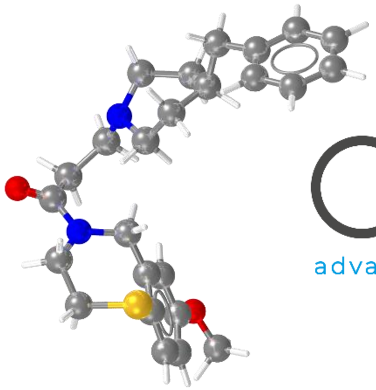
Mogul

2020.2 CSD Release



CCDC advancing structural science

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Introduction

This tutorial will introduce you to the Mogul Geometry Check included with Mercury under the CSD-Core toolsets.

Structural chemists can use the Mogul Geometry Check tool to validate the three-dimensional *conformation* of a particular molecule. The 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 inconsistencies 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.

Objectives

In this workshop you will learn:

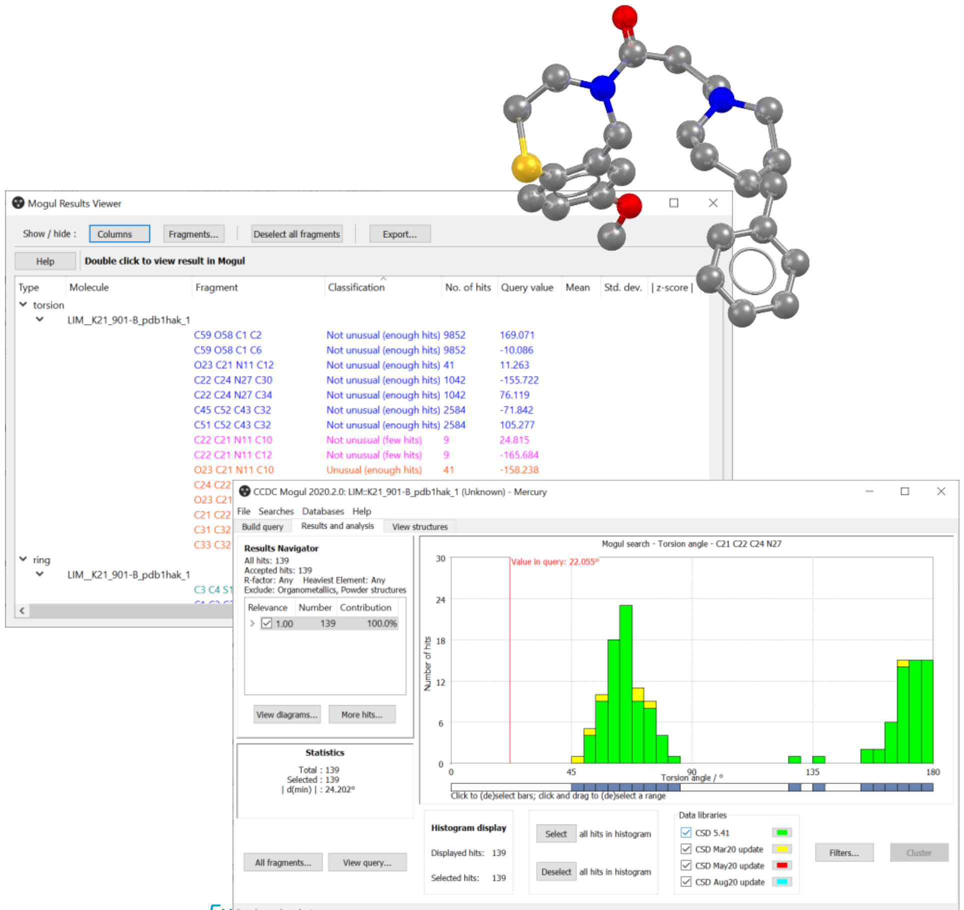
- How to use the Mogul geometry check from Mercury to assess the geometry of a molecule.
- How to launch Mogul from Mercury.
- How to run a geometry check on specific features (for example a torsional angle) of a molecule that you load.

The exercises in this handout will take approximately ***25 minutes*** to be completed.

Note: This handout was realised using the 2020.2 release of the CSD (data Aug20). Your results (e.g., number of hits and histogram colours) might differ based on the CSD version you are using.

Pre-required skills

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.



Example of the Mogul geometry assessment interface.

Materials

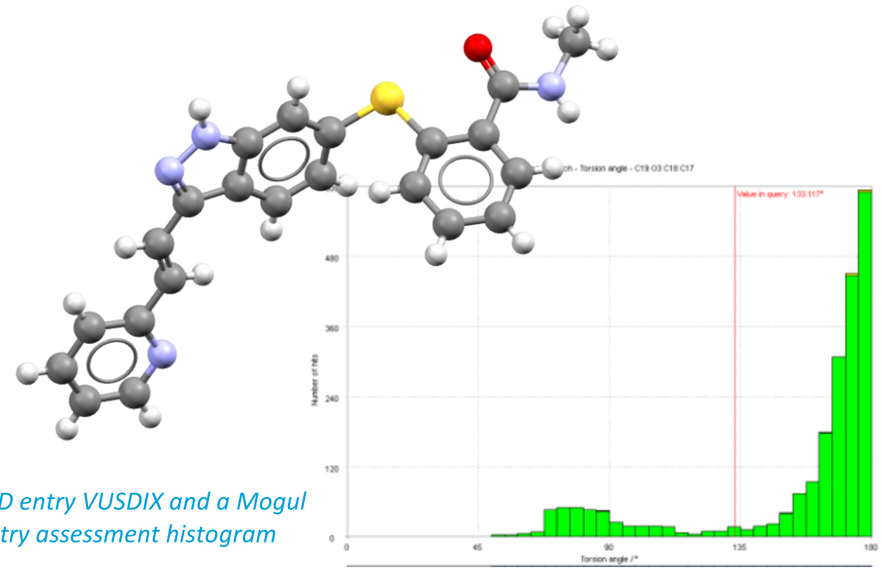
For this workshop we will use the file **1JR1_ligand.pdb** that you can download from this link.

