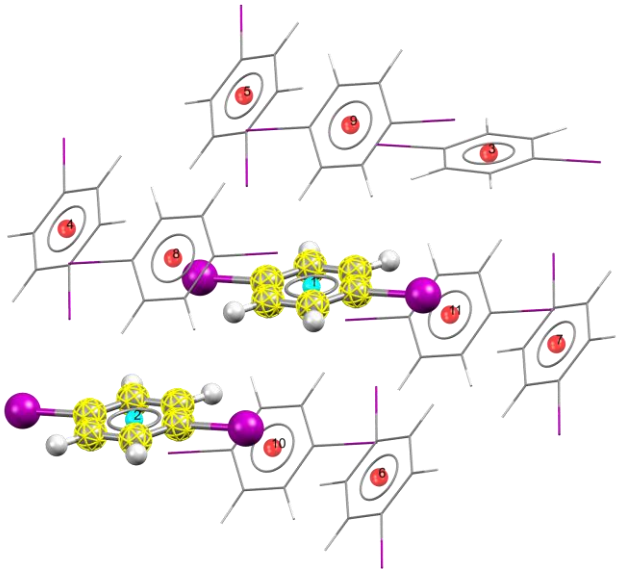
Aromatics Analyser

MAT-005

2023.3 CSD Release



advancing structural science

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Introduction

This tutorial will introduce you to the Aromatics Analyser in *CSD-Materials*.

The Aromatics Analyser tool in Mercury provides the user the ability to quickly and easily visualise and identify aromatic interactions within a crystal structure, including their distance and relative orientation.

You can learn more about the tool by watching the How To Aromatics Analyser video (https://www.youtube.com/watch?v=mYYpggxDt-E) and checking the Aromatics Analyser blog: (https://www.ccdc.cam.ac.uk/discover/blog/2020-04-17-new-for-20201-release-aromatics-analyser-in-merc/)

Learning Outcomes

After completing the workshop, you should be able to:

- Visualise aromatic interactions.
- Assess the strength of aromatics interactions in a crystal structure.
- Gain insight into the observed aromatic interactions by estimating their stabilising influence upon the crystal structure.
- Investigate aromatic interactions in polymorphs.

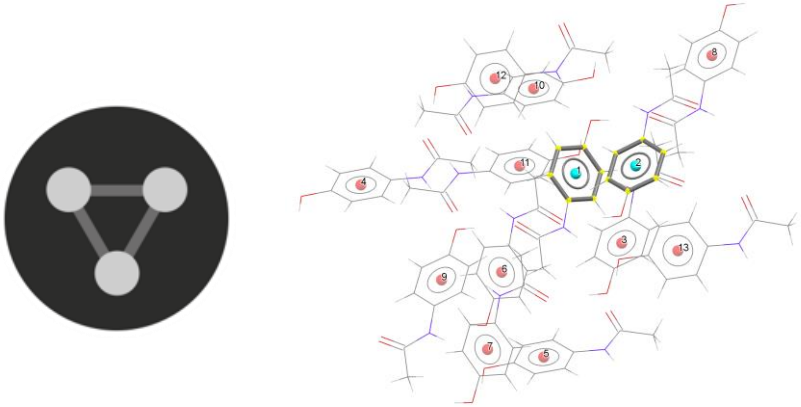
This workshop will take approximately ***2*** hours to be completed. The words in *Blue Italic* in the text are reported in the Glossary at the end of this handout.

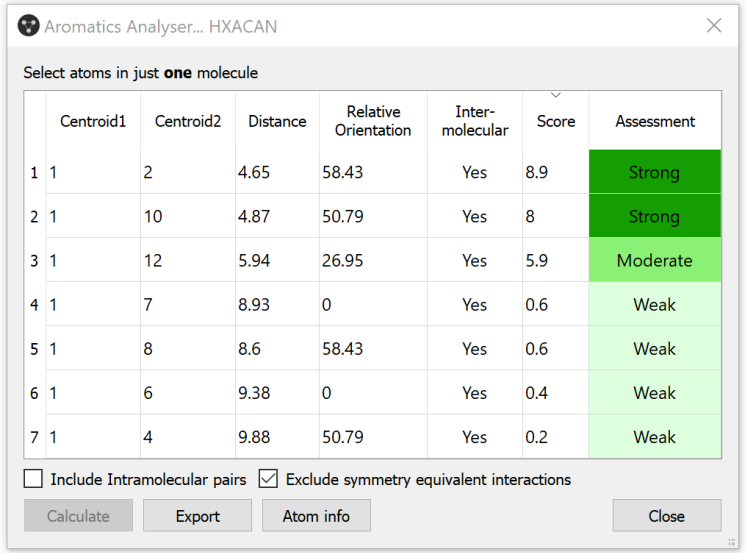
Pre-required Skills

Familiarity with the Mercury interface is important; you can access the Visualization in Mercury self-guided workshop here. In exercises 2a and 3a, we will show graphs obtained using Hydrogen Bond Propensities feature. If you want to learn more, you can read about it in the Glossary at the end of the handout, and we suggest working through the Hydrogen Bond Propensity Workshops on our website.

Materials

There are no additional materials required for this workshop.



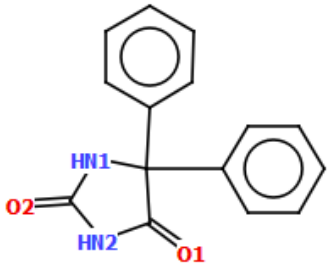


	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	1	2	4.65	58.43	Yes	8.9	Strong
2	1	10	4.87	50.79	Yes	8	Strong
3	1	12	5.94	26.95	Yes	5.9	Moderate
4	1	7	8.93	0	Yes	0.6	Weak
5	1	8	8.6	58.43	Yes	0.6	Weak
6	1	6	9.38	0	Yes	0.4	Weak
7	1	4	9.88	50.79	Yes	0.2	Weak

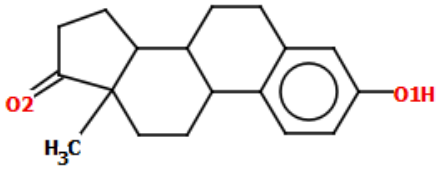
Example 1. Visualising aromatic interactions.

The presence and types of different aromatic interactions within crystal structures can be difficult to visualize and understand.

The two examples in this section illustrate how to visualise aromatic interactions and associated parameters using the Aromatics Analyser quickly and easily within *CSD-Materials.* These examples also introduce the use of the tool to analyse and assess the nature of the resulting aromatic interactions.



Phenytoin - CSD refcode ***PHYDAN01***



Estrone - CSD refcode ***ESTRON11***

1a. Example of favourable aromatic interactions (PHYDAN01)

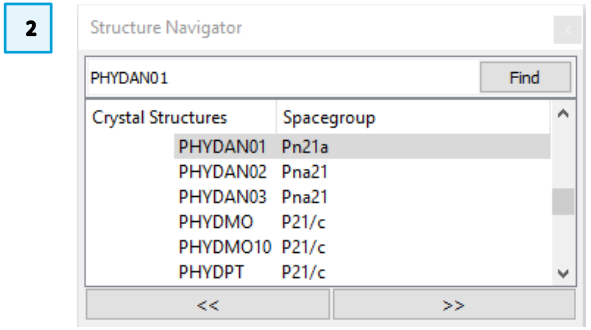
1. Open Mercury by double-clicking the Mercury icon on the desktop.

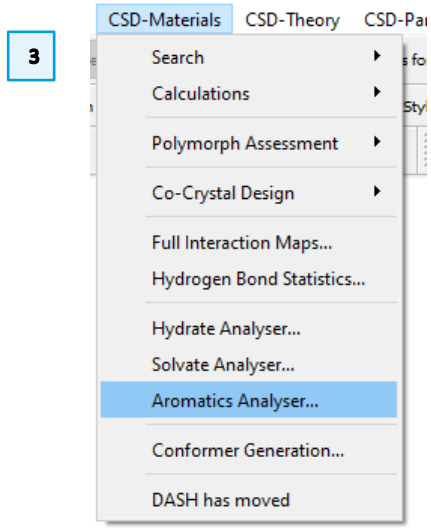
2. In the **Structure Navigator** window, type the refcode "PHYDAN01", to load the structure of phenytoin (Dilantin), an anti-seizure medication.

