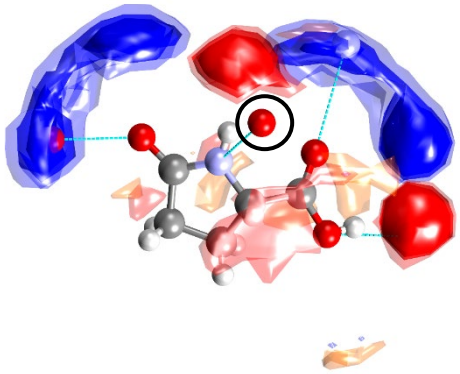
Advanced applications of Full Interaction Maps (MER-003)

2023.2 CSD Release



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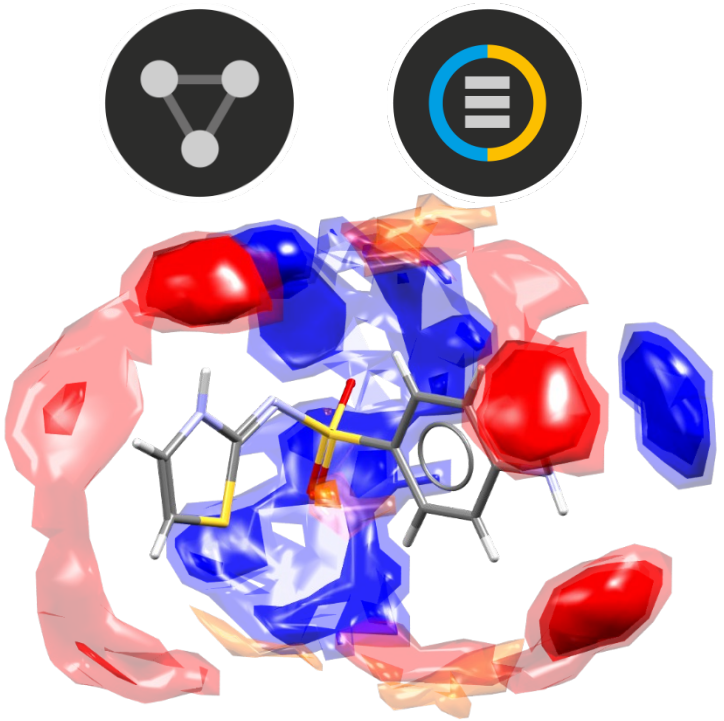
Introduction

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.

Before beginning this workshop, ensure that you have installed Mercury, CSD Main Data and CSD IsoStar Data. Full Interactions Maps module can be accessed from both the CSD-Materials and CSD-Discovery menu in Mercury.



Learning Outcomes

In this workshop you will learn about the Full Interaction Maps (FIMs) feature in Mercury, specifically you will learn:

- How to produce Full Interaction Maps (FIMs) and interpret the results.
- How the FIMs analysis can be used for co-crystal design.
- How FIMs can be used to assess polymorph stability.

This workshop will take approximately ***30*** minutes to be completed. The Glossary at the end of this handout contains useful terminology for the exercises.

Pre-required Skills

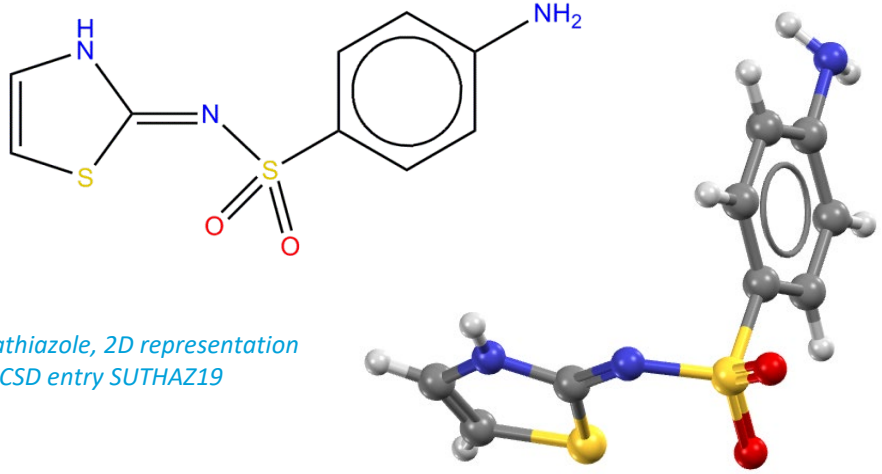
To complete this workshop, you need to be comfortable with the basics of Mercury visualization, including navigating the Mercury interface and interacting with structures. If you are not, we recommend the Structure Visualization Workshop (MER-001), available on this page. The introduction to Full Interaction Maps workshop on this page provides a basic introduction to FIMs (MER-002).

