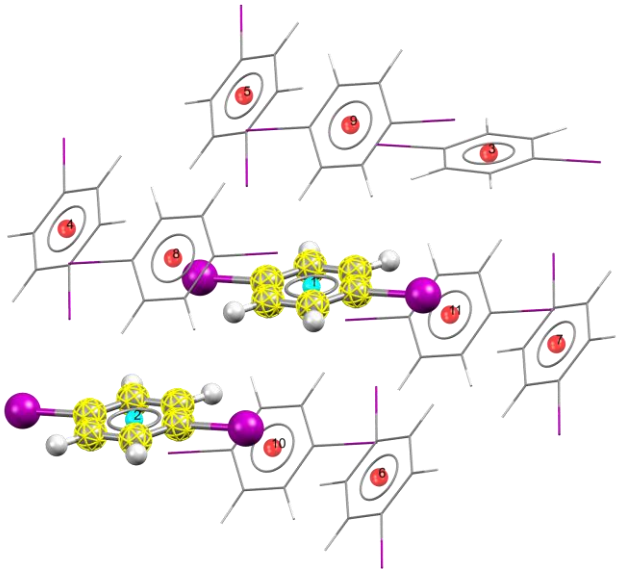
Aromatics Analyser

2020.2 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 with 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 this tool by watching the How To Aromatics Analyser video (https://www.youtube.com/watch?v=mYYpggxDt-E) or checking the Aromatics Analyser blog (https://www.ccdc.cam.ac.uk/Community/blog/2020-04-17-new-for-20201-release-aromatics-analyser-in-merc/).

Objectives

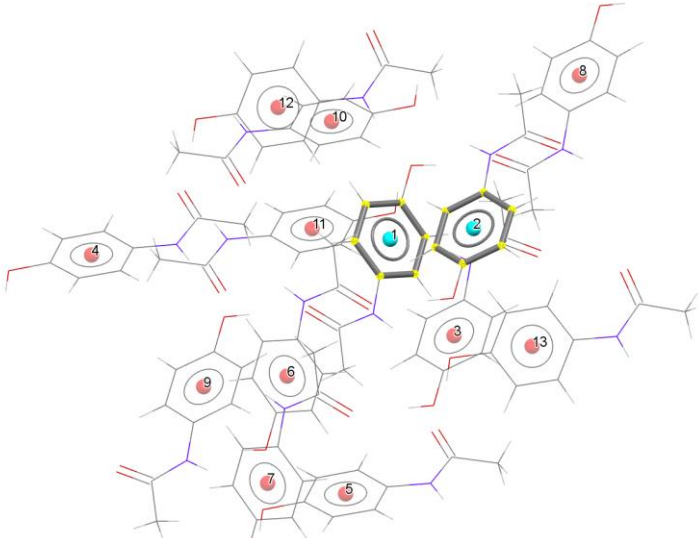
- Visualise Aromatic Interactions
- Assess the strength of Aromatics Interactions in a crystal structure
- Gain insight into the observed aromatic interactions by estimating their stabilising influence upon the crystal structure
- Investigating aromatic interactions for polymorphs such as:
    - Polymorphs with different H-bonding
    - Polymorphs with the same H-boding
    - Polymorphs with no H-bonding available
    - Polymorphs where Aromatic Interactions are more relevant

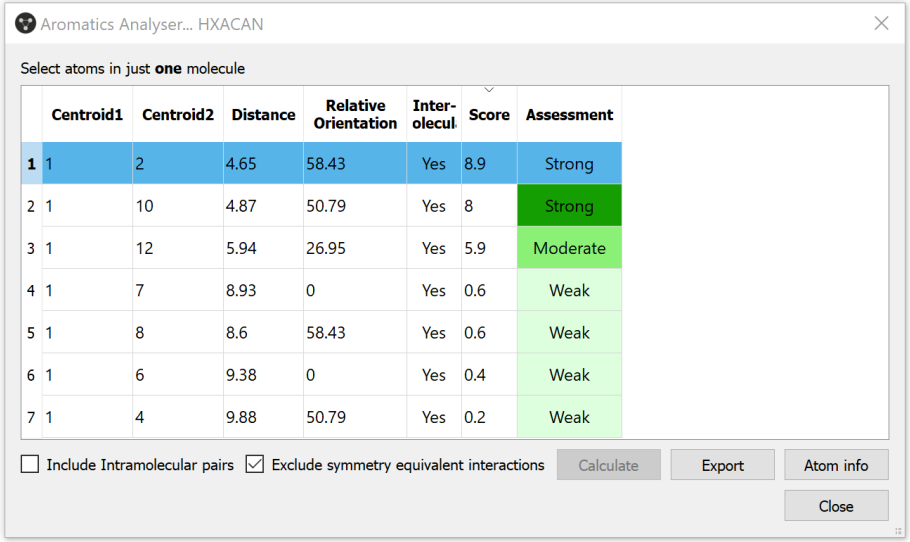
This workshop will take approximately ***45*** minutes to be completed.

Pre-required skills

For this tutorial, we recommend being familiar with the following:

- Mercury interface and basics of visualisation
- In Example1 and Example3, we will show graphs obtained using the Hydrogen Bond Propensities (HBP) feature. The presentation has introduced this concept to the level needed. If you want to learn more, you can read about it in the Dictionary at the end of the handout, and we suggest the Hydrogen Bond Propensity Workshop on our website. Completing the HBP workshop is not required today.