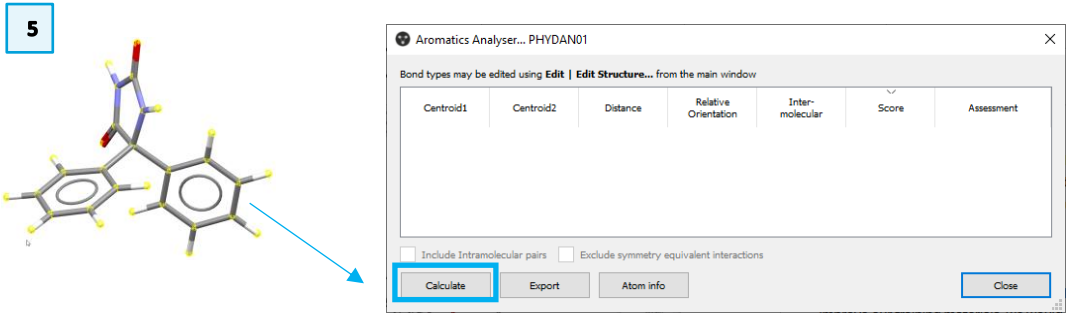
3. The structure will be displayed in the 3D visualiser.

4. From the top-level menu select *CSD-Materials > Aromatics Analyser* to launch the *Aromatics Analyser* dialog box

5. Select the molecule in the 3D visualiser by **Shift+Left-click**, then click on **Calculate** in the *Aromatics Analyser* dialog box to generate the aromatic interactions of the selected molecule and its neighbours. A packing shell is generated using a default value of van der Waals radii +0.5 Å.







6. A table of data relating to the aromatic interactions found in PHYDAN01 will now be displayed in the *Aromatics Analyser* dialog box. The refcode of the structure being analysed is displayed at the top of the dialogue box. A summary of the Aromatics Analyser dialog box can be found here.

7. The table is interactive: if you click within a row in the table, the aromatic rings involved in that interaction will be highlighted in the 3D visualiser. This allows a quick route to easily view the aromatic interactions present in the crystal structure and their associated geometric parameters.

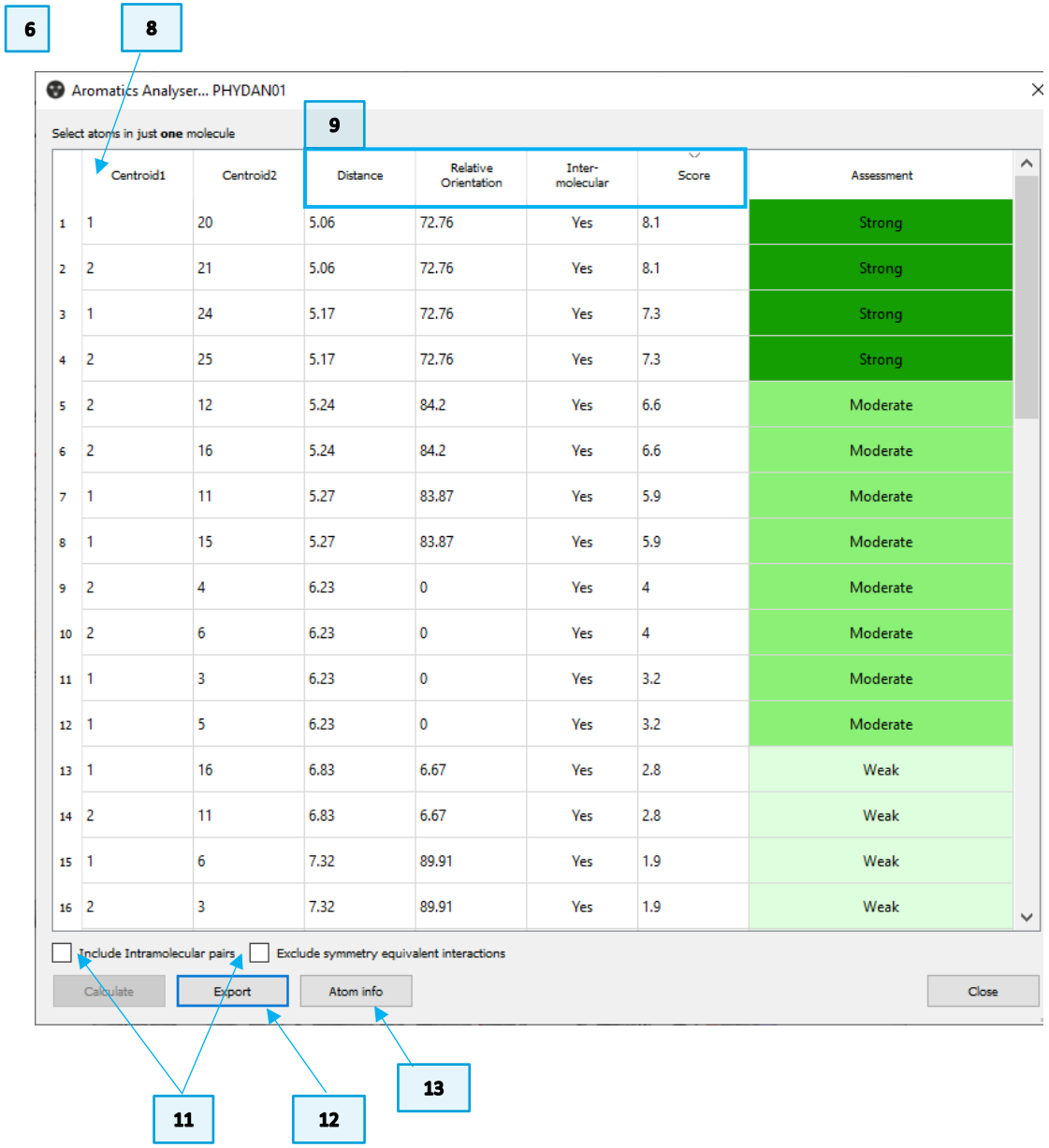
8. Data can be re-ordered by left-clicking in the desired column heading (e.g. high to low relative orientation).

9. The data in the table includes the distance between aromatic ring centroids (Å), relative orientation (°), as well as a score (0-10) assessing the strength of that interaction. Further information can be obtained by hovering the mouse over the column heading (e.g. definitions of parameters, units, how the score is classed for the '*Assessment*') or over the coloured assessment result (for the meaning of 'strong', 'moderate' and 'weak').

10. The numbering of aromatic rings in the *Centroid1* and *Centroid2* columns corresponds with those visible in the 3D visualiser (see image in step 14 below). The *Centroid1* column contains only aromatic ring(s) from within the originally selected molecule. For PHYDAN01, there are 2 aromatic rings in the structure, labelled as 1 and 2 in the *Centroid1* column.

11. You can **Include Intramolecular pairs** or **Exclude symmetry equivalent interactions** from the table by toggling on the checkboxes at the bottom of the *Aromatics Analyser* dialog. By default, intramolecular pairs are excluded, and symmetry inequivalent interactions are included. For example, excluding symmetry equivalent interactions in PHYDAN01 halves the number of rows.

12. The **Export** button allows you to generate a summary of the main table content in CSV format, to facilitate further investigations of the numerical data.



	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	1	20	5.06	72.76	Yes	8.1	Strong
2	2	21	5.06	72.76	Yes	8.1	Strong
3	1	24	5.17	72.76	Yes	7.3	Strong
4	2	25	5.17	72.76	Yes	7.3	Strong
5	2	12	5.24	84.2	Yes	6.6	Moderate
6	2	16	5.24	84.2	Yes	6.6	Moderate
7	1	11	5.27	83.87	Yes	5.9	Moderate
8	1	15	5.27	83.87	Yes	5.9	Moderate
9	2	4	6.23	0	Yes	4	Moderate
10	2	6	6.23	0	Yes	4	Moderate
11	1	3	6.23	0	Yes	3.2	Moderate
12	1	5	6.23	0	Yes	3.2	Moderate
13	1	16	6.83	6.67	Yes	2.8	Weak
14	2	11	6.83	6.67	Yes	2.8	Weak
15	1	6	7.32	89.91	Yes	1.9	Weak
16	2	3	7.32	89.91	Yes	1.9	Weak

13. By clicking the **Atom info** button, you can gain additional information about the atoms involved in the aromatic interaction highlighted in the main table, together with their distance, van der Waals adjusted distance and van der Waals overlap. Clicking on either of the atoms in a row will display the distance between that pair of atoms in the 3D visualiser.

