CCDC

Mogul Geometry Check

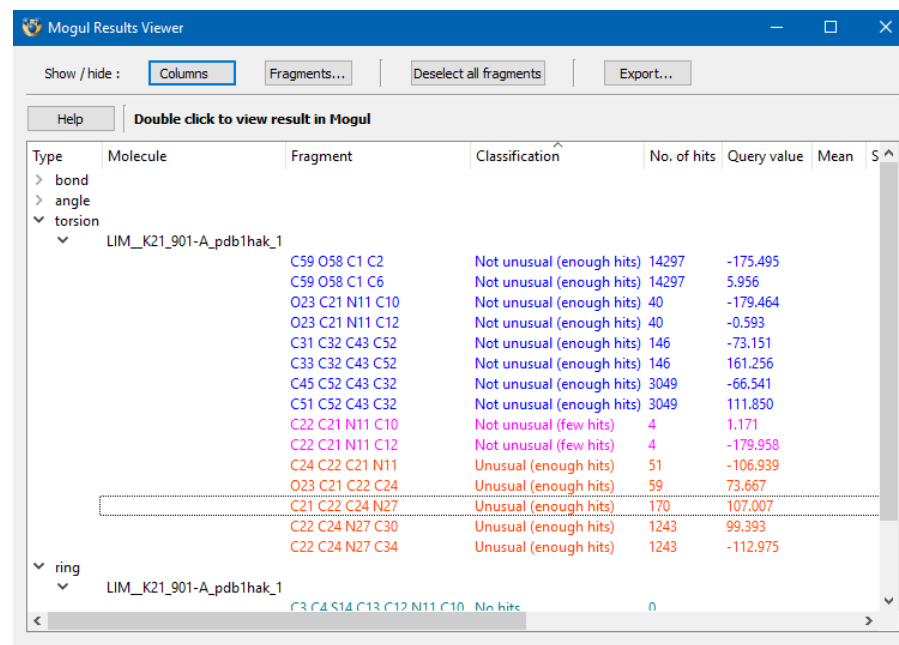**Version 2.0 – June 2019**
CSD v5.40

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Introduction

This tutorial will introduce you to the Mogul Geometry Check feature included with Mercury under the CSD-System toolset.

Structural chemists can use the Mogul Geometry Check tool to validate the three-dimensional conformation of a particular molecule. The metric data from structures in the CSD can be used to show the most likely values a particular bond, angle, torsion or ring should adopt. The information obtained from a Mogul check can help identify inconsistences within a crystal structure and can suggest values to be used for restraints during refinement. In addition, Mogul can also be run on 3D coordinates generated *in silico* as a validation of calculated structures.

The following exercises assume you have a working knowledge of the program Mercury, namely how to display and manipulate structures from a 3D coordinates file. There are many other features included with Mercury that are beyond the scope of this tutorial. For assistance with any aspect of Mercury, please ask your workshop instructor, or view the help guides included with the application.
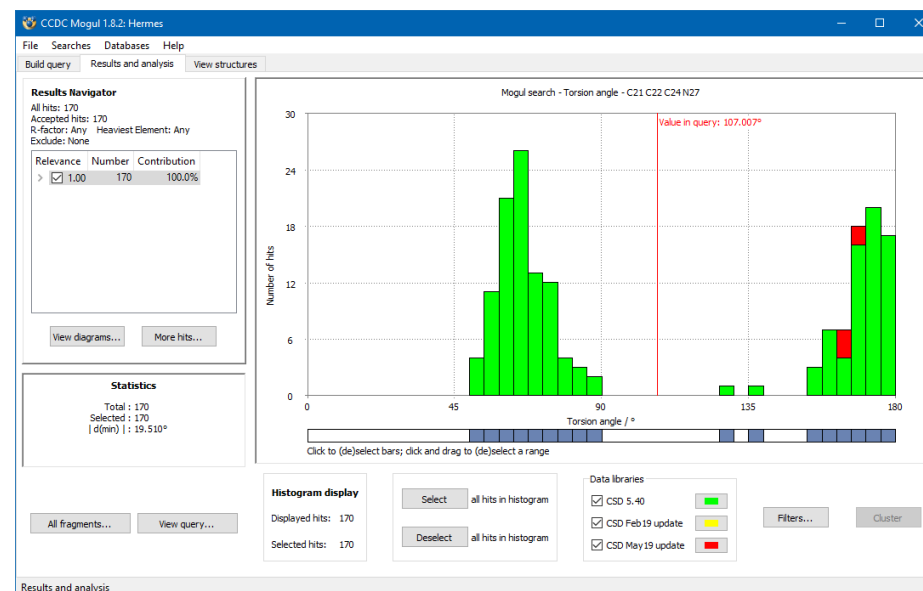
Example 1. Using Mogul to assess intramolecular geometry

