

How to analyse small molecules interactions with Full Interaction Maps



CCDC Virtual Workshop Summer 2021 – Session 2

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Khaled Takieddin, Eva Myers, Andy Maloney

July 2021

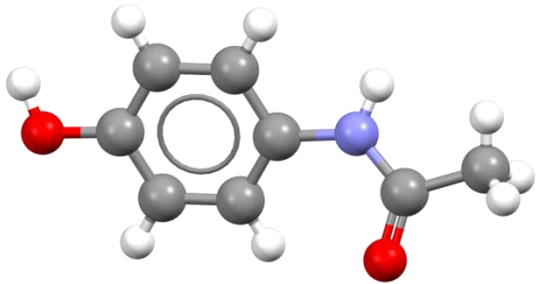


CCDC
advancing structural science

Learning outcomes for today

- Learn how informatics and data-driven approaches can be used to understand the solid state
- Familiarise yourself with what tools are available in the CSD-Materials suite and what they can be used to do
- Learn how to use Full Interaction Maps to analyse a structure

Solid form selection in product development

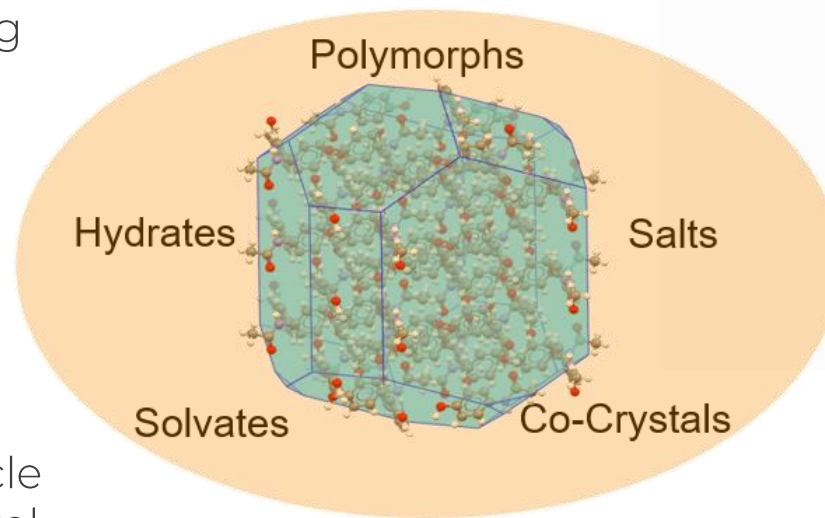


Melting
Point

Solubility

Particle
Control

Chemical & Physical Stability



Product Process
Control

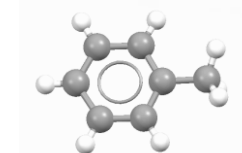
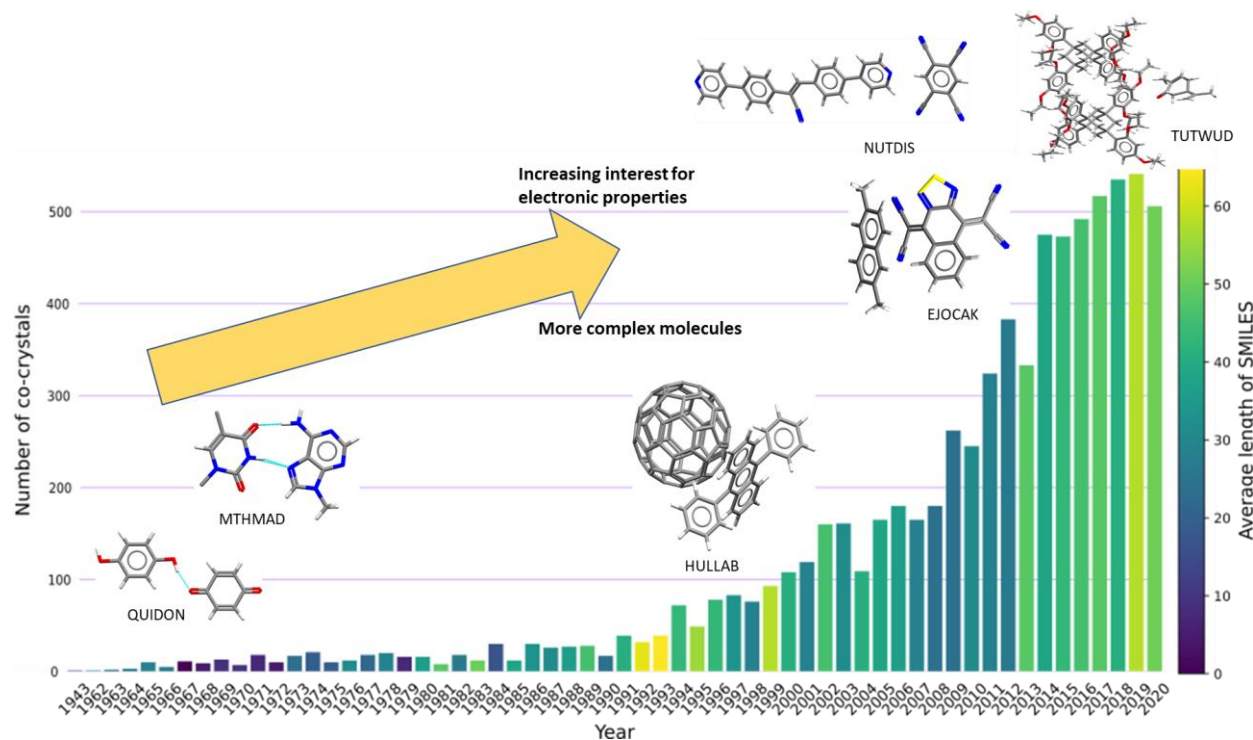
Morphology

