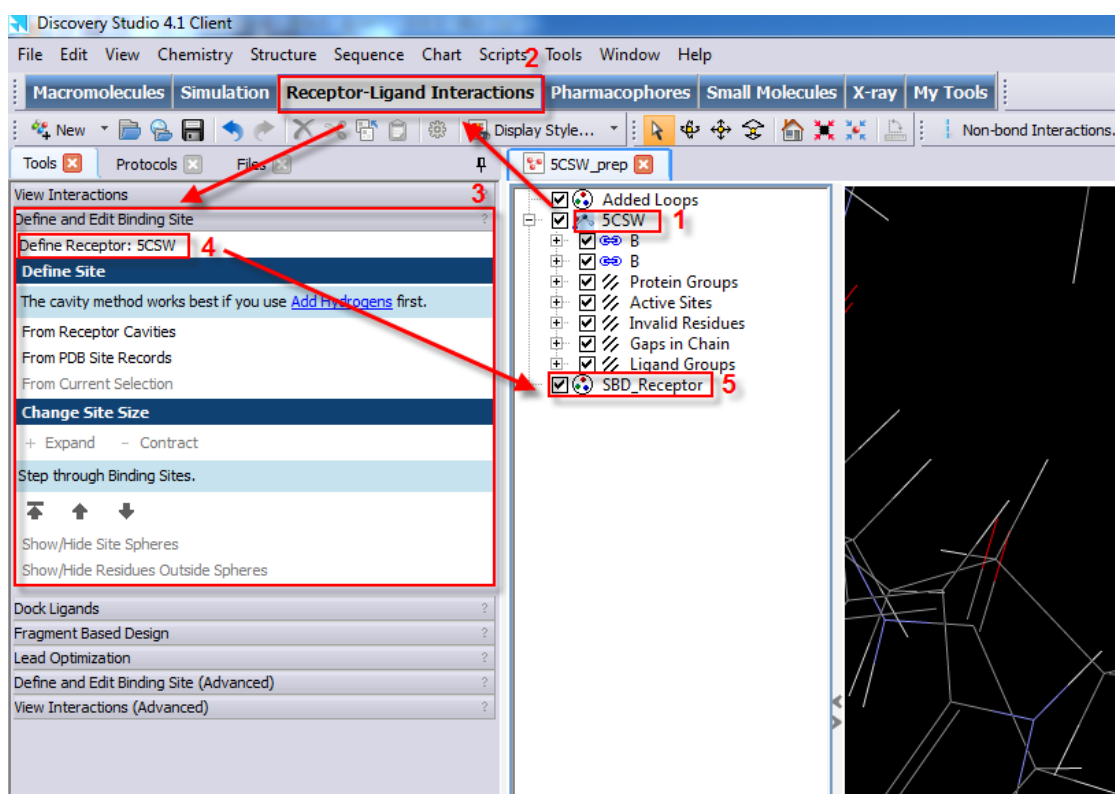
At this step, it is a good advice to save the prepared protein structure for future work (**File > Save As...**) as **\*.dsf** or **\*.pdb** format.

Once the protein structure is prepared (in this case a protein-ligand complex), the next step is to prepare it for structure-based (molecular docking) calculations. To easily access all the protein/ligand components, first close the **Results window**, click on the **Molecule window** where the protein structure is displayed and open the **Hierarchy tree view** by pressing **Ctrl + H** on the keyboard.



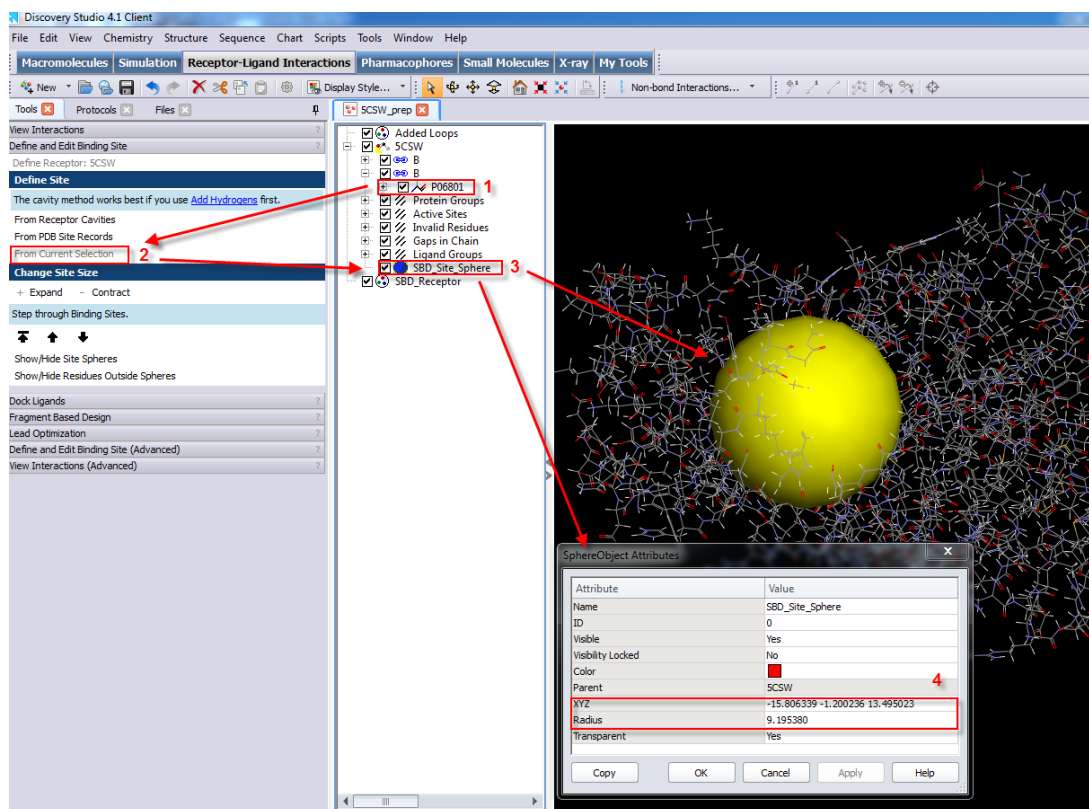
It should be noted however that during the Protein preparation step any other co-factors (e.g., metal ions) are not automatically removed from the structure and we should do it manually. This is somehow similar to the elimination of the water molecules described previously. Put differently, in the absence of a solid background to keep such co-factors and to use them in our calculations, we should remove them from the structure (see previous picture). In **Hierarchy tree view**, identify the unwanted co-factors, select them and press Delete (e.g., Cl<sup>-</sup> ion in the above example). Moreover, in the **Hierarchy tree view**, click on <Cell> and go to main menu (**Structure > Crystal Cell > Remove Cell**). This will remove the crystal cell covering the entire crystal structure.

