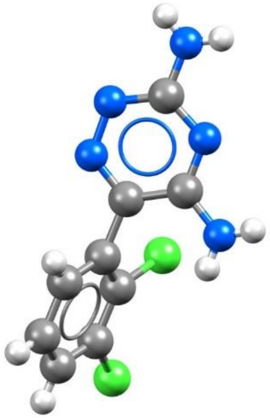
Introduction to Hermes

HERM-001

2020.3 CSD Release



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Introduction

Hermes is a visualisation program for the display and editing of protein and small molecule structures which hosts interfaces to GOLD, Mogul, SuperStar, the CSD Ligand Overlay, and descriptors for GOLD docking poses. Detailed information about Hermes can be found in the Hermes User Guide.

The MLL1 fusion protein

MLL1 is a fusion protein expressed by blood cancer cells. *S*-adenosyl-L-homocysteine (SAH) is a metabolite of the cofactor *S*-adenosyl methionine (SAM). Cofactor binding sites can be challenging in drug discovery projects due to the potential for off-target binding to related proteins. Interestingly, SAM is very flexible and adopts different conformations in different enzymes. Thus, SAM binding sites are considered druggable and currently investigated for the treatments of cancer and neuropsychiatric disorders.[1]

Objectives

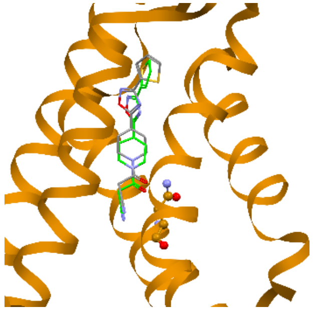
As an introduction to the Hermes interface, this tutorial will show you how to inspect and edit a complex between the MLL1 fusion protein and the cofactor product SAH, deposited in the PDB with the code 2w5y.

In this tutorial, you will learn how to:

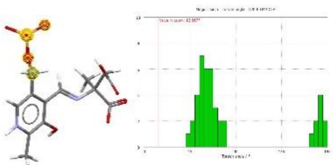
- Load, save and edit molecules
- Inspect the active site of your complex
- Focus on parts of the molecule
- Restrict the display of the molecule to its active site
- Label atoms and protein residues
- Measure distances
- Customise molecule rendering, colours and backgrounds

Material

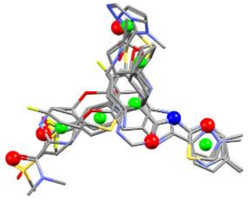
Please download the following folder and extract all files (including *2w5y.pdb*).



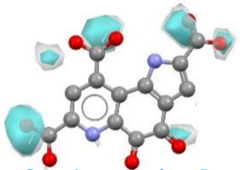
GOLD Docking and Descriptors



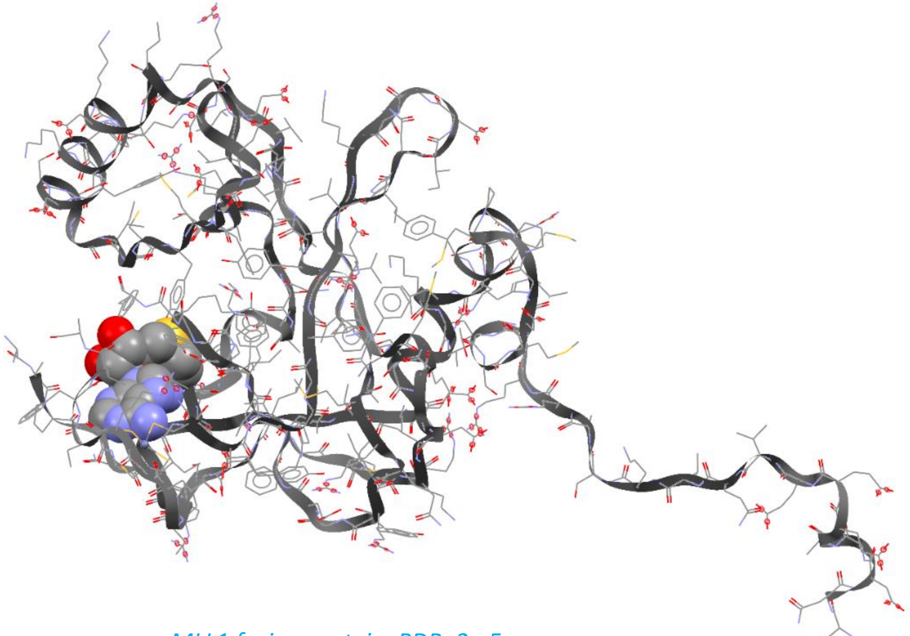
Mogul Geometry Analysis



CSD Ligand Overlay



SuperStar Interaction Prediction



MLL1 fusion protein, PDB: 2w5y

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[1] Arrowsmith, Cheryl H., *et al.* "Epigenetic protein families: a new frontier for drug discovery." *Nature Reviews Drug Discovery* (2012). **11**, 384-400.

Visualising and Editing the MLL1 fusion protein

Opening Files in Hermes

1. Launch Hermes by clicking the icon (on macOS, double click on hermes.app).

2. From the top-level menu, click **File** > **Open**. Browse to the folder where you saved the *2w5y.pdb* and double-click to open it.