Mechanical
Properties

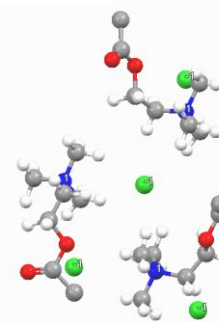
Purification



A wealth of data in the CSD

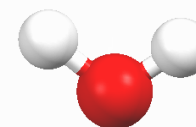


Solvates
>230,000

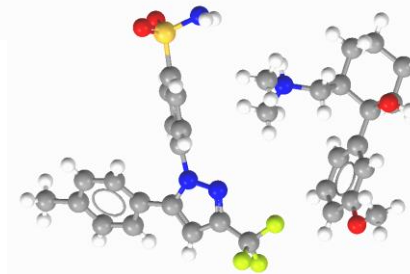


Salts

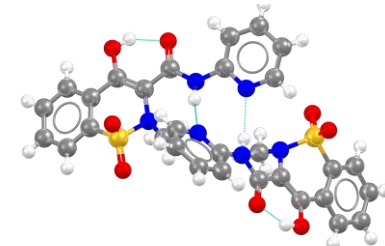
Hydrates
>140,000



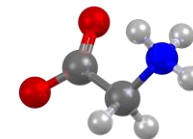
Co-Crystals



Polymorphs
>11,000 polymorphic families



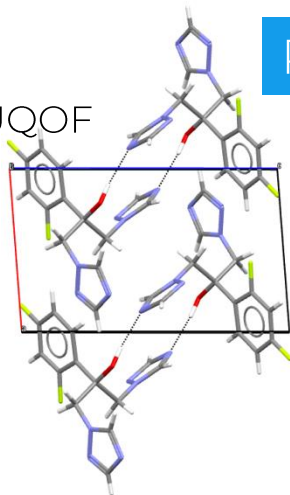
Refcode families
>1,000,000



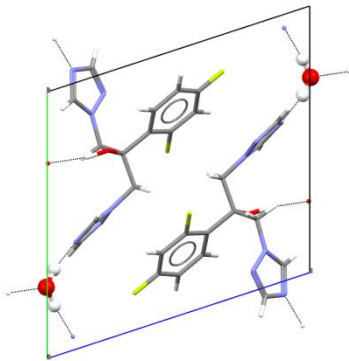
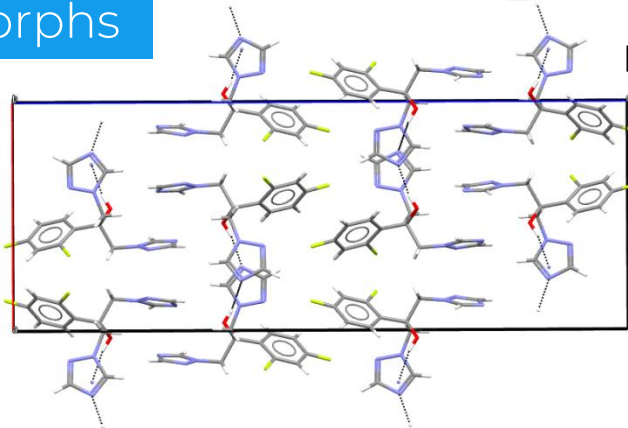
A solid form landscape

Polymorphs

IVUQOF



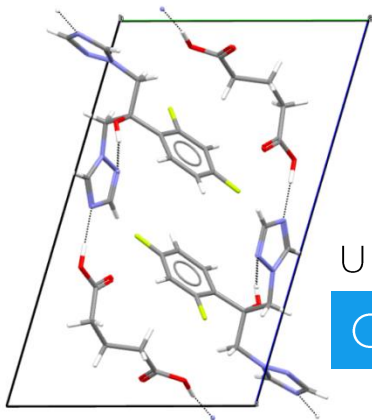
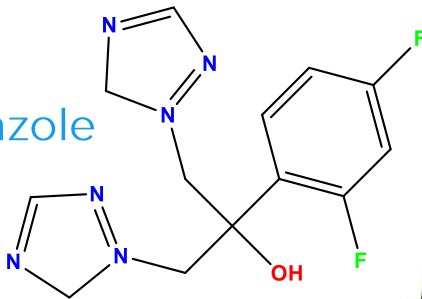
IVUQOF02



IVUQIZ

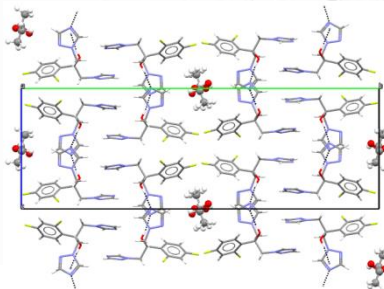
Hydrates

fluconazole



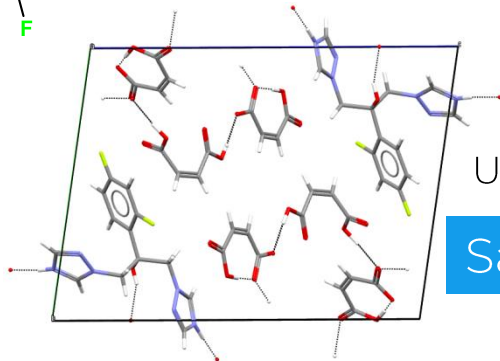
UPOQEW

Co-crystals



IVUQEV

Solvates



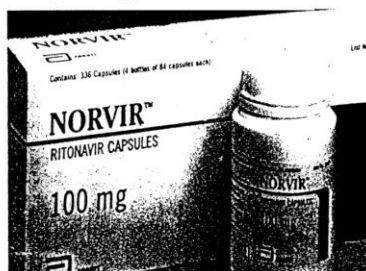
UPOQAS

Salts

Impact of Hydrogen Bonding on lattice stability -The Ritonavir story

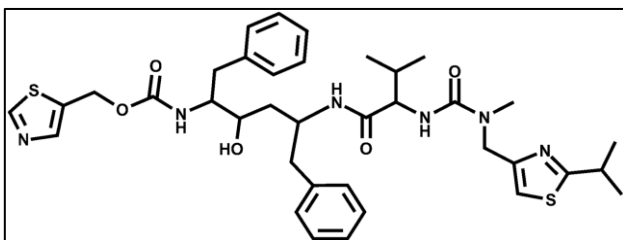
Manufacturing problems hit Abbott's HIV drug ritonavir

Capsules of Abbott Laboratories' protease inhibitor Norvir (ritonavir) are likely to become unavailable by the middle of August. The company has a problem with the manufacture of the anti-HIV capsules which it cannot resolve at present.

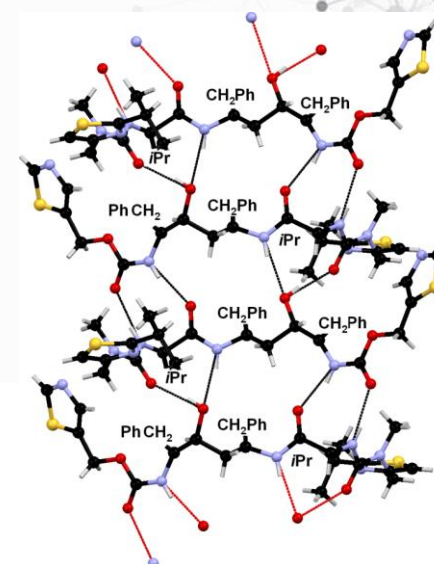
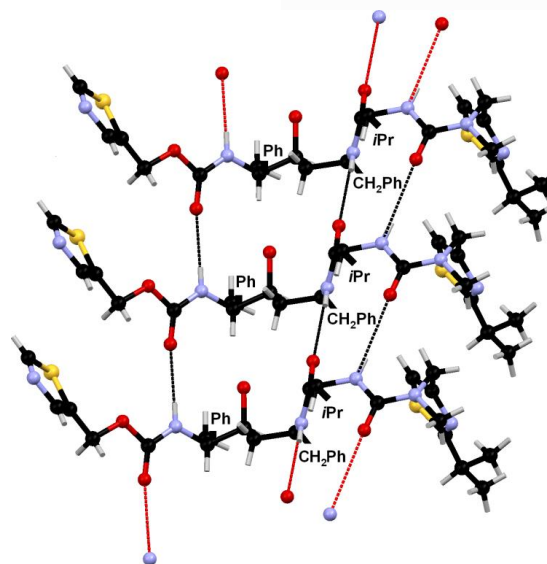


Capsules unlikely to be available from mid-August

The problem relates to "undesirable" crystal formation. Abbott says that a series of capsules from a number of marketed batches of capsules were examined and there was no



- ~5-fold decrease in solubility
- Change in Hydrogen Bonding



"Since the strength and completeness of the hydrogen bonding has attained the maximum possible in the Form II lattice, it is not thought possible that another undiscovered polymorph of ritonavir would exist with equivalent or lower solubility than that of Form II."

Structural Informatics

Which is the stable wall?