Materials

There are no additional materials required for this workshop.

Example 1. Using Full Interaction Maps to assess polymorph stability.

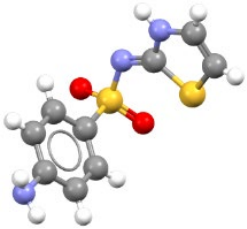
The stability of a given crystal structure is a balance between the intramolecular conformation and the intermolecular packing of the molecules in the crystalline state. One method for understanding the relative stability of crystal structures is to compare the observed intermolecular interactions with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

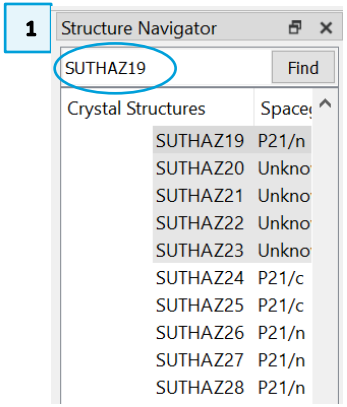


Sulfathiazole, 2D representation and CSD entry SUTHAZ19

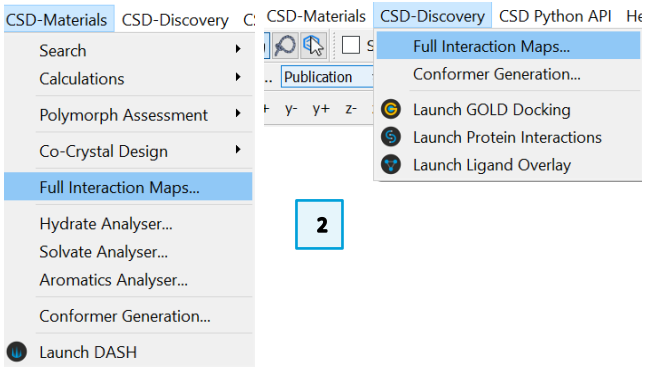
This example will look at two known polymorphs of sulfathiazole to answer the question: **How do the interactions in each polymorph compare with what is expected?** You will learn how to produce a Full Interaction Map for a given structure and how to interpret this map.

1. Launch Mercury by clicking its icon . In the **Structure Navigator** toolbar, type "SUTHAZ19" to bring up the structure for the Form V polymorph of sulfathiazole.



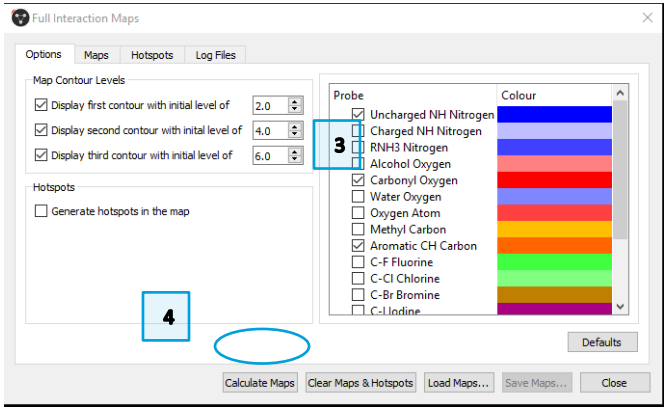


2. Click on the *CSD-Materials* menu or *CSD-Discovery* menu and select *Full Interaction Maps…* Note: If the CSD-Materials menu bar is inactive or there is a key icon next to the FIMs feature, you will need to activate the software with a licence key that includes the use of the CSD-Materials suite.