Setting Display Options

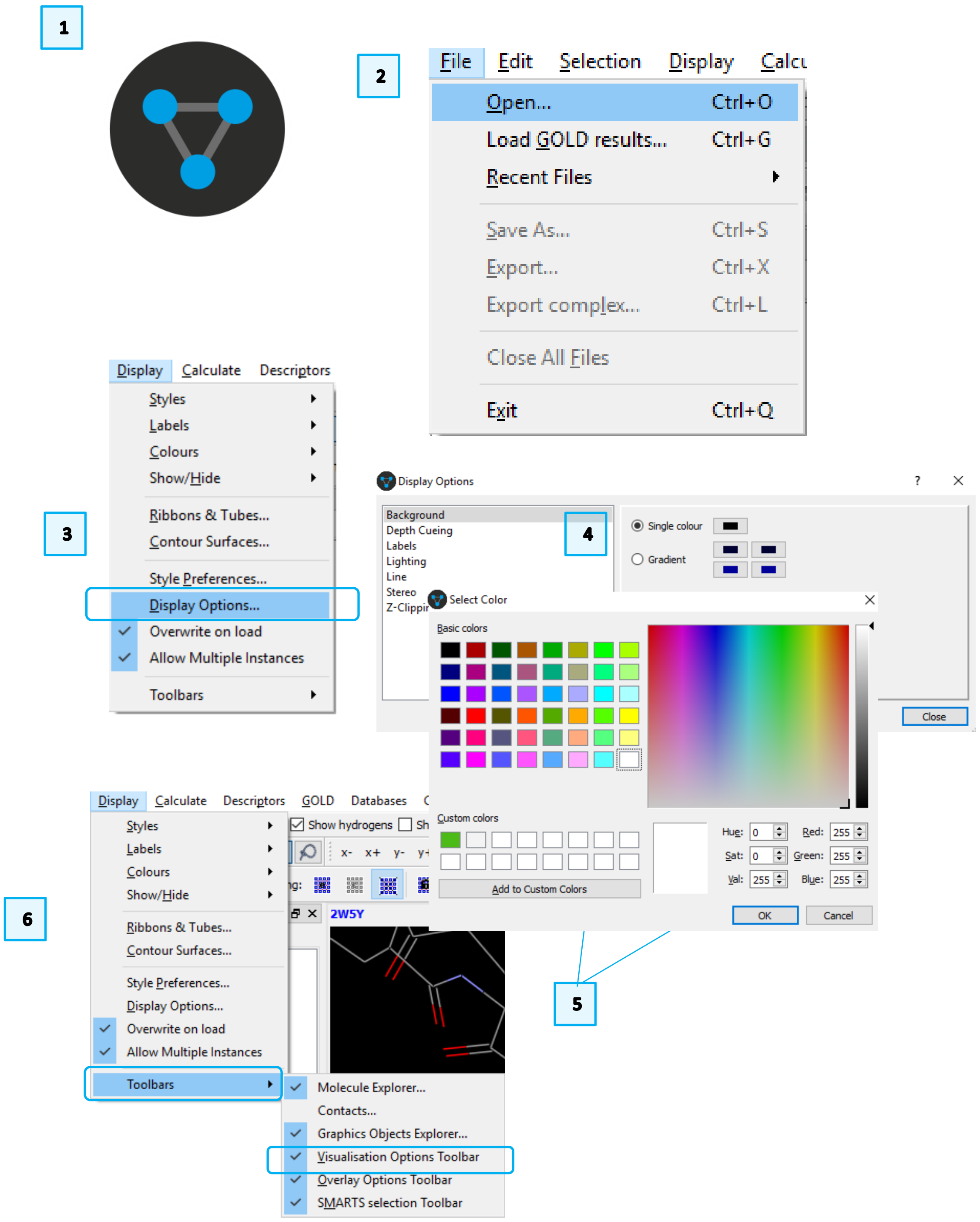
3. From the top-level menu, click **Display** > **Display Options** (on macOS: click **Hermes** > **Preferences**) to open the *Display Options* dialogue box.

4. In the *Display Options* dialogue box, click to select **Background** (on macOS: **Display** > **Colours** > **Background settings**) on the left side of the window. Make sure the radio button next to "Single colour" is ticked. Click on the colour button next to "Single colour" to bring up a colour panel.

5. From the *Select Color* dialogue box, you can click to select any colour you want, or type in the numerical values for Hue/Sat/Val or Red/Green/Blue. For the purposes of this example, click the white colour box as shown. Click **OK** to exit this window.

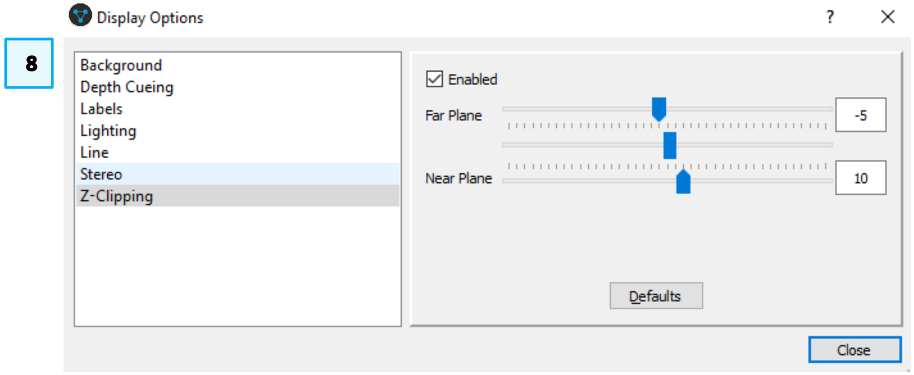
6. Tick **Depth Cueing** tick-box in the *Visualisation Options* toolbar to enable depth cueing. Depth cueing renders objects at the front of the display more brightly than those at the back. If this toolbar is not displayed, load it by selecting **Display** > **Toolbars** > **Visualisation Options Toolbar** from the top-level menu.