The
CCDC
c.1992



A

Great
Pyramid
of Giza
c.2560 BC

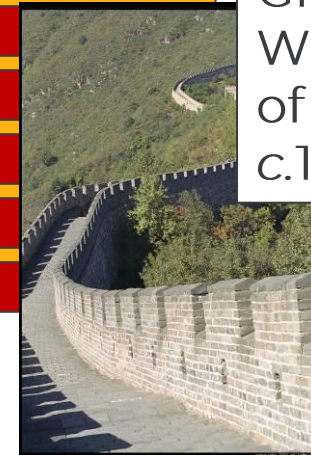


B

Hadrian's Wall
c.122



Great
Wall
of China
c.1368



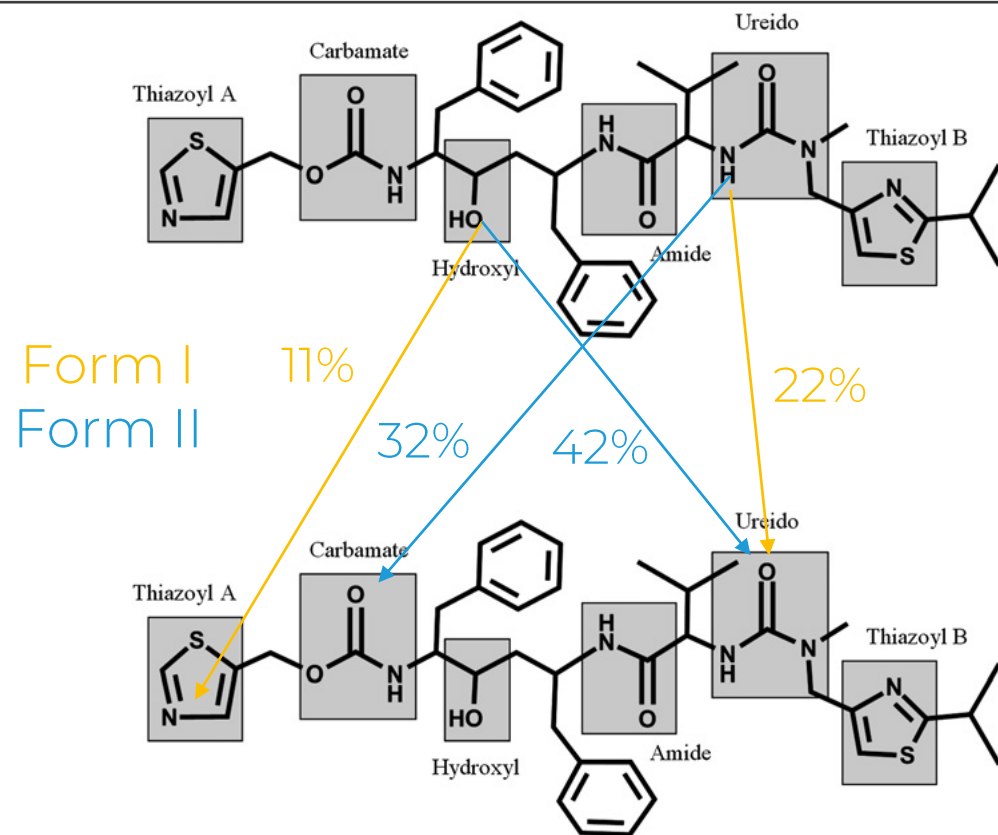
My
House
c.1967



The database of walls indicates that A is the frequently observed arrangement and therefore we can predict it is the most stable form

Predicting unlikely interactions

Predictive analytics is used to identify the likelihood of specific molecular interactions occurring from similar crystal structures



The integration of solid-form informatics into solid-form selection

Neil Feeder^a, Elna Pidcock^a, Anthony M. Reilly^a, Ghazala Sadiq^a, Cheryl L. Doherty^b, Kevin R. Back^b, Paul Meenan^c and Robert Docherty^b

One in half a million: a solid form informatics study of a pharmaceutical crystal structure

[Peter T. A. Galek](#),^{*a} [Elna Pidcock](#),^a [Peter A. Wood](#),^a [Ian J. Bruno](#)^a and [Colin R. Groom](#)^a

Navigating the Solid Form Landscape with Structural Informatics

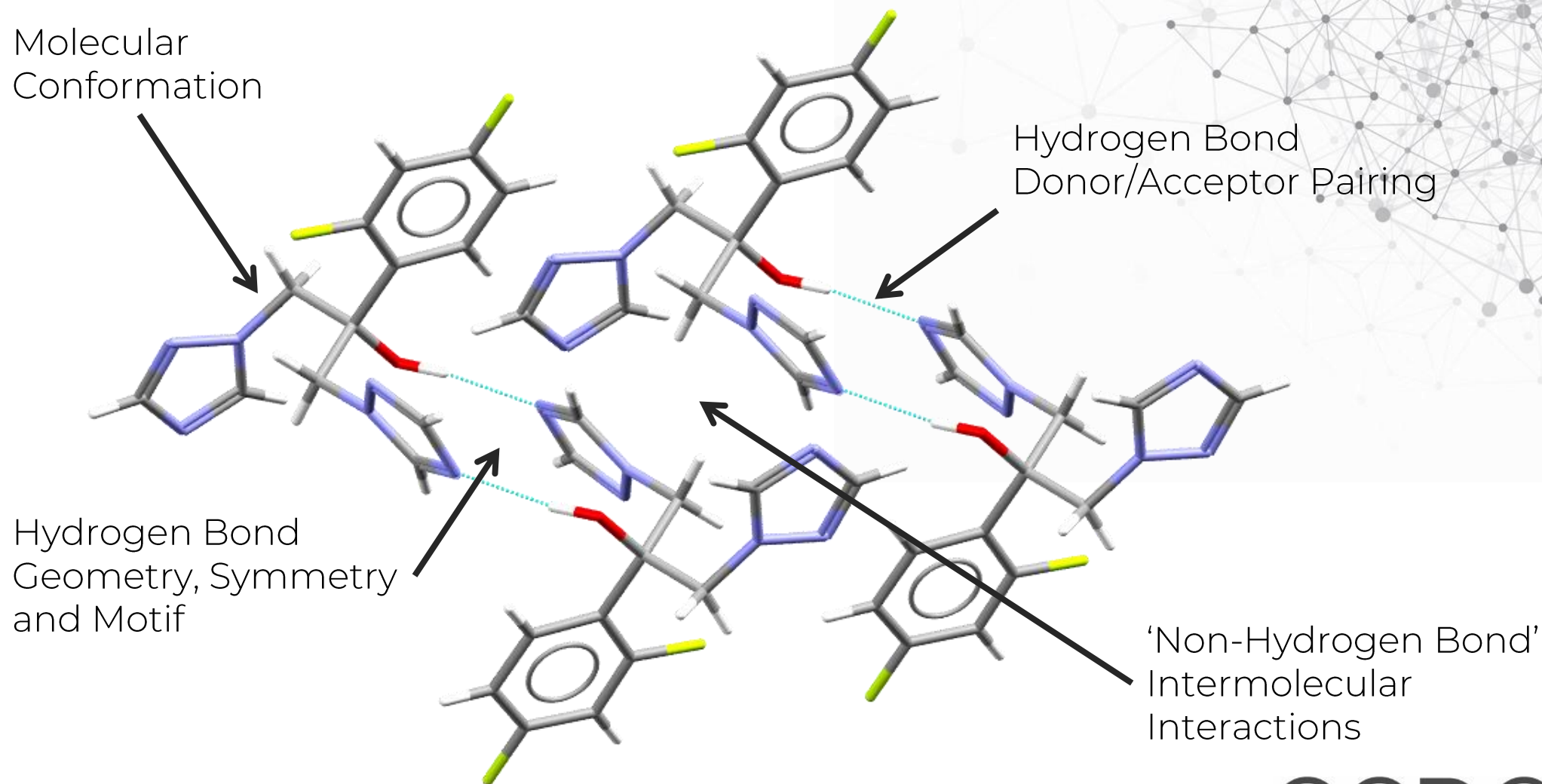
[Peter T. A. Galek](#), [Elna Pidcock](#), [Peter A. Wood](#), [Neil Feeder](#), [Frank H. Allen](#)

