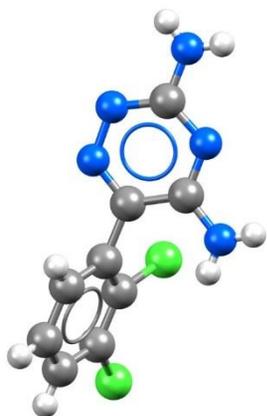


# Full Interaction Maps Mogul Geometry Check

Version 1.0 – April 2016



## Table of Contents

Introduction .....	2
Example 1: Using Full Interaction Maps to assess polymorph stability ....	3
Conclusions .....	5
Example 2: Investigating the potential for co-crystallization.....	6
Conclusions .....	7
Example 3: Investigating a series of halogenated molecules .....	8
Conclusions .....	10
Further Exercises.....	10
Example 4: Using Mogul to assess intramolecular geometry .....	11
Example 5: Using Mercury to predict geometry of a fragment .....	13
Conclusions .....	14
Further Exercises.....	14
Example 6: Using Mogul to explain activity data .....	15
Conclusions .....	18
Further Exercises.....	18

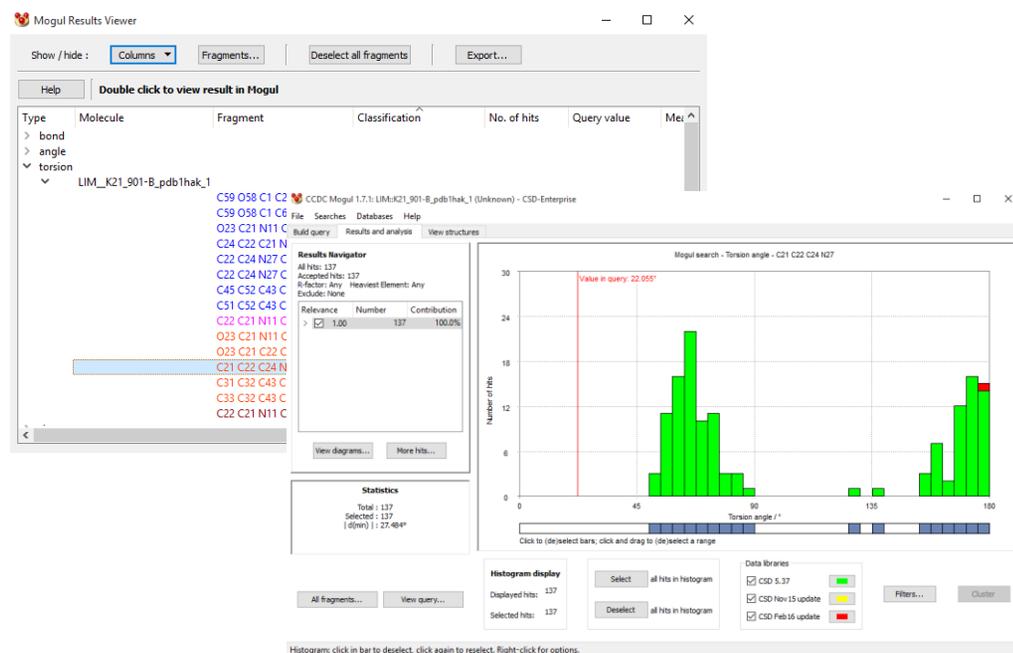
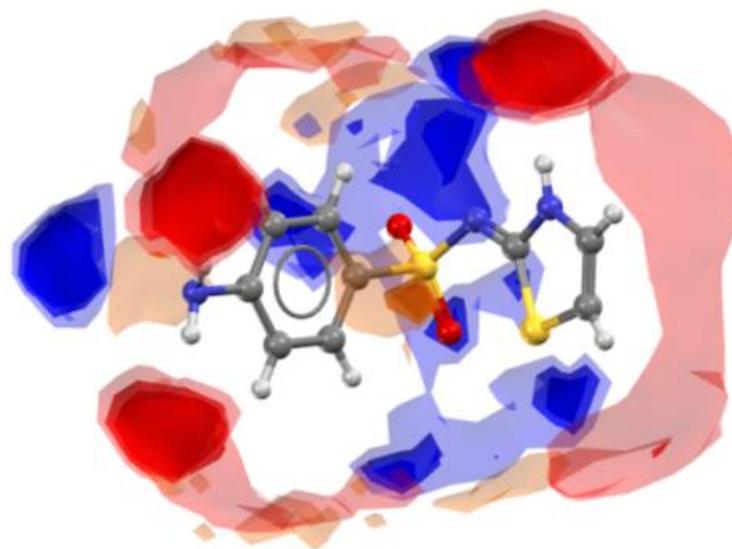
## Introduction

This tutorial will introduce you to the Full Interaction Maps and Mogul Geometry Check features included with Mercury under the CSD-Materials and CSD-System toolsets.

The Full Interaction Maps tool will generate a picture of the interaction landscape of your molecule from its three-dimensional coordinates. Using statistical distributions from the hundreds of thousands of structures included in the CSD, we can predict the most likely locations for a variety of functional groups. By comparing this distribution against a 3D packing diagram, we can determine whether a crystal structure fulfills the desired interactions of a particular conformation of a particular molecule. The Full Interaction Maps tool is instrumental in highlighting the potential for polymorphism of a given compound, assisting in the development of co-crystals, and understanding solid form stability.

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 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.

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.

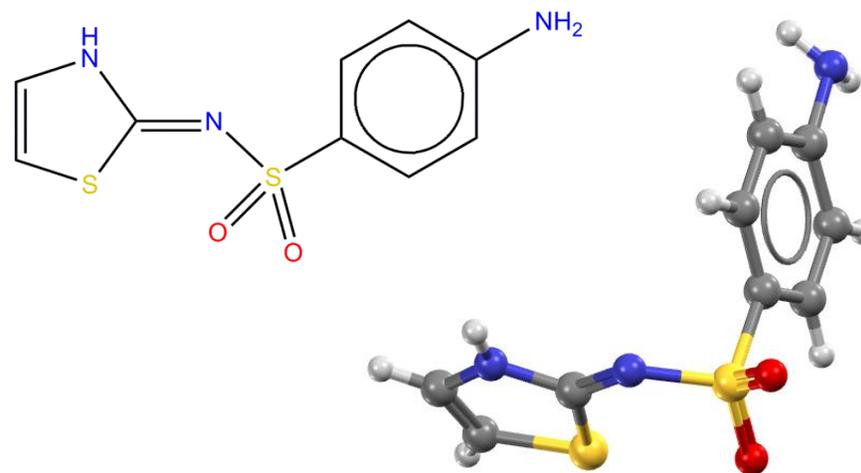


## Example 1: Using Full Interaction Maps to assess polymorph stability

The stability of a given crystal structure is a balance between the intramolecular conformation and the intermolecular packing of the molecules in the crystalline state. One method for understanding the relative stability of crystal structures is to compare the observed intermolecular interactions with preferred geometries for that type of interaction.

This example will look at two known polymorphs of sulfathiazole to answer the question: **How do the interactions in each polymorph compare with what is expected?** You will learn how to produce a Full Interaction Map for a given structure and how to interpret this map.

1. Launch Mercury by clicking its icon . In the Structure Navigator toolbar, type SUTHAZ19 to bring up the structure for Form V of sulfathiazole.
2. Click on the *CSD-Materials* menu and select *Full Interaction Maps...*
3. In the *Full Interaction Maps* dialogue box, you will see several options. On the left you will find options to change the display contour levels. On the right, you will see a list of functional groups to be used as probes. For the purposes of this tutorial, we will keep the default options. These typically work well for most situations, but if you know you are looking for a specific functional group, or if you want to change the look of the map, you will want to change these settings.
4. Click the **Calculate Maps** button to start.