14. Examine the aromatic interactions and data for PHYDAN01. There are a total of 48 aromatic interactions over a range of angles and centroid-centroid distances for the two, symmetry-related rings. These include (i) the strongest interactions approaching T-shape and (ii) parallel displaced interactions at slightly longer distances.

15. Of the aromatic interactions in PHYDAN01, 4 are assessed as ‘strong’ with higher scores – these are likely to be significantly stabilising in the structure. These are accompanied by a good range of moderately stabilising interactions, and several weaker interactions.

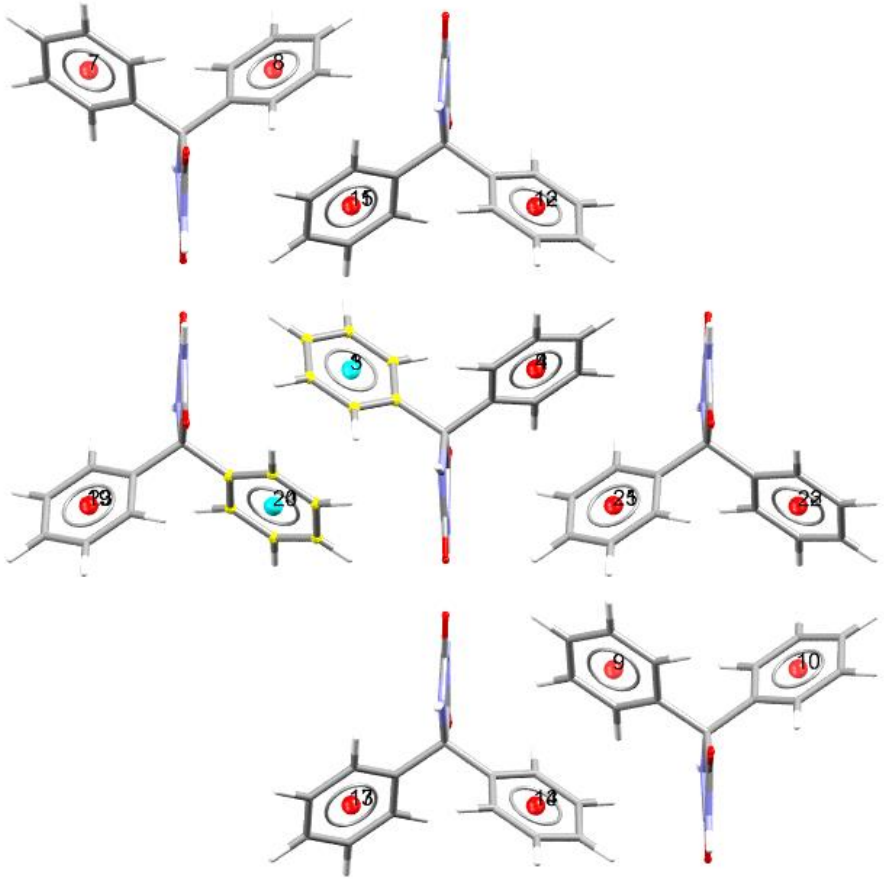
Conclusion

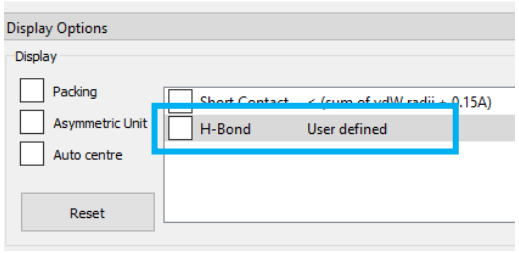
PHYDAN01 is an example of a structure that appears to be quite favourable in terms of aromatic interactions. It is the developed API (Active Pharmaceutical Ingredient) form, using the best hydrogen bonding network from HBP (Hydrogen Bond Propensity) – the packing satisfies both hydrogen bonding and aromatic interactions particularly well.

Exercise

Look at the hydrogen bonding and aromatic interactions for PHYDAN01 together to see how they complement one another. Tip: You can display the hydrogen bonding network by clicking on H-Bond in the Display Options menu and expand the network by clicking on the dangling contacts.

14





1b. Example of less favourable aromatic interactions (*ESTRON11*)

16. To look at a different structure, it must be selected in the 3D visualiser and the table updated by clicking Calculate.

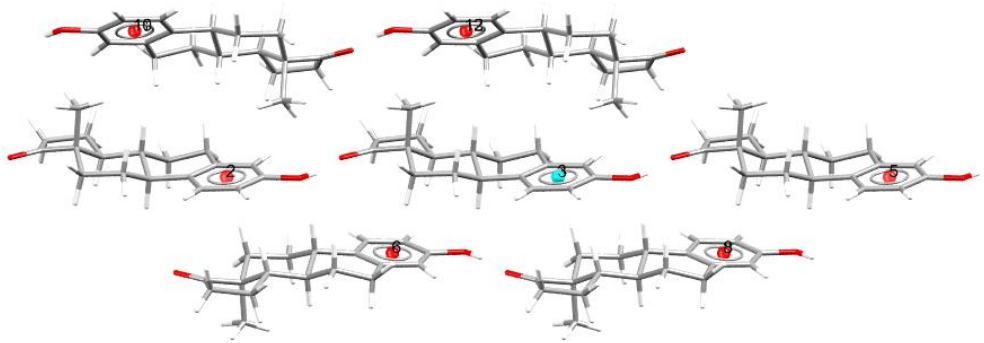
17. Examine the aromatic interactions for Estrone, an estrogen derivative. Type the refcode "ESTRON11" into the **Structure Navigator** window, select the molecule by **Shift+Left-click** and then click **Calculate** to view the aromatic interactions. Note the refcode identifier at the top of the *Aromatics Analyser* has now changed to ESTRON11.

18. There are only 12 aromatic interactions for ESTRON11 (6 symmetry equivalent interactions). None of these are classed as strongly or moderately stabilising – there are no close centroid-centroid distances and no 'high' or 'moderate' scores.

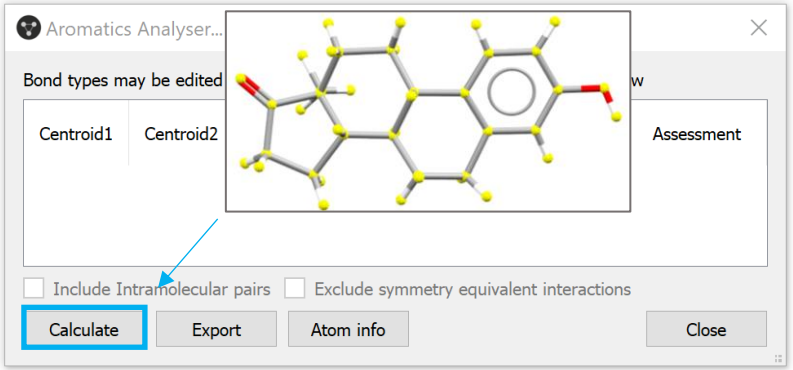
19. The **Close** button can be used to close the *Aromatics Analyser* dialog box.