Book Editor(s): [Yuriy A. Abramov](#)

Knowledge-based H-bond prediction to aid experimental polymorph screening

[Peter T. A. Galek](#),^{*ab} [Frank H. Allen](#),^a [László Fábián](#)^{ab} and [Neil Feeder](#)^c

Characteristics that influence stability



The CSD software

CSDEnterprise.

CSDMaterials.



DASH



Python API



Mercury

CSDDiscovery.



SuperStar



Python API



GOLD



CrossMiner



Mercury

CSDCore.



WebCSD



Mogul



MyStructures



ConQuest



CSD



IsoStar



Mercury



Hermes



Python API

CSDCommunity.



Mercury



enCIFer



Symmetry



Deposit



CellCheck



Educational



Access



MyStructures

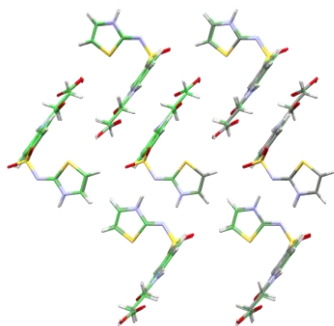
Professional
Services

Research
& Knowledge
partnerships

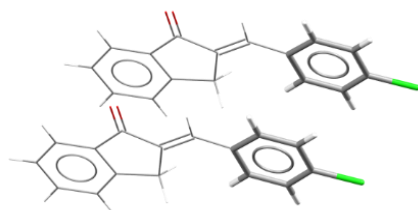
CSD-Materials overview



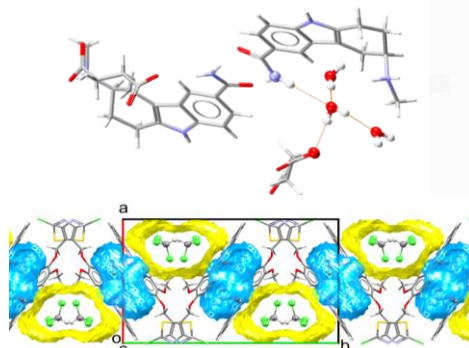
23



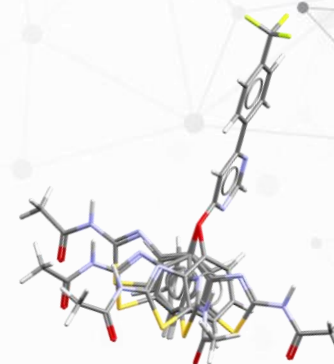
Crystal Packing
Similarity



Motif Search &
Packing Feature Search



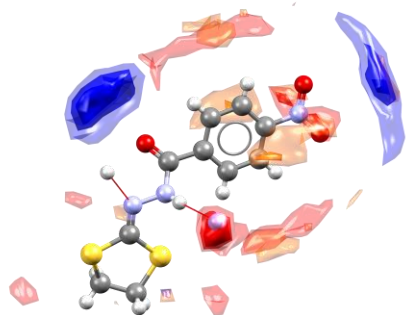
Hydrate Analyser &
Solvate Analyser



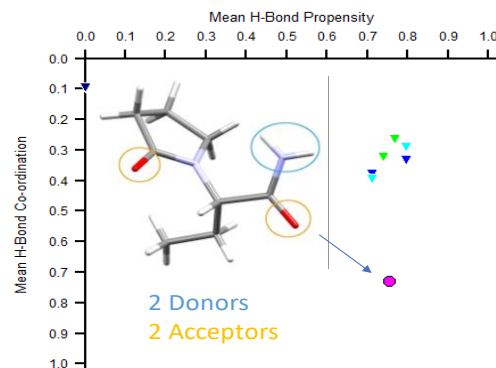
CSD Conformer
Generator

Detailed Structural Analysis

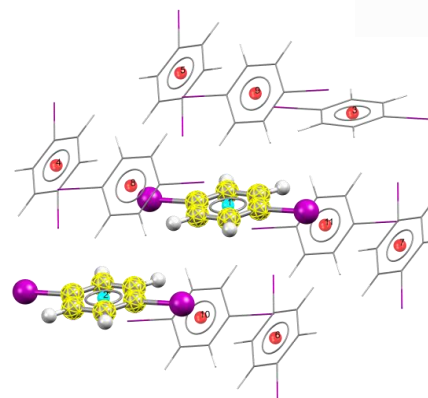
Solid Form Design



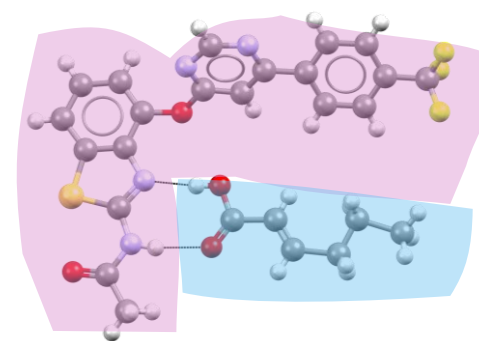
Full Interaction Maps



Hydrogen Bond Propensity



Aromatics Analyser



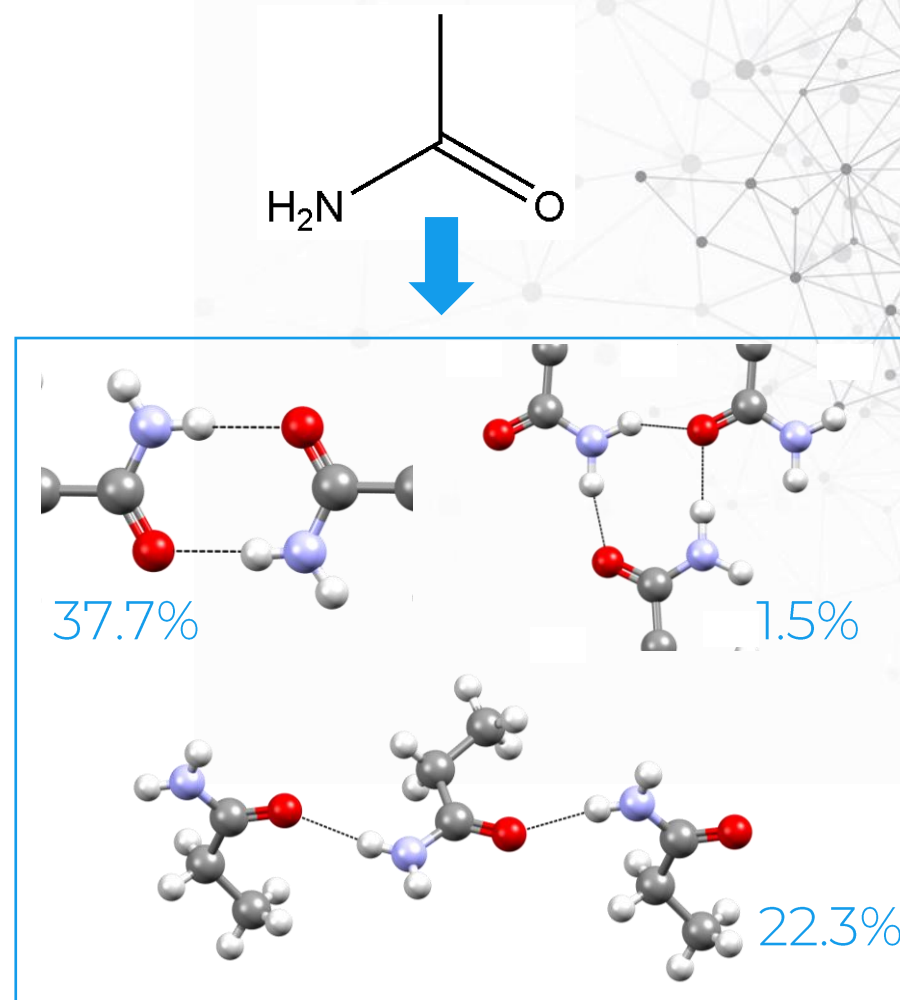
Molecular
Complementarity

Solid Form Risk Assessment

CCDC

Motifs

- Determine likely hydrogen bond motifs for a specified set of functional groups
- Assess motifs by their relative frequency of occurrence in the CSD
- Search for auto-generated and bespoke motifs
- Analyse the results of crystal structure prediction runs by identifying the range of predicted motifs



Frequency of occurrence of Primary Amide hydrogen bond motifs

Searching for motifs

CSD Refcode: JURZOO

JURZOO (C2) - Mercury

File Edit Selection Display Calculate CSD-Community CSD-Core CSD-Materials CSD-Discovery CSD Python API Help

Picking Mode: Lasso Atoms

Style: Ball and Stick Colour: by Element

Animate... Default view: b a b c a* b*

Search

- Calculations
- Polymorph Assessment
- Co-Crystal Design
- Full Interaction Maps...
- Hydrate Analyser...
- Solvate Analyser...
- Aromatics Analyser...