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5. The generated map will now be displayed in the main Mercury window. Notice the three different colors in the map. **Red** regions of the map denote areas in which there is a high probability of locating a hydrogen bond **acceptor**. **Blue** regions denote hydrogen bond **donors**, and **brown** regions indicate **hydrophobic** preferences.

6. Now we want to see how the overall packing of this polymorph fits with the Full Interaction Map we have generated. Tick the box for H-bond in the Display Options toolbar. Click **OK** to apply the change.

7. Double click the H-bond line to launch the *Define H-bonds* dialogue box. Then tick the box for "Require hydrogen atoms to be present". Click **OK** to apply the change.

8. Now you will see dashed lines in the Mercury window that indicate where hydrogen bonding interactions are present.

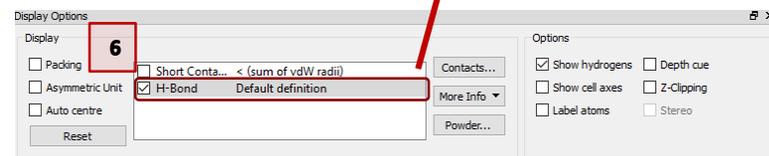
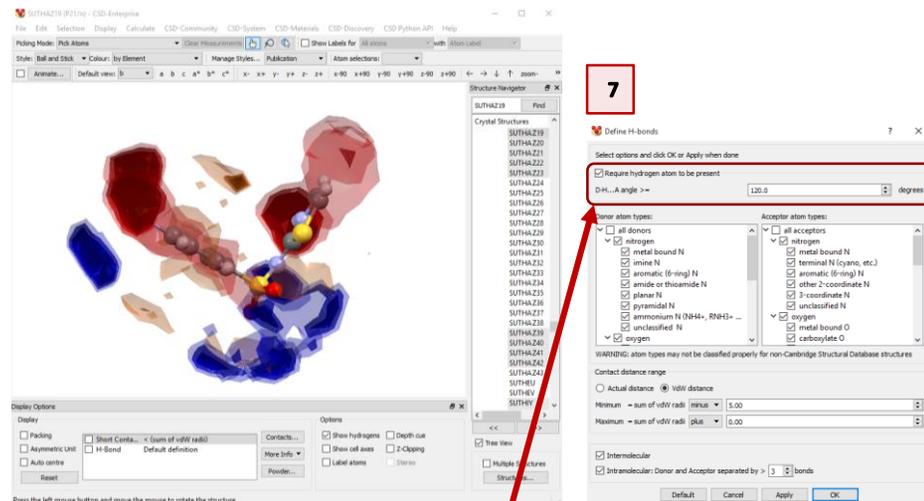
9. Click the contacts to generate nearby molecules. You will see that in each case, the interaction falls within the contour range for the expected type. This indicates that the packing of Form V satisfies the expected interaction landscape of this conformation of sulfathiazole.

10. Now let's look at Form I. In the Structure Navigator toolbar, type SUTHAZ16 to load this structure.

11. Click the **Reset** button in the Display Options toolbar to remove all the hydrogen bonding interactions.

12. Note that  $Z' = 2$  for Form I; meaning there are two unique molecules in the asymmetric unit. We will focus on one unique molecule in the Form I structure.

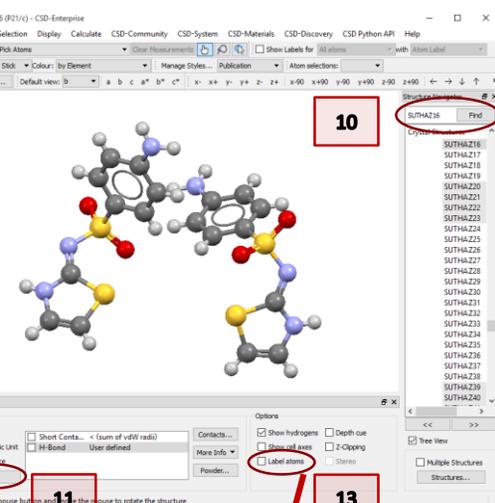
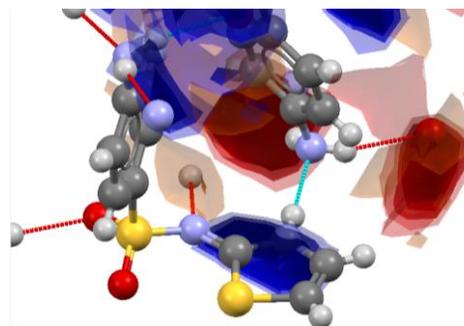
13. Tick the box to Label atoms in the Display Options toolbar. Locate which molecule contains N1. This is the molecule we will focus on. Once you have located it, remember which one it is, but untick the Label atoms box to keep the display clean.



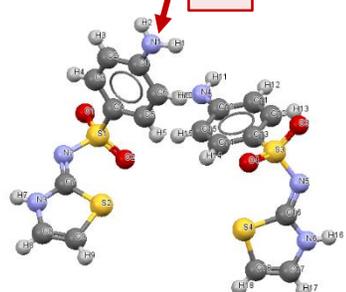
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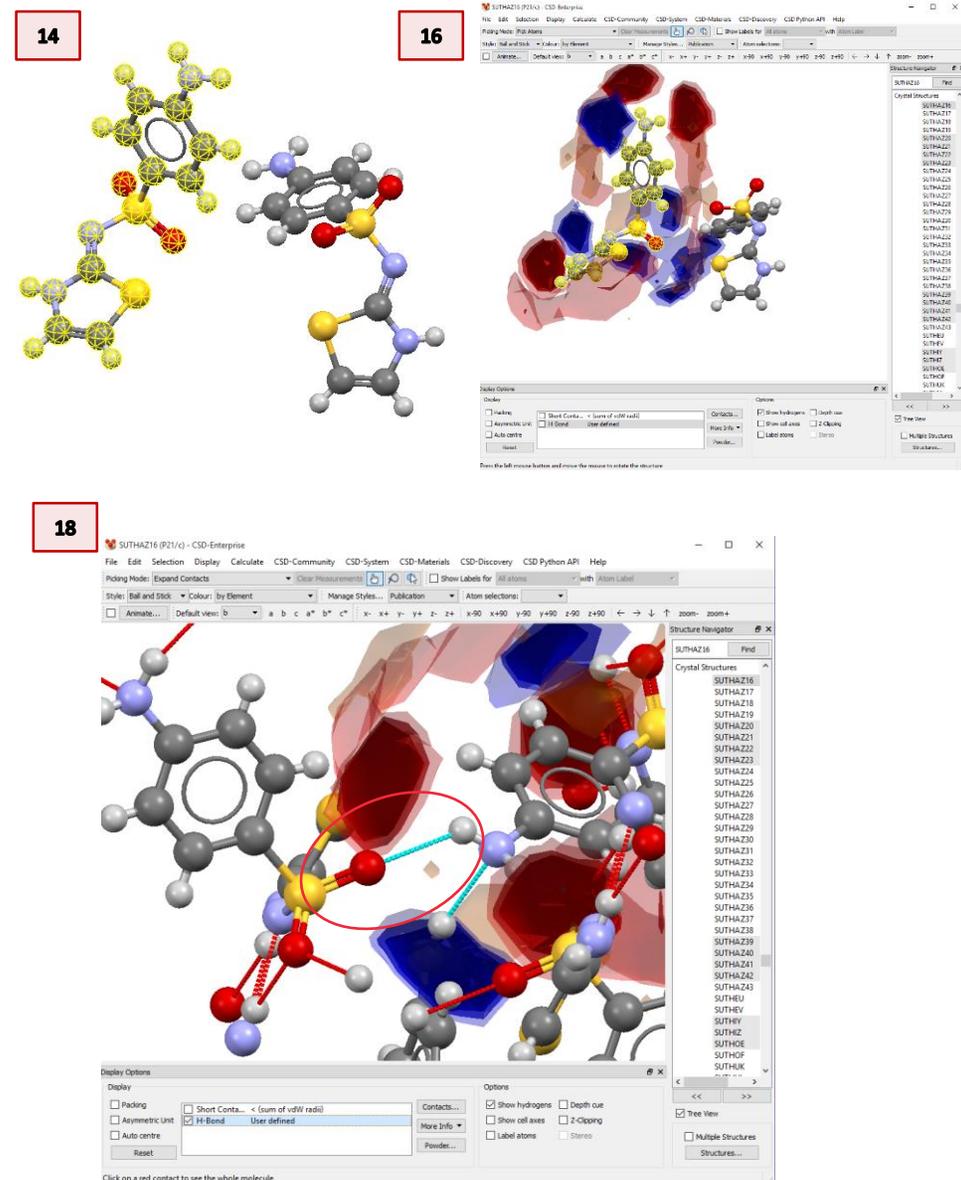
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14. Hold the Shift key and click the molecule that contains N1. This will select the entire molecule.
15. If the *Full Interaction Maps* dialogue box is still open, simply click **Calculate Maps** again. Otherwise, follow steps 2-4 to re-open the box.
16. You should now have a Full Interaction Map surrounding molecule 1.
17. Following steps 6-9 above, turn on the hydrogen bonding interactions and click to expand the interaction around N1.
18. Notice that one of the three interactions falls well outside the predicted region for a hydrogen bond acceptor. This suggests that this interaction has a non-ideal geometry and is likely to be significantly less stabilizing than the interactions in Form V.