Mogul is able to provide an assessment of a given structure's conformation by comparing it to the data from the hundreds of thousands of structures already in the CSD. By using the statistical distributions of similar fragments, Mogul can confirm your 3D geometry is appropriate, or flag values that are too far outside the norm.

In this example, you will see how to use Mogul to assess the geometry of a given molecule. Mogul can be run as a stand-alone application or from the Mercury or Hermes interfaces. For this tutorial, we will use Mercury to run Mogul.
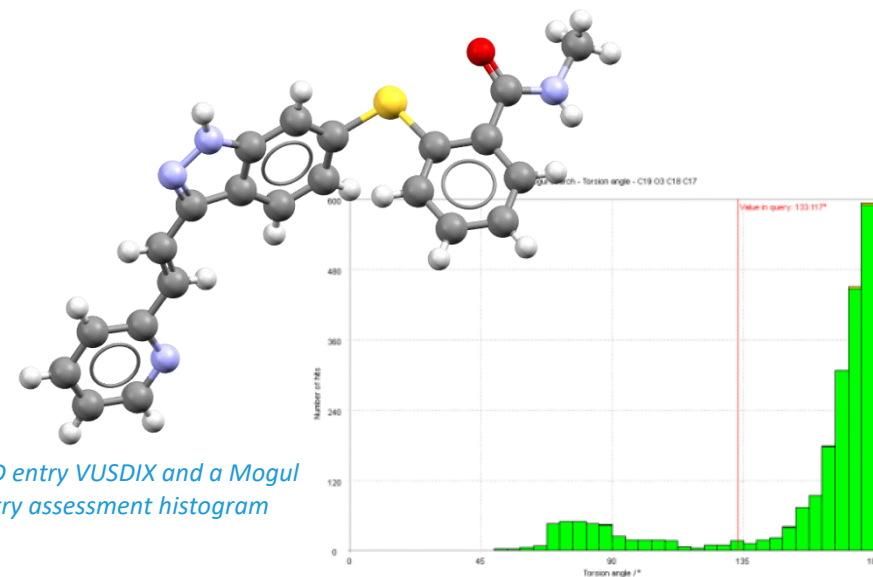
The CSD entry VUSDIX and a Mogul geometry assessment histogram

1. Launch Mercury and type VUSDIX in the Structure Navigator toolbar.

2. To start a geometry analysis, click the CSD-System menu and then click *Mogul Geometry Check* from the dropdown menu.

3. This brings up the *Mogul Search Settings* dialogue box. You can typically use the defaults in this window, but we can streamline our search by unticking the box for rings and ticking the boxes for *Apply Filters*, *Exclude Organometallics*, and *Exclude Powder structures*.

4. Click **Search** to start.

5. A dialogue box will pop up to warn you that you are going to check the entire molecule. Click **OK** to continue.

6. The search will begin to run. You can follow its progress in the *Search Progress* dialogue box.

7. When the search is complete, your results will be displayed in the **Mogul Results Viewer.**

8. The results are color-coded. Unusual values are flagged in red.

9. Scroll through the results until you find the angle for C20-C21-C22. Double-click this line to bring up the data from the Mogul library.