- Conformer Generation...

Motifs...

- Crystal Packing Feature...
- Crystal Packing Similarity...
- Manage Searches...
- Manage Motifs...

Search Options

Motif Search Wizard

Select the motif(s) you would like to search for

Select one of the following options and then press 'Next'. To build your own motifs 'Create' option.

Select motif option

- ☒ Select pre-defined motif(s)
- ☐ Create new motifs
- ☐ Open a motif file (gmxml, mxml)

Display Options

Display

- ☒ Packing
- ☐ Asymmetric Unit
- ☐ Auto centre
- ☐ Short Contact < (sum of vdW radii)
- ☐ H-Bond Default definition

hydrogens ☐ cell axes ☐ atoms ☐

Next Cancel

Press the left mouse button and move the mouse to rotate the structure

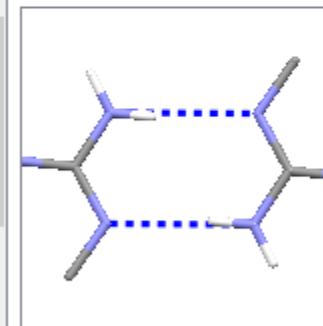
Select search motifs

Use the 'select' button to select motif search queries from the list of available motifs.

beta lactam chain
gamma lactam chain
delta lactam chain
hydroxy chain
trans amide chain
oxime R2,2(6)
NCCNH2 R2,2(10)
amino nitrile R2,2(10)
OCCOH R2,2(10)
COCONH R2,2(10)
SOOCH3 R2,2(8)
pyrazole R2,2(6)
pyrazole R3,3(9)
CONH2 R2,3(8)
CONH2 R2,3(8)

Select Motif

De-select Motif



NCNH2 R2,2(8)

homomeric

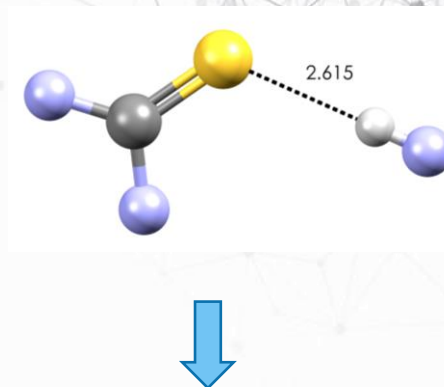
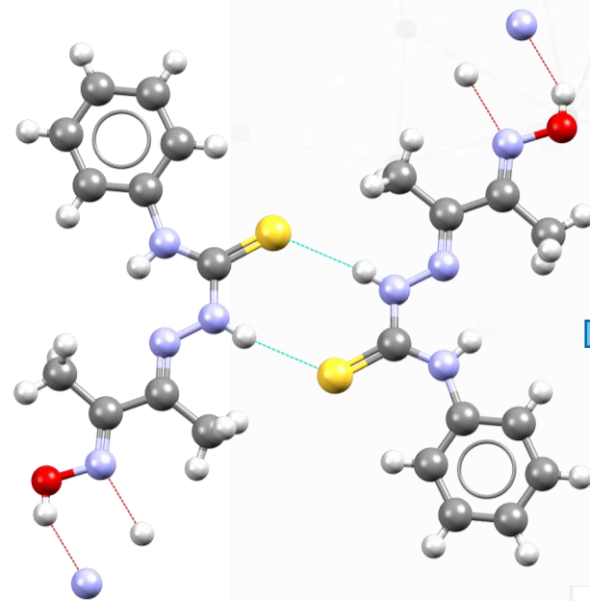
NCNH2 R2,2(8)

Next

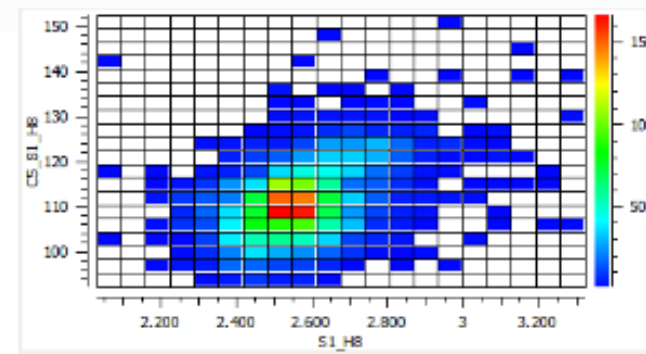
Cancel

Crystal Packing Feature Search

- Perform a substructure search
- Investigate conformations of molecules or bonded fragments
- Search for non-covalent interactions such as π - π or hydrogen bond interactions
- Search for particular spatial arrangements of functional groups
- Search for particular spatial arrangements of molecules



Query for S...H-N
interaction as found in
a thioamide derivative
(DUXXOJ01)



Searching for packing features

JURZOO (C2) - Mercury

File Edit Selection Display Calculate CSD-Community CSD-Cgre CSD-Materials CSD-Discovery CSD Python API Help

Picking Mode: Lasso Atoms

Style: Ball and Stick Colour: by Element

Animate... Default view: b a b c a* b*

Search

- Motifs...
- Crystal Packing Feature...
- Crystal Packing Similarity...
- Manage Searches...
- Manage Motifs...
- Post Search Options

Calculations

Polymorph Assessment

Co-Crystal Design

Full Interaction Maps...