The basic steps of calculating Aromatic Interactions

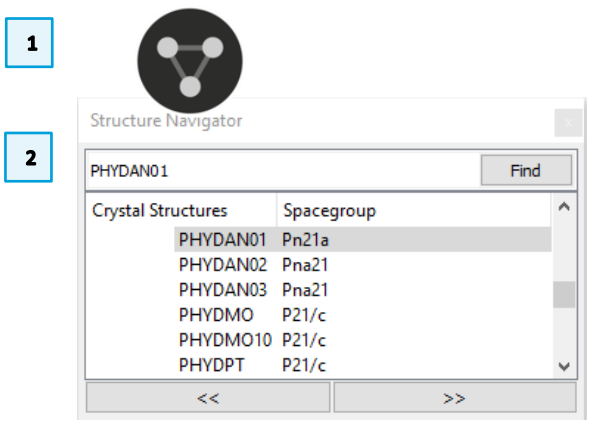
1. Open Mercury by double-clicking the Mercury icon on the desktop

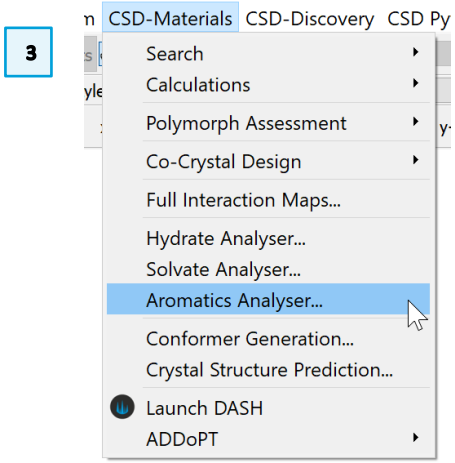
2. In the **Structure Navigator** window, type the refcode *PHYDAN01*, to load the structure of phenytoin (Dilantin), an anti-seizure medication

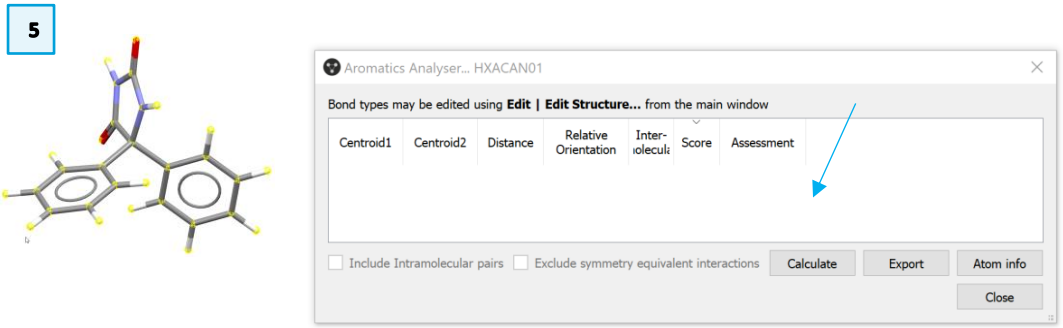
3. The structure will be displayed in the 3D visualiser.

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

5. Select one 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.



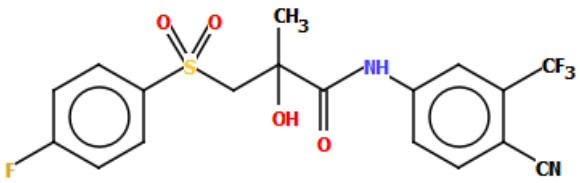




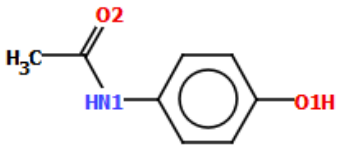
Investigating aromatic interactions for polymorphs

These sections look at comparing the nature and influence of aromatic interactions across different polymorphic forms using the *Aromatics Analyser*, both visually and quantitatively, and how these may align with other aspects.

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)

Example1. 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.

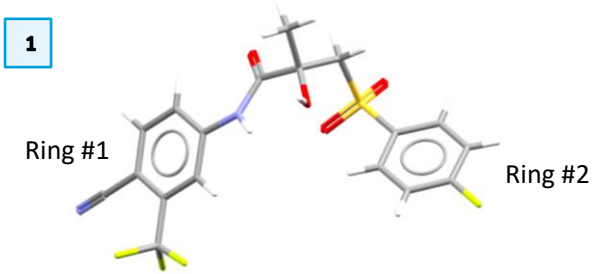
1. **Load Form I of bicalutamide, *JAYCES*.** Open Mercury, select the *JAYCES* molecule, and calculate the aromatic interactions (steps 1-5 of The basic steps of calculating Aromatic Interactions).

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

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

	Centroid1	Centroid2	Distance	Relative Orientation	Inter-olecul	Score	Assessment
1	2	20	4.39	0	Yes	8.6	Strong
2	1	17	4.68	0	Yes	7.5	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	12	6.26	64.29	Yes	3.2	Moderate
6	2	14	6.26	64.29	Yes	3.2	Moderate
7	2	22	6.88	0	Yes	3.1	Moderate
8	2	26	6.63	64.29	Yes	2.8	Weak
9	2	28	6.63	64.29	Yes	2.8	Weak
10	1	29	6.82	14.92	Yes	2.2	Weak
11	1	31	6.82	14.92	Yes	2.2	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. *JACES02* 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 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, which are drawn in red in the image on the side. Form I (*JAYCES*) is the best in HBP (Learn more about HBP in the *Dictionary* section), compared to both Form II *(JAYCES02*) and all other networks.

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

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.