Conclusion

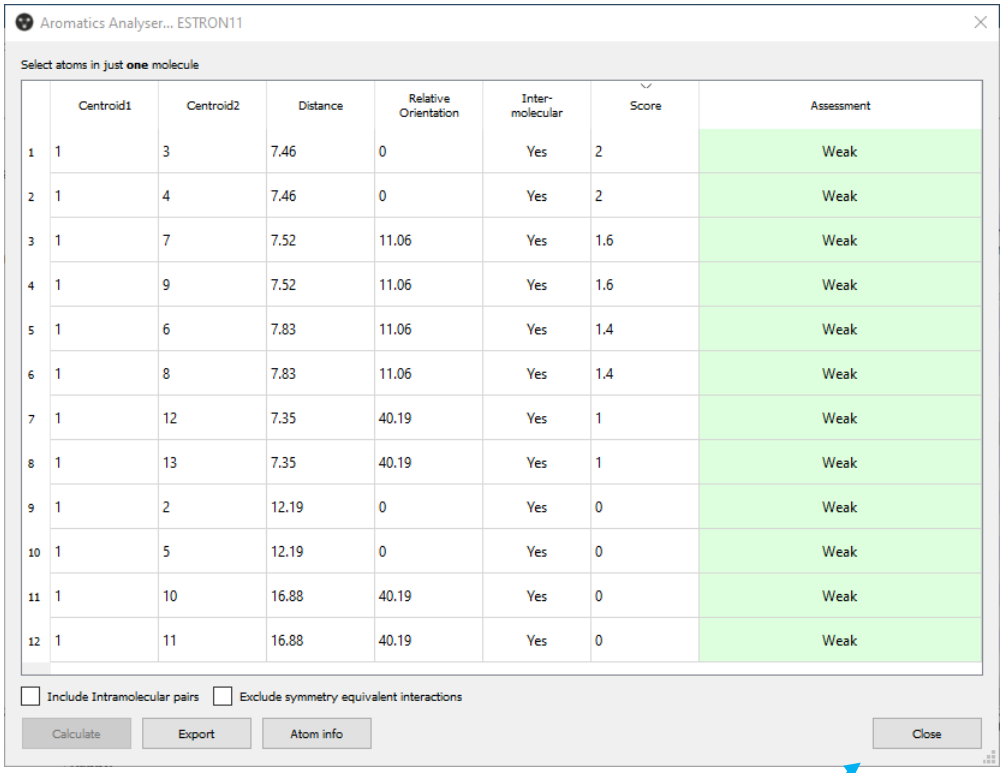
ESTRON is an example of a structure with less favourable aromatic interactions. The stabilising impact of aromatic interactions on this structure is expected to be minimal, and certainly none of these would be supposed to be structure-directing**.**



17



18



	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	1	3	7.46	0	Yes	2	Weak
2	1	4	7.46	0	Yes	2	Weak
3	1	7	7.52	11.06	Yes	1.6	Weak
4	1	9	7.52	11.06	Yes	1.6	Weak
5	1	6	7.83	11.06	Yes	1.4	Weak
6	1	8	7.83	11.06	Yes	1.4	Weak
7	1	12	7.35	40.19	Yes	1	Weak
8	1	13	7.35	40.19	Yes	1	Weak
9	1	2	12.19	0	Yes	0	Weak
10	1	5	12.19	0	Yes	0	Weak
11	1	10	16.88	40.19	Yes	0	Weak
12	1	11	16.88	40.19	Yes	0	Weak

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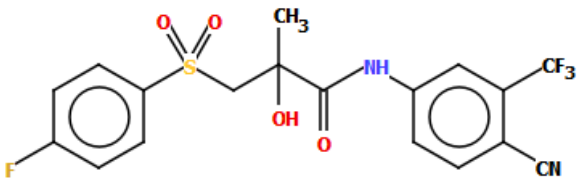
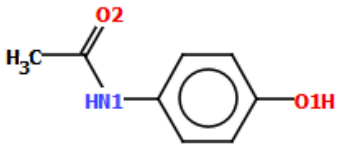
Example 2. Investigating aromatic interactions for polymorphs.

This section looks at comparing the nature and influence of aromatic interactions across different polymorphic forms using the *Aromatics Analyser*, both visually and quantitatively.

Examples include those with different and the same type of hydrogen bonding.



Bicalutamide - CSD refcodes
JAYCES (Form I)
JAYCES02 (Form II)



Paracetamol - CSD refcodes
HXACAN01 (Form I)
HXACAN (Form II)

2a. Bicalutamide Forms I and II (JAYCES and JAYCES02)

Bicalutamide (Casodex) is an antiandrogen medication primarily used to treat prostate cancer. Bicalutamide contains 2 different aromatic rings, and there are 2 reported forms in the CSD.

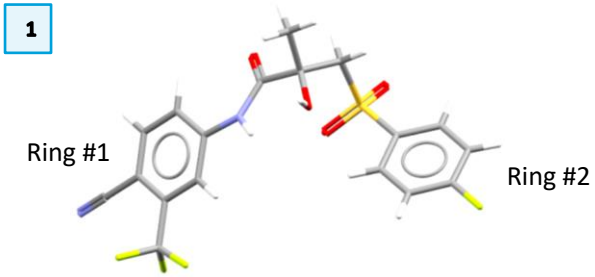
1. Load Form I of bicalutamide, JAYCES**.** Open Mercury, select the JAYCES molecule, and calculate the aromatic interactions (steps 1-5 for Example 1a).

2. Examine the interactions and data for JAYCES (Form I) in the 3D visualiser and resulting table. The identified aromatic interactions cover a range of different distances and relative orientations from parallel to tilted.

3. Assessment indicates there are many stabilising aromatic interactions for both ring #1 and ring #2 (see Centroid1 column), of which several are classed as ‘strong’ and ‘moderate’.

4. JAYCES therefore looks quite favourable in terms of aromatic interactions. *How does this compare with the second polymorph of bicalutamide?*

1



2

Aromatics Analyser... JAYCES

Select atoms in just **one** molecule

	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	2	20	4.39	0	Yes	8.4	Strong
2	1	17	4.68	0	Yes	7.4	Strong
3	1	14	5.13	25.81	Yes	6.7	Moderate
4	2	11	5.13	25.81	Yes	6.7	Moderate
5	2	22	6.88	0	Yes	3.3	Moderate
6	2	12	6.26	64.29	Yes	3.2	Moderate
7	2	14	6.26	64.29	Yes	3.2	Moderate
8	2	26	6.63	64.29	Yes	2.9	Weak
9	2	28	6.63	64.29	Yes	2.9	Weak
10	1	29	6.82	14.92	Yes	2.3	Weak
11	1	31	6.82	14.92	Yes	2.3	Weak
12	1	7	8.06	14.92	Yes	1	Weak

Include Intramolecular pairs Exclude symmetry equivalent interactions

Calculate Export Atom info Close

5. Look at Form II of bicalutamide, JAYCES02**.** Select the JAYCES02 molecule in *Mercury* and click Calculate in the *Aromatics Analyser* to update the table.

6. Examine the interactions and data for JAYCES02 (Form II) in the resulting table. The identified aromatic interactions cover a range of different distances, although in this case all the relative orientations are near-parallel.

7. JAYCES02 has two aromatic interactions with a high score (one per ring) that are likely to be significantly stabilising ('strong'), and one moderate interaction for ring #2. All the remaining interactions are relatively weak, and not likely to offer much in terms of lattice stabilisation. There are thus a few very good aromatic interactions in JAYCES02, although not that many.

8. **Comparison with Form I** (JAYCES) shows that the aromatic interactions are less favourable in both quality and quantity – lower scores for the aromatic interactions in Form II (JAYCES02) overall, and lower number of aromatic interactions identified.

9. The *Aromatics Analyser* thus indicates that Form I (JAYCES) is more favourable than Form II (JAYCES02) in terms of aromatic interactions. It also highlights the differences in relative orientations of the aromatic rings within the two crystal structures.

10. Form I and II of bicalutamide exhibit different hydrogen bonding. Form I (JAYCES) is the best in *Hydrogen Bond Propensities*, compared to both Form II *(*JAYCES02) and all other networks.

11. Form I (JAYCES) is the most thermodynamically stable Form*.

Conclusion

This example has shown an instance of aromatic interactions aligning with other evidence about the stability of Form I over Form II of bicalutamide.

* D. R. Vega, G. Polla, A. Martinez, E. Mendioroz, M. Reinoso, *Int. J. Pharm.*, **2007**, 328 (2), 112-118.