Now we should properly label the structure to be used for structure-based calculations. In the **Hierarchy tree view**, select the main structure tree (in our example it is named as 5CSW). Click on the **Receptor-Ligand Interactions** tool panel, go to **Tools** tab, open **Define and Edit Binding Site** tool collection and click on **Define Receptor** button. The structure label will appear in the **Hierarchy tree view** (see 5 on picture below).



While we are still in the **Hierarchy tree view**, we should also identify the ligand molecule in order to define the **binding site sphere** where docking calculations will be performed. The **binding site sphere** can be defined by selecting a ligand atom, a fragment or the entire ligand molecule in the **Hierarchy tree view**. Now under **Define Site** tools collection click on the **From Current Selection** button to create the **binding site sphere** (see next picture).





As demonstrated on the picture above, a new **SBD\_Site\_Sphere** item will be defined under the 5CSW tree in the **Hierarchy tree view**. Right-click on **SBD\_Site\_Sphere** item (blue sphere icon) and then click on **Attributes of SBD\_Site\_Sphere**. This will open a dialog named **SphereObject Attributes** where some default parameters parameters (XYZ coordinates and radius of the sphere) can be customized (see previous picture).

Now in **Hierarchy tree view** select again the ligand molecule and remove it from the structure. This can be done by a right click on the ligand in the **Hierarchy tree view** and click **Cut** on the shortcut menu. Open a new **Molecule window** (**File > New > Molecule Window**) and paste the ligand molecule here.

Visually inspect the ligand in the **Molecule window** for possible errors (e.g., atom valences), rename the ligand in **Molecular detail and navigation panel** (e.g., **5CSW\_ref**) and save the ligand molecule as **\*.mol** or **\*.sdf** file (**File > Save As...**).

When everything is properly prepared, the system is ready for the next step (Parameterization of SBD protocols for molecular docking).

## Parameterization of SBD protocols for molecular docking calculations

The parameterizations of the DS SBD protocols (e.g., CDOCKER, GOLD, etc.) for molecular docking calculations are mainly automatic. To open a SBD protocol switch to **Protocols tab** and navigate to the SBD protocol of your choice (**Protocols tab** > **Discovery Studio** > **Receptor-Ligand Interactions** > **Docking**). Double click on the selected SBD protocol (e.g. CDOCKER). The CDOCKER SBD protocol parameter window will open (see picture below).

| Dock Ligands (CDOCKER) |                                     |
|------------------------|-------------------------------------|
| Parameter Name         | Parameter Value                     |
| Input Receptor         | 5CSW_prep:5CSW                      |
| Input Ligands          | Molecule:All                        |
| Input Site Sphere      | -15.8063, -1.20024, 13.495, 9.19538 |
| Top Hits               | 3                                   |
| Random Conformations   | 10                                  |
| Orientations to Refine | 0                                   |
| Simulated Annealing    | True                                |
| Advanced               |                                     |
| Parallel Processing    | False                               |

Parameterize the protocol for your needs and when everything is prepared just click **Run** (green play button) in the **Toolbar**.

When the calculation is finished, open the Results in exactly the same way as for the Prepare Protein job explained above.

## Analysis of docked poses (RMSD of re-docked ligand molecule)

To analyze the docked poses click on **Docked Ligands** link in the Result window. This will open the docked poses in a new Molecule window. In order to compare how good our results are, we need to insert here the co-crystallized ligand we saved previously (**File** > **Insert From** > **File**). Rename the inserted original ligand molecules (e.g., **5CSW\_ref\_orig**) and enable visibility of all docked poses by putting check marks on visibility option (see picture below).

| Molecule (1) |       |               |   |                             |                             |         |                 |                             |             |            |
|--------------|-------|---------------|---|-----------------------------|-----------------------------|---------|-----------------|-----------------------------|-------------|------------|
|              | Index | Name          | Visible                                 | Tagged                      | Visibility Locked           | TopHits | -CDOCKER_ENERGY | -CDOCKER_INTERACTION_ENERGY | POSE_NUMBER | Resolution |
|              | 1     | 5CSW_ref      | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> No | 3       | 38.6522         | 66.2624                     | 1           | 2.66       |
|              | 2     | 5CSW_ref      | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> No | 3       | 37.9031         | 66.0536                     | 2           | 2.66       |
|              | 3     | 5CSW_ref      | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> No | 3       | 36.3867         | 65.9034                     | 3           | 2.66       |
|              | 4     | 5CSW_ref_orig | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> No |         |                 |                             |             | 2.66       |

inserted original co-crystallized ligand (renamed)

Now select the inserted original co-crystallized ligand (4<sup>th</sup> row in the previous picture) and label it as a reference molecule (main menu > **Structure** > **RMSD** > **Set Reference**) and open the **Molecule window**.

The screenshot displays the software interface with the 'Molecule (1)' window active. The window title bar includes 'SCSW\_prep', 'Molecule', and 'Molecule (1)'. A red circle highlights a button in the top right corner of the window, with a red arrow pointing to it and the text 'click here to open the Molecule window'.

The main area of the window shows a 3D molecular model of a complex organic molecule, likely a ligand, rendered in a stick representation. The molecule features a central ring system with various substituents, including a sulfonamide group (SO<sub>2</sub>NH<sub>2</sub>) and a carboxylic acid group (COOH).

On the left side of the window, there is a list of molecules with checkboxes for visibility and tagging. The list includes:

- SCSW\_ref (checked)
- SCSW\_ref (checked)
- SCSW\_ref (checked)
- SCSW\_ref (checked)
- SCSW\_ref\_orig (checked)
- SBD\_Pose\_Reference\_Ligand (checked)

At the bottom of the window, there is a table with the following columns: Index, Name, Visible, Tagged, Visibility Locked, TopHits, -CDOCKER\_ENERGY, -CDOCKER\_INTERACTION\_ENERGY, POSE\_NUMBER, Resolution, and REMARK99. The table contains four rows of data:

| Index | Name          | Visible                             | Tagged                   | Visibility Locked        | TopHits | -CDOCKER_ENERGY | -CDOCKER_INTERACTION_ENERGY | POSE_NUMBER | Resolution | REMARK99       |
|-------|---------------|-------------------------------------|--------------------------|--------------------------|---------|-----------------|-----------------------------|-------------|------------|----------------|
| 1     | SCSW_ref      | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 3       | 38.6522         | 66.2624                     | 1           | 2.66       | REMARK 99 M... |
| 2     | SCSW_ref      | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 3       | 37.9031         | 66.0536                     | 2           | 2.66       | REMARK 99 S... |
| 3     | SCSW_ref      | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 3       | 36.3867         | 65.9034                     | 3           | 2.66       | REMARK 99 M... |
| 4     | SCSW_ref_orig | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |         |                 |                             |             | 2.66       | REMARK 99 S... |