7. You can customise depth cueing options, by opening the **Display** > **Display Options...** dialogue box as in step 3 above and clicking **Depth Cueing** from the left side. Tick the **Enabled** box to type in values in the *Front brightness* and *Back brightness* boxes to control how bright an object at the front is compared to one at the back.



8. Z-Clipping allows you to display only objects that are located between two user-defined planes parallel to the screen. It restricts the depth of the display. In the *Display Options* dialogue box, click **Z-Clipping** on the left side.

9. Tick the **Enabled** box to turn on Z-clipping. Click and drag the slider buttons to change the values of the Far and Near Planes. See what effect this has on your display. Click and drag in the main display window to move the protein around with Z-clipping enabled. When you have finished, untick the box next to **Enabled** and click **Close** to exit the *Display Options* dialogue box.



☑ Enabled

Far Plane -5

Near Plane 10

More information on display settings can be found in Chapter 7 of the Hermes User Guide.

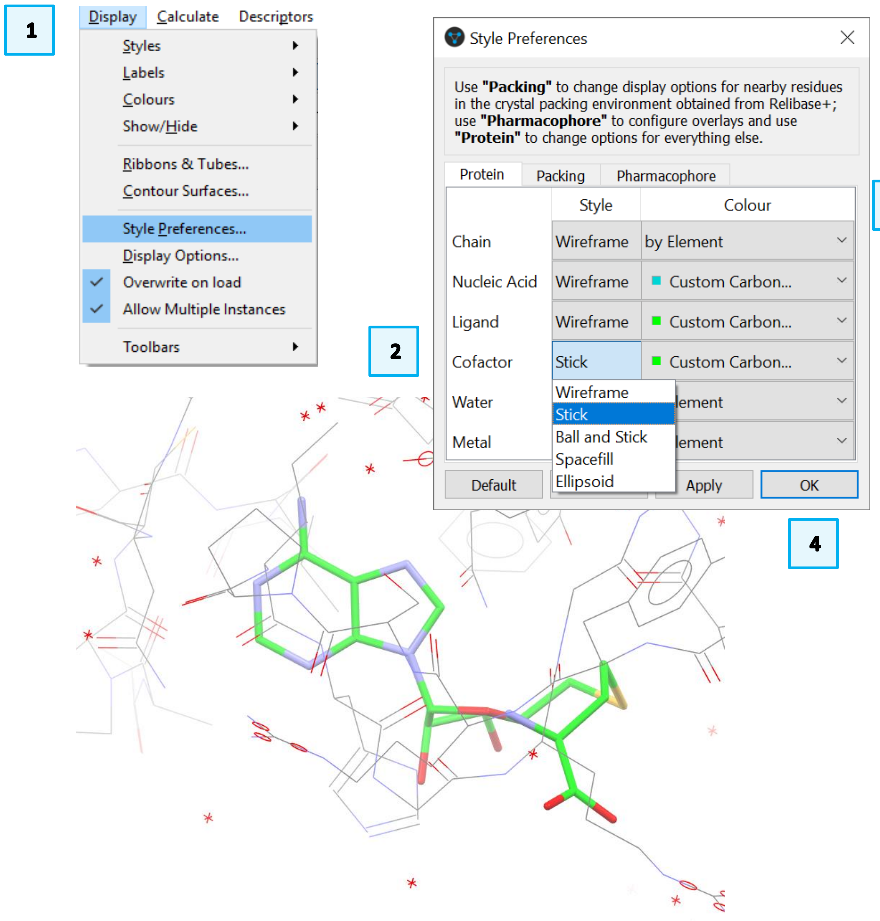
Setting Style Preferences

1. Open the *Style Preferences* dialogue box by clicking **Display** > **Style Preferences...** from the top-level menu.

2. The *Style Preferences* dialogue allows you to change the display style of the main protein or *Chain*, as well as any *Nucleic Acid* atoms, *Ligand* atoms, *Cofactor* atoms, *Water* molecules or *Metal* atoms that may be present. By default, everything is set to *Wireframe* except for metal atoms. Change the cofactor style by selecting *Stick* from the dropdown menu, as shown, and clicking **Apply**.

3. Similarly, you can choose different colouring options by selecting them from the appropriate dropdown boxes. Here the ligand is coloured such that carbon atoms are green (*Custom Carbon...*) but all heteroatoms are their normal (by element) colours.

4. Experiment with these various options to find a view that suits your needs, and click **OK** to exit the dialogue box.



Use **"Packing"** to change display options for nearby residues in the crystal packing environment obtained from Relibase+; use **"Pharmacophore"** to configure overlays and use **"Protein"** to change options for everything else.

	Style	Colour
Chain	Wireframe	by Element
Nucleic Acid	Wireframe	🟦 Custom Carbon...
Ligand	Wireframe	🟩 Custom Carbon...
Cofactor	Stick	🟩 Custom Carbon...
Water		lement
Metal		lement

Moving the Contents of the 3D Display Area

A complete description on how to move Hermes's display can be found in Chapter 5 of the Hermes User Guide.