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.



5. The generated map will now be displayed in the main Mercury window. Notice the three different colours 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.

7. Double click the *H-Bond* line to launch the *Define H-bonds* dialogue. In this dialogue, tick the box for **Require hydrogen atom to be present**. Click **OK** to apply the change.

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

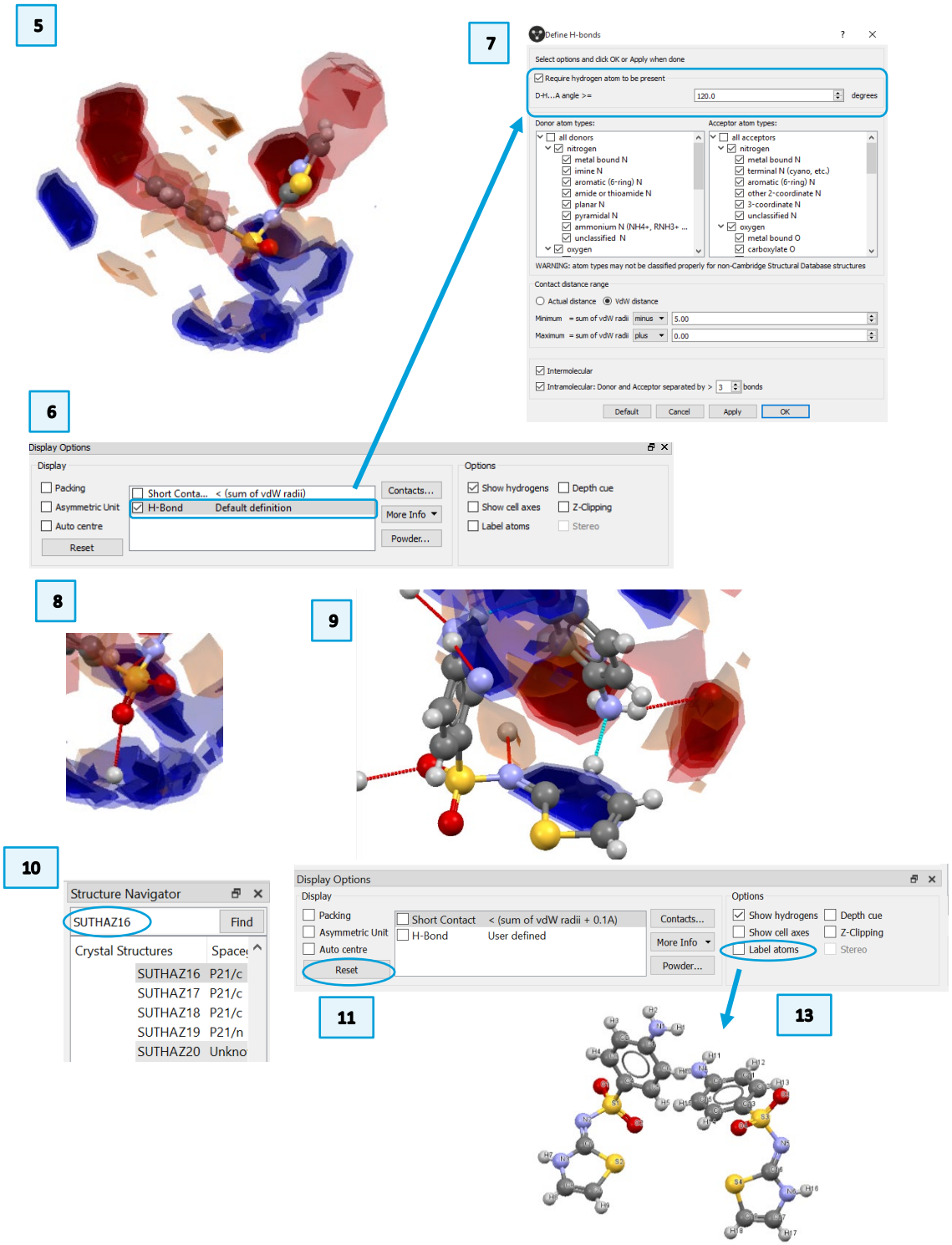
9. Click on these contacts to generate nearby molecules. You will see that in each case, the interaction falls within the contour range for the expected type. This indicates that the packing of Form V satisfies the expected interaction landscape of this conformation of sulfathiazole.