Note: The words in *Blue Italic* in the text are reported in the Glossary at the end of this handout.

Example 1. Using Mogul to assess intramolecular geometry

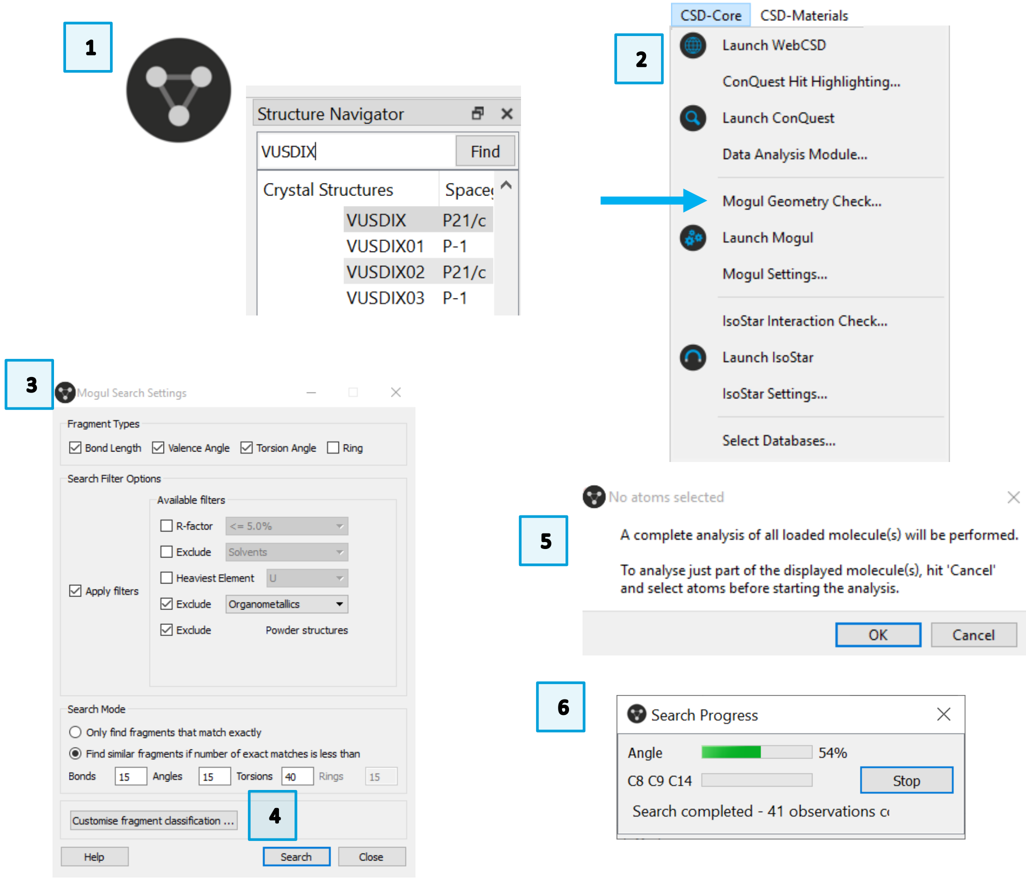
Mogul can provide an assessment of a given structure's *conformation* by comparing it to the data from the over one million structures already in the CSD. By using the statistical distributions of similar *fragments*, Mogul can confirm your 3D geometry is appropriate, or flag values that are too far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

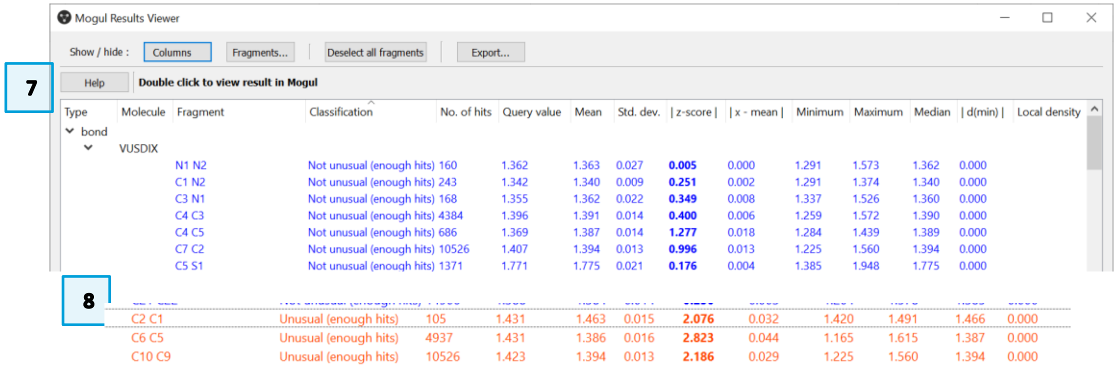
8. The results are colour-coded. Unusual values are flagged in orange. Please, be aware that the number of hits might differ based on the version of the data update. The data in this workshop are obtained with the Aug20 update.