10. The red line marks the value of the angle from your molecule (the query).

11. The histogram shows the data from the CSD, color coded by update. (Note, you can double-click the color swatches to change what color is shown.)

12. To see which structures contribute to a certain bar on the histogram, first click **Deselect**, and then click the bar directly under the red query line. This will highlight that particular bar of the histogram.

13. Now click the *View structures* tab, near the top of the window, to see a list of refcodes included in this bin. The default view for this window is the 2D diagram. Scroll through the refcodes on the right side of the window to view different structures.

14. Click the **Information** button on the left to see further details about the structure.

15. Click the **3D Visualiser** button to see a 3D rotatable view of the structure. The fragment of the molecule used for comparison will be highlighted with the value displayed in green.

16. Continue to investigate other unusual parameters. You can always return to view the structure in Mercury to see which parameter you are querying.

Example 2. Using Mogul to explain activity data

Mycophenolic acid (A) is an immunosuppressant that binds to inosine monophosphate dehydrogenase (IMPDH) with an IC_{50} of 0.02μM. There are two close analogues (B and C) which are less active, with C much less so. How can Mogul help explain this decrease in activity?

In this example you will see how to use Mogul to correlate improved function with geometric preferences. You will need the file `1JR1_ligand.pdb` for this example

A successful target molecule will be able to form two favourable hydrogen bonds in the protein binding site, as shown. The angle of the allylic torsion angle should be in the range of 110-115° for this interaction to be achieved. We know that molecule A is a successful target but molecules B and C are not. What does Mogul have to say about these structures?

A
0.02 μM

B
0.14 μM

C
1.00 μM
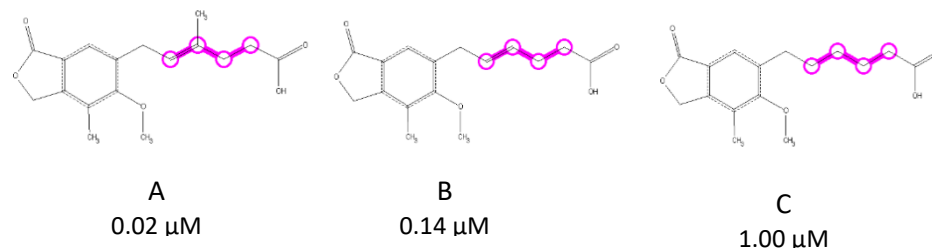
Mycophenolic acid (A) bound to a protein and analogues (B&C)

PDB: 1JR1
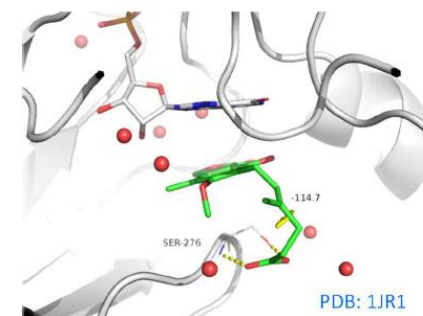
1. Launch ConQuest and click on the **Name/Class** query type.

2. In the box for Compound Name type "mycophenol" and then click **Add**.

3. Click **Search** and then **Start Search** for the *Search Setup* dialogue box.

4. The search should return 8 results. MYCPHA and MYCPHA01 are the neutral species. KIWQUC is a sodium salt. WAJYUC is a neutral derivative. The others are co-crystals.