6

Aromatics Analyser... JAYCES02

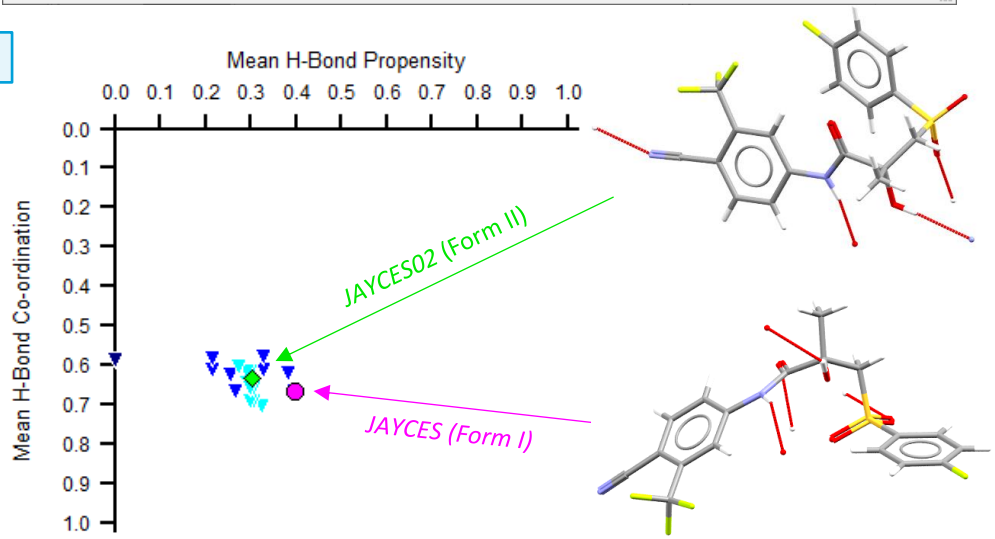
Select atoms in just **one** molecule

	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	1	4	3.89	13.3	Yes	7.7	Strong
2	2	13	3.89	13.3	Yes	7.7	Strong
3	2	24	5.19	0	Yes	5.8	Moderate
4	1	17	7.24	0	Yes	2.3	Weak
5	2	28	7.28	0	Yes	2.3	Weak
6	1	15	7.46	0	Yes	1.8	Weak
7	1	24	7.46	13.3	Yes	1.8	Weak
8	2	23	7.46	13.3	Yes	1.8	Weak
9	1	18	8.15	13.3	Yes	1.1	Weak
10	1	20	8.14	13.3	Yes	1.1	Weak
11	2	17	8.15	13.3	Yes	1.1	Weak
12	2	19	8.14	13.3	Yes	1.1	Weak

Include Intramolecular pairs Exclude symmetry equivalent interactions

Calculate Export Atom info Close

10



2b. Paracetamol Forms I and II (HXACAN01 and HXACAN)

1. Load Form I of paracetamol, HXACAN01. Select the HXACAN01 molecule in Mercury and calculate the aromatic interactions (steps 1-5 for Example 1a).

2. Examine the interactions and data for HXACAN01 (Form I) in the resulting table. The identified aromatic interactions cover a range of different distances in parallel and T-shape orientations. Assessment indicates there is one stronger aromatic interaction, accompanied by some moderately stabilising interactions and a range of weaker interactions.

3. Load Form II of paracetamol, HXACAN. Select the HXACAN molecule in the 3D visualiser and click **Calculate** to update the table.

4. Examine the interactions and data for HXACAN (Form II) in the resulting table. The identified aromatic interactions cover a range of different distances and orientations. Assessment indicates there are four stronger aromatic interactions, accompanied by a few moderately stabilising interactions and a range of weaker interactions.

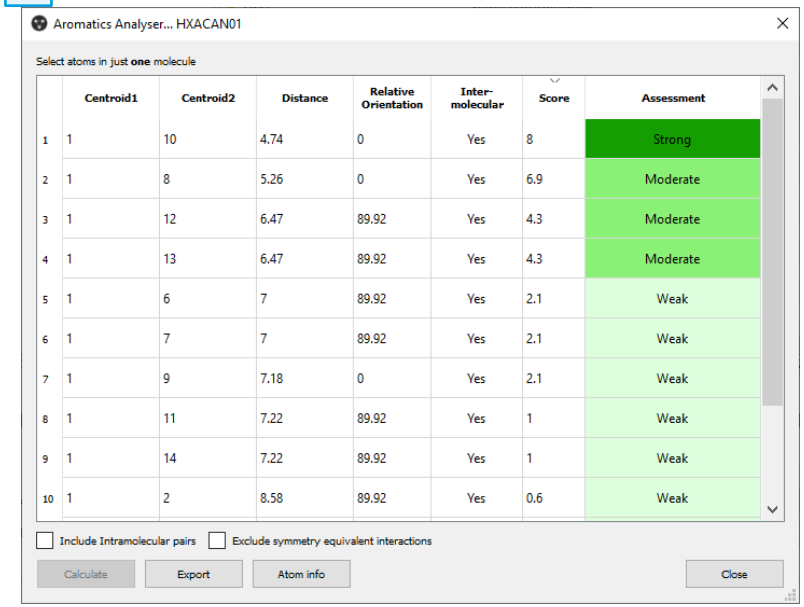
5. Compare and contrast the data on the aromatic interactions for Form I (HXACAN01) and Form II (HXACAN) of paracetamol. Both have a similar top-ranked interaction (similar score and distance). There are a larger number of high scores for HXACAN (strong interactions over close distances), although there is a larger quantity of aromatic interactions overall for HXACAN01.

6. Form I (HXACAN01) is the more thermodynamically stable Form*. In this case, both forms exhibit the same type of hydrogen bonding. Analysis using the *Aromatics Analyser* reveals the additional stabilisation for Form I does not appear to originate from better individual aromatic interactions. This is reinforced by comparison with DFT calculations**, which show the aromatic interactions in Form II (HXACAN) are associated with slightly better energies.

* G. L. Perlovich, T. V. Volkova, A. Bauer-Brandl, *J. Them. Anal. Cal.*, **2007**, 89 (3), 767-774

** B3LYP-D3/6-311G** calculations on benzene dimers extracted from the crystal structures → estimated energy (kJ mol^{-1}) for the top 3 ranked aromatic interactions.

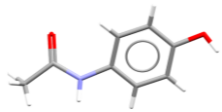
2



Energy*
-12.5
-10.9
-6.9
-6.9
-2.3

6

DFT (kJ mol^{-1})



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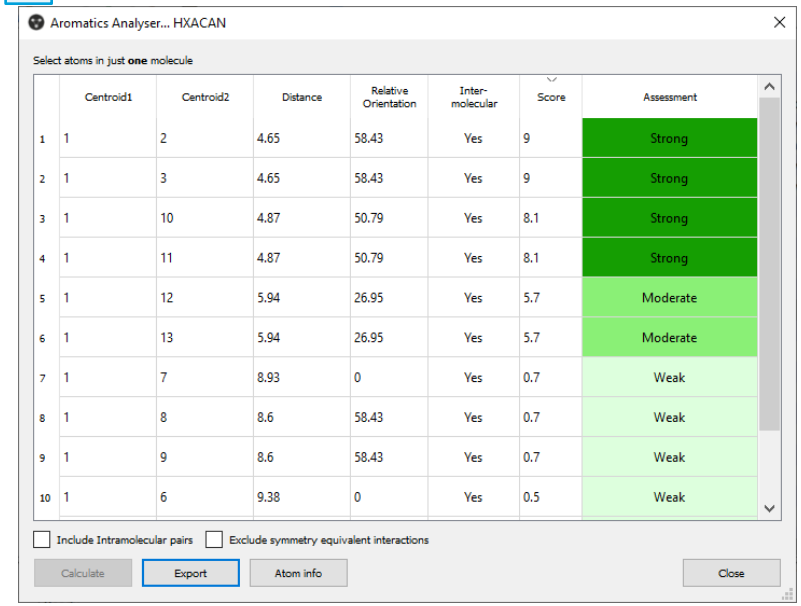
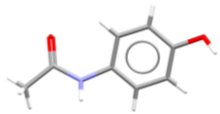


Energy*
-15.3
-15.3
-13.5
-13.5
-9.2
-9.2

6

DFT (kJ mol^{-1})



Example 3. Investigating cases where aromatic interactions may be more relevant in structure stability.

This section looks at comparing the nature and influence of aromatic interactions for solid forms where aromatic interactions may be considered particularly pertinent to assessing structure stability.

Examples include cases with no hydrogen bonding, or where there is limited or unfavourable information from other areas.

3a. Tesaglitazar (MATXUD)

Tesaglitazar is PPARα/γ agonist proposed for the management of type 2 diabetes. The structure investigated here is the commercially developed solid form, yet it exhibits some less than favourable aspects including HBP outcome and morphology.