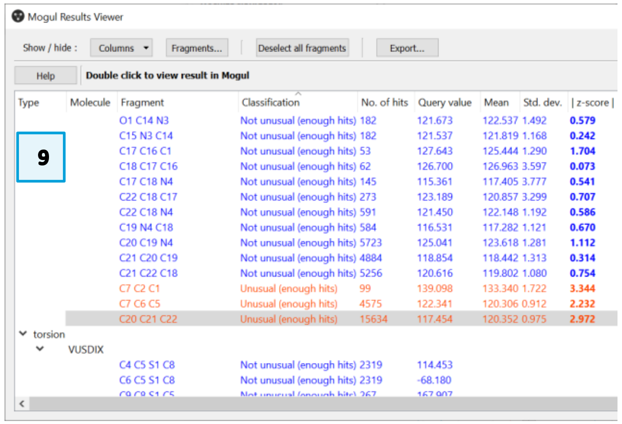
9. Scroll through the results until you find the angle for C20-C21-C22. Double-click this line to bring up the data from the Mogul library.

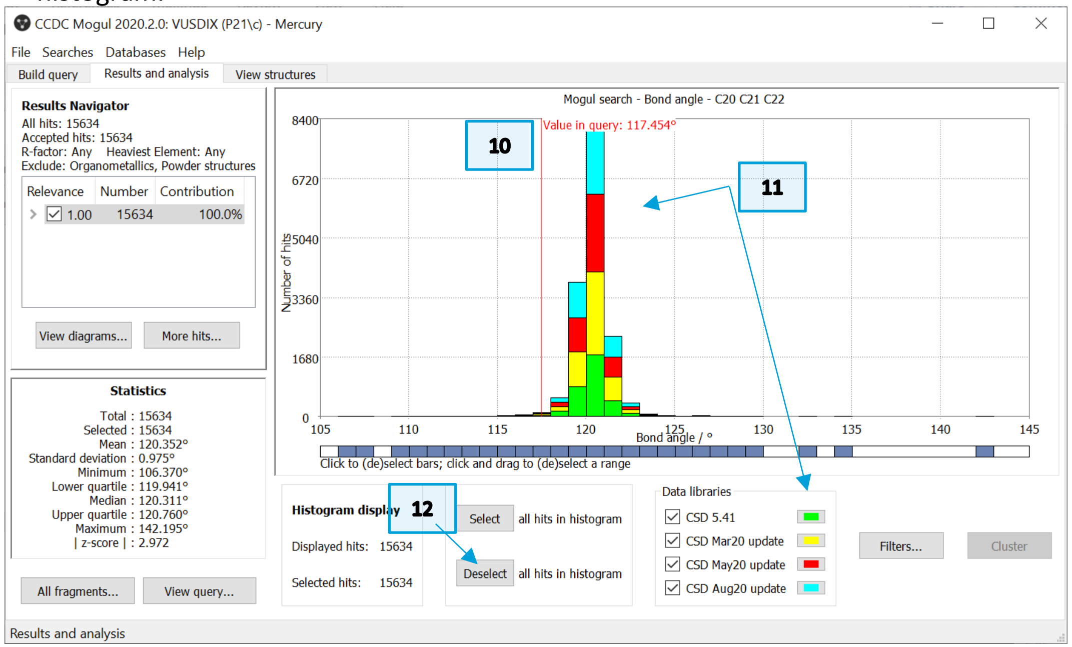
10. The red line marks the value of the angle from your molecule (the query).

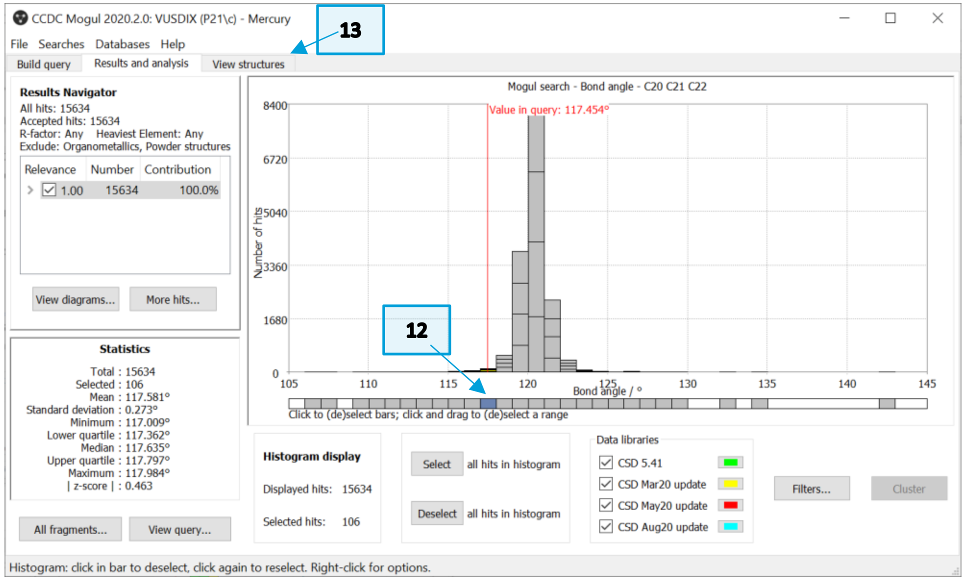
11. The histogram shows the data from the CSD, colour coded by update. (Note: you can double-click the colour swatches to change what colour is shown.)

12. To see which structures contribute to a certain bar on the histogram, first click **Deselect** (all the bars will turn grey), and then click the bar directly under the red query line. This will highlight with colours that specific bar of the histogram.