5. Use the *3D Visualiser* tab to view the MYCPHA and KIWQUC structures noting the different conformations. Which one is the preferred orientation?
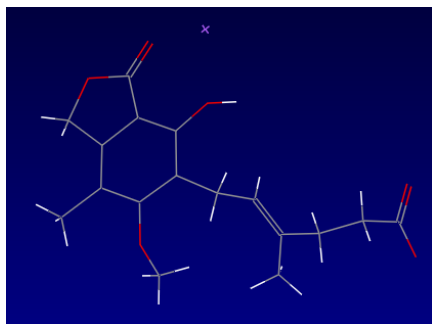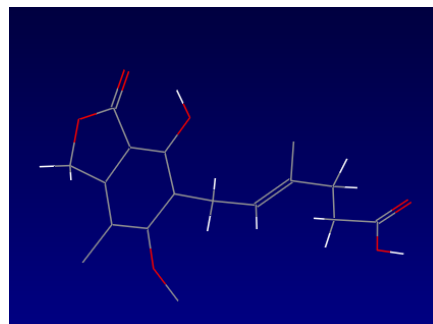
6. Launch Mogul (*via* the desktop icon, or *via* Mercury). We will first do a torsion search on the ligand as it appears in the protein crystal structure.

7. Click **Load…** and select the file 1JR1_ligand.pdb (provided for you along with this example). When the file is imported, Mogul will prompt you to edit the structure to assign bond types and add hydrogen atoms if necessary. Click **OK** to accept these changes.

8. Click to select the four carbon atoms that define the C2=C3-C4-C5 torsion angle. These will appear in the *Current Selection* box as you click.

9. Click **Search** when all atoms are selected.

10. The resulting histogram shows that the query value (114.654°) falls in a highly populated region of the histogram.

11. Now let's investigate the other two analogues in comparison to the bound ligand. We can do this by editing the ligand structure in the Mogul interface.

12. In the *Build query* tab, click **Edit…** This will launch the *Edit Structure* dialogue box. At the bottom of this box, under "Remove" click **Atoms & Bonds**. Then click on the methyl atoms (C and 3H) to delete them from the structure.

13. Once the atoms are deleted, at the top of the *Edit Structure* dialogue box under "Add" click **Hydrogen Atoms**. Make sure the value is set to 1 and then click the carbon atom from which you just deleted the CH3. This will add an idealized hydrogen at this position. Click **Close** when you are finished.