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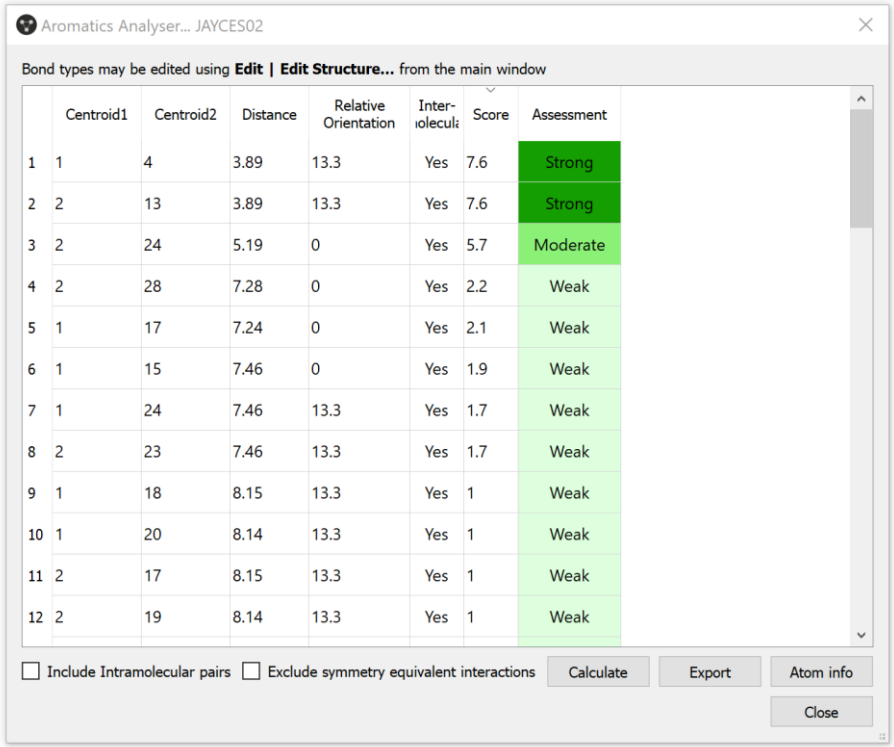
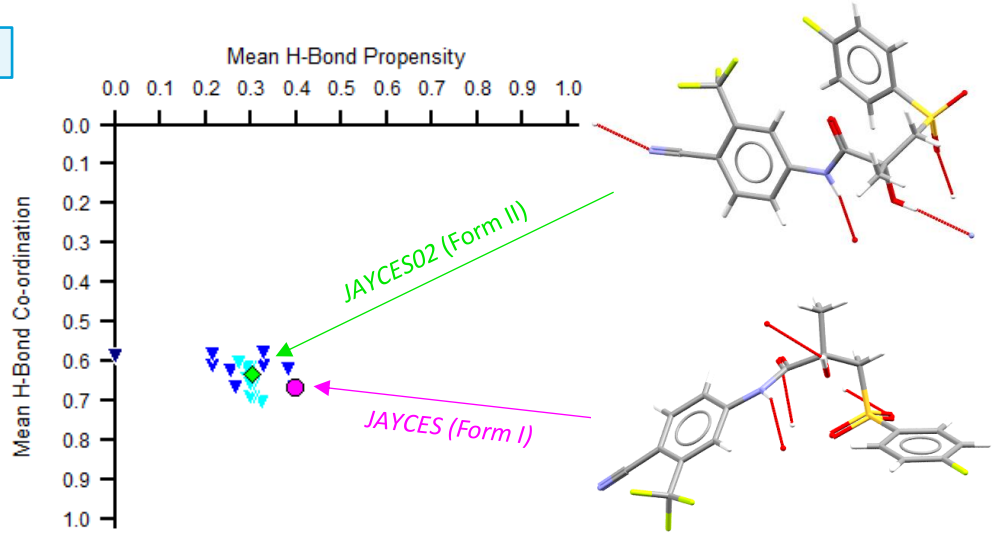


	Centroid1	Centroid2	Distance	Relative Orientation	Inter-olecula	Score	Assessment
1	1	4	3.89	13.3	Yes	7.6	Strong
2	2	13	3.89	13.3	Yes	7.6	Strong
3	2	24	5.19	0	Yes	5.7	Moderate
4	2	28	7.28	0	Yes	2.2	Weak
5	1	17	7.24	0	Yes	2.1	Weak
6	1	15	7.46	0	Yes	1.9	Weak
7	1	24	7.46	13.3	Yes	1.7	Weak
8	2	23	7.46	13.3	Yes	1.7	Weak
9	1	18	8.15	13.3	Yes	1	Weak
10	1	20	8.14	13.3	Yes	1	Weak
11	2	17	8.15	13.3	Yes	1	Weak
12	2	19	8.14	13.3	Yes	1	Weak

10



Example 2. 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 of The basic steps of calculating Aromatic Interactions).

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 that there are four stronger aromatic interactions, accompanied by a few moderately stabilising interactions and a range of weaker interactions.

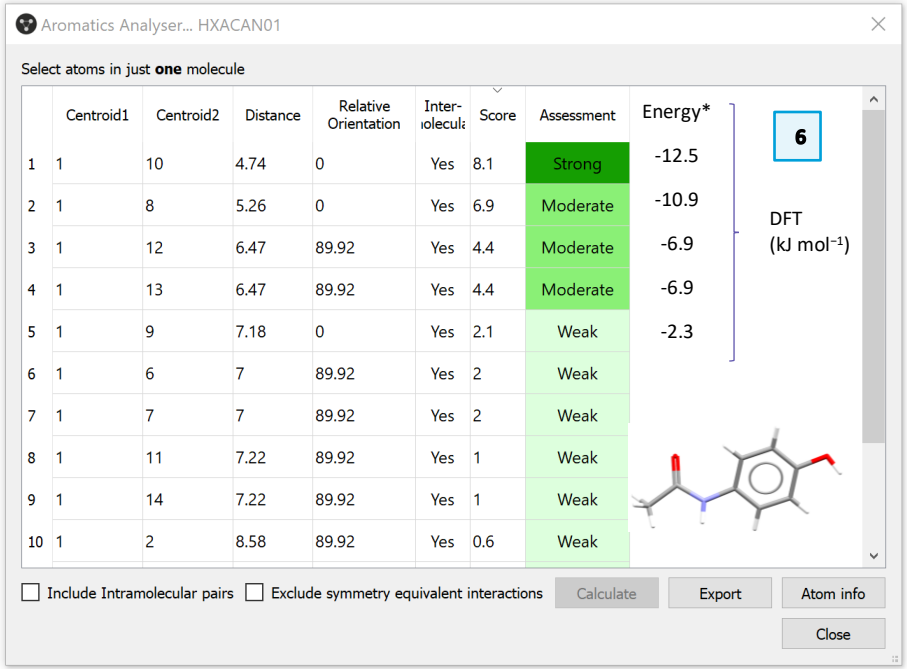
5. **Compare and contrast** the data on the aromatic interactions for Form I (*HXACAN01*) and Form II (*HXACAN*) of paracetamol. Both have a similar top-ranked interaction (similar score and distance). There are a larger number of high scores for *HXACAN* (strong interactions over close distances), although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