## Conclusions

The observed polymorphs of sulfathiazole exhibit different interactions, but also noticeably different geometries for those interactions. We can use knowledge-based approaches to compare the observed intermolecular interactions in two polymorphs with the preferred geometries for these interaction types. Full Interaction Maps indicate that Form V (known to be the most stable of the sulfathiazole polymorphs) has interactions which are near to ideal, whereas Form I (known to be metastable) has non-ideal interactions.

**You should now know how to generate a Full Interaction Map of a molecule through Mercury and how to explore hydrogen bonding interactions in a crystal structure in relation to the predicted interaction landscape.**

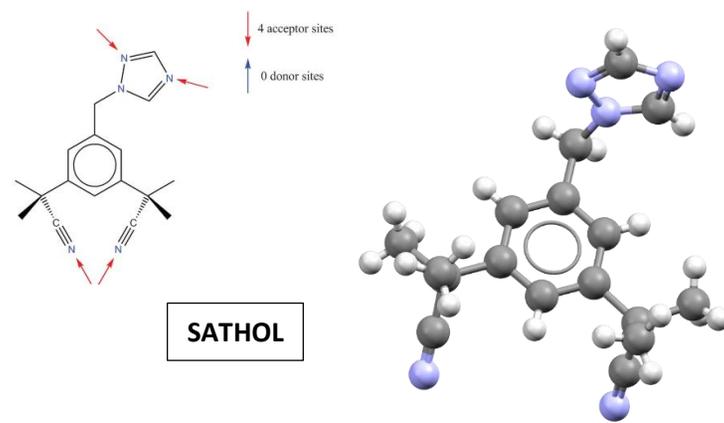


## Example 2: Investigating the potential for co-crystallization

For this tutorial, we will investigate the molecule anastrozole. This compound is a non-steroidal aromatase inhibitor used to treat breast cancer. The only published crystal structure is of the pure form. The molecule also contains no conventional hydrogen bond donors.

In this example, you will generate a Full Interaction Map for this molecule and investigate the interaction landscape. You will see how this information can be used to design a co-crystal.

1. In the Mercury window, type SATHOL in the Structure Navigator toolbar to load the structure of anastrozole.
2. Click the *CSD-Materials* menu and select *Full Interaction Maps...* from the dropdown menu.
3. As in the previous example, we will keep the default settings.
4. Click **Calculate Maps** to generate the Full Interaction Map for SATHOL.
5. The resulting map shows several areas for hydrogen bond donors; two high-probability areas near the nitrogen atoms of the triazole ring, and two slightly lower probability regions near the cyano groups.
6. While there are no true hydrogen bond donors in this structure, the C-H groups in the triazole ring could interact with possible hydrogen bond acceptors.
7. There is also a small brown region indicating the possibility for a hydrophobic or  $\pi$ - $\pi$  interaction.



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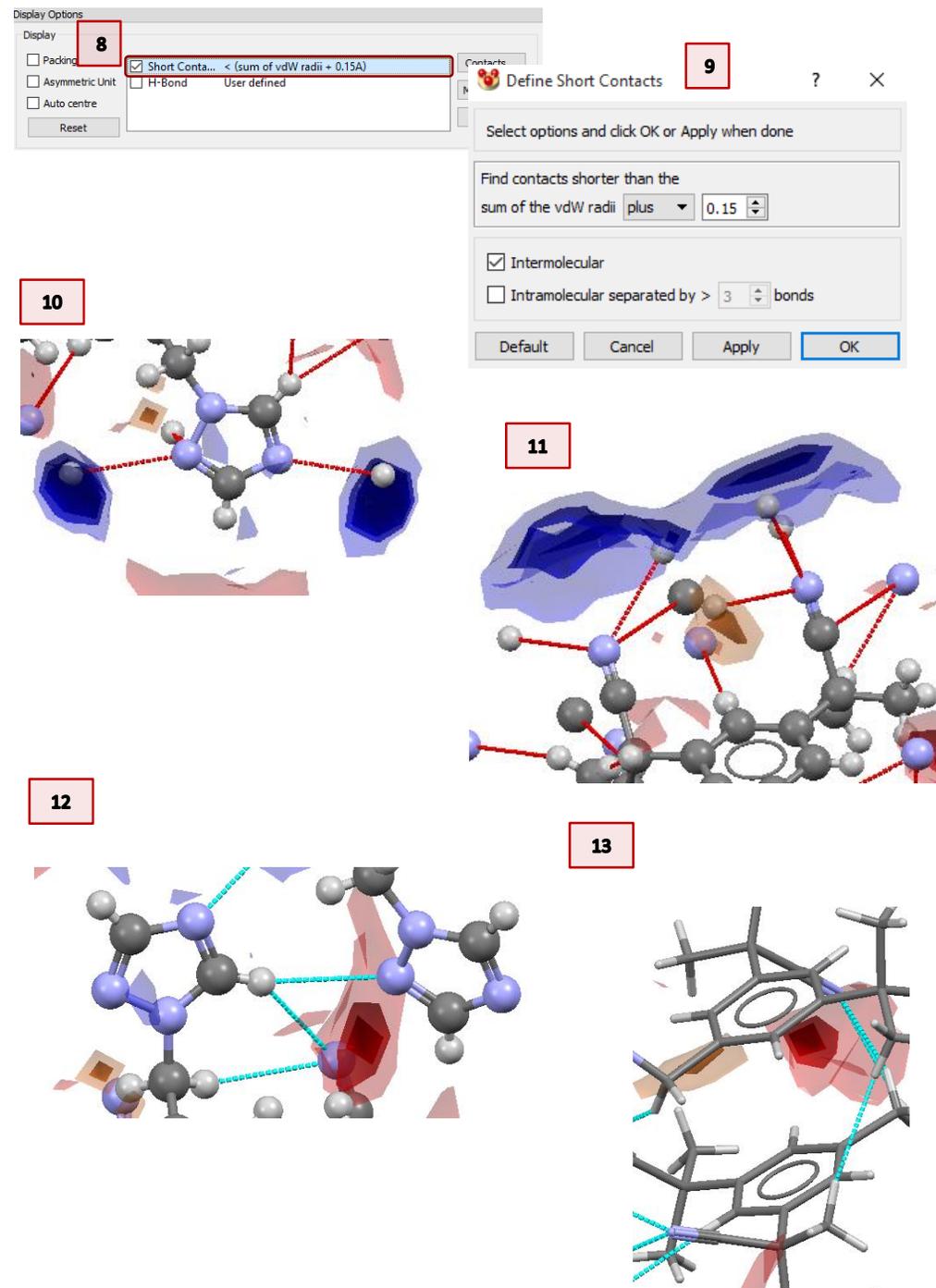
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- As there are no conventional hydrogen-bond donors in this structure, there will be nothing to display by ticking the H-bond box in the Display Options toolbar. Instead, tick the Short Contacts box.
- Double click this bar to open the *Define Short Contacts* dialogue box. Change this so that we find contacts shorter than the sum of the vdW radii **plus** 0.15Å. Click **OK** to save your changes.
- Let's first look at the region around the triazole ring. We can see that there are two C-H donors that will satisfy the interaction preferences of the two N acceptors in the triazole ring. You can click the two contacts to generate the neighboring molecules.
- Looking at the region around the cyano groups, there are some short contacts available for interactions, but these are not directed toward the high-probability areas.
- From the acceptor probe maps (red contours), we can see that the main region of acceptor preference is only weakly satisfied by the cyano group from one molecule and the triazole ring from another. Click the contacts to expand nearby molecules. The other acceptor regions are not satisfied at all.
- Finally, there is a weak  $\pi$ — $\pi$  interaction between the two phenyl rings that matches with one of the hydrophobic regions.