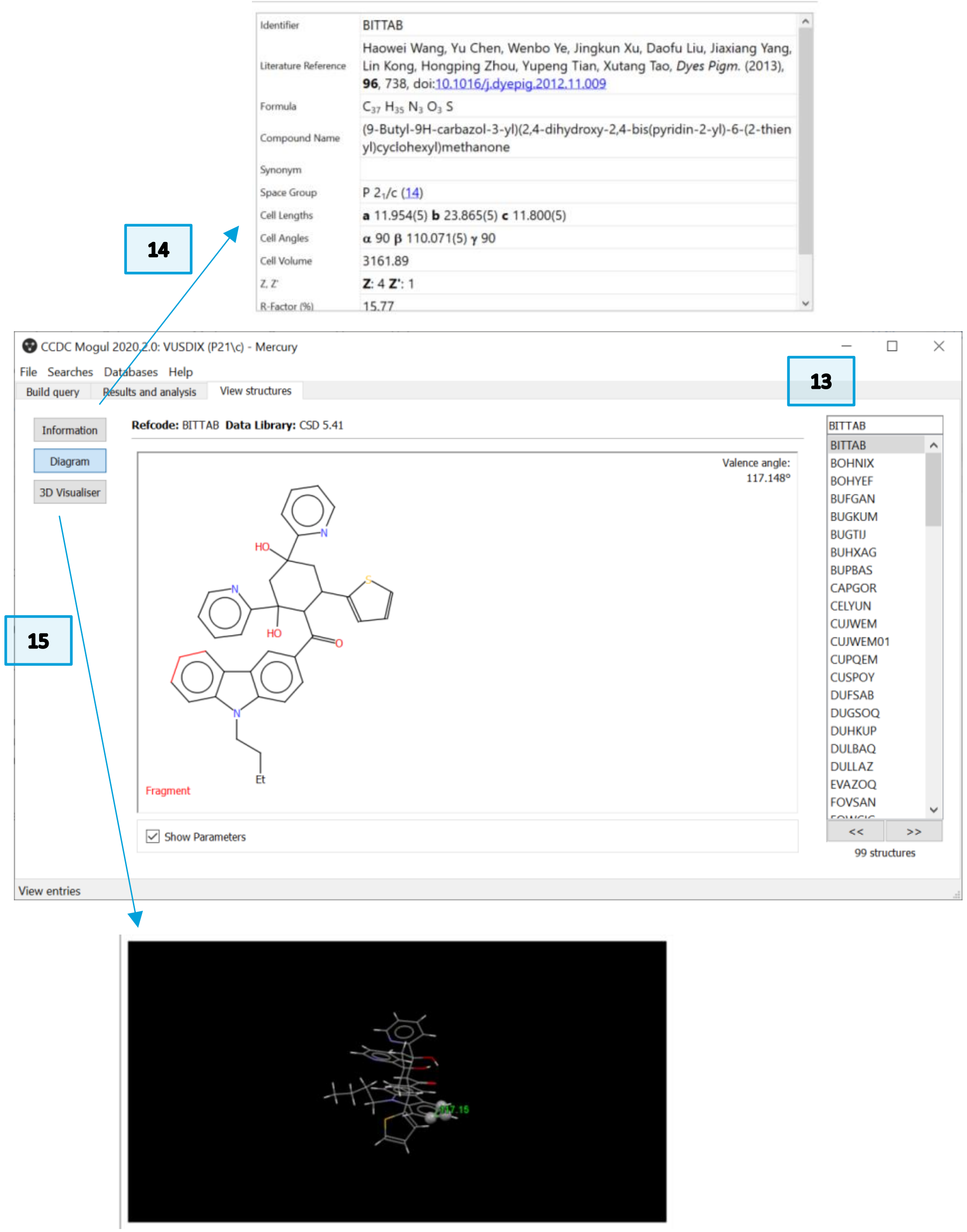


13. Now click the *View structures* tab, near the top of the window, to see a list of refcodes included in this bin. The default view for this window is the 2D diagram. Scroll through the refcodes on the right side of the window to view different structures. You will see that the *fragment* of interest is drawn in red and its value at the top right.

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.



Conclusions for Example 1

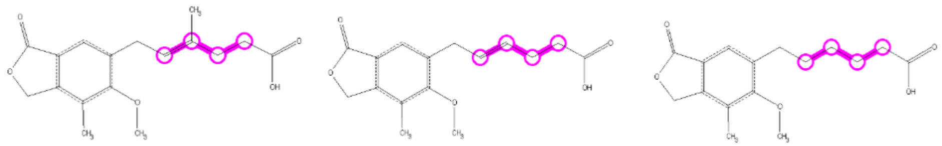
In this exercise we have performed a Mogul Geometry Check on a molecule from the CSD. We have learnt how to run a Mogul Geometry Check from the CSD-Core menu in Mercury and how to read and analyse the results.

Example 2. Using Mogul to explain activity data

Mycophenolic acid (A) is an immunosuppressant that binds to inosine monophosphate dehydrogenase (IMPDH) with an [*IC₅₀*] 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 activity with geometric preferences. You will need the file `1JR1_ligand.pdb` for this example (downloadable from [Materials section]).

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?