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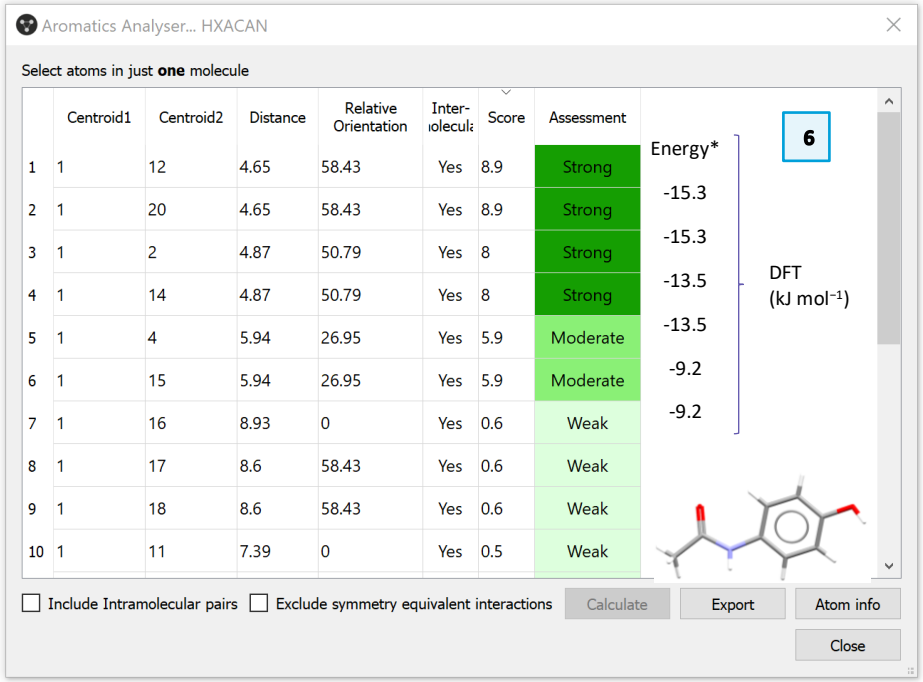


Summary

We have applied the *Aromatics Analyser* tool for polymorphic structures, containing both different H-bonding and the same H-bonding.

This has facilitated (1) easy visualisation and identification of aromatic interactions, and (2) a measure of quantitative assessment of their strength.

Further Exercises (Bonus)

- Analyse a structure of interest to you – what can you learn?
- Pick one of the examples and probe the aromatic interactions further in conjunction with another aspect (e.g. packing, hydrogen bonding, overlap of rings between molecules). What does it reveal?
- What would you consider bad / concerning / not well satisfied in terms of aromatic interactions?
- Is *quality* of aromatic interactions always more important than *quantity*?

Bonus Exercises. Polymorphs where aromatic interactions may be more relevant

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.

This example includes a case where there is limited and unfavourable information from other areas.

Example 3. 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.

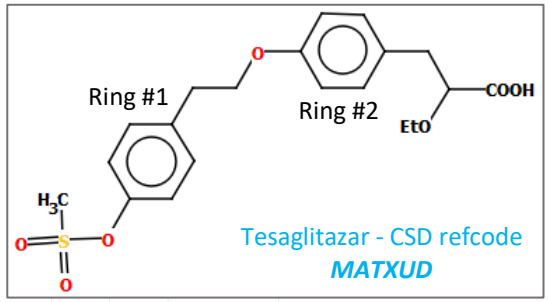
1. **Load the structure of tesaglitazar (*MATXUD*)**. Select the *MATXUD* molecule in Mercury and calculate the aromatic interactions (steps 1-5 for The basic steps of calculating Aromatic Interactions).

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). 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

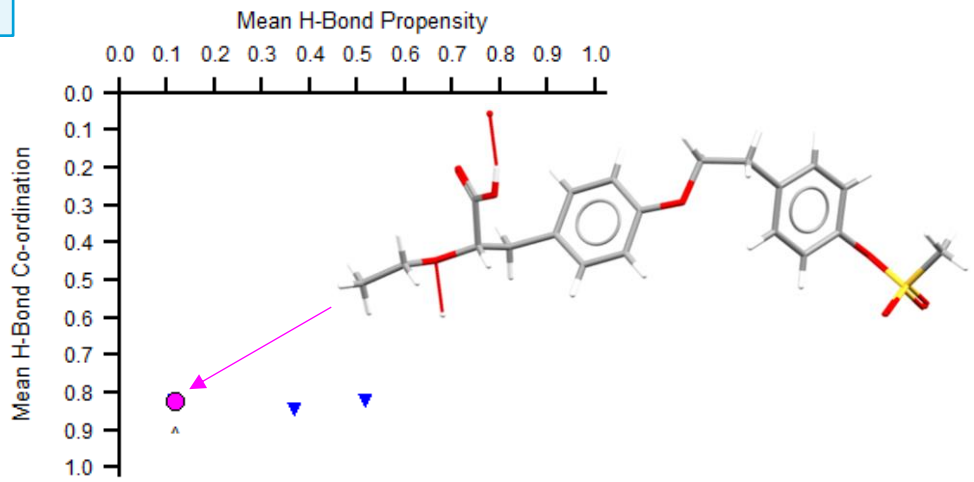


Aromatics Analyser... MATXUD

Select atoms in just **one** molecule

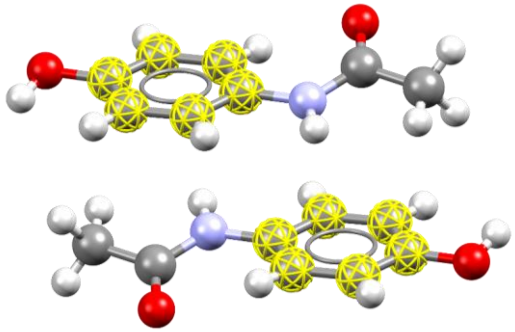
	Centroid1	Centroid2	Distance	Relative Orientation	Inter-olecul	Score	Assessment
1	1	15	5.16	58.54	Yes	6.5	Moderate
2	1	19	5.16	58.54	Yes	6.5	Moderate
3	1	3	5.76	0	Yes	6.3	Moderate
4	1	5	5.76	0	Yes	6.3	Moderate
5	1	16	5.78	82.59	Yes	5.1	Moderate
6	2	19	5.78	82.59	Yes	5.1	Moderate
7	2	4	5.76	0	Yes	5	Moderate
8	2	6	5.76	0	Yes	5	Moderate
9	2	28	7.34	28.22	Yes	2	Weak
10	2	30	7.34	28.22	Yes	2	Weak

3



Review. *Aromatics Analyser* Definitions

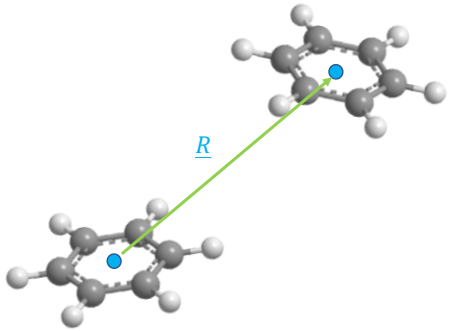
This uses a neural network model* to provide a score between 0 and 10 based on how stabilising an aromatic ring interaction is expected to be, and assessment into 'strong', 'moderate' and 'weak' interactions.