10. Now let's look at the Form I polymorph. 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.



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 is still open, simply click **Calculate Maps** again. Otherwise, follow steps 2-4 to re-open the dialogue.

16. You should now have a Full Interaction Map surrounding molecule 1.

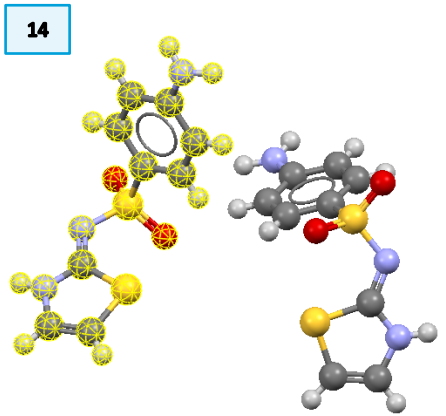
17. Following steps 6-9 above, turn on the hydrogen bonding interactions and click to expand the interaction around N1.

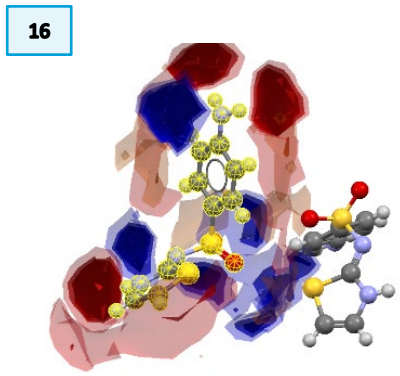
18. Notice that one of the three interactions falls well outside the predicted region for a hydrogen bond acceptor. This suggests that this interaction has a non-ideal geometry and is likely to be significantly less stabilizing that the interactions in Form V.

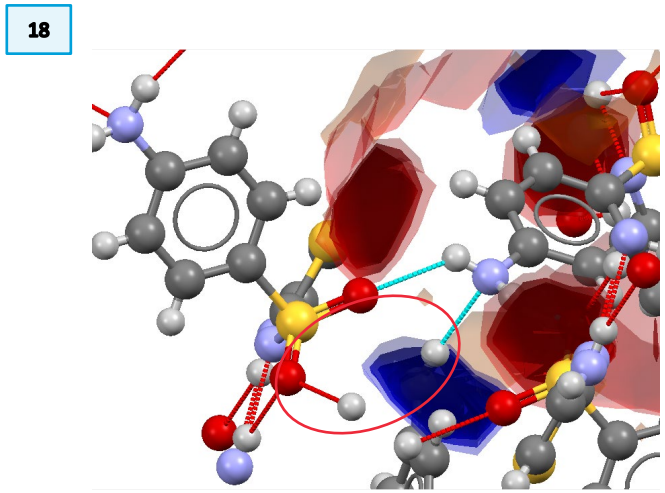
Conclusions

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.