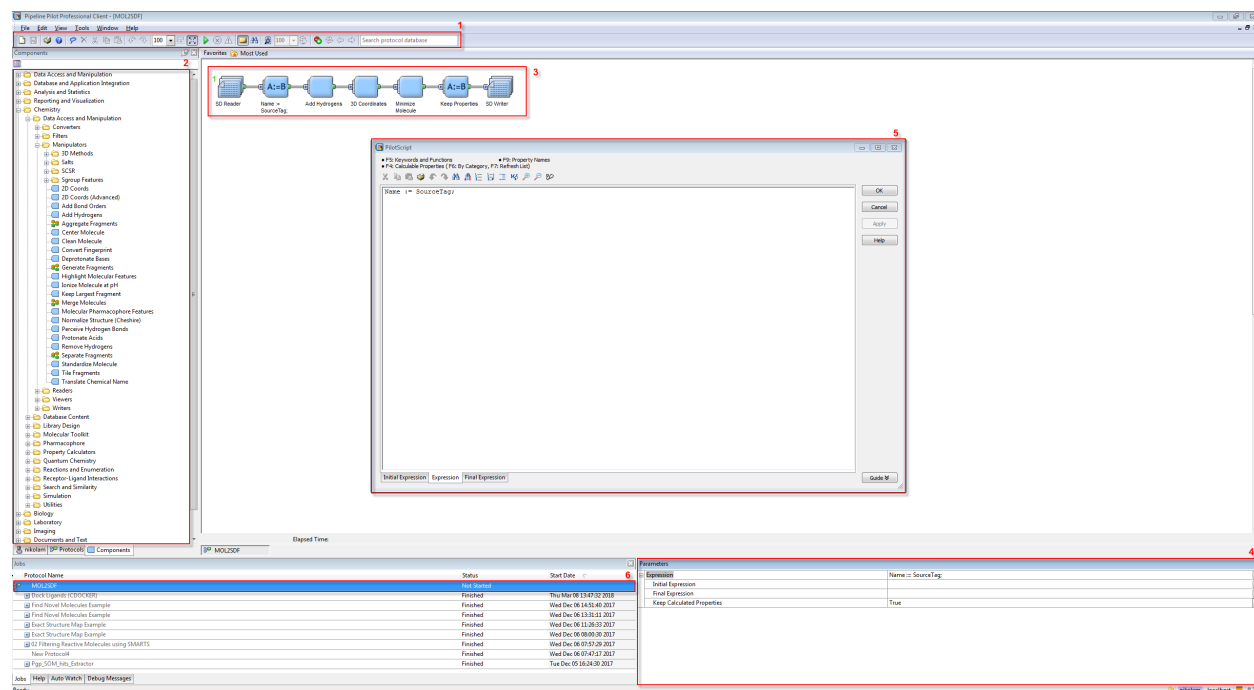
In order to calculate the RMSD (it should be  $\leq 2.0$  Å), go to main menu (**Structure** > **RMSD** > **Heavy Atoms**). This will open the RMSD Report window where all RMSD comparisons are displayed.

| 5CSW_ref_orig - RMSD Report <span>✕</span> |                 |          |
|--|-----------------|----------|
| Heavy Atom RMSD to 5CSW_ref_orig 4         |                 |          |
| Name                                       | Reference       | RMSD (Å) |
| 5CSW_ref 1                                 | 5CSW_ref_orig 4 | 0.4246   |
| 5CSW_ref 2                                 | 5CSW_ref_orig 4 | 0.5746   |
| 5CSW_ref 3                                 | 5CSW_ref_orig 4 | 1.2021   |
| 5CSW_ref_orig 4                            | 5CSW_ref_orig 4 | 0.0000   |

As demonstrated, all docked poses have RMSD below 2.0 Å (that is also visually true), i.e., the docking protocol is properly parameterized and ready to be used for performing molecular docking calculations on new compounds.

While still open, switch to **5CSW\_prep** tab and save as a new \*.dsv file (e.g., **5CSW\_prep\_final.dsv**).

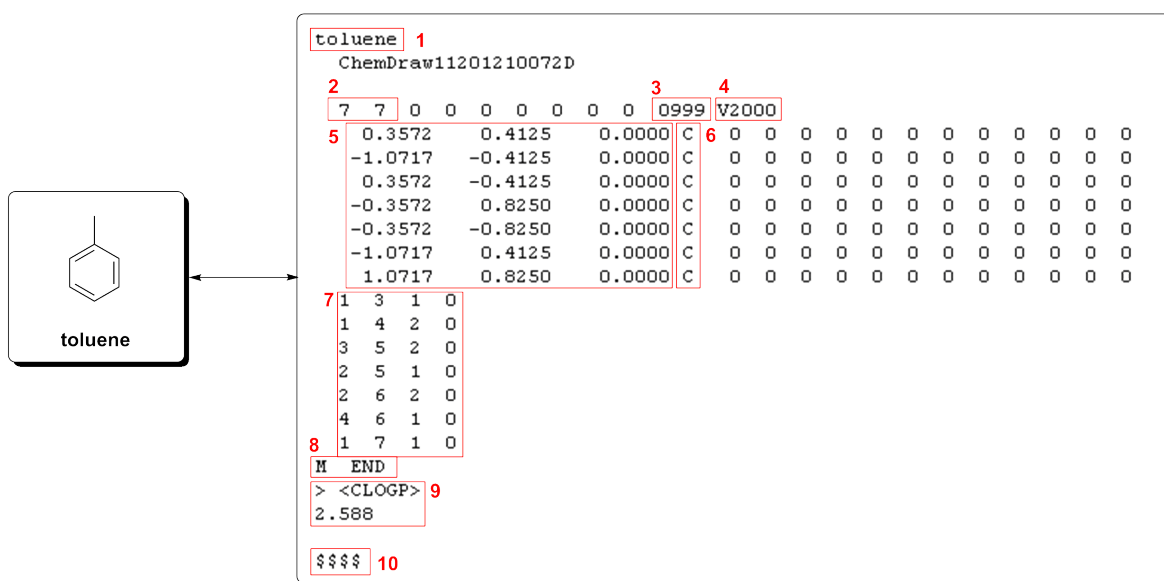
# A quick introduction to Pipeline Pilot (PP) user interface



1. Main PP tool panel
2. Components collections
3. PP protocol (assembled of piped components)
4. Protocol parameters
5. PilotScript interface
6. Jobs explorer

## Preparation of a ligands library for molecular docking calculations

Regardless of the origin of ligands we would like to dock (e.g., commercially available compounds, ligands scrutinized from the literature, or even *de novo* virtually assembled ligands not commercially available), they should be properly pre-treated for molecular docking calculations. This means that all of them should be adequately prepared in a machine-readable format (e.g., \*.mol, \*.sd/\*.sdf, SMILES, etc.). Comparing to the \*.mol file format (commonly known as a connection table) that contains structural information (e.g., atoms, bonds and their connectivity) related to a single ligand, the \*.sdf file format in a broader sense can be regarded as a database of significantly higher number of ligands. In fact, \*.sdf format contains the same information as a single \*.mol file, where each ligand (encoded in form of connection tables) are separated by "\$\$\$\$" delimiter. Moreover, these file formats can store various information related to the ligand(s) (e.g., various physico-chemical properties, chemical names, etc.). A snippet of these file formats (e.g., molecule of toluene) is given in the picture below.