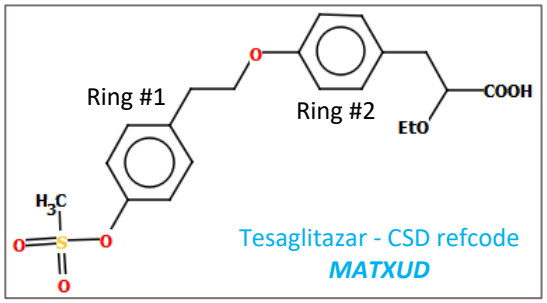
1. Load the structure of tesaglitazar (MATXUD). Select the MATXUD molecule in Mercury and calculate the aromatic interactions (steps 1-5 for Example 1a).

2. Examine the interactions and data for MATXUD in the resulting table. There are a decent number of good stabilising aromatic interactions (scores between 5 and 6.5) across both of the aromatic rings (#1 and #2). The structure appears reasonably favourable in terms of aromatic interactions, and would be expected to be quite supportive in terms of lattice energy stabilisation.

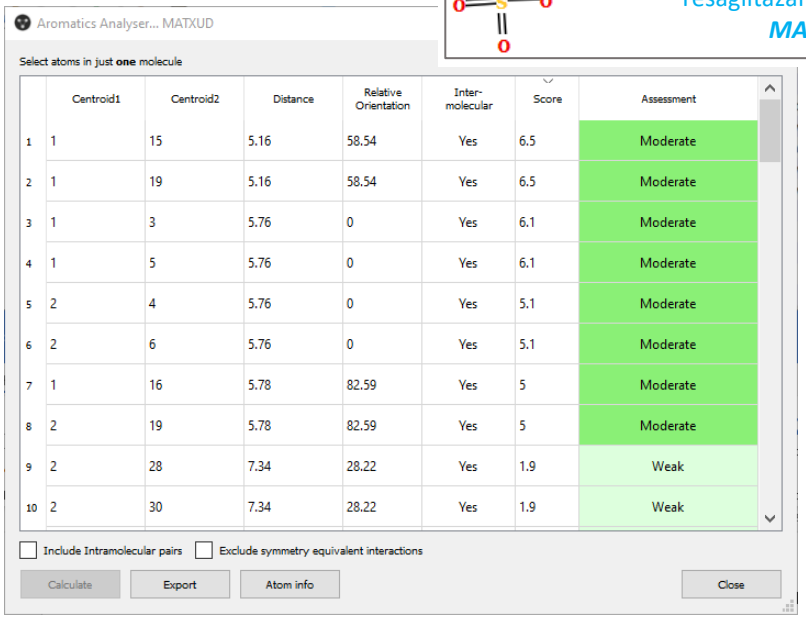
3. The hydrogen bonding in MATXUD involves donation from the carboxylic acid OH to one of the ether C-O groups. This results in the worst outcome in HBP (best arises from sulfonyl S=O accepting). The morphology for MATXUD is also sub-optimal, resulting in needles.

4. The aromatic interactions look quite reasonable for MATXUD, aligning with it being chosen as the solid form for development despite other caveats.

2

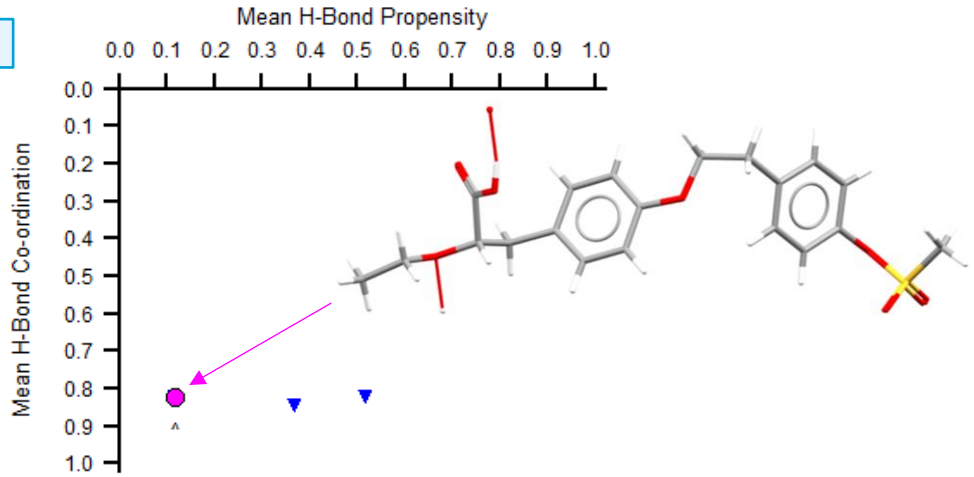


Tesaglitazar - CSD refcode ***MATXUD***



	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	1	15	5.16	58.54	Yes	6.5	Moderate
2	1	19	5.16	58.54	Yes	6.5	Moderate
3	1	3	5.76	0	Yes	6.1	Moderate
4	1	5	5.76	0	Yes	6.1	Moderate
5	2	4	5.76	0	Yes	5.1	Moderate
6	2	6	5.76	0	Yes	5.1	Moderate
7	1	16	5.78	82.59	Yes	5	Moderate
8	2	19	5.78	82.59	Yes	5	Moderate
9	2	28	7.34	28.22	Yes	1.9	Weak
10	2	30	7.34	28.22	Yes	1.9	Weak

3



3b. Risperidone Forms I and II (WASTEP and WASTEP01)

Risperidone (Risperdal) is used as an antipsychotic. It exists as two polymorphs, one of which has Z' = 2. There are no donor protons in the structure, so the solid forms cannot be assessed via hydrogen bonding.

1. Load the structure of Form I of risperidone (WASTEP). Select the WASTEP molecule in Mercury and calculate the aromatic interactions (steps 1-5 for Example 1a).

2. Examine the interactions and data for WASTEP in the resulting table.

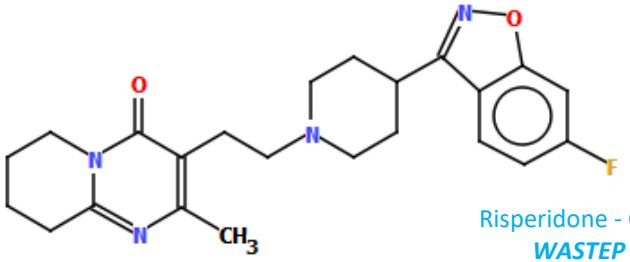
3. Load the structure of Form II of risperidone (WASTEP01). Select the WASTEP01 molecule in the 3D visualiser. This form has Z' = 2, so we will need to select which molecule to analyse first. Toggle on 'show labels' for the non-CH atoms at the top of Mercury, and select the molecule containing O1, then click Calculate to update the table in the *Aromatics Analyser* dialogue box.

4. Examine the interactions and data for the 1st molecule of WASTEP01 in the resulting table.

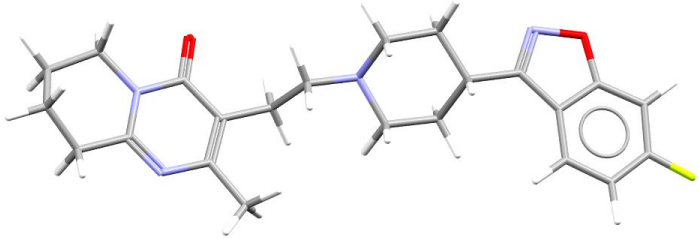
5. Examine the interactions and data for the 2nd molecule of WASTEP01. Repeat the same process, but this time selecting the molecule containing O3 for WASTEP01: click the **Reset** button below the 3D visualiser, then select the required molecule and update the results by clicking **Calculate** in the *Aromatics Analyser* dialogue box.

6. Compare and contrast the results for Form I (WASTEP) and Form II (WASTEP01). There is one 'strong' interaction in WASTEP (score of 8.8), which forms molecular dimers through aromatic interactions (benzoxazole --- benzoxazole). This is accompanied by many aromatic interactions that would only be considered to weakly contribute to lattice stability at best. For WASTEP01, however, molecule #1 has no identified interactions and molecule #2 interacts in dimeric pairs, bonded through two symmetry-related interactions: benzoxazole --- pyrimidine and pyrimidine --- benzoxazole at the opposite end of the molecule.