## Conclusions

The Full Interaction Maps for SATHOL show that the highest probability regions for interactions are quite nicely satisfied: the donor regions for the triazole N atoms. However, this comes at the cost of satisfying the interactions that would fulfill the acceptor sites. Since anastrozole has no classical H-bond donors of its own to fulfill those interactions, a molecule with one or more H-bond donors would be a good choice for a potential co-crystallization agent.

There are no co-crystals or solvates of anastrozole yet found in this CSD.

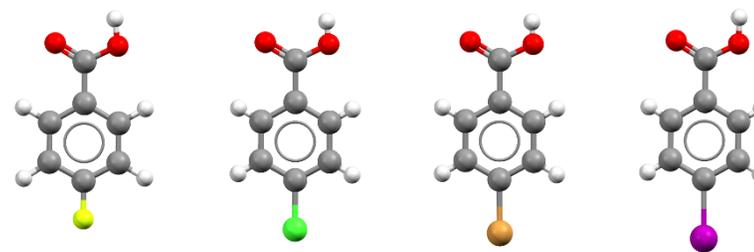


## Example 3: Investigating a series of halogenated molecules

When designing molecules to fit a specific purpose, chemists will often make subtle changes to a single functional group; for example, replacing fluorine with chlorine, bromine or iodine. We can use Full Interaction Maps to investigate the differences in the interaction preferences of a molecule when these substitutions are made across a series.

This example will look at the series of halogenated benzoic acids to compare what differences there are across the series.

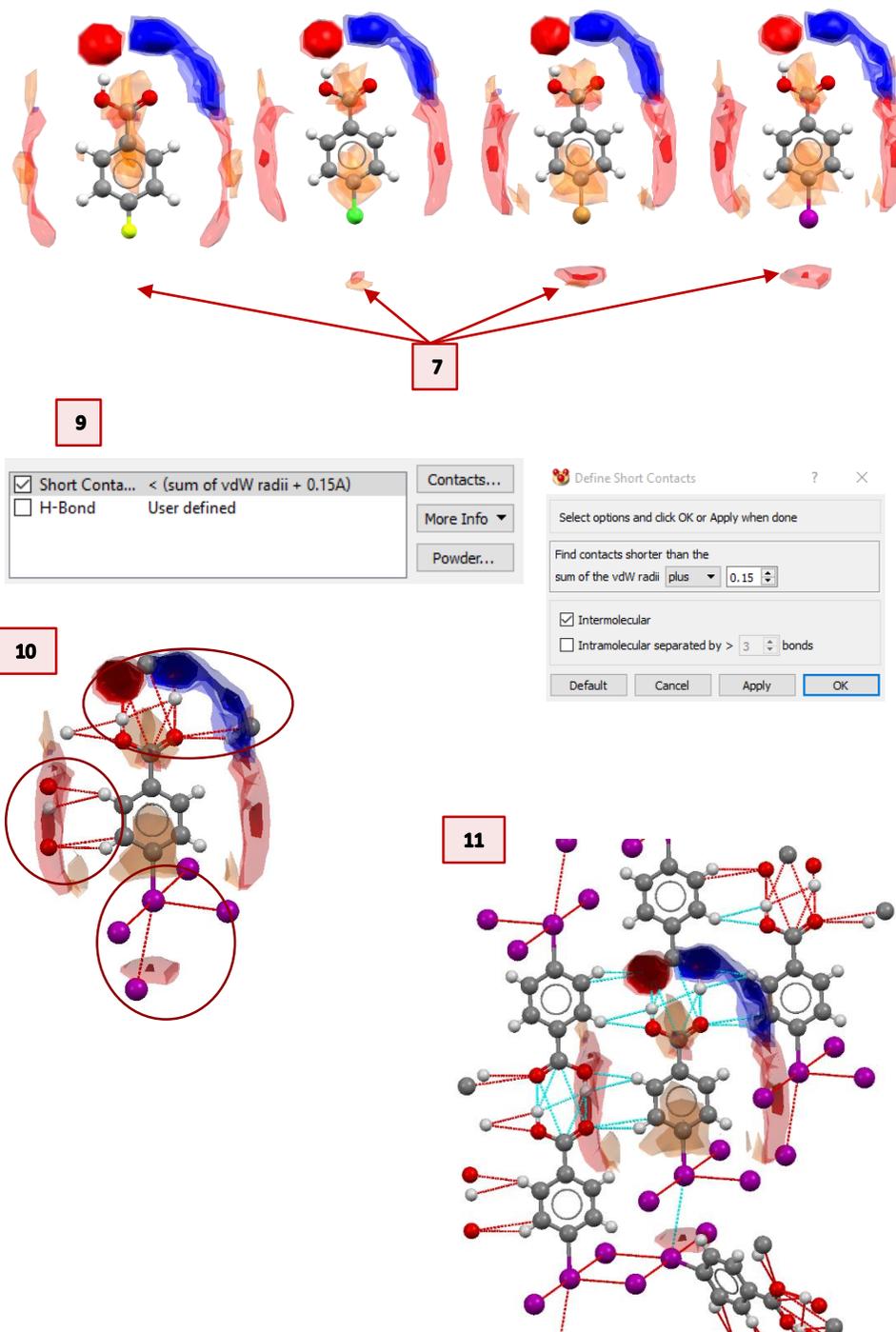
1. Launch Mercury and type PFBZAD15 in the Structure Navigator tool bar to bring up one of the parafluorobenzoic acid entries.
2. Click the *CSD-Materials* menu and choose *Full Interaction Maps...* from the drop-down menu.
3. We will again use the default settings.
4. Click **Calculate Maps** to generate the Full Interaction Map for parafluorobenzoic acid.
5. Repeat steps 1-4 for the other molecules in this series. Open a new instance of Mercury each time so you can easily compare the results. Use refcodes CLBZAP10 for the Cl analogue, BRBZAP01 for the Br analogue, and BENMOW07 for the I analogue. These particular entries were chosen because they are relatively recent structure determinations at low temperatures.
6. Now let's compare the maps for each molecule in the series.