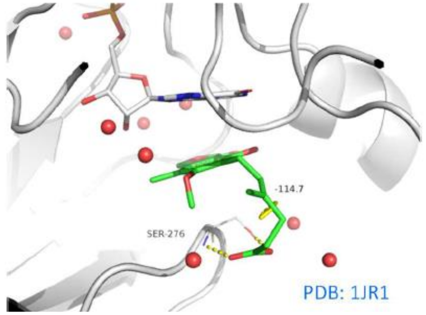


A
0.02 µM

B
0.14 µM

C
1.00 µM

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

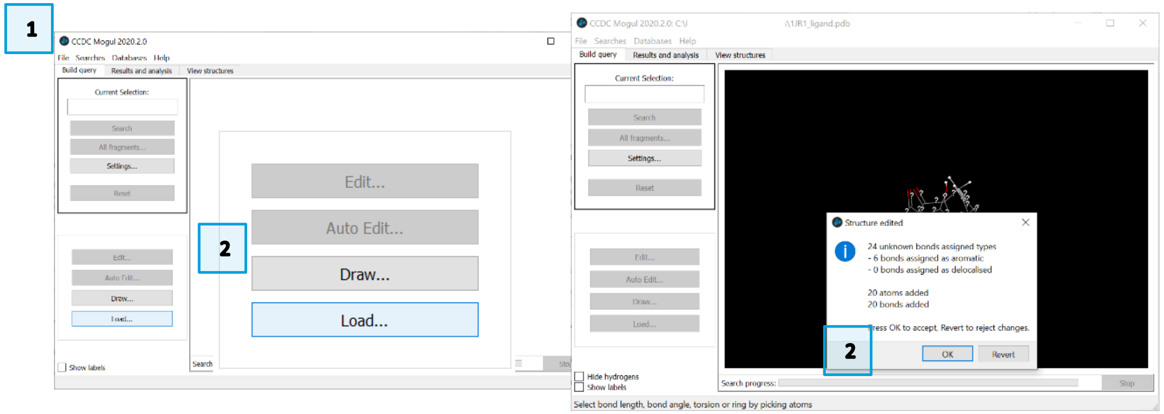


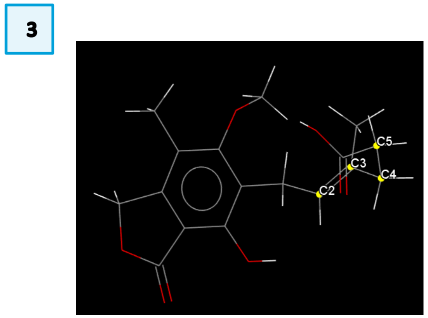
1. Launch Mogul (*via* the desktop icon, or *via* Mercury). We will first do a torsion search on the ligand as it appears in the protein crystal structure.

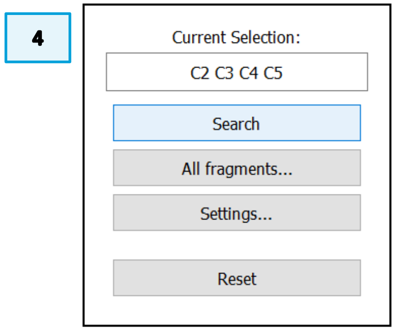
2. Click **Load…** and select the file 1JR1_ligand.pdb (provided for you along with this example). When the file is imported, Mogul will prompt you to edit the structure to assign bond types and add hydrogen atoms if necessary. Click **OK** to accept these changes.

3. 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. You can tick Show Labels at the bottom left of the window as an aid to identify the four atoms. **Note**: the order of selection is important when defining a torsion. In this case, follow the order as they are bonded together.

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







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

6. Now let's investigate the other two molecules and compare them to the ligand just seen. We can do this by editing the ligand structure in the Mogul interface.

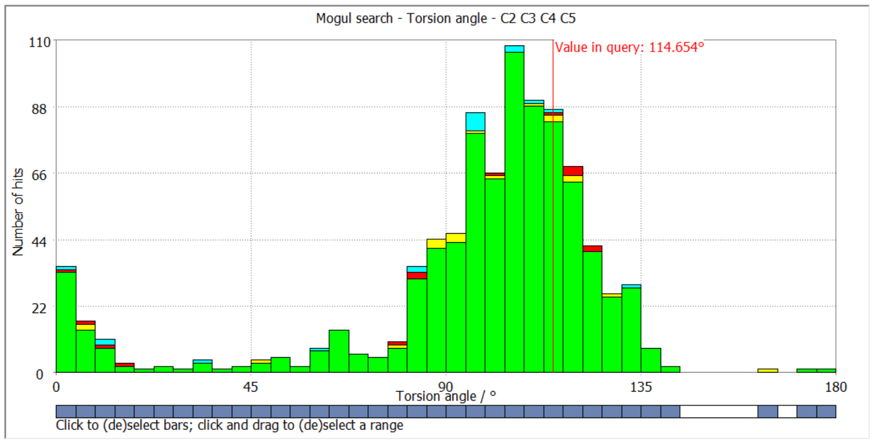
7. In the *Build query* tab, click **Edit...** This will launch the *Edit Structure* dialogue box. At the bottom of this box, under "Remove" click **Atoms & Bonds**. Then click on the *methyl* atoms (atoms C9, and the 3 H bonded to it) to delete them from the structure.

8. 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 (carbon C3). This will add an idealized hydrogen at this position. Click **Close** when you are finished.

9. As in step 3 above, select the four carbon atoms of the C=C-C-C group, and then click **Search** to start Mogul running.

10. You will see the resulting histogram has shifted slightly, indicating 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.