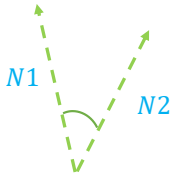
** The model is based on a geometric description of aromatic interactions involving the position of two benzene rings relative to each other, in order to estimate the associated energy with an aromatic interaction, presented as a 'score'. The influence of non-H substituents is not explicitly accounted 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.*

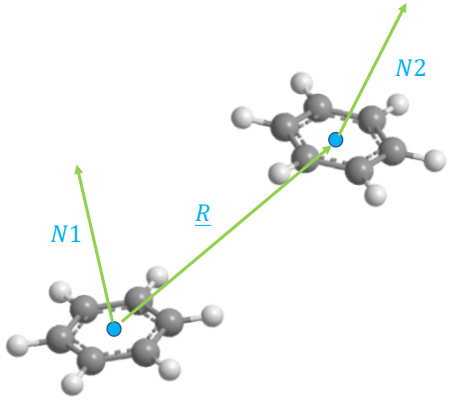
Packing shell:
van der Waals
radii +0.5 Å

Distance:
centroid-centroid
distance (Å)



Relative orientation:
angle between
ring normals (°)



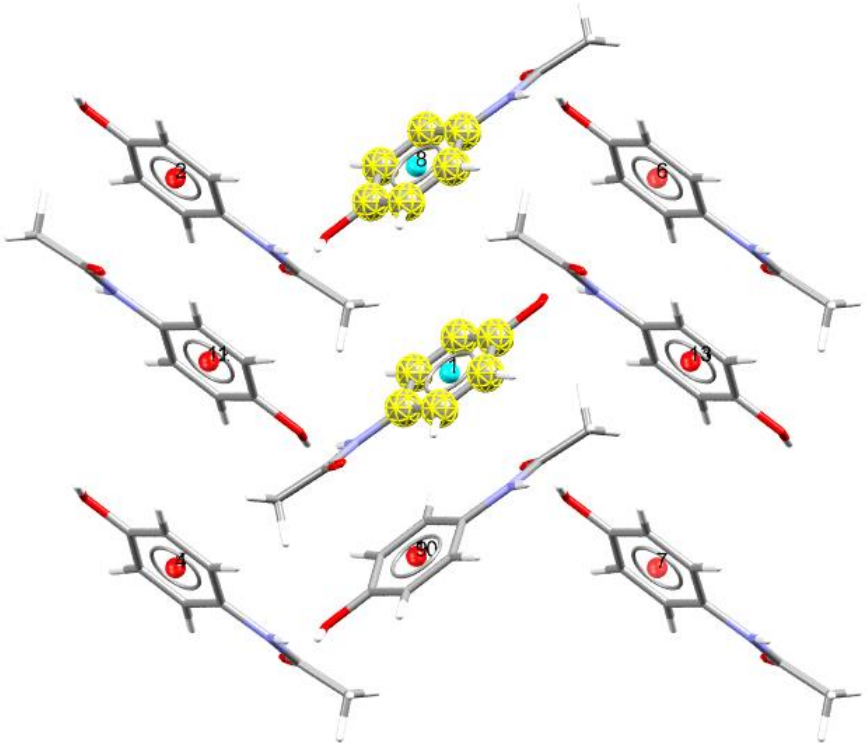


Aromatics Analyser score

- **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

Review. *Aromatics Analyser* interface

The *Aromatics Analyser* is interactive with the 3D visualiser in Mercury, and it 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)

Aromatics Analyser... HXACAN01

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

	Centroid1	Centroid2	Distance	Relative Orientation	Inter-olecula	Score	Assessment
1	1	10	4.74	0	Yes	8.1	Strong
2	1	8	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	9	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

Hover for info, click to re-order

☐ Include Intramolecular pairs ☐ Exclude symmetry equivalent interactions

Calculate | Export | Atom info | Close

Tailor which interactions are specified

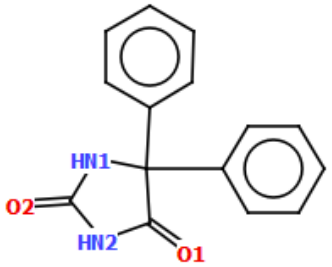
Save a .csv file

More info for atoms involved in interaction

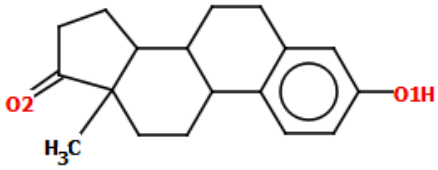
Review. Visualising aromatic interactions

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

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



Phenytoin - CSD refcode ***PHYDAN01***



Estrone - CSD refcode ***ESTRON11***

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

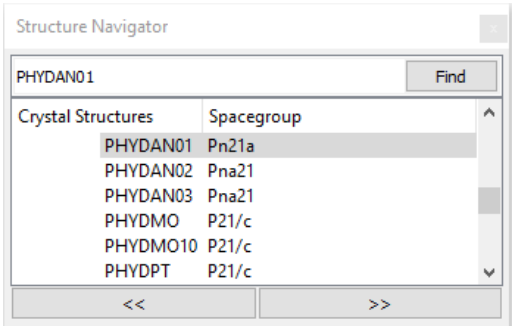
3. The structure will be displayed in the 3D visualiser.