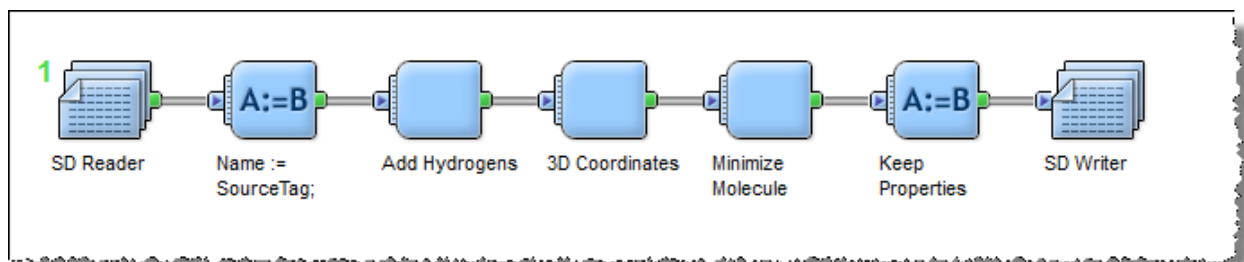


- 1 Molecule name: toluene
- 2 Number of atoms and bonds in the molecules: 7 atoms and 7 bonds
- 3 Format limitation: maximum 999 characters
- 4 Mol file format: V2000 or V3000 (for larger structures)
- 5 Cartesian coordinates: 2D structures (X and Y) or 3D structures (X, Y, and Z)
- 6 Atom symbol: C, H, ...
- 7 Connectivity information: how the atoms in the molecule are inter-connected
- 8 End of the connection table: M END
- 9 Property name and value: CLOGP = 2.588
- 10 Delimiter "\$\$\$\$": without (\*.MOL file; one molecule per file), with (\*.SD/\*.SDF file format; one or more molecules per file)

Assuming that our ligands are represented as 2D structures (see previous picture) it should be stressed that such a representation is not very recommended for performing molecular docking calculations. Put differently, prior to perform molecular docking calculations, all ligands should be:

- Converted to 3D structures,
  - All hydrogen atoms should be added (2D structures are lacking of H-atoms),
- and optionally
- They should be geometrically minimized (e.g., to remove any *van der Waals* clashes).

Finally and also preferably, all ligands should be assembled as one database in an appropriate molecular machine-readable format (e.g., \*.sdf). In order to do all these crucial steps in a concomitant fashion, we will construct a Pipeline Pilot (PP) protocol (see picture below).

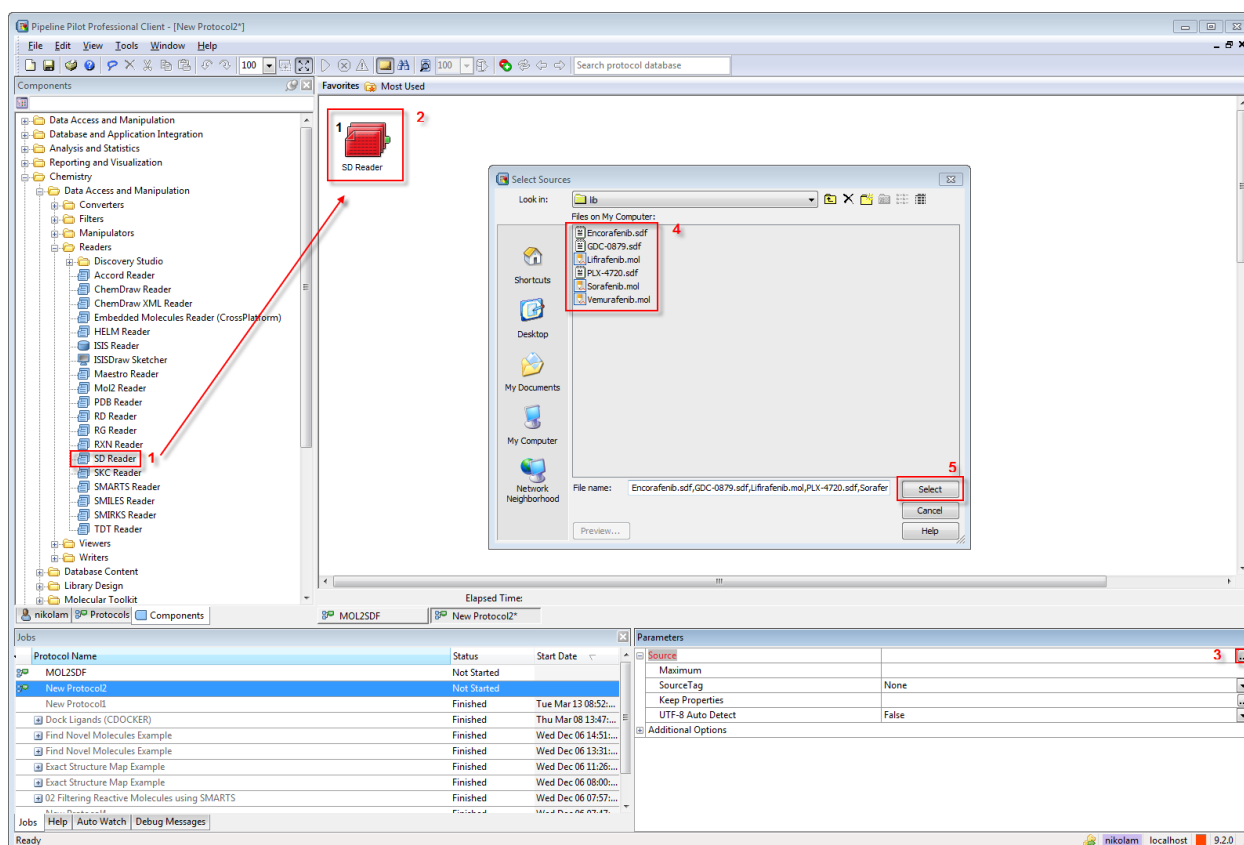


Let's assume that our ligands we scrutinized from different sources (e.g., literature, online structural databases, etc.) represent separate 2D molecules, which are either in \*.mol or \*.sdf format. In order to construct a PP protocol (like the one represented above) that will automate all the steps described above, we will use PP interface.