14. As in step 8 above, select the four carbon atoms of the C=C-C-C group, and then click **Search** to start Mogul running.
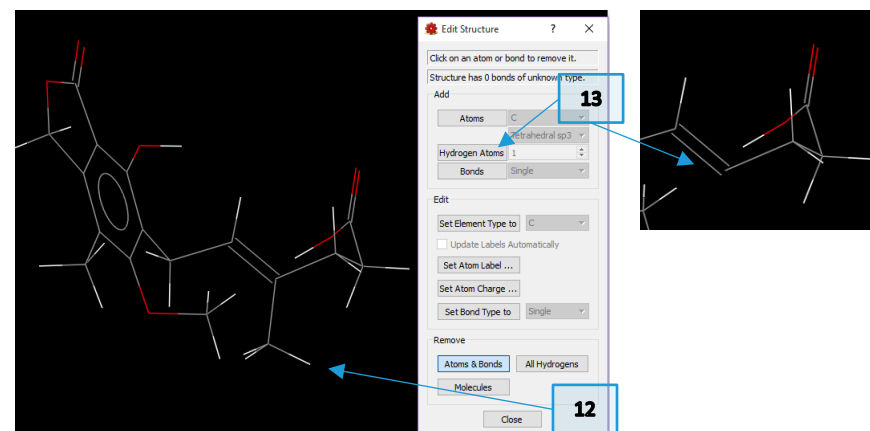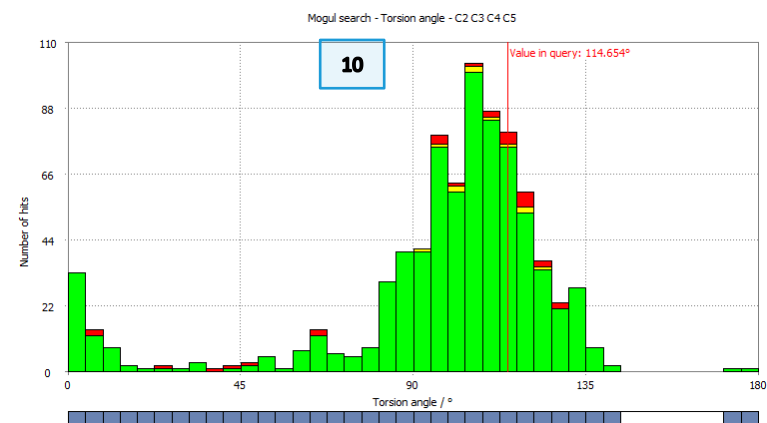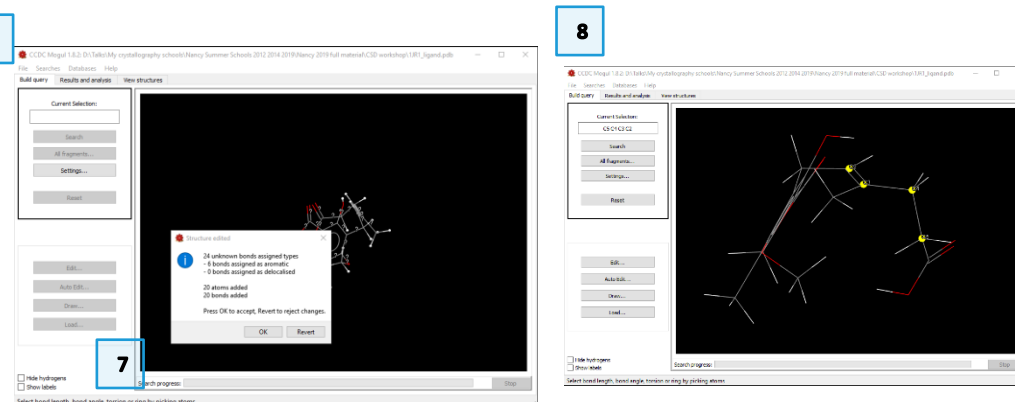
15. You will see the resulting histogram has shifted slightly, indicated the change in *chemistry* of the query fragment (des-methyl vs. methyl). However, the query *value* stays the same because we did nothing to alter the geometry of our query fragment. This shift in the predicted geometry indicates a slight loss of potency in this target molecule (B, above).

16. Finally, to investigate molecule C above, we need to make one more change. This molecule lacks the double bond that is present in molecules A and B.

17. Once again, return to the *Build query* tab and click **Edit...**

18. This time in the *Edit Structure* dialogue box click **Set Bond Type to** and choose *Single* from the drop-down menu beside it. Then click on the double bond to change it to a single bond.

19. Now, as in step 13 above, in the "Add" section, click **Hydrogen Atoms** and make sure the value is set to 1. Click the two carbon atoms on either side of what had been the double bond, to ensure they are fully saturated. Click **Close** to exit the dialogue box.