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

5. Select one 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.

1

2



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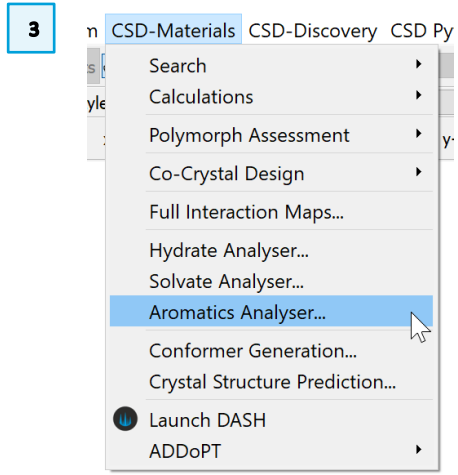

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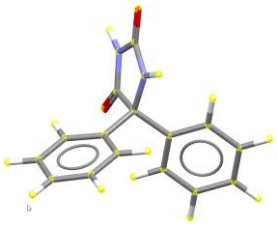
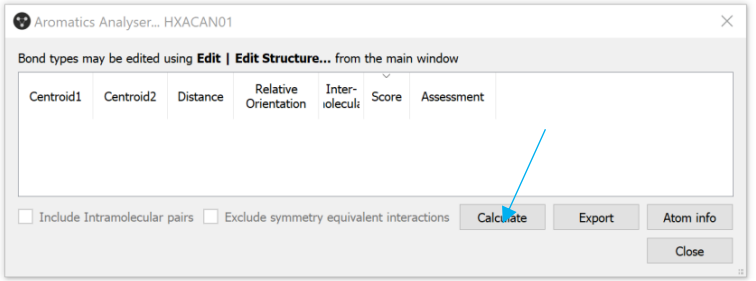




6. A table of data relating to the aromatic interactions found in *PHYDAN01* will now be displayed in the *Aromatics Analyser* dialog box. The refcode of the structure being analysed is displayed at the top of the dialogue box.

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 viewing the aromatic interactions present in the crystal structure and their associated geometric parameters.

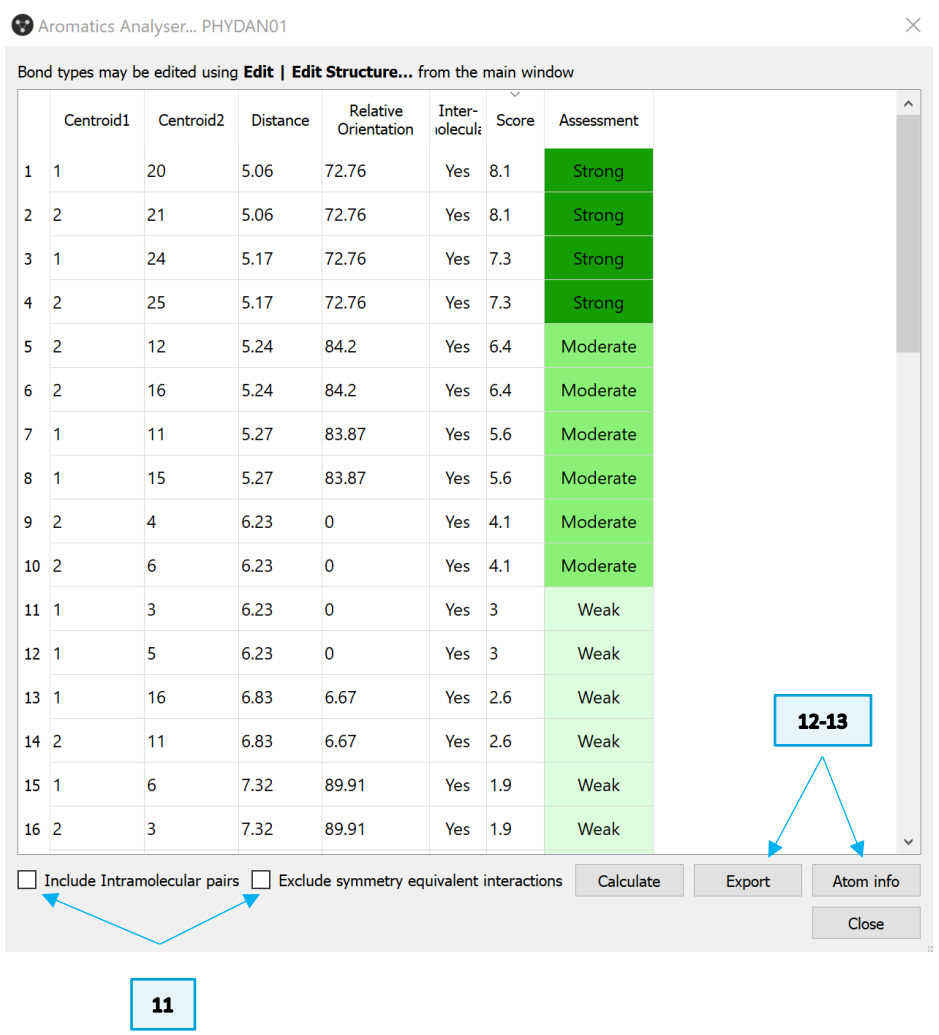
8. Data can be re-ordered by left-clicking in the desired column heading (e.g. high to low relative orientation).

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. 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-olecul	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	6.4	Moderate
6	2	16	5.24	84.2	Yes	6.4	Moderate
7	1	11	5.27	83.87	Yes	5.6	Moderate
8	1	15	5.27	83.87	Yes	5.6	Moderate
9	2	4	6.23	0	Yes	4.1	Moderate
10	2	6	6.23	0	Yes	4.1	Moderate
11	1	3	6.23	0	Yes	3	Weak
12	1	5	6.23	0	Yes	3	Weak
13	1	16	6.83	6.67	Yes	2.6	Weak
14	2	11	6.83	6.67	Yes	2.6	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.

16. 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.