So, here is the step-by-step guide:

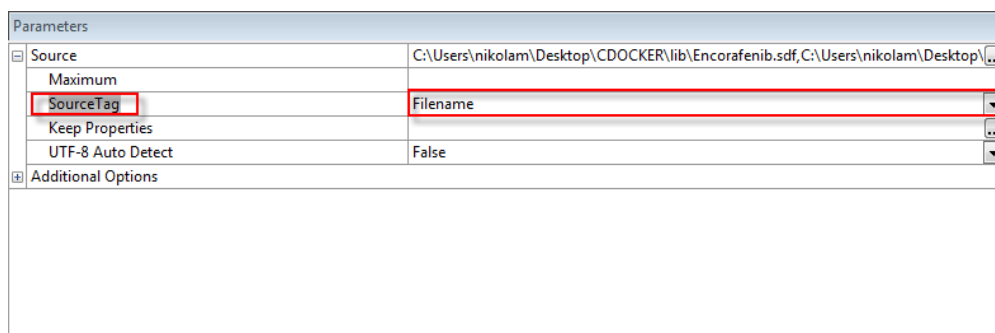
As a very first step, we should read all the ligands we collected (\*.mol or \*.sdf files). Since, both file formats are practically very similar, we will use the so-called **SD Reader** PP component, which is capable to read both formats.

To do this, in the **Components Collection** tab, locate **SD Reader** component (stored in **Chemistry > Data Access and Manipulation > Readers**) and double-click on the **SD Reader** component to put it on the working layout (see picture below). At first, the **SD Reader** component is red, which means that we should add some data to it. Select the red **SD Reader** component on the working layout and in the **Parameters** window, under **Source** click the corresponding button as depicted in the picture to open the file browser dialog.



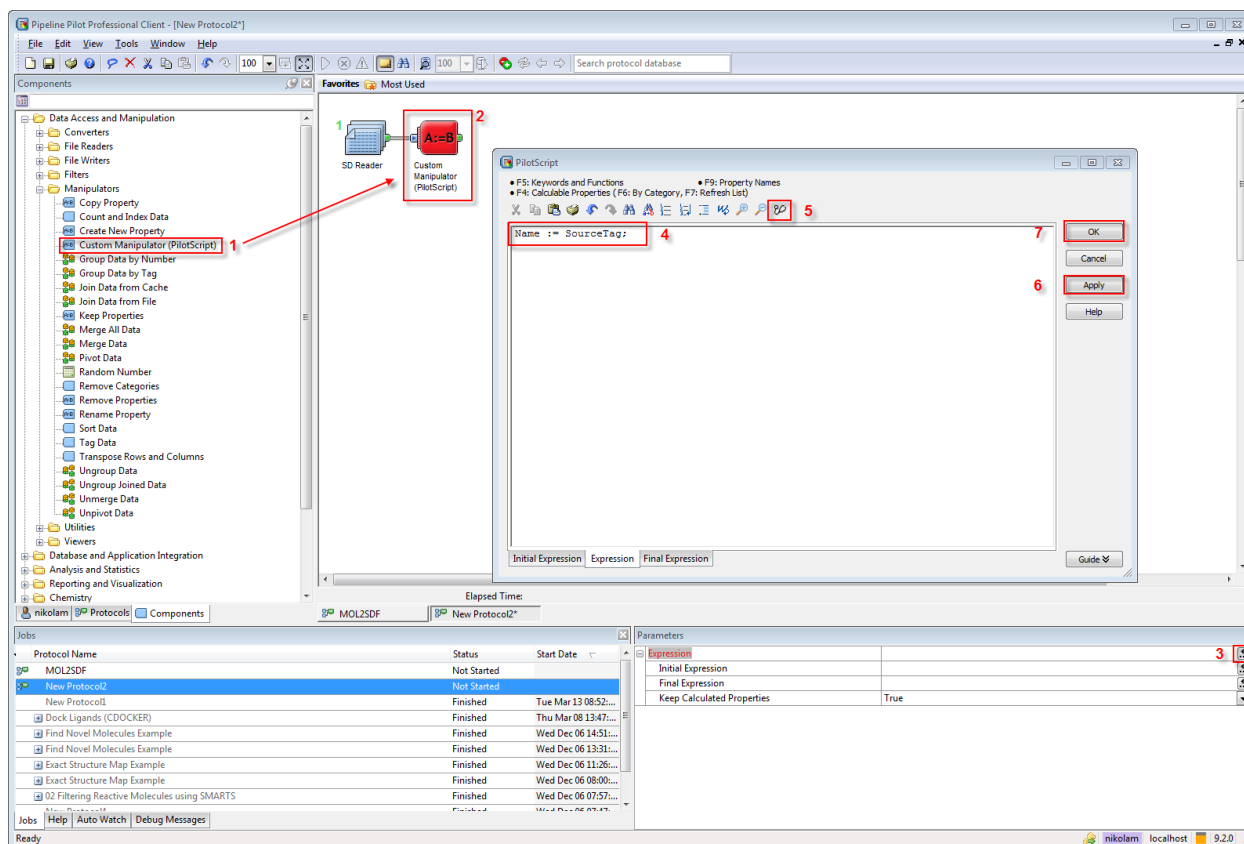
Navigate to the directory where your ligands are stored, select all ligands, and click on the **Select** button to select them. In this way, the **SD Reader** component will become blue, while in the **Parameters** window all \*.mol and \*.sdf files we selected will be separated by commas. The parameters for a particular component in the **Parameters** window will be visible only in case the target component is selected in the working layout!

As we can see on the picture above, the filenames of our ligands are actually their names, so it is not a bad idea to use these information in the final \*.sdf file (the ligand library we are constructing) for easier ligand's recognition. While we have still open the **Parameters** for the selected **SD Reader** component, locate the **SourceTag** parameter and from the corresponding list select **Filename** (see picture below).