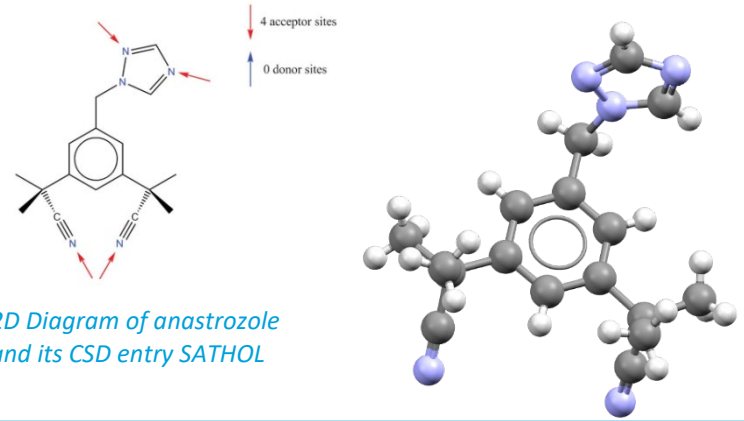




Example 2. Investigating the potential for co-crystallisation.

For this example, 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.



2D Diagram of anastrozole and its CSD entry SATHOL

1. In the Mercury window, type "SATHOL" in the Structure Navigator toolbar to load the structure of anastrozole.

2. Click the *CSD-Materials* menu or *CSD-Discovery* menu and select *Full Interaction Maps…* from the dropdown menu.

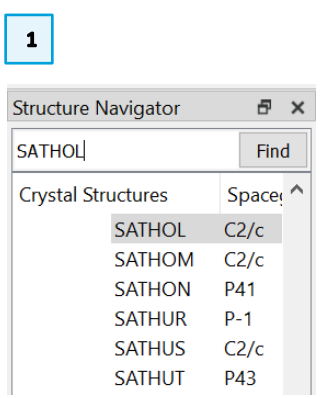
3. Keep the default settings.

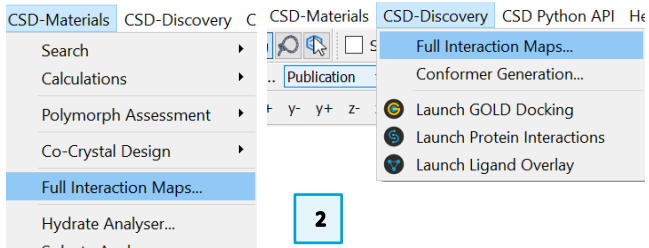
4. Click **Calculate Maps** to generate the Full Interaction Map for SATHOL.

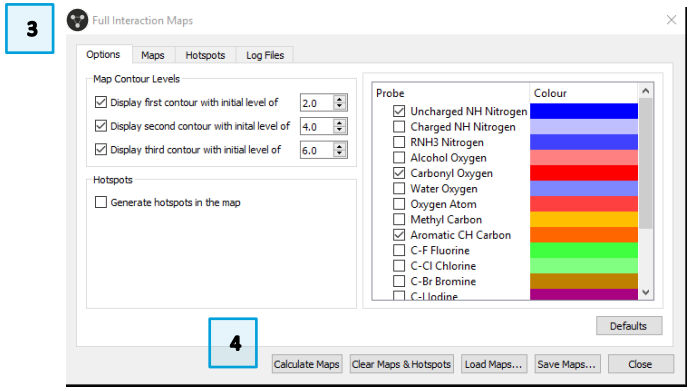
5. The resulting map shows several areas for hydrogen bond donors (blue regions); two high-probability areas near the nitrogen atoms of the triazole ring, and two slightly lower probability regions near the cyano groups.

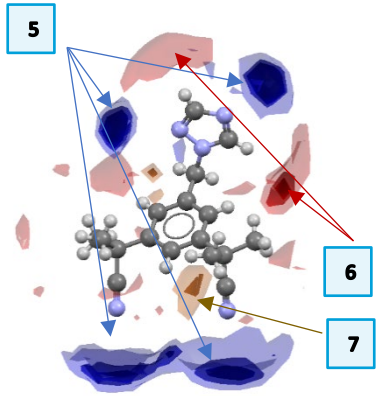
6. While there are no true hydrogen bond donors in this structure, the C-H groups in the triazole ring could interact with possible hydrogen bond acceptors (red regions).

7. There is also a small brown region indicating the possibility for a hydrophobic or *π—π interaction*.









8. 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 Contact** box.