1



Risperidone - CSD refcodes
WASTEP (Form I)
WASTEP01 (Form II)



2

Aromatics Analyser... WASTEP

Select atoms in just **one** molecule

	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	1	11	4.29	0	Yes	8.8	Strong
2	1	4	7.22	30.45	Yes	1.1	Weak
3	1	5	7.22	30.45	Yes	1.1	Weak
4	1	10	8.3	0	Yes	1	Weak
5	1	2	9.77	0	Yes	0.4	Weak
6	1	3	9.77	0	Yes	0.4	Weak
7	1	6	18.59	30.45	Yes	0	Weak
8	1	7	12.44	30.45	Yes	0	Weak
9	1	8	12.44	30.45	Yes	0	Weak
10	1	9	18.59	30.45	Yes	0	Weak

Include Intramolecular pairs Exclude symmetry equivalent interactions

Calculate Export Atom info Close

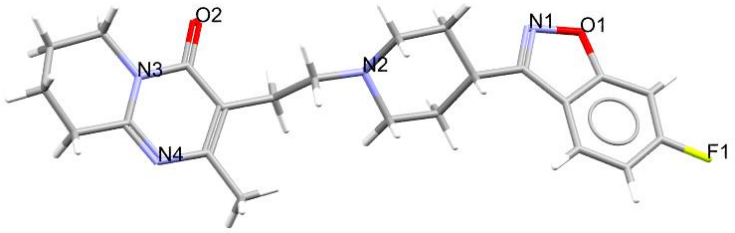
7. Form I (WASTEP) looks significantly more favourable than Form II (WASTEP01) from aromatic interactions, although distinguishing between the forms effectively comes down to distribution and relative strength of aromatic interactions.

8. Assessment from the *Aromatics Analyser* contrasts with the relative stability – Form I (WASTEP) is considered more favourable as the Form II transforms to Form I: approaching the melting point* and agrees with the observed thermodynamic stability**.

* https://patents.google.com/patent/EP1982980A1/en **[0038]**

** *D. Mealey, M.Svärd, Å. C. Rasmuson, Fluid Phase Equilibr., 2014, 375, 73-79*

4 WASTEP01, Molecule #1



Aromatics Analyser... WASTEP01

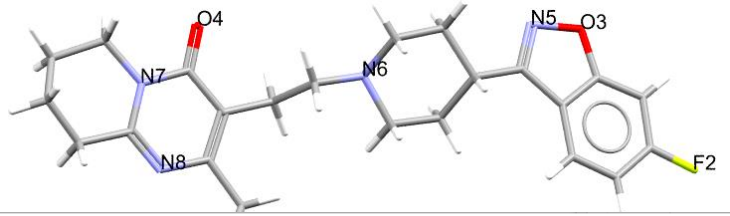
Select atoms in just **one** molecule

	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	1	10	6.87	14.58	Yes	1.8	Weak
2	1	2	6.97	14.58	Yes	1.2	Weak
3	1	5	7.66	0	Yes	1.1	Weak
4	1	3	9.94	0	Yes	0.4	Weak
5	1	4	9.94	0	Yes	0.4	Weak
6	1	6	18.24	0	Yes	0	Weak
7	1	7	15.6	0	Yes	0	Weak
8	1	8	26.12	0	Yes	0	Weak
9	1	9	18.58	14.58	Yes	0	Weak
10	1	11	19.68	14.58	Yes	0	Weak

Include Intramolecular pairs Exclude symmetry equivalent interactions

Calculate Export Atom info Close

5 WASTEP01, Molecule #2



Aromatics Analyser... WASTEP01

Select atoms in just **one** molecule

	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	1	12	5.97	0	Yes	4	Moderate
2	1	4	6.87	14.58	Yes	1.8	Weak
3	1	2	6.97	14.58	Yes	1.2	Weak
4	1	10	9.94	0	Yes	0.4	Weak
5	1	11	9.94	0	Yes	0.4	Weak
6	1	3	19.68	14.58	Yes	0	Weak
7	1	5	18.58	14.58	Yes	0	Weak
8	1	6	15.03	14.58	Yes	0	Weak
9	1	7	14.74	14.58	Yes	0	Weak
10	1	8	21.8	14.58	Yes	0	Weak

Include Intramolecular pairs Exclude symmetry equivalent interactions

Calculate Export Atom info Close

Exercises

- Investigate the overlap of phenyl and heterocycle rings between molecules for the two forms.
- How differently do the symmetrically inequivalent molecules in WASTEP01 behave in terms of aromatic interactions?

Summary

In this workshop, you have learnt how to use the Aromatics Analyser tool in Mercury for investigating aromatic interactions in several structures, including systems with no hydrogen bonding and polymorphic forms. You should now be able to:

- Visualize aromatic interactions in your system and analyse the results.
- Investigate aromatic interactions and its stabilizing influence on a crystal structure.
- Investigate aromatic interactions for polymorphs.

Next Steps

Hydrogen Bond Propensity maps were mentioned in this workshop but not fully explained. We recommend working through our workshops on using the Hydrogen Bond Propensity tool in Mercury that is available from the CSD-Materials workshops page (https://www.ccdc.cam.ac.uk/community/training-and-learning/workshop-materials/csd-materials-workshops/). The Hydrogen Bonds Statistics workshop also provides more complementary tools for the Aromatics Analyser.

Feedback

We hope this workshop improved your understanding of the *Aromatics Analyser* 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 MAT-005. Thank you!

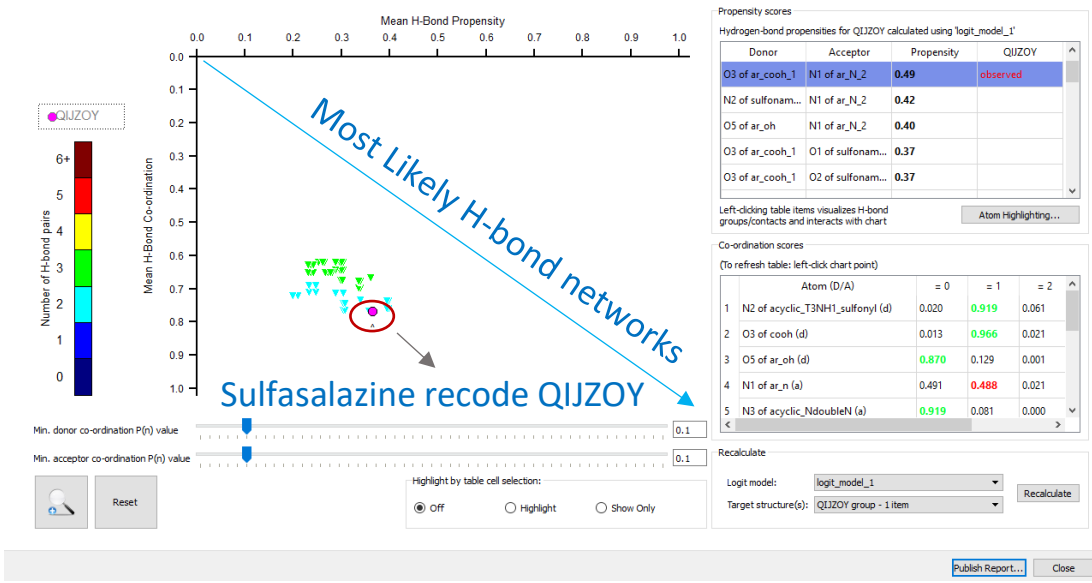
Glossary

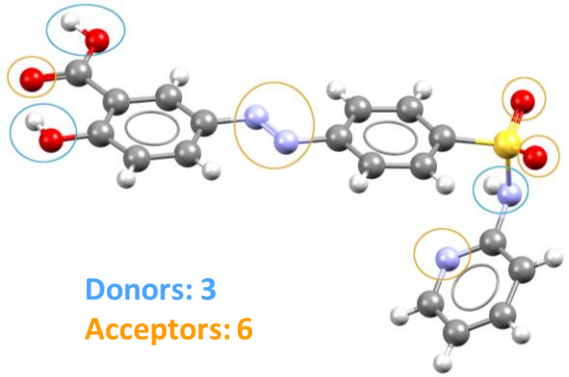
Hydrogen Bond Propensity (HBP)

- The HBP tool in Mercury>CSD-Materials evaluates the relative likelihoods of possible H-bonding networks in any observed polymorphs of a target system.
- Probabilities for hydrogen bond pairings to form in the target system are calculated from a statistical model built from relevant structures in the CSD. The model encapsulates information regarding the environment of the functional groups, which ensures the prediction is specific to the target molecule.
- Combining probabilities of hydrogen bond formation with a statistical model that captures information regarding how often a functional group participates allows the generation of chemically sensible alternative structures.
- The view of the solid-state landscape of an active ingredient afforded through the combination of propensity and coordination addresses questions such as how likely polymorphism is and whether there is the possibility of a more stable form. Specifically, you can:
    - Predict likely hydrogen bonds for a given molecule.
    - Assess crystal forms e.g. by identifying sub-optimal hydrogen bonding.
    - Calculate hydrogen bond propensities for individual donor and acceptor groups.
    - Perform a comprehensive analysis of hydrogen bonding on a set of structures.