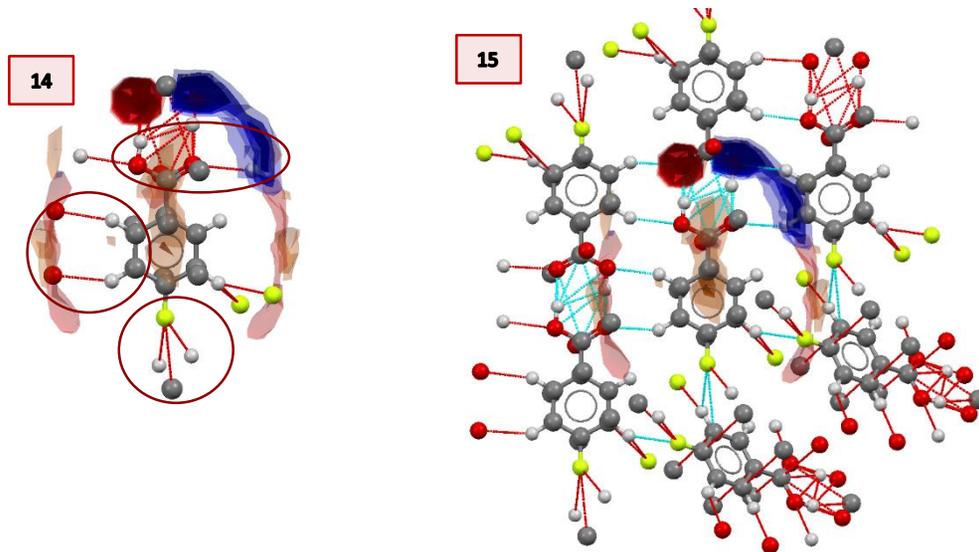
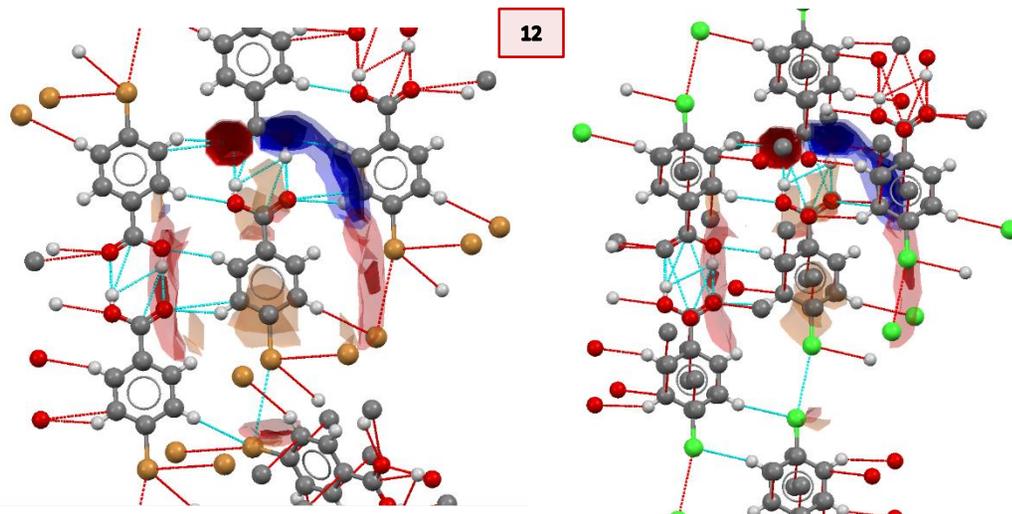
The screenshots illustrate the workflow in Mercury:

- 1**: The Structure Navigator window shows the molecule PFBZAD15 selected.
- 2**: The *CSD-Materials* menu is open, and *Full Interaction Maps...* is selected.
- 3**: The *Full Interaction Maps* dialog box is shown with the **Calculate Maps** button circled in red.
- 4**: The resulting Full Interaction Map is displayed, showing the molecule with colored surfaces representing interaction hotspots.

7. Look at the maps generated across the series. You should notice that as the size of the halogen increases across the series, there is an increased likelihood of finding an acceptor interacting with the halogen. This interaction is non-existent for the fluoro species, but fairly well defined for the iodo analogue.
8. Now we will investigate how this affects the packing in each crystal structure.
9. Start with the iodo analogue. In the Display Options make sure the Short Contacts settings are for "sum of vdW radii + 0.15Å." If not, double click that line to open the Define Short Contacts dialog and change the settings. Click **OK** to accept these changes. Then tick the box to display Short Contacts.
10. With the short contacts displayed, you should see that most of the interactions are satisfied. The two high-probability donor and acceptor sites near the carboxylic acid group are satisfied, as are the weaker acceptor sites near the aromatic hydrogen atoms on the phenyl ring. The iodine from a neighboring molecule serves as the acceptor for a halogen-halogen interaction.
11. Click the interactions highlighted in Figure 10 to expand these neighboring molecules. You will notice that while the acceptor contours on either side of the phenyl ring are roughly equivalent, only one region is satisfied well by an interaction. Iodine atoms from neighboring molecules fill this region on the opposite side.



12. Repeat steps 9-11 for the Br and Cl analogues. What similarities and differences do you see across the series so far? What do you expect to see for the fluoro analogue?
13. For the fluoro analogue, follow step 9 to generate the short contacts.
14. You will see that the interactions for the carboxylic acid group and for the two weak C-H donors on the phenyl ring are satisfied. However, there is no probability of an acceptor for the fluorine, and consequently there is only C and H in this region.
15. Click these contacts to expand the neighboring molecules. Now you can see that there is no halogen-halogen interaction involving the fluorine.



## Conclusions

It is well understood that iodine forms halogen-halogen interactions more so than the other halogen atoms. Using Full Interaction Maps, we can clearly see how the probability of these interactions affects the overall packing in a crystal structure.

## Further Exercises

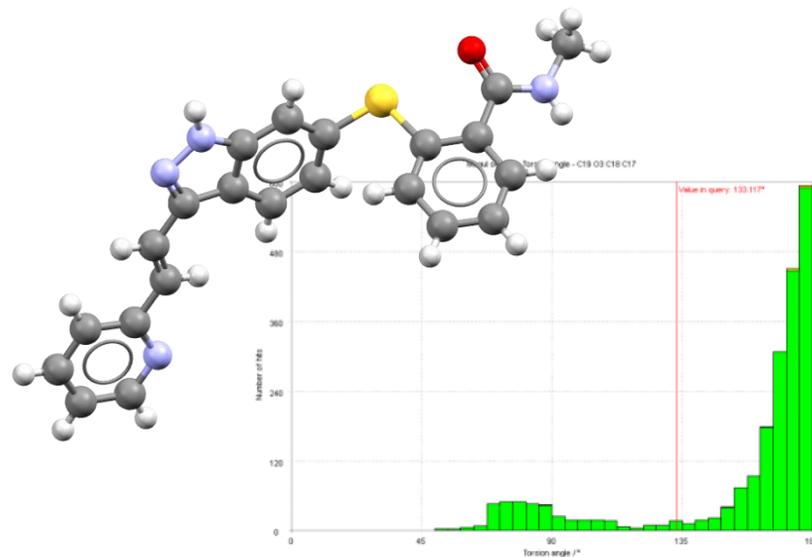
- Try calculating Full Interaction Maps using only the C-F and C-Cl probes. Do the results match your expectations?
- Investigate the hydrophobic interactions among the halogenated benzoic acid molecules in this series.
- Try looking at ortho- or meta- substituted halogenated benzoic acid species. Do your results match your expectations?
- Run a Full Interaction Maps calculation on your own molecules.
- **Advanced:** Try designing a ConQuest search to return just the molecules we used for this example. How close can you get? *Tips: You may want to try using the **Formula** and **Author/Journal** query types, too.*

## Example 4: 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 interface. For this tutorial, we will use Mercury to run Mogul.