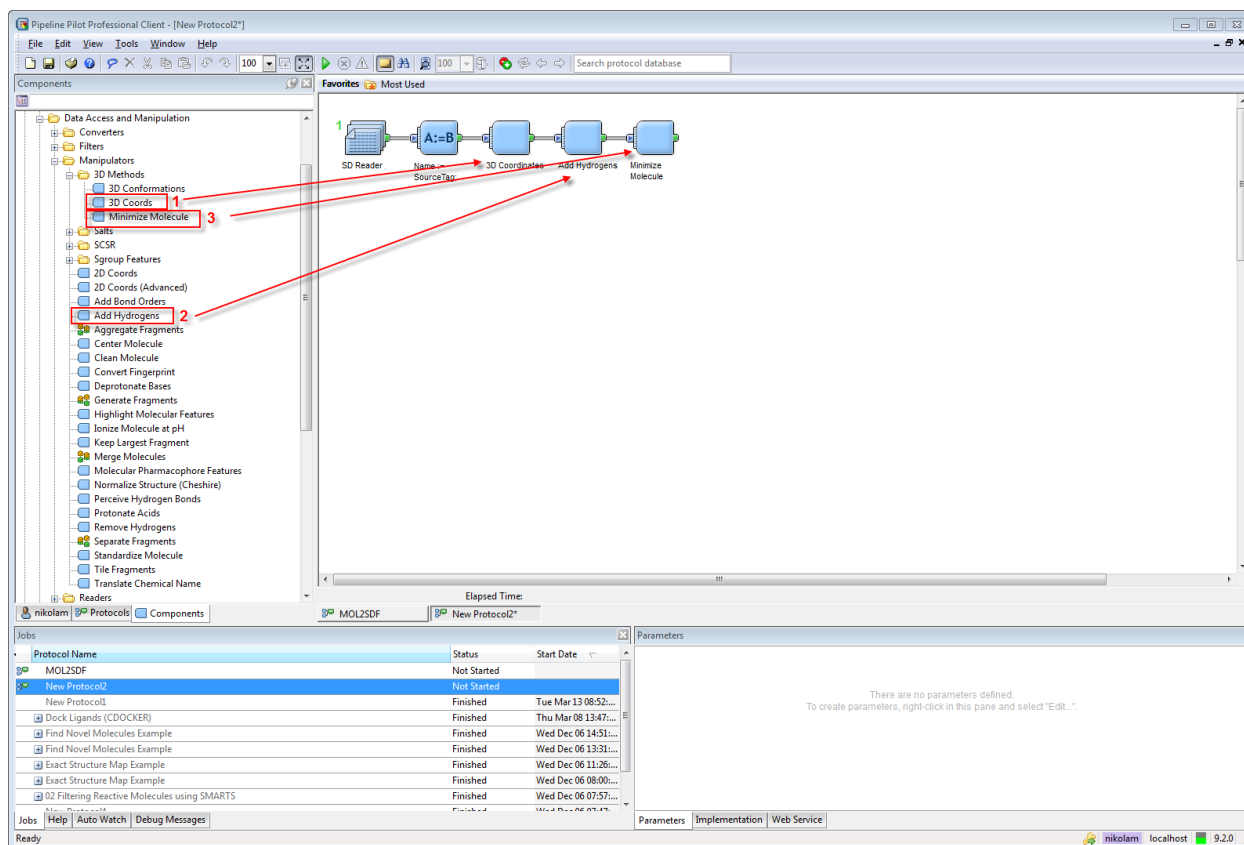
Now, navigate to the **Components Collection** tab, locate the **Custom Manipulator (PilotScript)** component (stored in **Data Access and Manipulation > Manipulators**) and double-click it to automatically pipe it to the **SD Reader** component (see picture below).



Once piped, select the **Custom Manipulator (PilotScript)** component and in the **Parameters** window click the **Expression** button to open the **PilotScript** interface. Here, define the **Name** for each ligand as demonstrated on the picture above (**Name := SourceTag**). In this way we constructed a new property named "Name" that contain names of our ligands. Check if the **PilotScript** is correct (5), click on the **Apply** button (6) and finally click on the **OK** button (7) to close the **PilotScript** interface.

Now navigate again to the **Components Collection** tab and find the following components: **3D Coords** (located in **Chemistry > Data Access and Manipulation > Manipulators > 3D Methods**), **Add Hydrogens** (located in **Chemistry > Data Access and Manipulation > Manipulators**) and **Minimize Molecule** (located in **Chemistry > Data Access and Manipulation > Manipulators > 3D Methods**). Double-click each of these components in the same order (**3D Coords > Add Hydrogens > Minimize Molecule**) to pipe them automatically (see next picture). So, the **3D Coords** component will update the 2D connection table of the input ligands with Z-coordinate,

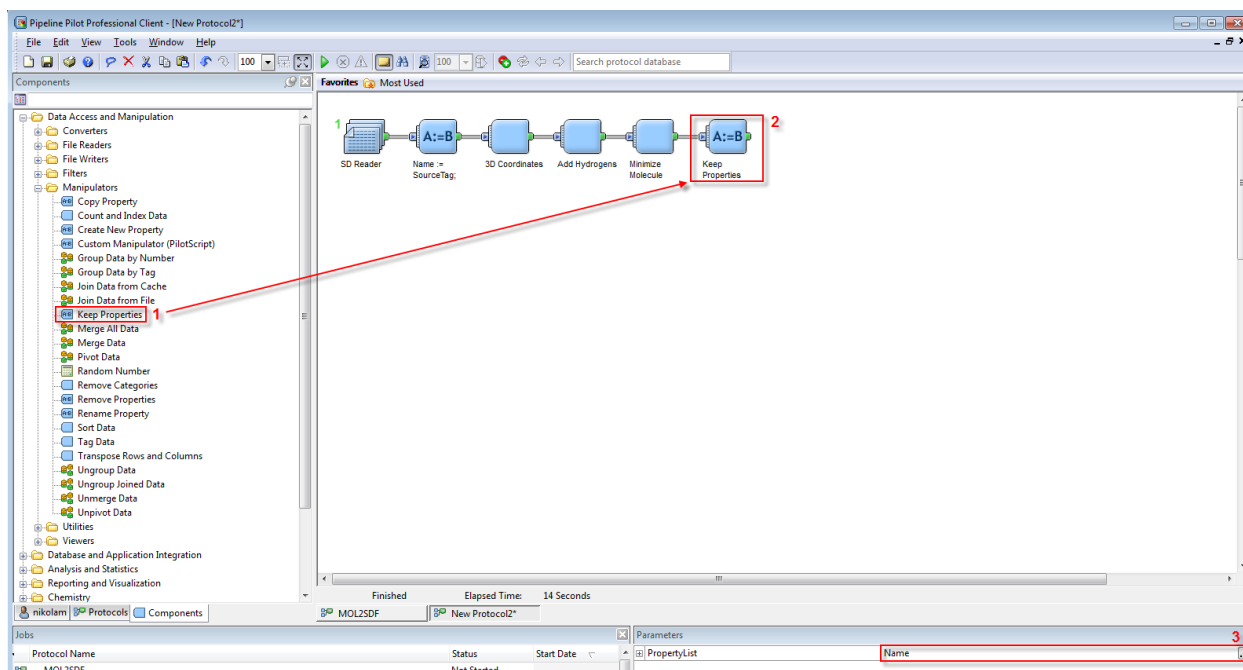
the **Add Hydrogens** component will also update each input ligand by adding H-atoms, while **Minimize Molecule** will minimize the energy of all input ligands.