1. Left-click the mouse and drag the pointer **to rotate** the display (x and y axes).

2. **To translate** in the plane of the screen, click the middle mouse button or Ctrl-left-click while dragging.

3. To **rotate in the plane** of the screen (z axis), Shift-left-click and drag.

4. To **zoom** in and out, right-click and drag up (zoom in) and down (zoom out).

5. You can also use the *Alignment and Orientation Operations* toolbar in Hermes to move the model without having to click in the display window.

6. If the toolbar is not visible, right-click in the area around the top-level menu and toolbars and choose **Alignment and Orientation Operations** from the dropdown menu.

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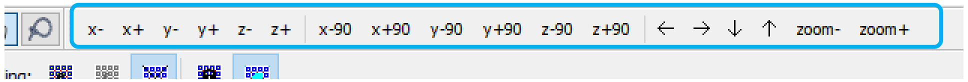

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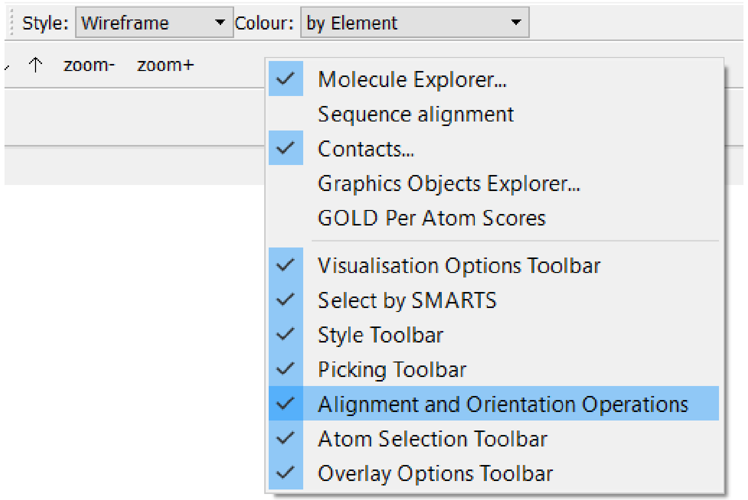


Select and Centre with *Molecule Explorer*

1. Ensure that *Molecule Explorer* is displayed by clicking **Display** then **Toolbars** and checking that **Molecule Explorer** is ticked.

2. The *Molecule Explorer* window can be selected with the left mouse button, moved within the Hermes interface or detached and dragged to any position on the screen.

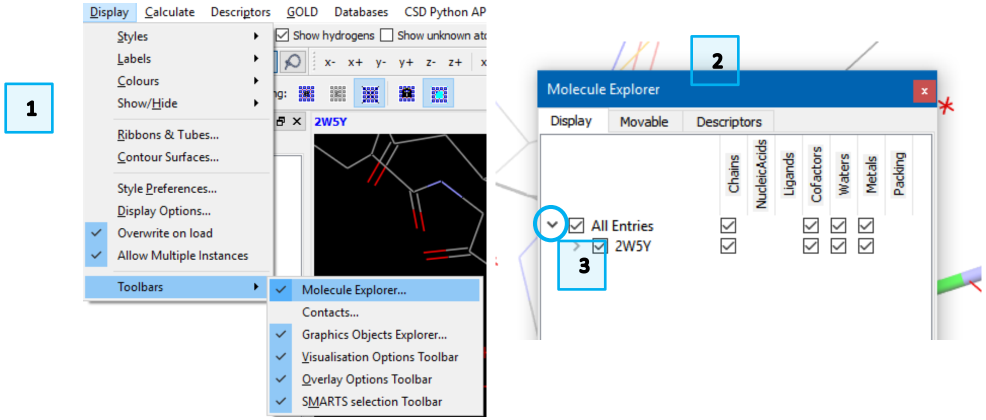
3. In *Molecule Explorer* window, individual components of the model can be opened by selecting the “>” to the left for Windows. Click on “>” adjacent to *2W5Y* under *All Entries*.