9. 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.

10. 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. Click on the two contacts (dashed red lines) to generate the neighbouring molecules.

11. 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.

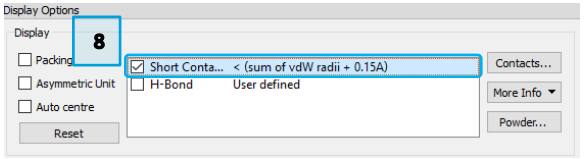
12. From the acceptor probe maps (red contours), we can see that the main region of acceptor preference is only weakly satisfied by the cyano group from one molecule and the triazole ring from another. Click the contacts to expand nearby molecules. The other acceptor regions are not satisfied at all.

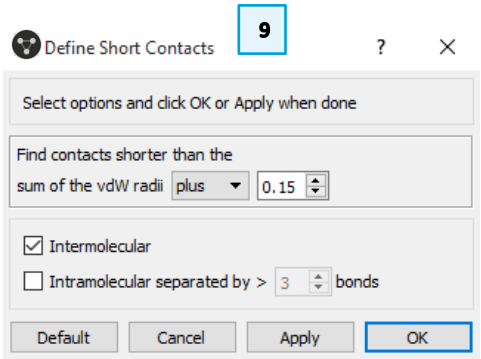
13. Finally, there is a weak π—π interaction between the two phenyl rings that matches with one of the hydrophobic regions.

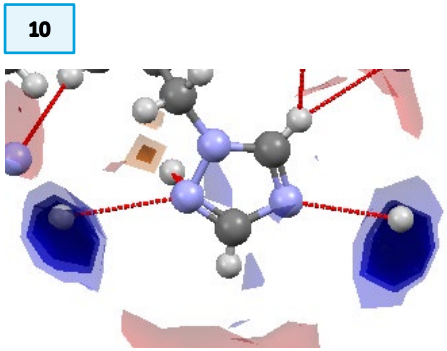
Conclusions

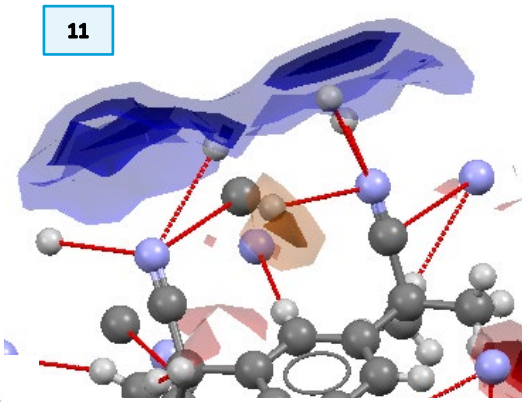
The Full Interaction Maps for SATHOL show that the highest probability regions for interactions, the donor regions for the triazole N atoms, are quite nicely satisfied. However, this comes at the cost of satisfying the interactions that would fulfill the acceptor sites. Since anastrozole has no classical 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-crystallisation agent.

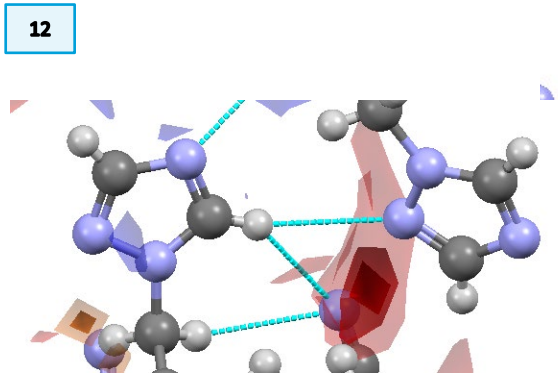
There are no co-crystals or solvates of anastrozole yet found in this CSD.