Hydrate Analyser...

Solvate Analyser...

Aromatics Analyser...

Conformer Generation...

Launch DASH

Packing Feature Search Wizard

Allow variable atom and bond types

Select the atoms and bonds you wish to vary and press 'Modify'. Or simply press 'Next'.

atoms bonds

atom	residue	elements	hydrogen	bonds
N2	1	N	2	3
H1	1	H		1
N1	1	N	0	2
H2	1	H		1
H1	2	H		1
N2	2	N	2	3
H2	2	H		1
N1	2	N	0	2
C1	2	C	0	3
C1	1	C	0	3

Search Options

Modify

Reset

Add Constraint

- ☒ Number of hydrogens
- ☒ Number of bonds
- ☐ Charge
- ☐ Cyclicity

Next Cancel

Display Options

Display

- ☒ Packing
- ☐ Asymmetric Unit
- ☐ Auto centre

Short Contact < (sum of vdW radii)

H-Bond Default definition

Reset

Options

- ☒ Show hydrogens
- ☒ Show cell axes
- ☐ Label atoms
- ☐ Depth cue
- ☐ Z-Clipping
- ☐ Stereo

Contacts...

More Info

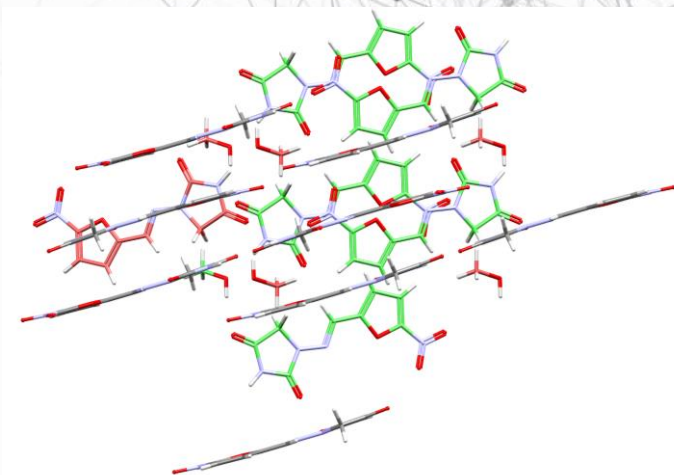
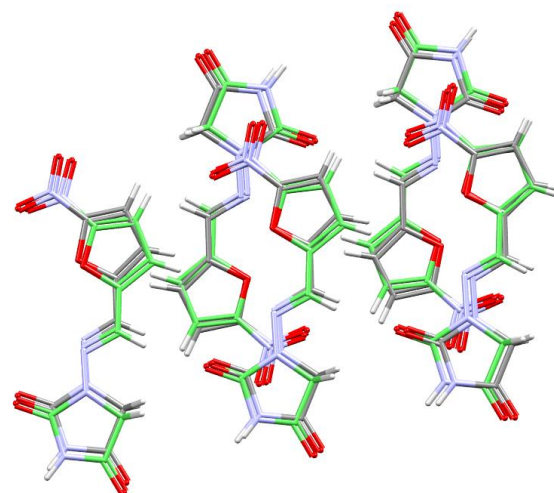
Powder...

Press the left mouse button and move the mouse to rotate the structure

CCDC

Crystal Packing Similarity

- Determine whether two crystal structures are the same
- Identify, from a list of structures, the number of distinct polymorphic forms
- Identify iso-structurality in solvates, salts, hydrates & co-crystals
- Find an experimentally observed structure within a prediction list
- Quantify similarity between polymorphs, solvates, salts, hydrates & co-crystals



Packing Similarity analysis for:

- Nitrofurantoin (Refcode: AZAXEG)
- and its hydrated structure (Refcode: ULECAQ)

Molecules depicted in:

- green show the match between the two structures
 - 5 out of 15 molecules are a match
- pink show where they differ

Searching for packing similarity

CSD Refcodes: JURZOO
JURZOO01

JURZOO (C2) - Mercury

File Edit Selection Display Calculate CSD-Community CSD-Cgre CSD-Materials CSD-Discovery CSD Python API Help

Picking Mode: Lasso Atoms

Style: Ball and Stick Colour: by Element

Animate... Default view: b a b c a* b*

Search

- Motifs...
- Crystal Packing Feature...
- Crystal Packing Similarity...
- Manage Searches...
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- Post Search Options

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Solvate Analyser...

Aromatics Analyser...

Conformer Generation...

Launch DASH

Packing Similarity Wizard

Select structures to compare

This tool allows you to identify similarity in crystal packing between structures containing the same compound. All structures added to the 'reference' list will be compared with all structures added to the 'comparison' list.

Reference Structures

JURZOO
JURZOO01

Select...
Add Refcode...
Remove

Comparison Structures

JURZOO
JURZOO01

Select...
Add Refcode...
Remove

Compare Next Cancel

Display Options

Display

☒ Packing ☐ Short Contact < (sum of vdW radii)