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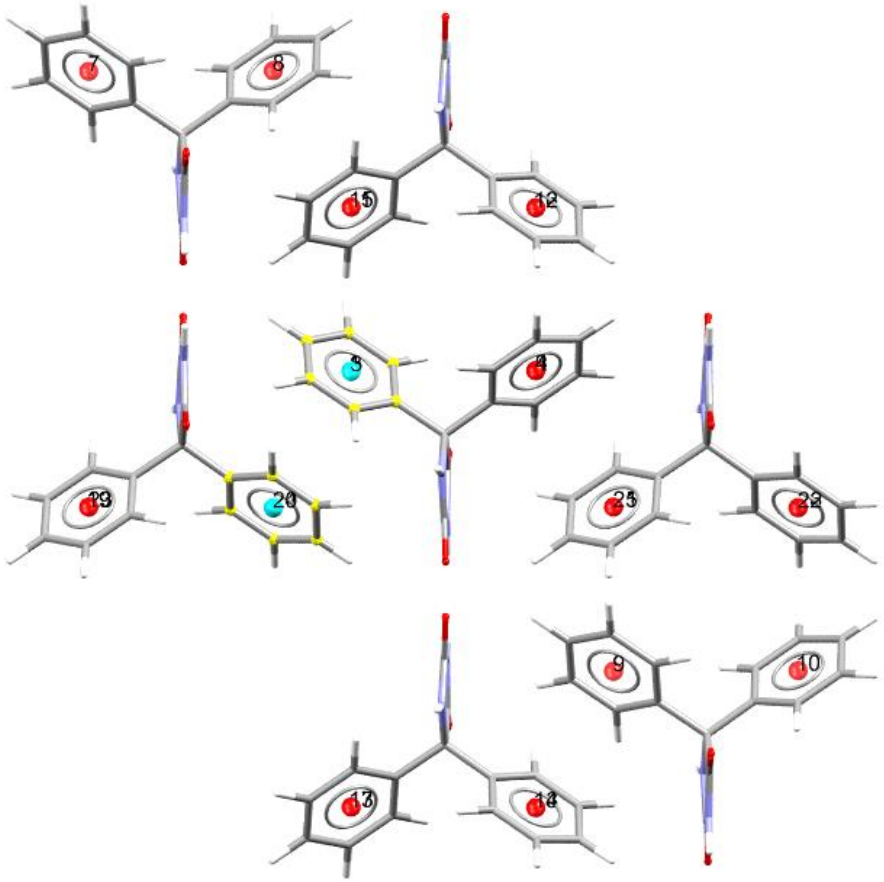


Further Exercises

- Look at the hydrogen bonding and aromatic interactions for *PHYDAN01* together to see how they complement one another

Example of less favourable aromatic interactions (*ESTRON11*)

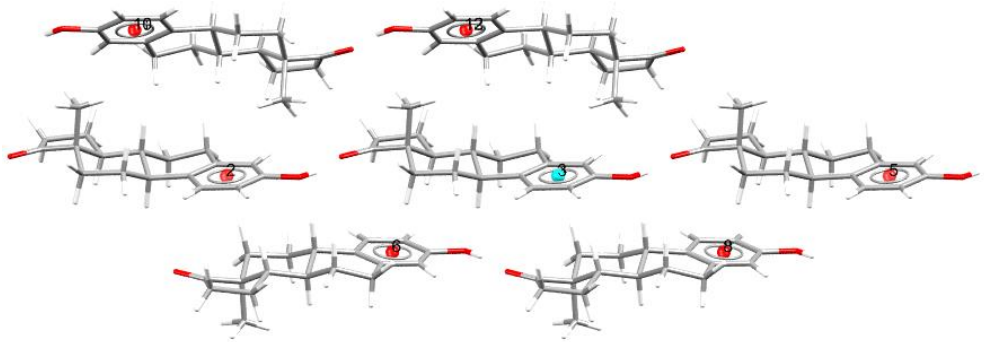
17. **To look at a different structure**, it must be selected in the 3D visualiser and the table updated by clicking Calculate.

18. **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.

19. 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.

20. 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**.**

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



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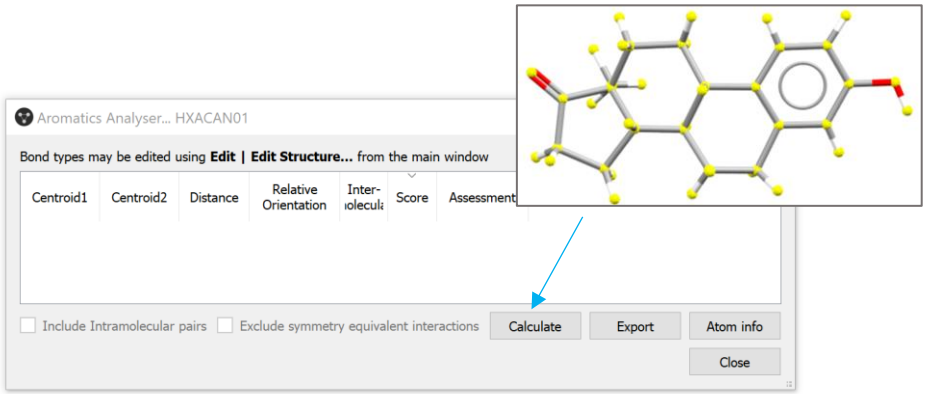