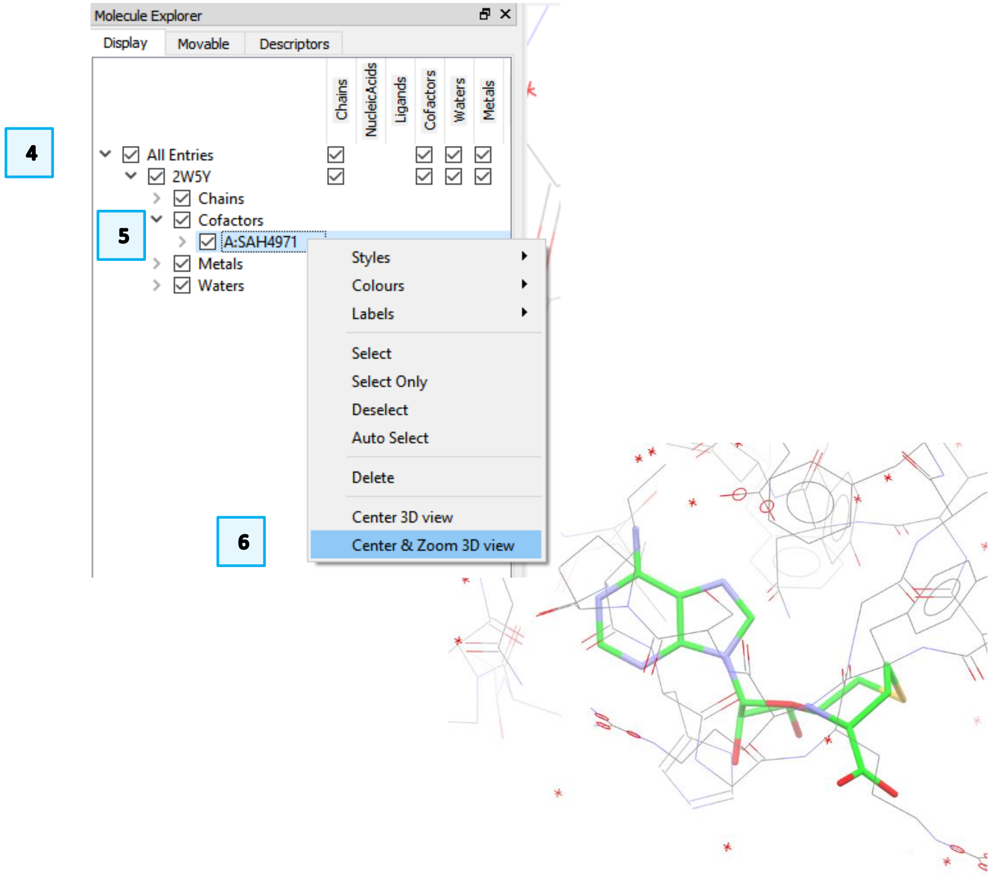
4. The various components of the model are now displayed: *Chains*, *Nucleic Acids*, *Ligands*, *Cofactors*, *Metals* and *Waters*. Each of these has a corresponding “>”. By clicking on each “>” each component is broken down further. This way it is possible to identify specific protein residues or atoms in a ligand.

   Click the “>” next to “*Cofactors*” to expand this category further.

5. Right-click on *A:SAH* to bring up the dropdown menu controlling the content and style of the display.

6. Select **Center & Zoom 3D View** to focus on the active site, this will centre the display on the *Cofactor A:SAH* and automatically zoom in.





Labelling

1. Click on an atom in the Display area to select it. The atom will be then highlighted in yellow.

2. Right-click on or near the selected atom to bring up a dropdown menu.

Depending on the exact position of your mouse, the selection of options may slightly vary, but a sub-option **Labels** should always be available.

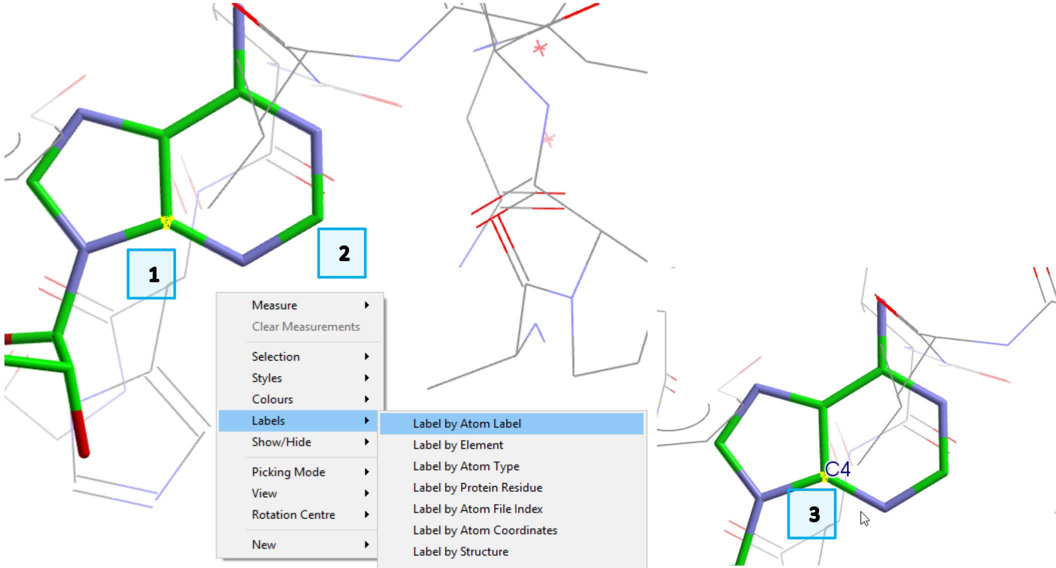
3. In the menu select **Labels** > **Label by Atom Label**. The label will then appear by the selected atom.

4. To label all residues, press Ctrl-A to select all atoms, or right-click in the display and choose **Selection** > **Select All** from the dropdown menu. All atoms will be highlighted in yellow.

5. With all atoms selected, right-click in the display and choose **Labels** > **Label Alpha Carbons by Protein Residue** from the dropdown menu. Note that there may be a short delay before the residue labels appear but this will show the Protein Residue and the relative residue number.

In addition, it is possible to select specific molecules by using the **Selection** > **Select Molecules.** Then, clicking on one atom will select all the atoms belonging to that molecule. Note that the same result is obtained by using Shift+ click on an atom.

6. To change the colours of the labels, right-click in the Display area and choose **Labels** > **Label colour…** from the dropdown menu. Choose a colour from the menu and click **OK**.