☐ Asymmetric Unit ☐ H-Bond Default definition

☐ Auto centre

Reset

Options

☒ Show hydrogens ☐ Depth cue

☒ Show cell axes ☐ Z-Clipping

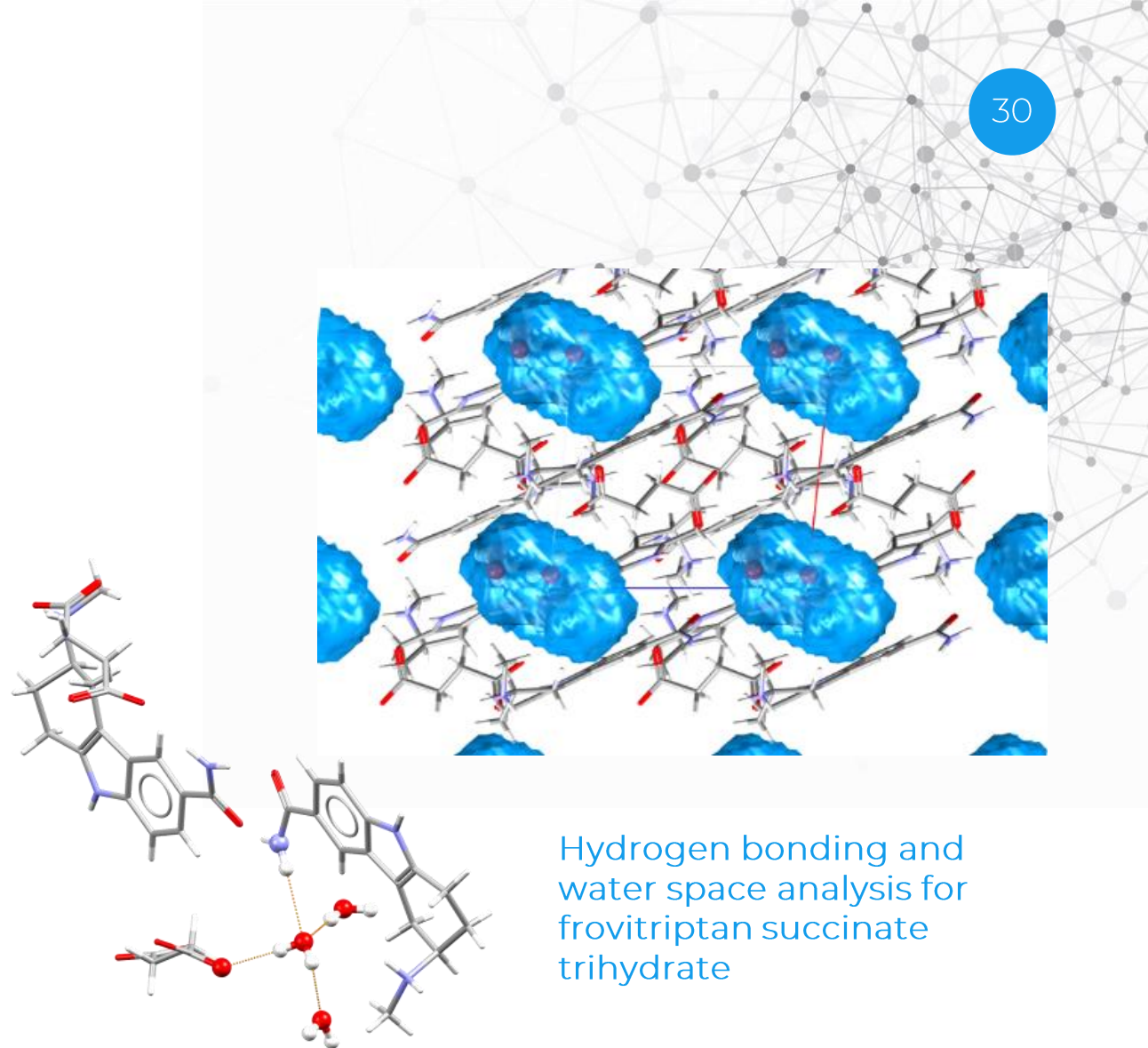
☐ Label atoms ☐ Stereo

Contacts...
More Info
Powder...

Press the left mouse button and move the mouse to rotate the structure

Hydrate Analyser

- Quickly obtain a summary describing features of a hydrated phase
- Assess hydrogen bonding motifs involving water molecules
- Interpret the space occupied in the lattice by water molecules
- Analyse extended structural features such as coordination polymers including water
- Obtain reports on the assessments made



Hydrogen bonding and water space analysis for frovotriptan succinate trihydrate

CSD Refcode: AAGAGG10

Using the Hydrate Analyser

AAGAGG10 (P212121) - Mercury

File Edit Selection Display Calculate CSD-Community CSD-Core CSD-Materials CSD-Discovery CSD Python API Help

Picking Mode: Lasso Atoms

Style: Ball and Stick Colour: by Element

Animate... Default view: b a b c a* b*

Search
Calculations
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Co-Crystal Design
Full Interaction Maps...
Hydrate Analyser...
Solvate Analyser...
Aromatics Analyser...
Conformer Generation...
Launch DASH

Labels for: All atoms

Atom selections: -90 y+90 z-90 z+90 < >

Structure Overview Water H-Bonding Water Space Water Interaction Maps Coordination Polymer

Current structure: AAGAGG10

	Motif #	Hits	Thumbnail
1	zero	0	
2	one_d	0	
3	two_dd	0	
4	three_a	0	
5	four_aa	0	
6	five_dda	2	
7	six_ddaa	0	
8	seven_da	0	
9	eight_daa	0	
10	nine_ddaaa	0	

Row selection shows 3D search hits

Browse multiple hits (of 0): 0

Highlighting style...

Close

Display Options

Display

☒ Packing ☐ Short Contact < (sum of vdW radii)

☐ Asymmetric Unit ☐ H-Bond Default definition

☐ Auto centre

Reset

Options

☒ Show hydrogens ☐

☒ Show cell axes ☐

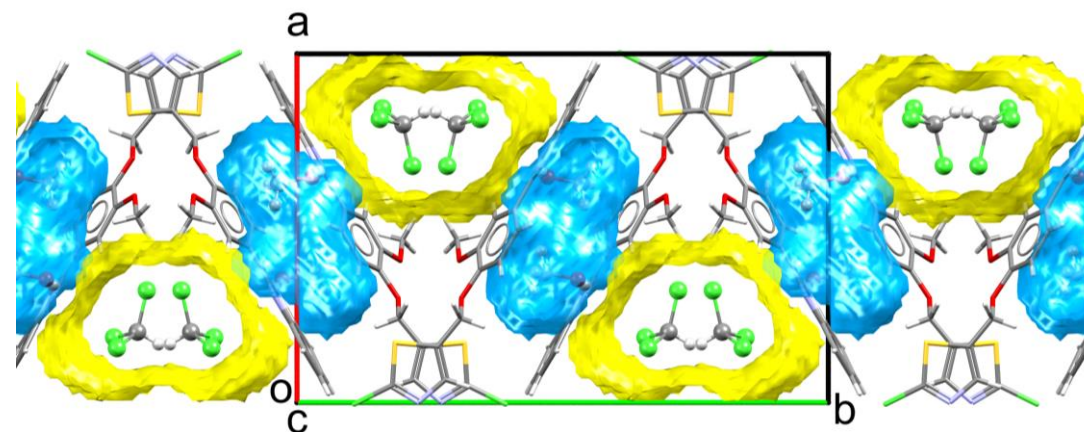
☐ Label atoms ☐

Contacts... More Info Powder...

Press the left mouse button and move the mouse to rotate the structure

Solvate Analyser

- Quick analysis of the structures containing one or more solvent molecules
- Easy selection of solvent molecule(s)
- Assessment of any hydrogen bonding motifs to/from the solvents
- Calculation and display of the space occupied by each of the different solvent molecules
- Obtain reports on the assessments made



Using the Solvate Analyser

ZOJLIV (P212121) - Mercury

File Edit Selection Display Calculate CSD-Community CSD-Cgre CSD-Materials CSD-Discovery CSD Python API Help

Picking Mode: Lasso Atoms

Style: Ball and Stick Colour: by Element

Animate... Default view: b a b c a* b*

Search
Calculations
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Solvate Analyser...
Aromatics Analyser...
Conformer Generation...
Launch DASH

Solvate Analyser

Solvent Selection and Space Calculation Solvent H-Bonding Structure Summary

Add Solvent From Selected Remove Solvent Calculate Space

	1	2	3
Solvent	Ethanol	Acetonitrile	Water
Formula	C ₂ H ₆ O ₁	C ₂ H ₃ N ₁	H ₆ O ₃
Volume (%)	6.7	5.6	4.2
Volume (Å³)	327.64	274.87	206.52
Show Space	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Show Solvent	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Select Solvent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Inside Colour			
Inside Opacity	0.45	0.45	0.45
Outside Colour			
Outside Opacity	0.45	0.45	0.45

☐ Hide all molecules Packing...