The Chart*:*

- plots Mean H-bond Propensity vs the Mean H-Bond Co-ordination
- target structure is represented as a magenta circle
- the most likely H-bonding network is displayed in the lower-right corner, the outcome should be read along the diagonal
- QIJZOY refcode has the most likely H-bonding network for sulfasalazine listed first in the lower right-hand corner

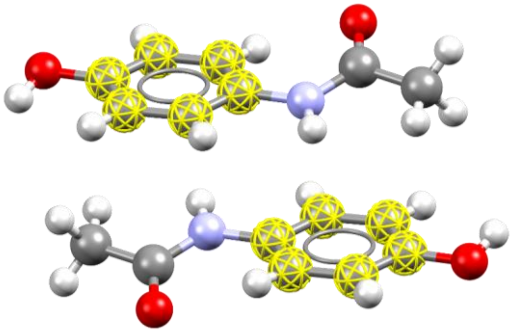




Eg.: Sulfasalazine exhibits 3 potential donors and 6 acceptors that might compete in forming H-bond interactions. HBP can be used to evaluate which of these potential interactions are more likely to form.

Aromatics Analyser

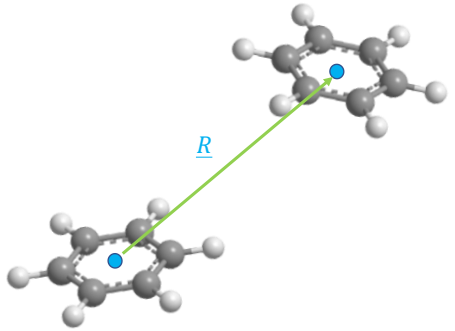
This uses a neural network model* to provide a score between 0 and 10 based on how stabilising an aromatic ring interaction is expected to be, and assessment into 'strong', 'moderate' and 'weak' interactions.



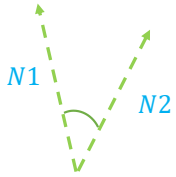
** The model is based on a geometric description of aromatic interactions involving the position of two benzene rings relative to each other, in order to estimate the associated energy with an aromatic interaction, presented as a 'score'. The influence of non-H substituents are not explicitly accounted for (model based on phenyl…phenyl aromatic interactions). The tool can be applied for aromatic rings that incorporate non-carbon atoms, but in such cases the interpretation should be approached with more care, because all the atoms will be treated as carbon (since the model is based on benzene rings), and the results can be less relevant.*

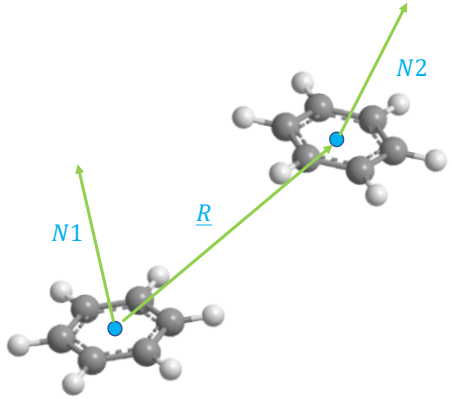
Packing shell:
van der Waals radii +0.5 Å

Distance:
centroid-centroid distance (Å)



Relative orientation:
angle between ring normals (°)



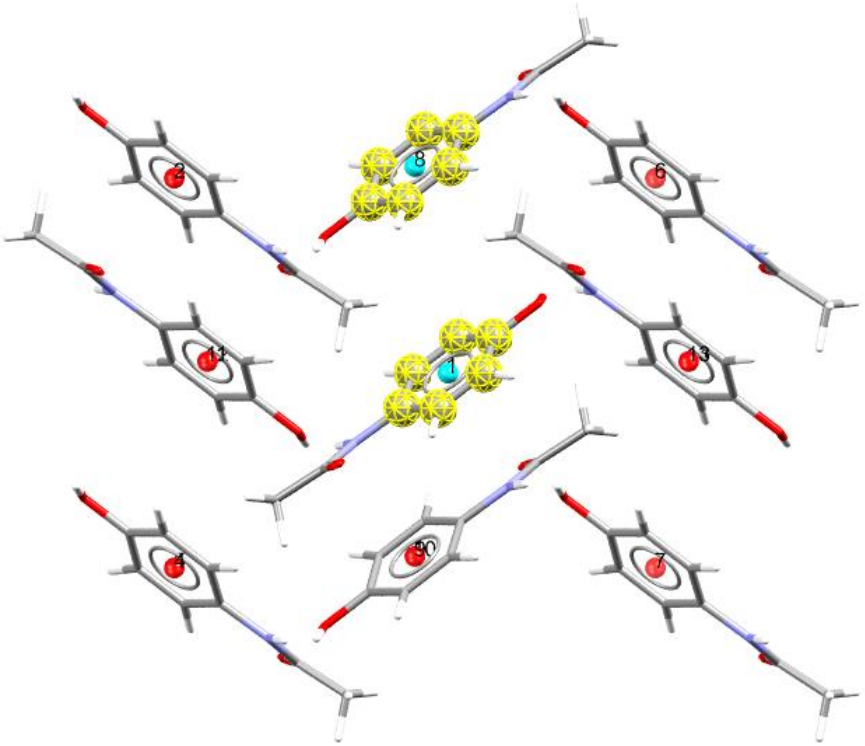


Aromatics Analyser score

- **Strong (10 → 7)**: Likely to be significantly stabilising and potentially structure-directing.
- **Moderate (7 → 3)**: Likely to be noticeably stabilising, but less optimal geometries.
- **Weak (3 → 0)**: Likely to have a low contribution to lattice stabilisation.

Summary of *Aromatics Analyser* interface

The *Aromatics Analyser* is interactive with the 3D visualiser in Mercury, and is simple to use (select a molecule and click *Calculate*).



Overview of dialogue box & associated actions

Structure analysed

Centroid-centroid distance (Å)

Angle between ring normals (°)

Scale of 0 (weak) to 10 (strong)

Hover for info, click to re-order

Aromatics Analyser... HXACAN01

Bond types may be edited using **Edit** | **Edit Structure...** from the main window

	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	1	9	4.74	0	Yes	8.1	Strong
2	1	10	5.26	0	Yes	6.9	Moderate
3	1	12	6.47	89.92	Yes	4.4	Moderate
4	1	13	6.47	89.92	Yes	4.4	Moderate
5	1	8	7.18	0	Yes	2.1	Weak
6	1	6	7	89.92	Yes	2	Weak
7	1	7	7	89.92	Yes	2	Weak
8	1	11	7.22	89.92	Yes	1	Weak
9	1	14	7.22	89.92	Yes	1	Weak
10	1	2	8.58	89.92	Yes	0.6	Weak
11	1	4	8.58	89.92	Yes	0.6	Weak
12	1	3	9.2	89.92	Yes	0.4	Weak
13	1	5	9.2	89.92	Yes	0.4	Weak

☐ Include Intramolecular pairs ☐ Exclude symmetry equivalent interactions

Calculate | Export | Atom info | Close

Tailor which interactions are specified

Save a .csv file

More info for atoms involved in interaction