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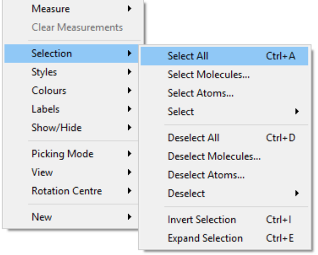

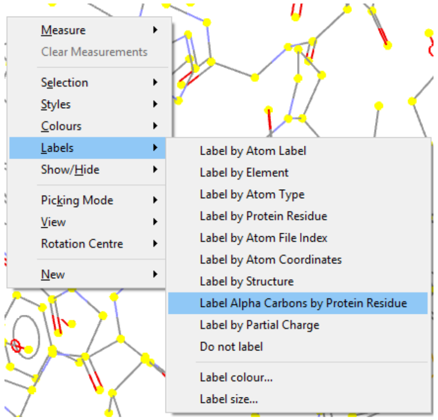

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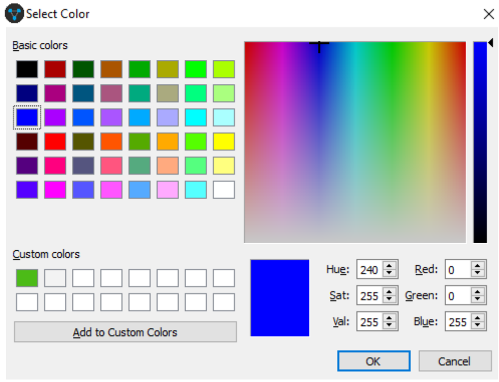
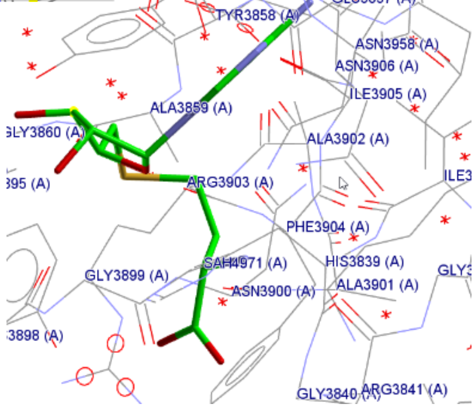


Hue: 240
Sat: 255
Val: 255
Red: 0
Green: 0
Blue: 255



Restrict the Display to Selected Residues

To inspect an active site, you may wish to restrict the display to residues interacting with your ligand or cofactor.

1. Left-click on any atom in the cofactor, then right-click on the atom to bring up the Molecule Area Pull Down Menu (MAM). Choose **Selection** > **Select Molecule** to select the atoms in the cofactor.

2. Ensure only the atoms in the cofactor are highlighted in yellow, then, in the top-level menu, click on **Selection** > **Define Complex Selection**. This will open the *Select atoms in 2W5Y* dialogue.

3. Enter "*AS*" as a name for your selection in the **Protein subset name** text box.

4. In the *Choose Atoms…* section, tick the **Residues that are within** radio button and change the value to "6" Å in the text box.

5. Press the **Add** button to add all atoms within this range to the selection.

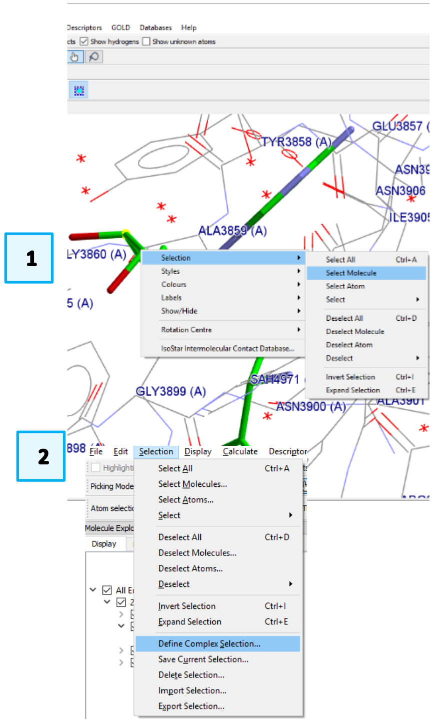
6. These atoms will now appear in the *Atoms currently selected* section.

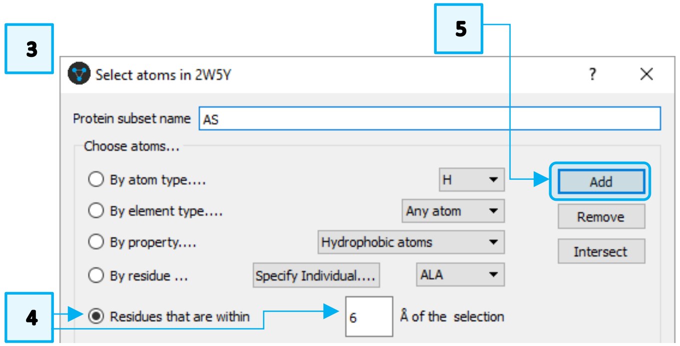
7. Click **Save** in the *Select atoms* dialogue to save your subset and then **Close** to close the *Select atoms* dialogue.

8. The defined subset will become then visible in the **Atom selections:** drop down in the menu bar. Click the dropdown menu and select *AS*. The selected atoms will be highlighted in yellow.

9. Right-click in the Display area and choose **Show/Hide** > **Show only** to restrict your display to the AS selection.