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.



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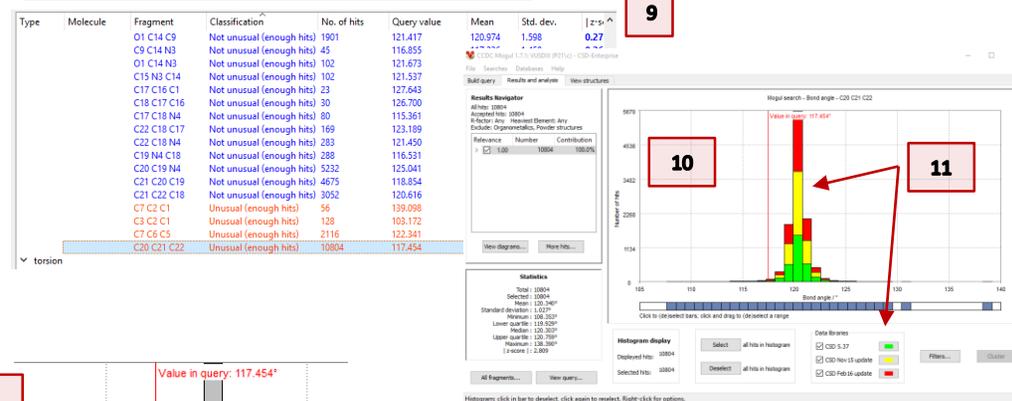
Mogul Results Viewer

Show/hide: Columns Fragments... Deselect all fragments Export...

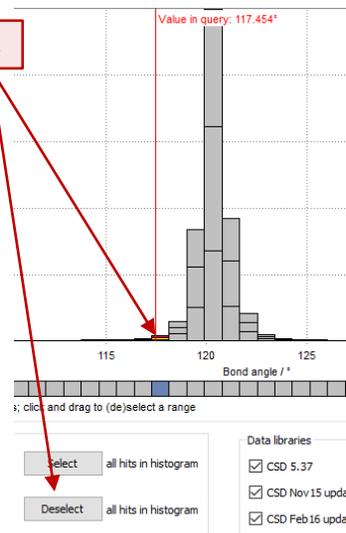
Help Double click to view result in Mogul

Type	Molecule	Fragment	Classification	No. of hits	Query value	Mean	Std. dev.	Z-score
bond	VUSDX	N1 N2	Not unusual (enough hits)	52	1.362	1.363	0.03	0.01
		C1 N2	Not unusual (enough hits)	182	1.342	1.341	0.008	0.20
		C2 N2	Not unusual (enough hits)	113	1.355	1.354		0.36
		C4 C3	Not unusual (enough hits)	2373	1.396	1.39		
		C4 C5	Not unusual (enough hits)	323	1.369	1.38		
		C7 C2	Not unusual (enough hits)	8542	1.407	1.38		
		C5 S1	Not unusual (enough hits)	835	1.771	1.71		
		C8 S1	Not unusual (enough hits)	2963	1.781	1.71		
		C9 C8	Not unusual (enough hits)	578	1.387	1.46		
		C11 C10	Not unusual (enough hits)	10576	1.367	1.38		
		C11 C12	Not unusual (enough hits)	10301	1.378	1.377	0.00	0.02
		C13 C8	Not unusual (enough hits)	5275	1.387	1.399	0.016	0.31
		C9 C14	Not unusual (enough hits)	2199	1.493	1.499	0.016	0.18
		O1 C14	Not unusual (enough hits)	7799	1.224	1.229	0.017	0.26
		C14 N3	Not unusual (enough hits)	128	1.339	1.329	0.011	0.64
		C15 N3	Not unusual (enough hits)	1831	1.450	1.451	0.017	0.07
		C16 C1	Not unusual (enough hits)	40	1.450	1.453	0.017	0.17
		C16 C17	Not unusual (enough hits)	3132	1.323	1.326	0.025	0.13
		C18 C17	Not unusual (enough hits)	284	1.471	1.467	0.021	0.17
		C18 N4	Not unusual (enough hits)	419	1.342	1.346	0.013	0.31
C19 N4	Not unusual (enough hits)	5407	1.334	1.341	0.016	0.40		
C20 C19	Not unusual (enough hits)	5446	1.360	1.376	0.023	0.68		
C20 C21	Not unusual (enough hits)	10301	1.360	1.377	0.020	0.86		

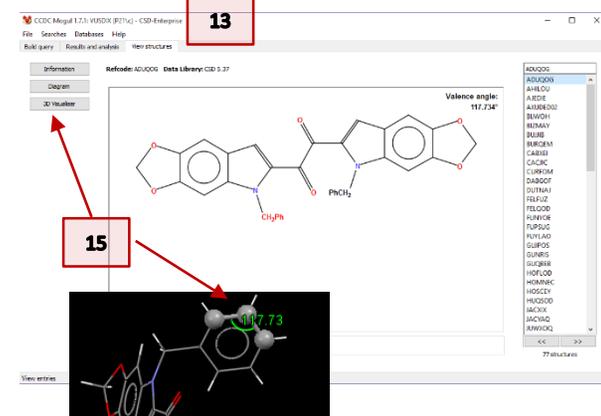
Not unusual (enough hits)	10576	1.388	1.384	0.015
Unusual (enough hits)	67	1.431	1.463	0.015
Unusual (enough hits)	4128	1.431	1.385	0.015
Unusual (enough hits)	8542	1.423	1.394	0.014



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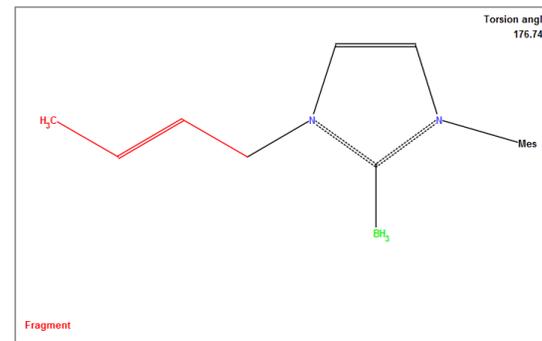
- When the search is complete, your results will be displayed in the **Mogul Results Viewer**.
- The results are color-coded. Unusual values are flagged in **red**.
- Scroll through the results until you find the angle for C20-C21-C22. Double-click this line to bring up the data from the Mogul library.
- The red line marks the value of the angle from your molecule (the query).
- 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.)
- 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.
- Now click the **View Structures** tab 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.
- Click the **Information** button on the left to see further details about the structure.
- Click the **3D Visualizer** 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.
- Continue to investigate other unusual parameters. You can always return to view the structure in Mercury to see which parameter you are querying.

## Example 5: Using Mogul to predict geometry of a fragment

Sometimes you may be investigating a molecule or fragment for which there is no crystal structure. You can still use Mercury to predict the most likely conformation for your molecule or fragment of interest.

**In this example, you will learn how to use Mercury to predict the orientation of a fragment from a 2D drawing.**

1. From the Mercury window click the *CSD-System* menu and choose *Launch Mogul* from the drop-down menu. It doesn't matter if there is a structure loaded in Mercury or not.
2. This will open a new instance of Mogul with no queries loaded. We will need to add our own query.
3. Click the **Draw...** button to launch the **Draw** window. This is very similar to what you may have seen in ConQuest.
4. First, make sure you tick the box for Add Hydrogens, Manually.
5. Then click in the white space and drag to create a 2-carbon chain. Click the second carbon and drag again to create 3 carbons, and repeat once more to create a 4-carbon chain.
6. Click the *Bond* drop-down menu and choose *Double*.
7. Now click the bond between the two central carbons to change this to a double bond.
8. Finally, right-click each of the two central carbon atoms and choose *Hydrogens* and then *Generate* from the drop-down menu. This will add one hydrogen to each of these carbon atoms.
9. When you are finished drawing click the **Done** button to return to Mogul.