5



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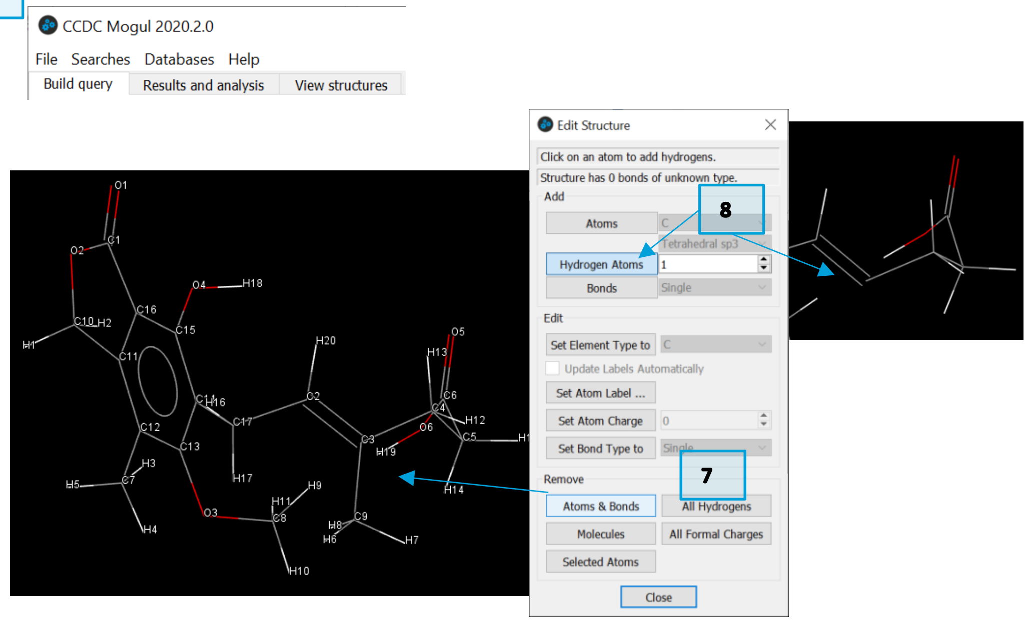

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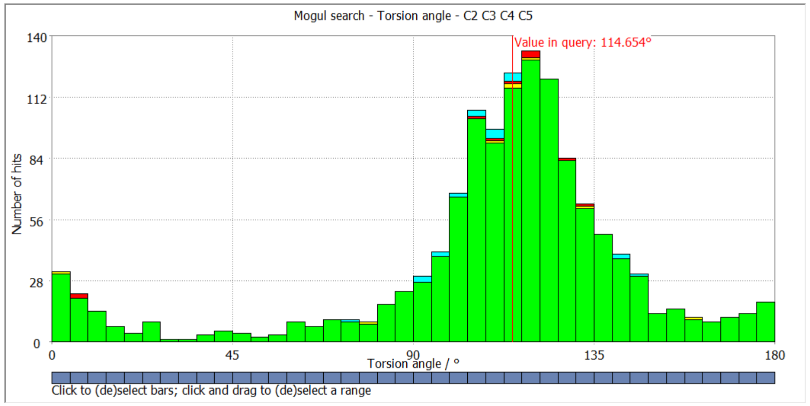


11. Finally, to investigate molecule C above, we need to make one more change. This molecule lacks the double bond that is present in molecules A and B.

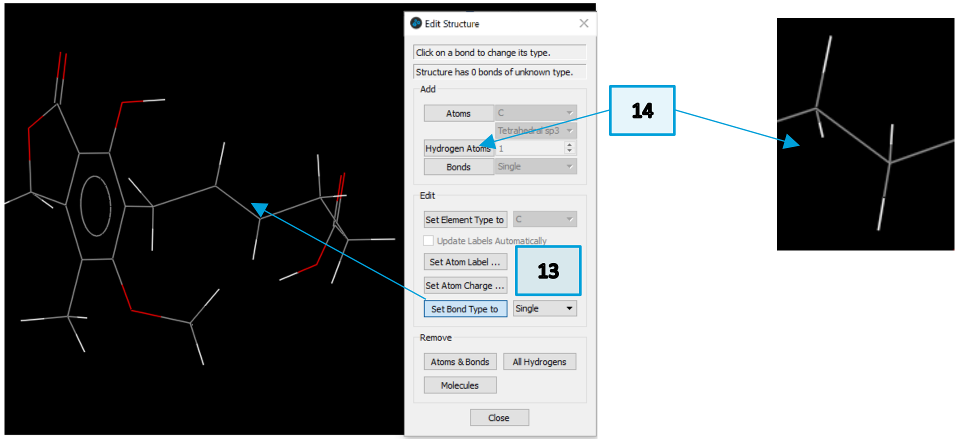
12. Once again, return to the *Build query* tab and click **Edit…**

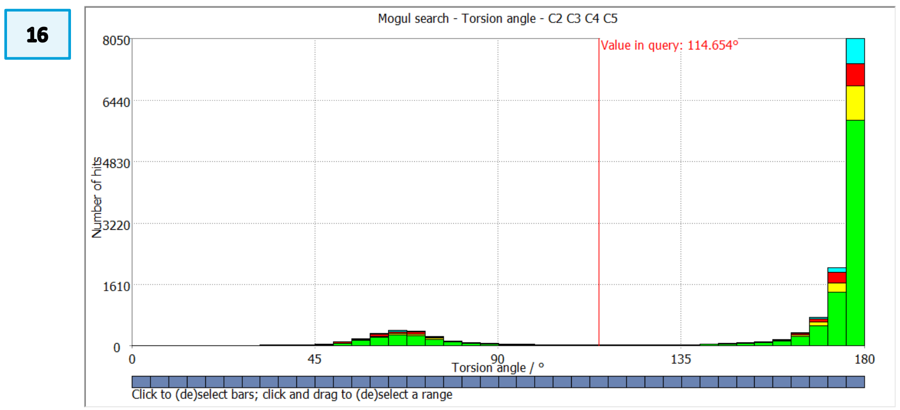
13. This time in the *Edit Structure* dialogue box click **Set Bond Type to** and choose *Single* from the drop-down menu beside it. Then click on the double bond C2=C3 to change it to a single bond.