10. You will see the cofactor with the active site residues on your screen.





Protein subset name AS

Choose atoms…

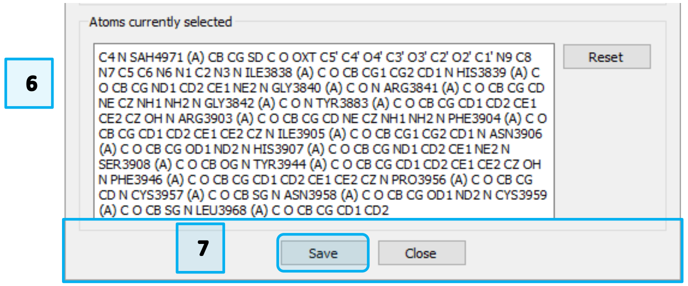
○ By atom type…. H

○ By element type…. Any atom

○ By property…. Hydrophobic atoms

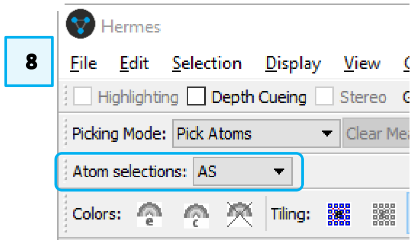
○ By residue … Specify Individual…. ALA

● Residues that are within 6 Å of the selection

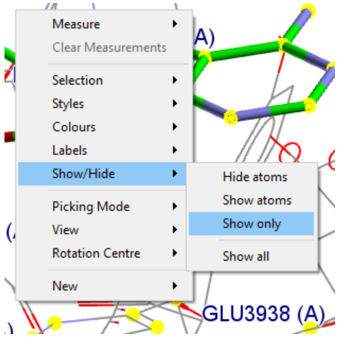


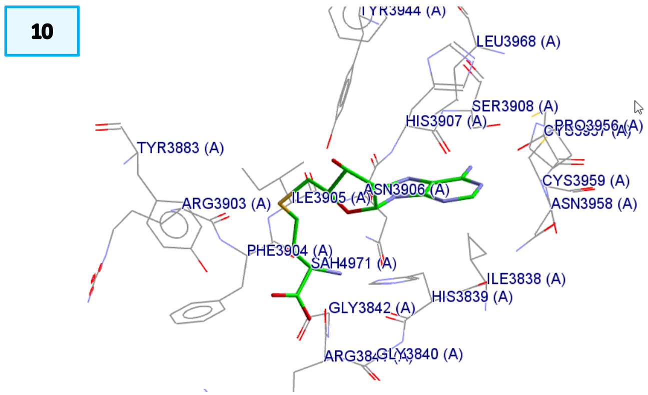
Atoms currently selected

C4 N SAH4971 (A) CB CG SD C O OXT C5' C4' O4' C3' O3' C2' O2' C1' N9 C8 N7 C5 C6 N6 N1 C2 N3 N ILE3838 (A) C O CB CG1 CG2 CD1 N HIS3839 (A) C O CB CG ND1 CD2 CE1 NE2 N GLY3840 (A) C O N ARG3841 (A) C O CB CG CD NE CZ NH1 NH2 N GLY3842 (A) C O N TYR3883 (A) C O CB CG CD1 CD2 CE1 CE2 CZ OH N ARG3903 (A) C O CB CG CD NE CZ NH1 NH2 N PHE3904 (A) C O CB CG CD1 CD2 CE1 CE2 CZ N ILE3905 (A) C O CB CG1 CG2 CD1 N ASN3906 (A) C O CB CG OD1 ND2 N HIS3907 (A) C O CB CG ND1 CD2 CE1 NE2 N SER3908 (A) C O CB OG N TYR3944 (A) C O CB CG CD1 CD2 CE1 CE2 CZ OH N PHE3946 (A) C O CB CG CD1 CD2 CE1 CE2 CZ N PRO3956 (A) C O CB CG CD N CYS3957 (A) C O CB SG N ASN3958 (A) C O CB CG OD1 ND2 N CYS3959 (A) C O CB SG N LEU3968 (A) C O CB CG CD1 CD2



Atom selections: AS





Measure Distances, Angles and Torsions

Metric parameters, such as distances, angles, and torsions can be measured for sets of atoms – whether bonded or not – by the following procedure. We want to measure the distances between the amide nitrogen of ASN3958 and the peptide oxygen of ILE3838.

1. Right-click in the Display are and choose **Measure** > **Measure Distances** from the dropdown menu.

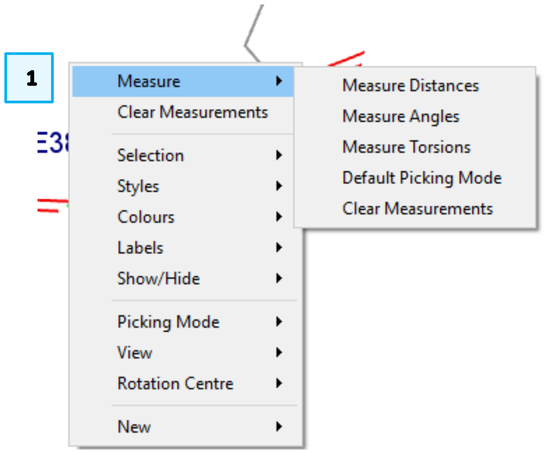
2. Click on the two atoms you would like to measure. The distance measurement will appear in the Display.