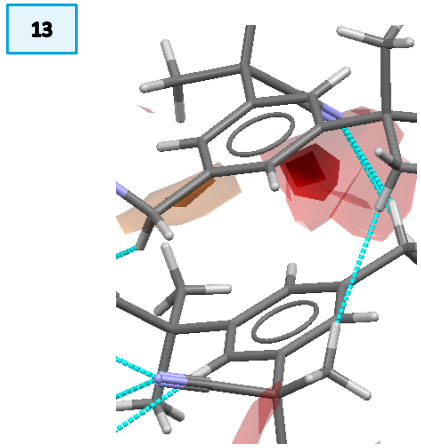












Summary

After this workshop you should be able to:

- Produce Full Interaction Maps (FIMs) for a given molecule and interpret the results.
- Explore and assess the hydrogen bonding interactions in a crystal structure in relation to the interaction landscape predicted by FIMs.
- Utilize FIMs analysis for co-crystal design.

Next Steps

After this workshop, you can explore more self-guided workshops available from the CSD-Materials workshops area and the CSD-Discovery workshops area on our website. If you are interested in CSD-Materials, we suggest trying the Hydrogen Bond Propensity or the Hydrogen Bond Statistics workshop, which presents complementary tools to the Full Interaction Maps in assessing solid forms.
https://www.ccdc.cam.ac.uk/Community/educationalresources/workshop-materials/

Feedback

We hope this workshop improved your understanding of *Full Interaction Maps* and you found it useful for your work. As we aim to continuously improve our training materials, we would love to hear 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 MER-003. Thank you!

Glossary

Contour level
The number of times more than random an interaction is likely to occur in a specific region of space.

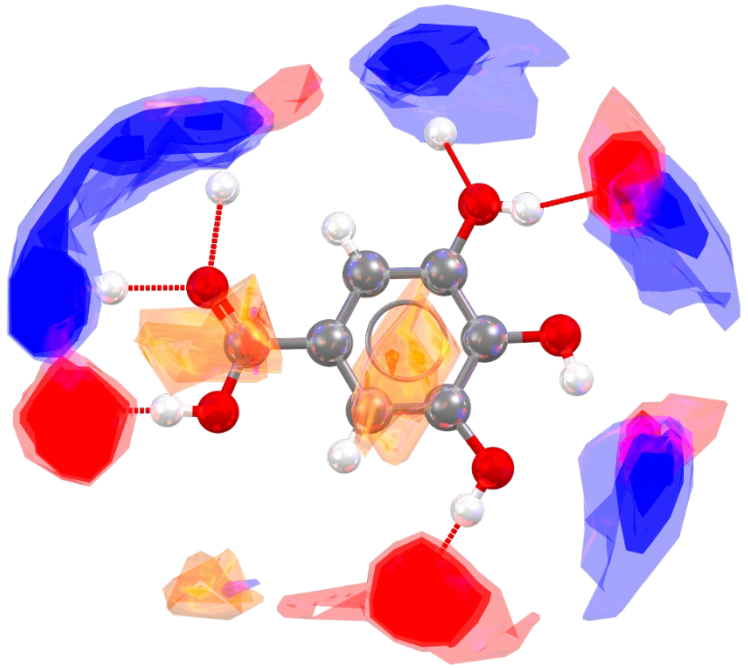
Hotspots
Hotspots represent the positions of highest local density for each contour Surface.

Van der Waals, Aromatic and Hydrogen Bond Interactions

Van der Waals forces are formed between atoms or molecules that are in each other's close proximity and are driven by induced electrical interaction. They are the weakest of all type of intermolecular attractions between molecules. However, with a lot of Van der Waals forces interacting between two molecules, the interaction can be very strong.

Aromatic Interactions are noncovalent interactions formed between aromatic rings. These interactions are important in material science since they will contribute to the overall crystal structure stability. The orientation of the aromatic ring can vary from parallel to T-shape, and we found during our DFT calculations that the T-shape interactions are very close in strength to the parallel displaced ones. Their strength is found between 0 and 16 kJ/mol based on DFT calculations.

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.



Interaction type	*Strength (kJ/mol)*
Van der Waals	**0.4-4.0**
Aromatics	**0-16**
Hydrogen Bonds	**12-30**