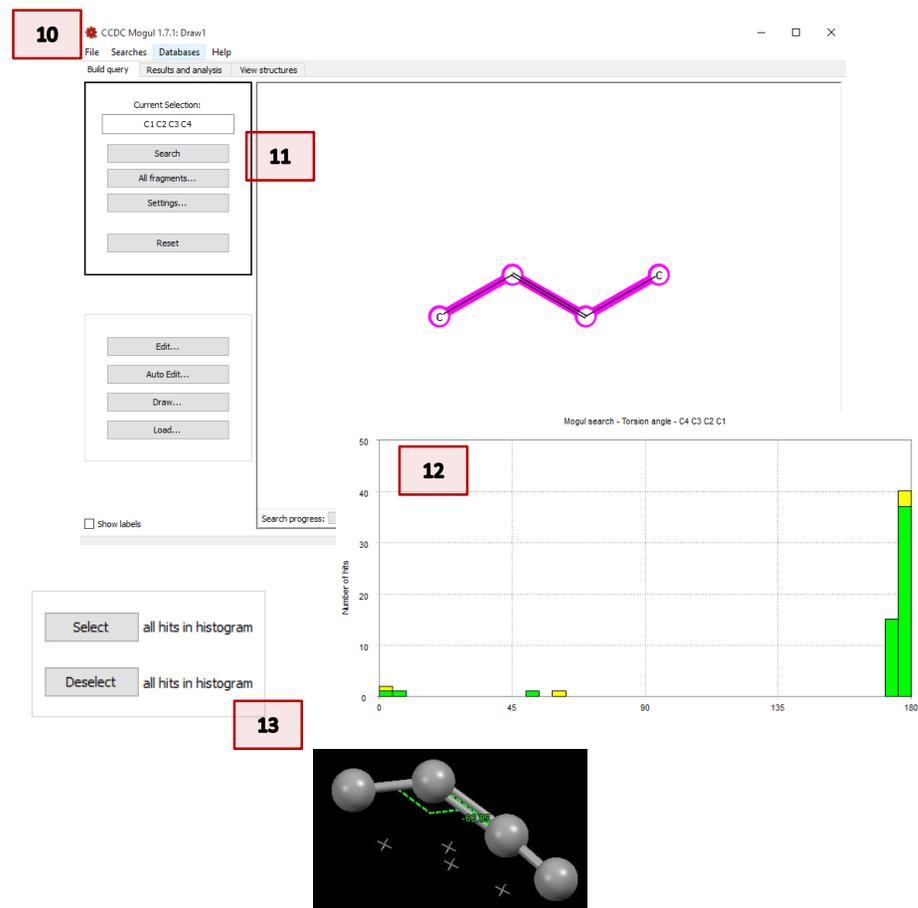
10. Now you should see your fragment in Mogul. We want to query the torsion angle around this double bond to see which is the more likely conformation, *cis* or *trans*. Click to select all four carbon atoms in order. You should see the atom numbers listed under "Current Selection".
11. To search the search for this fragment click **Search**.
12. Now you will see the histogram of the results, showing that the overwhelming preference for this fragment is the *trans* geometry.
13. Click the **Deselect** button and then click the two bars of the histogram near 45°. Click the *View Structures* tab to investigate these outliers. You can see one of these is highly disordered.

## Conclusions

Mogul is a powerful program that can help you assess the geometry of your crystal structures or help you predict what geometry a given fragment will adopt. You can also use Mogul to help you design new molecules to fit specific geometric constraints.

## Further Exercises

- Load one of your own crystal structures into Mercury and perform a Mogul search. What do you find?
- Try drawing other chemical fragments to see what geometries are predicted. For instance, what do you find when you search bipyridine or diethyl ether vs. hexane?



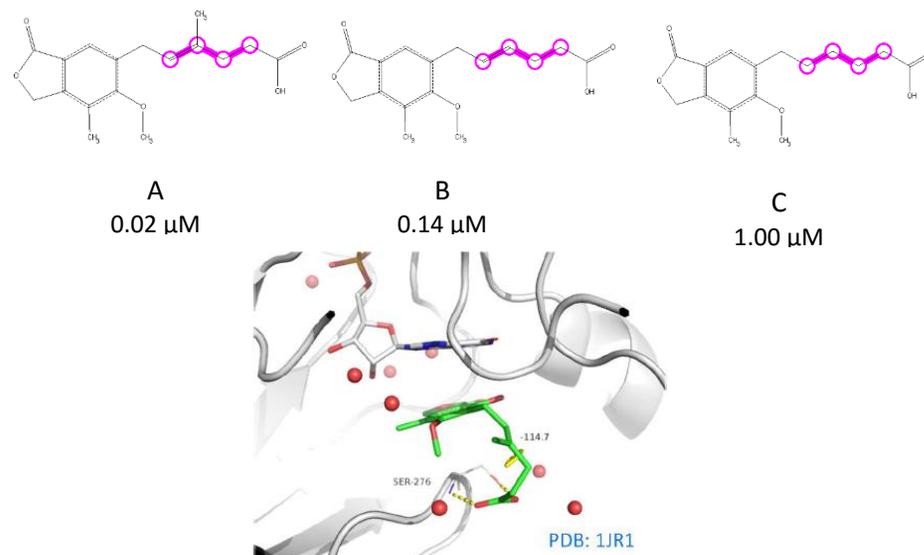
## Example 6: Using Mogul to explain activity data

Mycophenolic acid (A) is an immunosuppressant that binds to inosine monophosphate dehydrogenase (IMPDH) with an  $IC_{50}$  of  $0.02\mu\text{M}$ . 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?

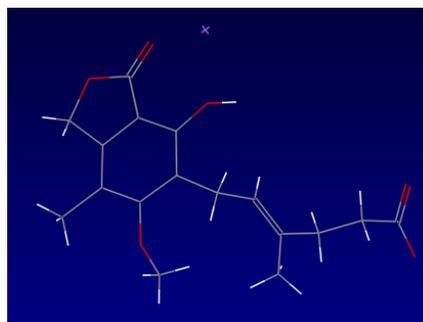
In this example you will see how to use Mogul to correlate improved function with geometric preferences.

You will need the file 1JR1\_ligand.pdb for this example

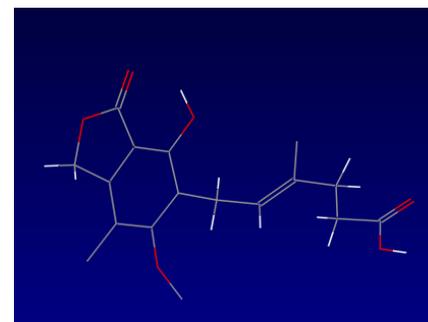
A successful target molecule will be able to form two favorable hydrogen bonds in the protein binding site, as shown. The angle of the allylic torsion angle should be in the range of  $110-110^\circ$  for this interaction to be achieved. We know that molecule A is a successful target but molecules B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