20. Once again, click to select the same four carbon atoms and then click **Search** to start Mogul running.

21. Now you will see the resulting histogram for this alkyl chain has shifted far away from the query value for mycophenolic acid. This means that this chemical change will not satisfy the necessary orientation for effective binding and explains the loss of potency in molecule C.
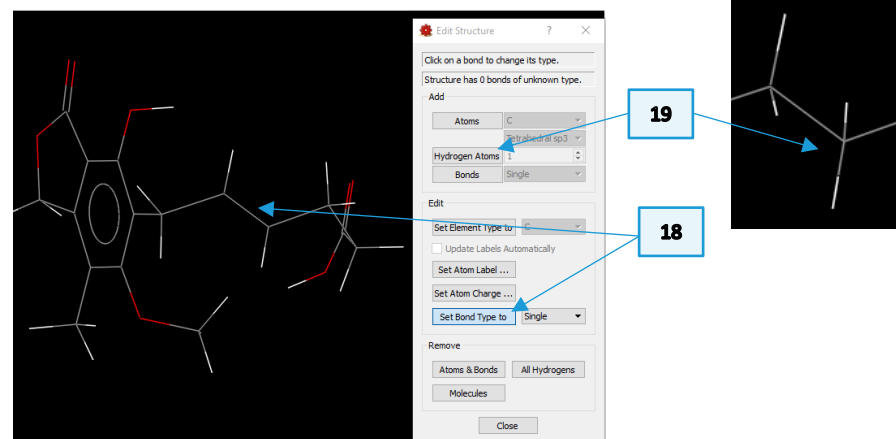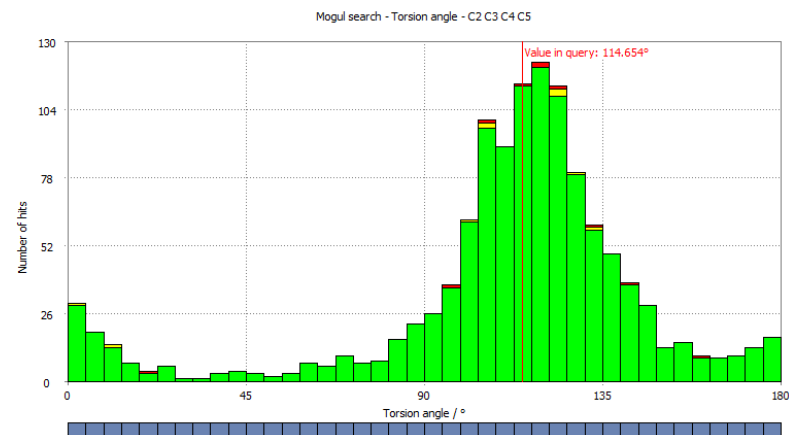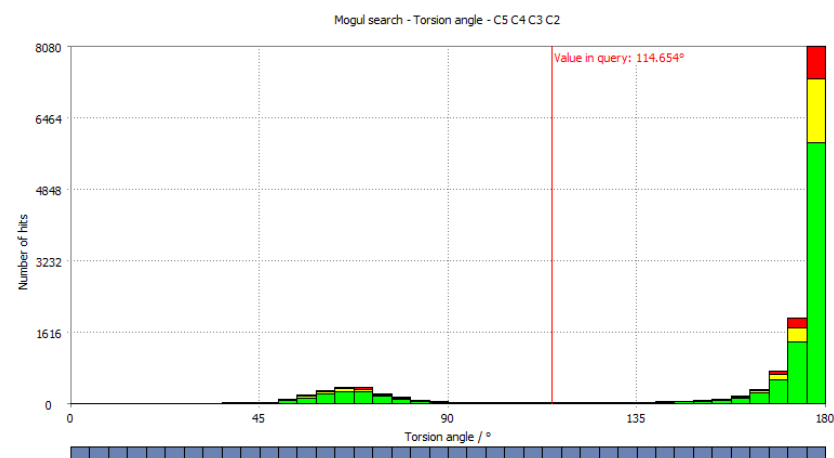
Conclusions

The skewed conformation for the crucial torsion in mycophenolic acid is the preferred orientation, although the neutral form of the molecule itself adopts a planar conformation for this torsion in the small molecule crystal structure. An analysis of conformational preferences rationalized the observed activity data for similar compounds.

Mogul can be an effective tool in explaining pharmacophore activity in relation to changes in substituents and bonding patterns. You should now be able to use Mogul to make changes to your own structures to see what functional groups can be altered in order to produce desired conformations or geometries.

Further Exercises

- Use Mogul to investigate subtle changes to your own molecules, or others that you find in the CSD.

- Using what you know of Full Interaction Maps, is there an explanation for the planar torsion angle of MYCPHA?

MYCPHA
syn conformation

1JR1 ligand
skewed conformation