14. Now, as in step 8 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, i.e., C2 and C3, to ensure they are fully saturated. Click **Close** to exit the dialogue box.

15. Once again, click to select the same four carbon atoms (C2-C3-C4-C5, as in steps 3 and 9) and then click **Search** to start Mogul running.

16. 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.



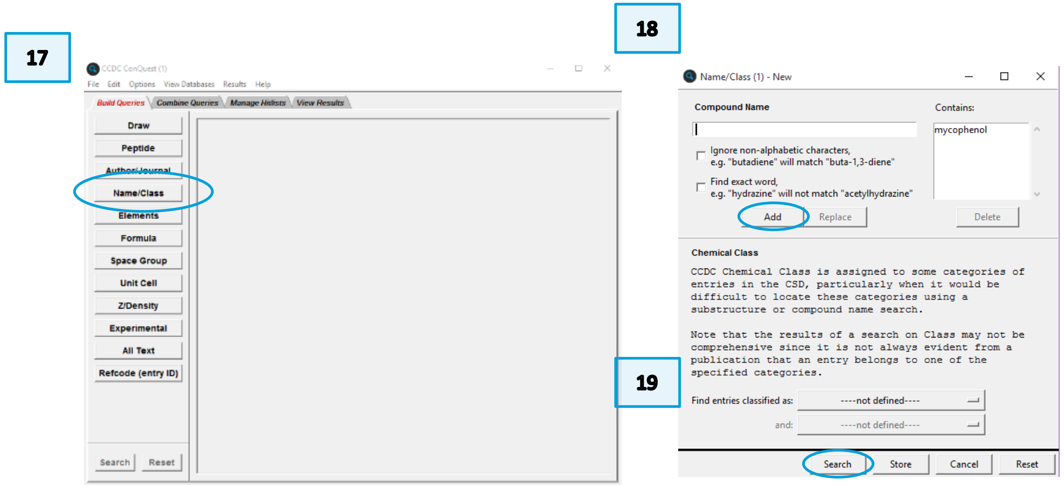


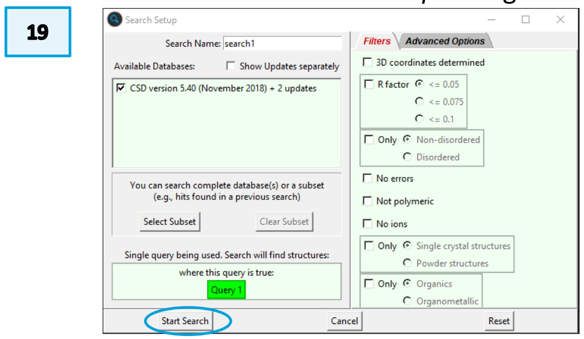
Extra Exercise: Find these molecules in Conquest and assess the preferred orientation

17. Launch ConQuest and click on the **Name/Class** query type.

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

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

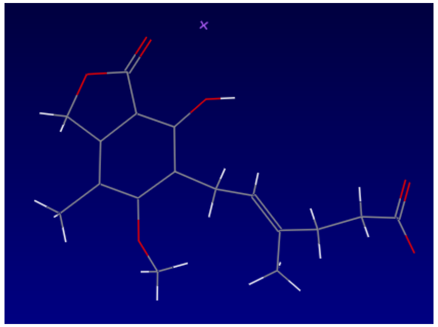




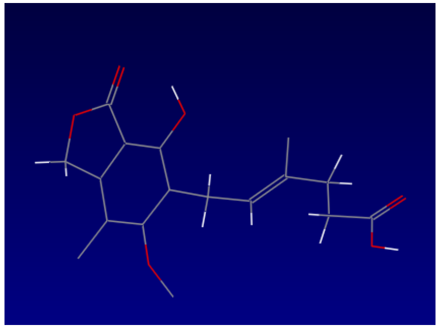
20. The search should return 8 results. MYCPHA and MYCPHA01 are the neutral species. KIWQUC is a sodium salt. WAJYUC is a neutral derivative. The others are co-crystals.

21. Use the *3D Visualiser* tab to view the MYCPHA and KIWQUC structures noting the different conformations. Based on what we have learnt from Mogul, which one is the preferred orientation?

21



KIWQUC

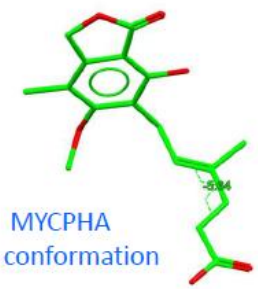


MYCPHA

Conclusions for Example 2

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.