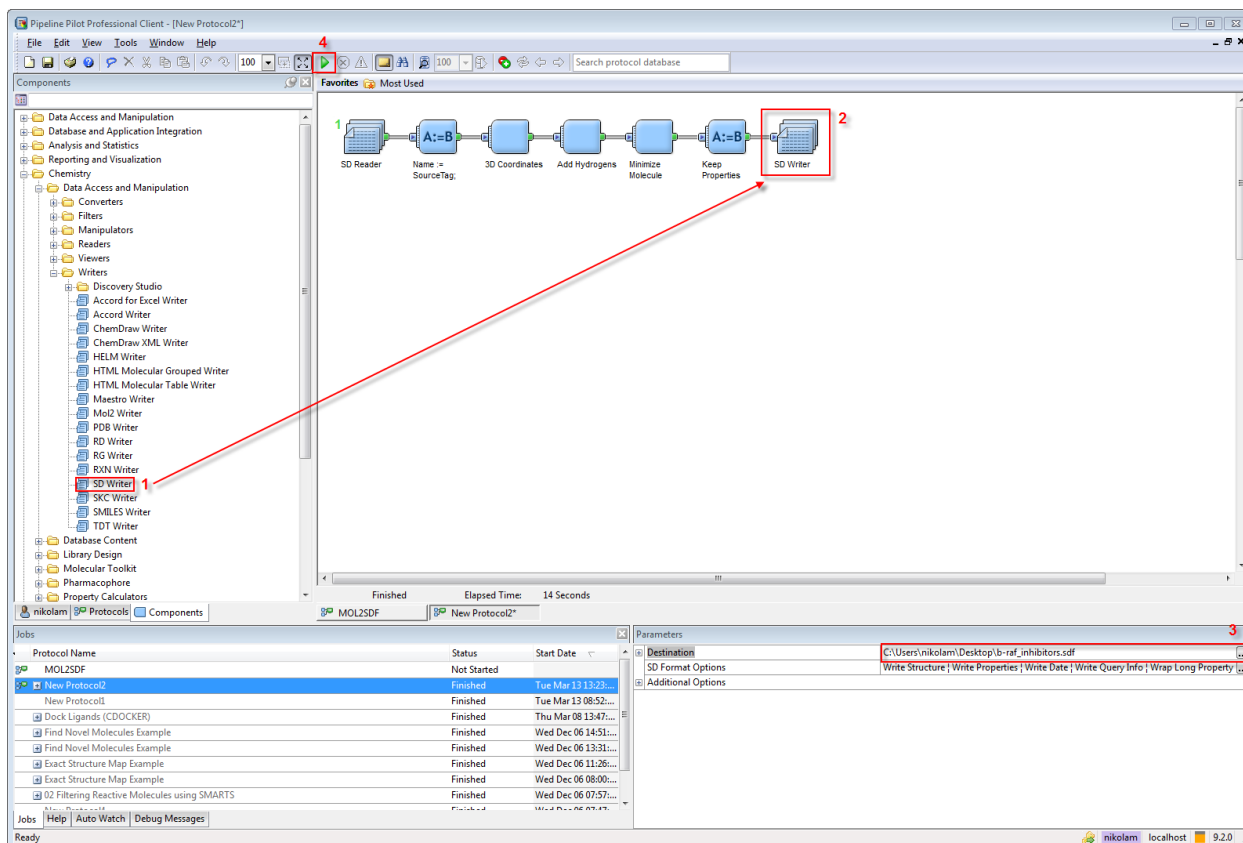
Before to finalize the protocol, we should keep in mind that the final \*.sdf library can contain some residual properties (e.g., SourceTag, Minimized Energy) that will be generated when the protocol will be run.

Except the "**Name**" property we created, we actually don't need any other property. In order to keep just the "**Name**" property, we will add one more component (double-click on it) named **Keep Properties** (located in **Data Access and Manipulation > Manipulators**) to our protocol (see next picture).

After adding the **Keep Properties** component, select it in the working layout and in the **Parameters** window type the name of the property (e.g., **Name**) for the needed **PropertyList** parameter (see next picture). In this way our \*.sdf library will contain only one property, i.e., "**Name**".



Finally, we will finish our protocol by adding the last component named **SD Writer** (located in **Chemistry > Data Access and Manipulation > Writers**).

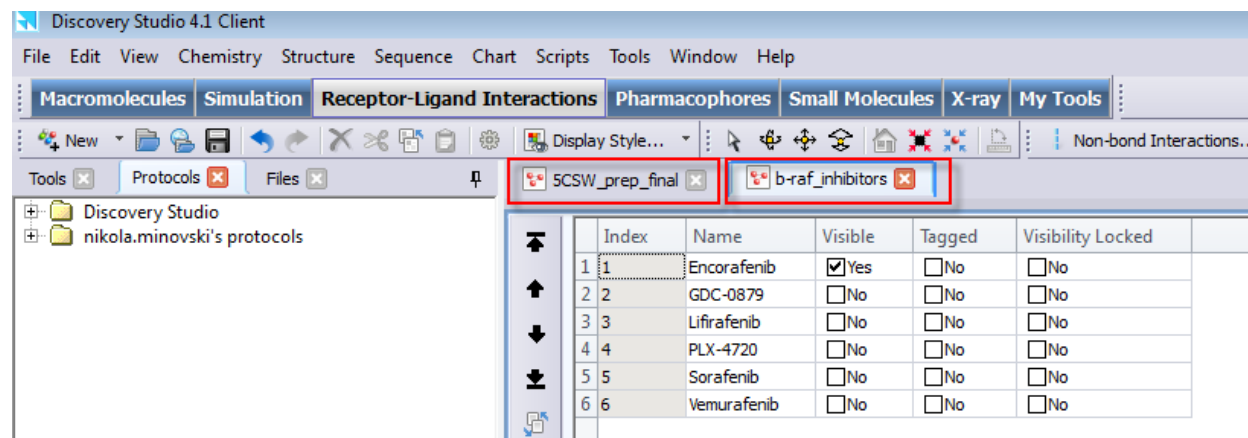


Select **SD Writer** component in the working layout and in the **Parameters** window, under the **Destination** parameter, type the full path and file name with extension (e.g. C:\Users\username\Desktop\library\_filename.sdf), where **username** is **your username** and **library\_filename.sdf** is the name of the ligand library in \*.sdf format (e.g., in this case **b-raf\_inhibitors.sdf**). Finally, **run the protocol** by clicking the **green play button** from the **main PP tool panel** (3) and wait for it to finish. Moreover, save the protocol for further use (goto **File > Save Protocol As...**) in your home directory.

## Molecular docking calculations using DS CDOCKER protocol

The procedure of performing molecular docking calculations for our previously constructed ligand library is actually very similar to the re-docking of the co-crystallized ligand conformation within its binding site (see pages 9-10). Previously, we saved our molecular docking settings as a \*.dsv file named **5CSW\_prep\_final.dsv**, which contains all the important information we obtained from the re-docking validation step (e.g., prepared protein, defined appropriate calculation sphere as well as the corresponding calculation parameters).