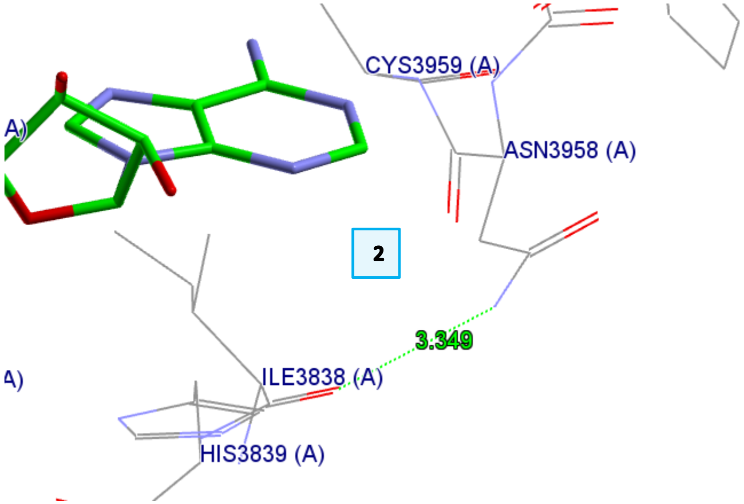
3. To measure angles, right-click in the Display area and choose **Measure** > **Measure Angles**. Click to select three atoms to measure the angle between them.

Note: The atoms must be clicked in order, such that the second atom selected will be the vertex of the angle.

4. To measure torsions, again, right-click in the Display area and choose **Measure** > **Measure Torsions**. Click to select four atoms to measure the torsion angle.

Note: The atoms must be clicked in order, such that the second and third atoms form the line around which the torsion will be measured.

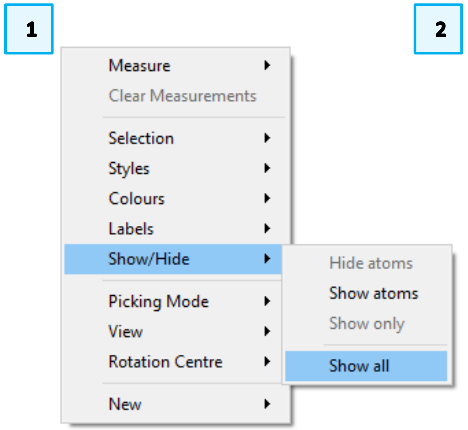


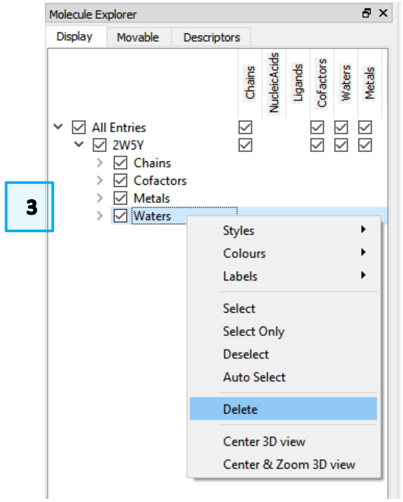


Edit Complexes with *Molecule Explorer*

Molecule Explorer window allows you to delete components of your macromolecule.

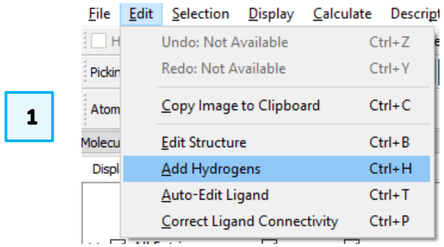
1. If your Display only shows the atoms in the *AS* selection as in the section above, right-click in the Display area and choose **Show/Hide** > **Show All** to display all the atoms of the model.
2. In the *Molecule Explorer* window, click *“>”* to expand *2W5Y* if it is not already expanded as shown.
3. Right-click *Waters* to bring up a dropdown menu and choose **Delete** to delete all water molecules from the complex.
4. In the same way as steps 2 and 3, delete the cofactor SAH (not illustrated).

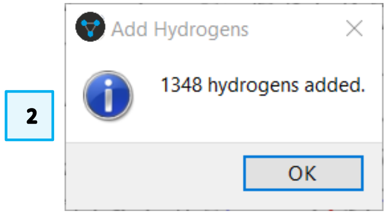




Adding Hydrogens

1. To add hydrogens to your model, select **Edit** > **Add Hydrogens** from the main menu.
2. Hermes will notify you that 1348 hydrogen atoms have been added. Click **OK** to exit the pop-up window.

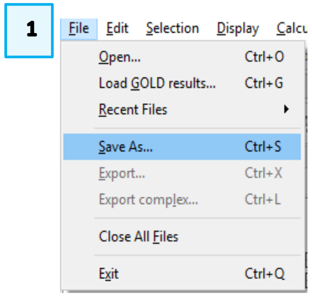




1348 hydrogens added.

Saving files

1. To save the current edited molecule in *mol2* format, from the top-level menu, choose **File** > **Save As…** Ensure you pick *mol2* for **Save as type**, enter *2w5y_protonated.mol2* as the name for your molecule and click **Save** to finish.



Feedback

We hope this workshop improved your understanding of Hermes and you found it useful for your work. As we aim to continuously improve our training materials, we would love to get your feedback. Click on this link to a survey (link also available from workshops webpage), it will take less than 5 minutes to complete. The feedback is anonymous. You will be asked to insert the workshop code, which for this self-guided workshop is HERM-001. Thank you!