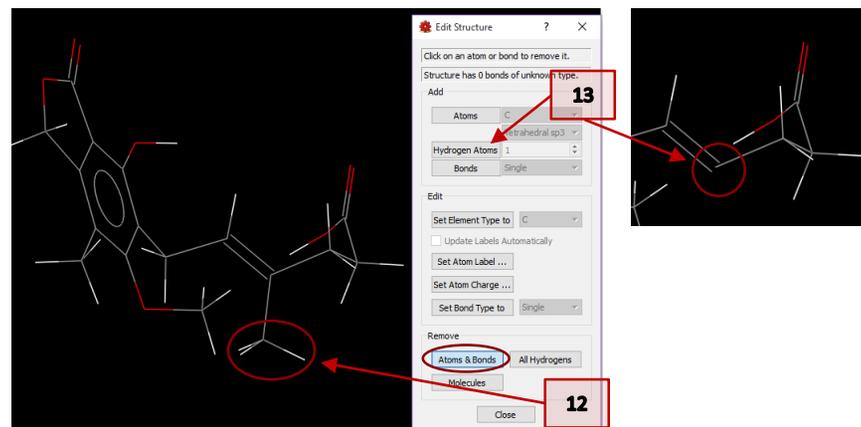
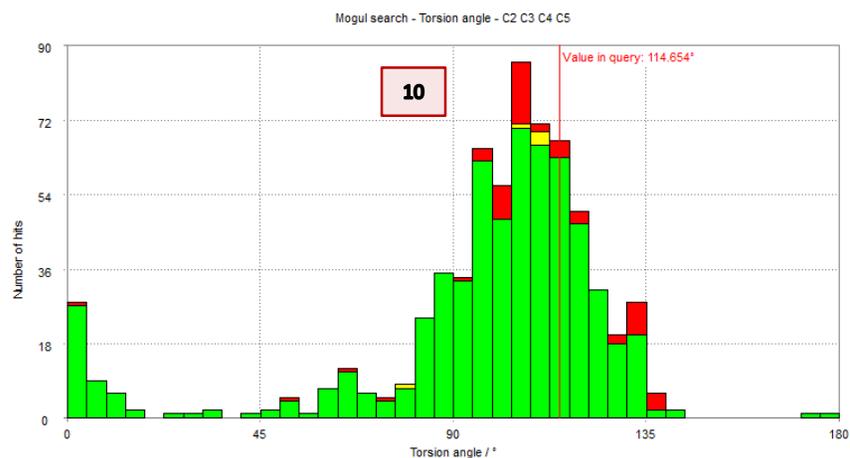
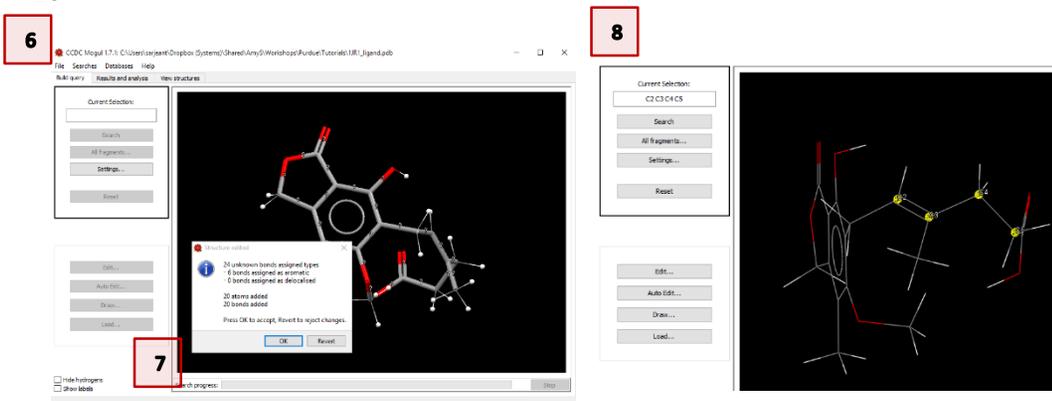
1. Launch ConQuest and click on the **Name/Class** query type.
2. In the box for Compound Name type “mycophenol” and then click **Add**.
3. Click **Search** and then **Start Search** for the *Search Options* dialogue box.
4. The search should return 4 results. MYCPHA and MYCPHA01 are the neutral species. KIWQUC is a sodium salt. WAJYUC is a neutral derivative.
5. Use the *3D Visualiser* tab to view the MYCPHA and KIWQUC structures noting the different conformations. Which one is the preferred orientation?



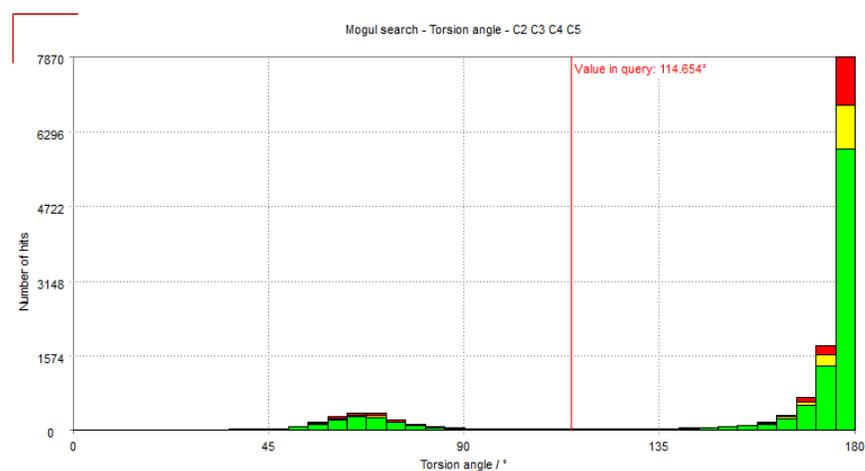
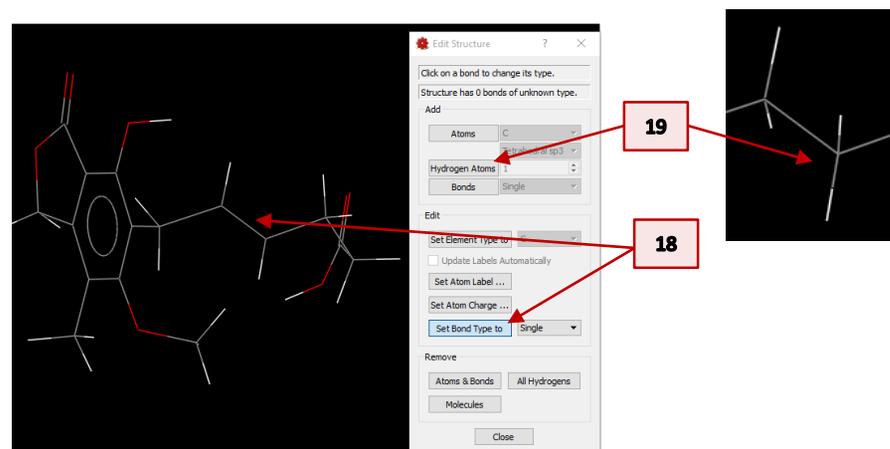
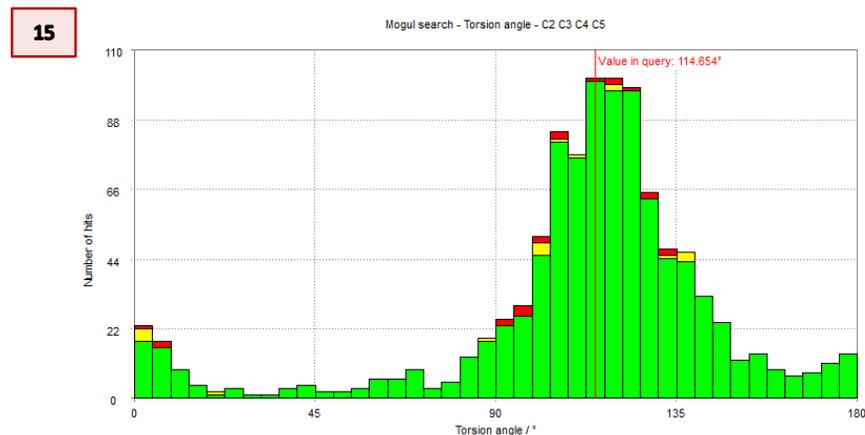
5



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. 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 atoms that define the C=C-C-C 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 CH<sub>3</sub>. 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 mycophenolica 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?