In order to perform molecular docking calculations for our previously constructed ligand library, in Discovery Studio first we will open our well-validated system (goto **File > Open...** and then locate and load the file **5CSW\_prep\_final.dsv**). After this, we will open our prepared ligand library as \*.sdf format (**b-raf\_inhibitors.sdf**) in a new **Molecule window** (see picture below).



Next, switch back on the protein (click on **5CSW\_prep\_final** tab). From **Protocols** tab navigate to the SBD protocol of your choice (**Protocols** tab > **Discovery Studio** > **Receptor-Ligand**

**Interactions > Docking**). Double click on the selected SBD protocol (e.g. CDOCKER). The CDOCKER SBD protocol parameter window will open (see next picture).

| Dock Ligands (CDOCKER) |                                |
|------------------------|--------------------------------|
| Parameter Name         | Parameter Value                |
| Input Receptor         | 5CSW_prep_final:5CSW           |
| Input Ligands          | b-raf_inhibitors:All           |
| Input Site Sphere      | -15.8061, -1.20006, 13.495, 10 |
| Top Hits               | 3                              |
| Random Conformations   | 10                             |
| Orientations to Refine | 0                              |
| Simulated Annealing    | True                           |
| Advanced               |                                |
| Parallel Processing    | False                          |

Parameterize the protocol as demonstrated on the picture above and click **Run** (green play button) in the **Toolbar** to start the docking calculation for our ligands.

When the calculation is finished, in the **Jobs** tab double-click to open the **Results** (2) and then click on the **View Results** button (3). This will open a new **Molecule window** (4) containing our protein structure and the docked poses (5) for the ligands (see picture below).

The screenshot shows the Discovery Studio 4.5 Client interface. The 'Jobs' tab is active, displaying a list of docking jobs. A red box highlights the 'Dock Ligands (CDOCKER)' job, with a red arrow pointing to it and the text '1 double-click to open results'. Another red box highlights the 'View Results' button in the job's details, with a red arrow pointing to it and the text '3'. A third red box highlights the 'Dock Ligands (CDOCKER)' window, which shows the protein structure and docked poses, with a red arrow pointing to it and the text '4'. A fourth red box highlights the 'Parameters' tab in the window, with a red arrow pointing to it and the text '5'.

## Analysis & selection of the most favorable docked poses

For the selection of the most favorable docked poses, first we will focus on the values for the scoring functions (in our case, **-CDOCKER\_ENERGY** and **-CDOCKER\_INTERACTION\_ENERGY**) calculated by the CDOCKER protocol. These scoring functions demonstrating the binding affinity of our ligands in kcal/mol give a first insight about the quality of the results (see picture below).

|  | Index | Name        | Visible                             | Tagged | Visibility Locked                   | POSE_NUMBER | -CDOCKER_ENERGY | -CDOCKER_INTERACTION_ENERGY | LoopList      | Resolution | REMARKS | SECRES | PartialCharge/Method | UseResidueTemplateCharge | Forcefield | ForcefieldBase | Initial RMS Gradi |
|--|-------|-------------|-------------------------------------|--------|-------------------------------------|-------------|-----------------|-----------------------------|---------------|------------|---------|--------|----------------------|--------------------------|------------|----------------|-------------------|
|  | 1     | SCSW        | <input checked="" type="checkbox"/> | No     | <input checked="" type="checkbox"/> | 1           | 20.4381         | -47.8047                    | 0:SCSW.A.P... | 2.66       |         |        |                      |                          |            |                |                   |
|  | 2     | Encorafenib | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 1           | 19.1216         | -51.0081                    |               |            |         |        |                      |                          |            |                |                   |
|  | 3     | Encorafenib | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 2           | 19.1216         | -51.0081                    |               |            |         |        |                      |                          |            |                |                   |
|  | 4     | Encorafenib | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 3           | -193.979        | -1.1964                     |               |            |         |        |                      |                          |            |                |                   |
|  | 5     | GDC-0879    | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 1           | 16.8529         | -42.5307                    |               |            |         |        |                      |                          |            |                |                   |
|  | 6     | GDC-0879    | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 2           | 18.0384         | -38.6495                    |               |            |         |        |                      |                          |            |                |                   |
|  | 7     | GDC-0879    | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 3           | 18.1339         | -40.8887                    |               |            |         |        |                      |                          |            |                |                   |
|  | 8     | Lifirafenib | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 1           | 34.2423         | -42.8188                    |               |            |         |        |                      |                          |            |                |                   |
|  | 9     | Lifirafenib | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 2           | -41.6088        | -27.3291                    |               |            |         |        |                      |                          |            |                |                   |
|  | 10    | Lifirafenib | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 3           | -61.7208        | -22.3663                    |               |            |         |        |                      |                          |            |                |                   |
|  | 11    | PLX-4720    | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 1           | 22.3926         | -43.5849                    |               |            |         |        |                      |                          |            |                |                   |
|  | 12    | PLX-4720    | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 2           | 21.5333         | -40.3133                    |               |            |         |        |                      |                          |            |                |                   |
|  | 13    | PLX-4720    | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 3           | 21.2565         | -40.241                     |               |            |         |        |                      |                          |            |                |                   |
|  | 14    | Sorafenib   | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 1           | 16.7085         | -40.2365                    |               |            |         |        |                      |                          |            |                |                   |
|  | 15    | Sorafenib   | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 2           | 15.8127         | -40.5167                    |               |            |         |        |                      |                          |            |                |                   |
|  | 16    | Sorafenib   | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 3           | 15.1815         | -39.458                     |               |            |         |        |                      |                          |            |                |                   |
|  | 17    | Vemurafenib | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 1           | 16.3346         | -45.2259                    |               |            |         |        |                      |                          |            |                |                   |
|  | 18    | Vemurafenib | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 2           | 15.2522         | -43.5978                    |               |            |         |        |                      |                          |            |                |                   |
|  | 19    | Vemurafenib | <input type="checkbox"/>            | No     | <input type="checkbox"/>            | 3           | 12.304          | -42.1318                    |               |            |         |        |                      |                          |            |                |                   |

Here, it is important to take into account the pre-defined "minus" sign of these scoring functions (see above picture). Put differently, if **-CDOCKER\_ENERGY** and **-CDOCKER\_INTERACTION\_ENERGY** for a docked pose are both positive values, then we are talking about an energetically favorable ligand pose (ligand poses framed in green). Conversely, if negative values are obtained, then these docked poses are energetically unfavorable (ligand poses framed in red) and consequently we can reject them for further assessments.

Since, we are interested solely for the energetically favorable docked poses (framed in green), we can extract them and further analyze visually within the binding pocket (e.g., ligand spatial orientation, interaction of the ligands with the protein's key amino acid residues, etc.).