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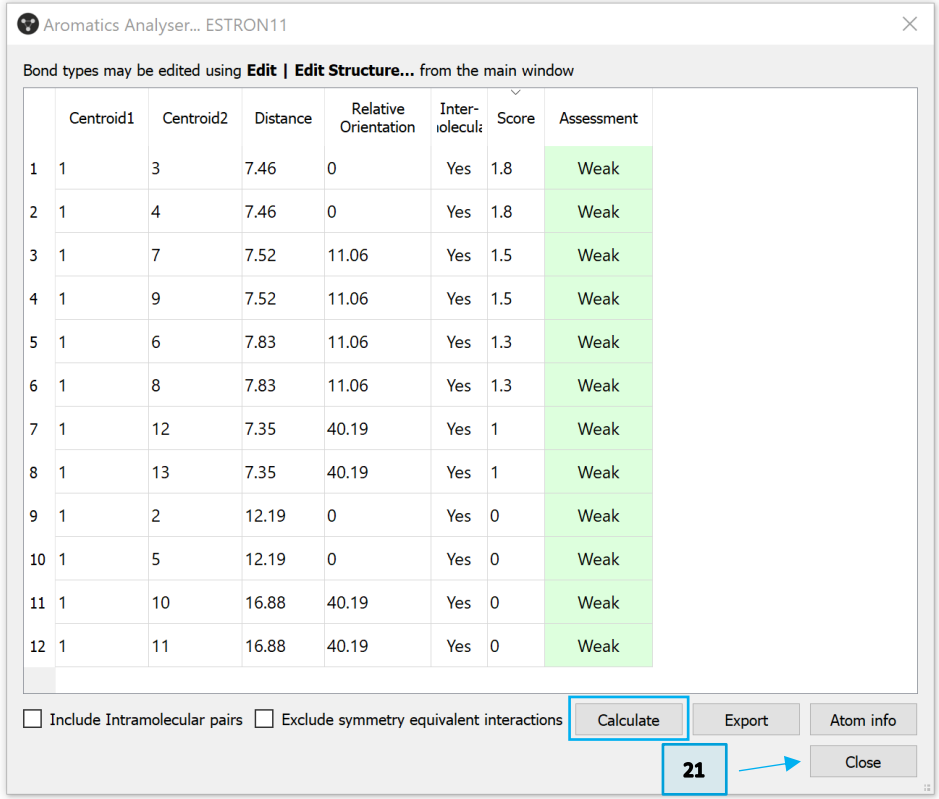


	Centroid1	Centroid2	Distance	Relative Orientation	Inter-	Score	Assessment
1	1	3	7.46	0	Yes	1.8	Weak
2	1	4	7.46	0	Yes	1.8	Weak
3	1	7	7.52	11.06	Yes	1.5	Weak
4	1	9	7.52	11.06	Yes	1.5	Weak
5	1	6	7.83	11.06	Yes	1.3	Weak
6	1	8	7.83	11.06	Yes	1.3	Weak
7	1	12	7.35	40.19	Yes	1	Weak
8	1	13	7.35	40.19	Yes	1	Weak
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

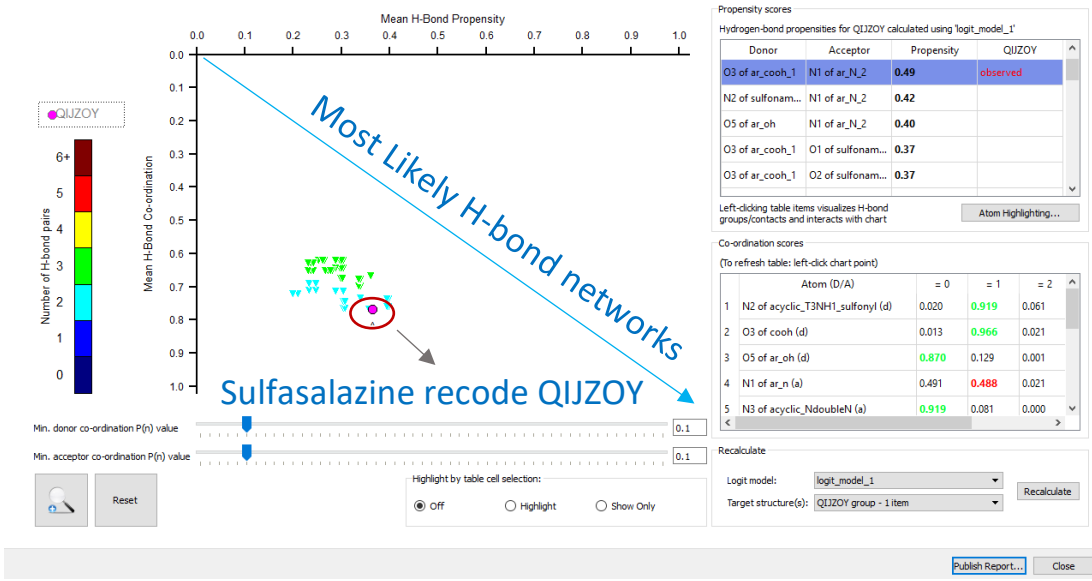
Dictionary

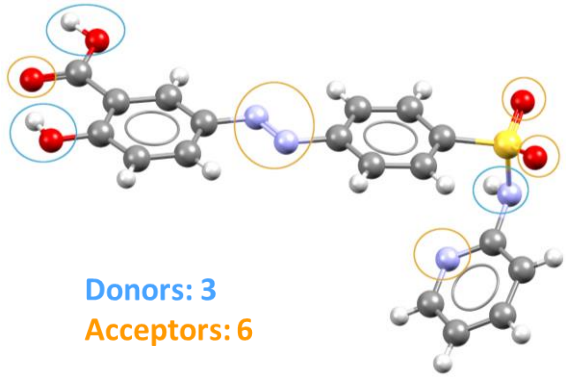
Hydrogen Bond Propensity (HBP)

- 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.

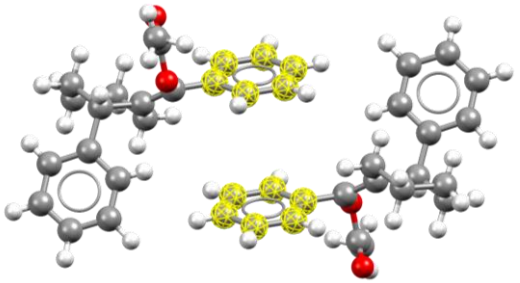
Van der Waals, Aromatic and Hydrogen Bond Interactions

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.

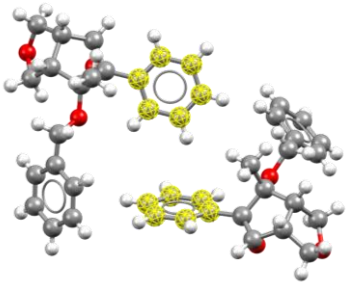
Aromatic Interactions are noncovalent interactions formed between aromatic rings. These interactions are important in material science since they will contribute to the overall crystal structure stability. The orientation of the aromatic ring can vary from parallel to T-shape, and we found during our 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**



Refcode AACMHX10
Parallel displacement
DFT: -11.037 kJ/mol



Refcode PAGBUX
T-shape
DFT: -11.427 kJ/mol