MYCPHA
syn conformation

1JR1 ligand
skewed conformation

Conclusions

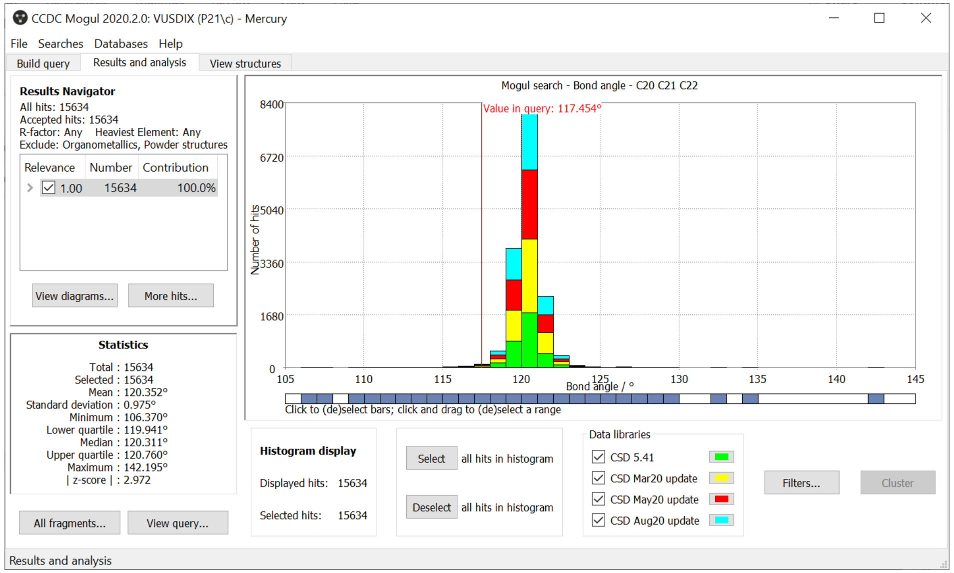
After this workshop you will be able to assess the geometry of a molecule of interest using Mogul in Mercury. In particular, you will:

- Know how to access Mogul and the Mogul Geometry Check from Mercury.
- Know how to run the Mogul Geometry Check on a molecule of interest.
- Be able to explain the results of the Mogul Geometry Check analysis, in particular the colour code of the tables and the histograms.
- Know how to load a file in Mogul and run a geometry check on specific features (for example a torsional angle) of a molecule.
- Know how to edit a molecule in Mogul to assess the geometry for different groups.

Next steps

After this workshop, you can explore more exercises in the self-guided workshops available in the [CSD-Materials workshops area](https://www.ccdc.cam.ac.uk/Community/educationalresources/workshop-materials/csd-materials-workshops/) on our website. We suggest trying the Full Interactions Maps workshop, which complement the Mogul geometry Check in the assessing of stability.

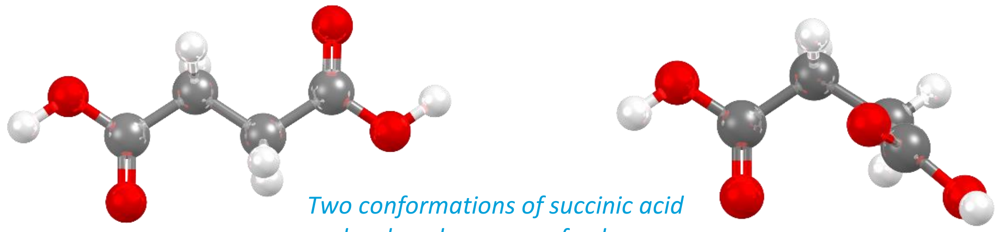
https://www.ccdc.cam.ac.uk/Community/educationalresources/workshop-materials/csd-materials-workshops/



Glossary

Conformation

The shape, or more precisely, the spatial arrangement of a molecule is called conformation. The same molecule can present different conformations (different shapes).



Two conformations of succinic acid molecules, shown on refcodes SUCACB02 (left) and SUCACB19 (right)

Des-methyl

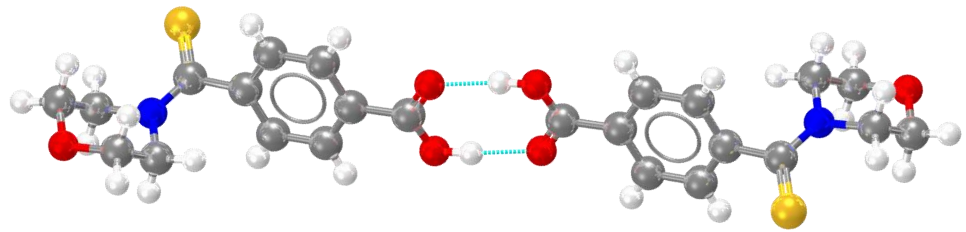
When a *methyl* group is removed from a structure, the adjective des-methyl is used for such structure.

Fragment

Fragment is the generic word used in Mogul for a bond, valence angle or torsion.

Hydrogen Bonds

Hydrogen Bonding occurs between donor-acceptor interactions precisely involving hydrogen atoms. The H-bonds interactions are classified as: strong (mostly covalent), moderate (mostly electrostatic) and weak (electrostatic).
Their strength is observed to be between 12 and 30 kJ/mol.



In light blue, example of hydrogen bonds for refcode MULWIC.

IC_{50}

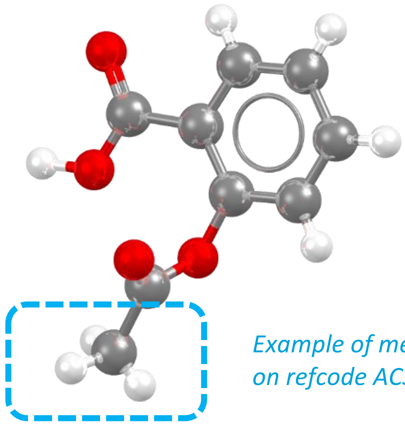
IC_{50} is a measure of the inhibition power of the substance. The lower the value the better, as less of the substance is needed to inhibit the process by 50%.

In silico

The expression *in silico* is used to refer to values that are generated via computer calculations or simulations.

Methyl

The methyl group is composed by a carbon atom linked to three hydrogen atoms. Its formula is CH_3.



Example of methyl group shown on refcode ACSALA

Torsion Angles

Torsion angles are used to describe conformations around rotatable bonds. The torsion angle between 4 atoms A-B-C-D is the angle by which the vector A-B must be rotated in order to eclipse the vector C-D when viewed along the vector B-C.