Settings

Probe Radius: 1.2 Å

Approx. Grid Spacing: 0.3 Å

Calculate using the Contact Surface

Results

Volume 16.5 % of unit cell volume

809.03 Å³

Defaults

Close

Display Options

Display

☒ Packing ☐ Short Contact < (sum of vdW radii)

☐ Asymmetric Unit ☐ H-Bond Default definition

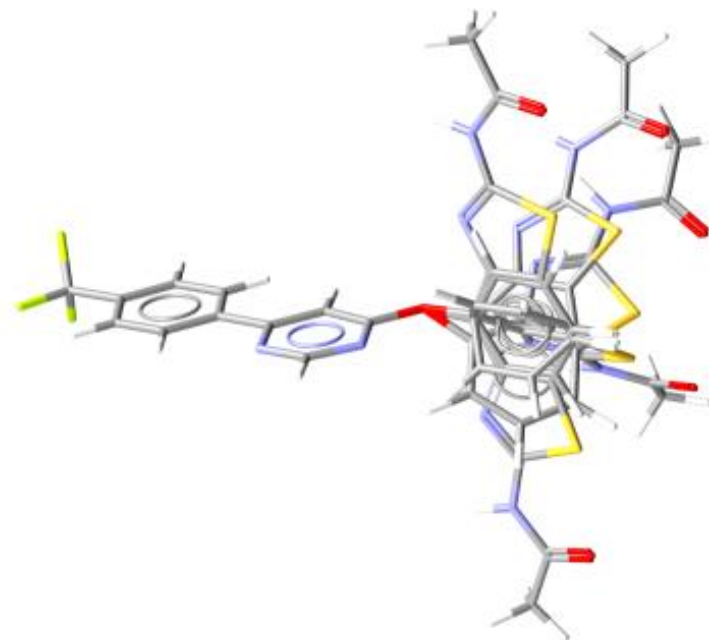
☐ Auto centre

Reset

Press the left mouse button and move the mouse to rotate the structure

CSD Conformer Generator

- Generate conformers based on geometrical statistics from the CSD
- Visualise overlays of generated conformers
- Export conformers and further analyse e.g. in a co-crystal screen



Ensemble of diverse conformations of AMG517 generated by the CSD conformer generator.

Generating conformers

JURZOO (C2) - Mercury

File Edit Selection Display Calculate CSD-Community CSD-Cgre CSD-Materials CSD-Discovery CSD Python API Help

Picking Mode: Lasso Atoms

Style: Ball and Stick Colour: by Element

Animate... Default view: b a b c a* b*

Search
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Hydrate Analyser...
Solvate Analyser...
Aromatics Analyser...
Conformer Generation...
Launch DASH

Labels for: All atoms with
Atom selections:

Maximum Number of Conformations: 200
Maximum Unusual Rotamers: 2
Maximum Conformations to Sample: 1000000
Minimum Rotamer Probability: 0.05
Minimise input molecule: ☒

Source molecule
☒ From Mercury: JURZOO
☐ From file: Browse

Working directory
C:\temporary Browse

Output format(s)
☒ mol2 ☐ sdf

☒ Show advanced options

Defaults

Conformer Generator status
Click "Calculate" to start

Calculate

Close

Display Options

Display
☒ Packing
☐ Asymmetric Unit
☐ Auto centre
☐ Short Contact < (sum of vdW radii)
☐ H-Bond Default definition

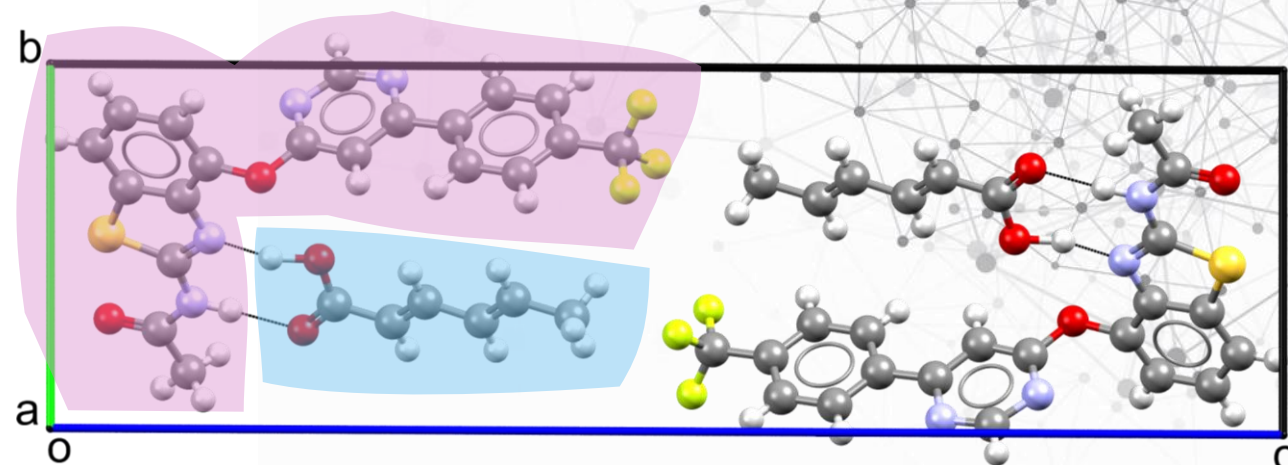
Options
☒ Show hydrogens
☒ Show cell axes
☐ Label atoms
☐ Depth cue
☐ Z-Clipping
☐ Stereo

Contacts...
More Info
Powder...
Reset

Press the left mouse button and move the mouse to rotate the structure

Molecular complementarity co-former screening

- Rapidly screen a set of co-formers against an Active Ingredient
- Assess how molecular descriptors vary across a set of molecules
- Submit multiple conformations of one or more molecules and compare them
- Designed to filter out molecules **unlikely** to form co-crystals



	ML axis ratio	S axis (Å)	SL axis ratio	Dipole Moment (/Debye)	Fraction of NO
Sorbic Acid	0.50	4.17	0.38	1.03	0.25
AMG 517	0.66	6.46	0.35	1.65	0.20
AMG 517:Sorbic Acid Delta	0.16	2.29	0.03	0.62	0.05
Delta Pass Criteria	<0.32	<3.2	<0.28	<5.8	<0.29
AMG 517:Sorbic Acid Delta Meets Criteria	Yes	Yes	Yes	Yes	Yes

Performing molecular complementarity

JURZOO (C2) - Mercury

File Edit Selection Display Calculate CSD-Community CSD-Cgre CSD-Materials CSD-Discovery CSD Python API Help

Picking Mode: Lasso Atoms

Style: Ball and Stick Colour: by Element

Animate... Default view: b a b c a* b*

Search
Calculations
Polymorph Assessment
Co-Crystal Design
Full Interaction Maps...
Hydrate Analyser...
Solvate Analyser...
Aromatics Analyser...
Conformer Generation...
Launch DASH

Labels for: All atoms with Atom Label

Atom selections:

Screen by Molecular Complementarity...

Display Options

Display

☒ Packing ☐ Short Contact < (sum of vdW radii)

☐ Asymmetric Unit ☐ H-Bond Default definition

☐ Auto centre

Reset

Options

☒ Show hydrogens ☐ Depth cue

☒ Show cell axes ☐ Z-Clipping

☐ Label atoms ☐ Stereo

Contacts...
More Info
Powder...

Press the left mouse button and move the mouse to rotate the structure

Molecular Complementarity Screening Wizard

Configure Settings

Use this tool to help identify molecules most likely to form co-crystals with one or more candidate active molecules.

Note that the method has only been validated on neutral molecules.

Please cite [this article](#).

Descriptor Settings

☒ Fraction N, O atoms ☒ M/L axis ratio

☒ S axis ☒ Dipole moment magnitude

☒ S/L axis ratio

Output Settings

Create: ☒ Multi-mol2 ☐ Folder of mol2s

For:

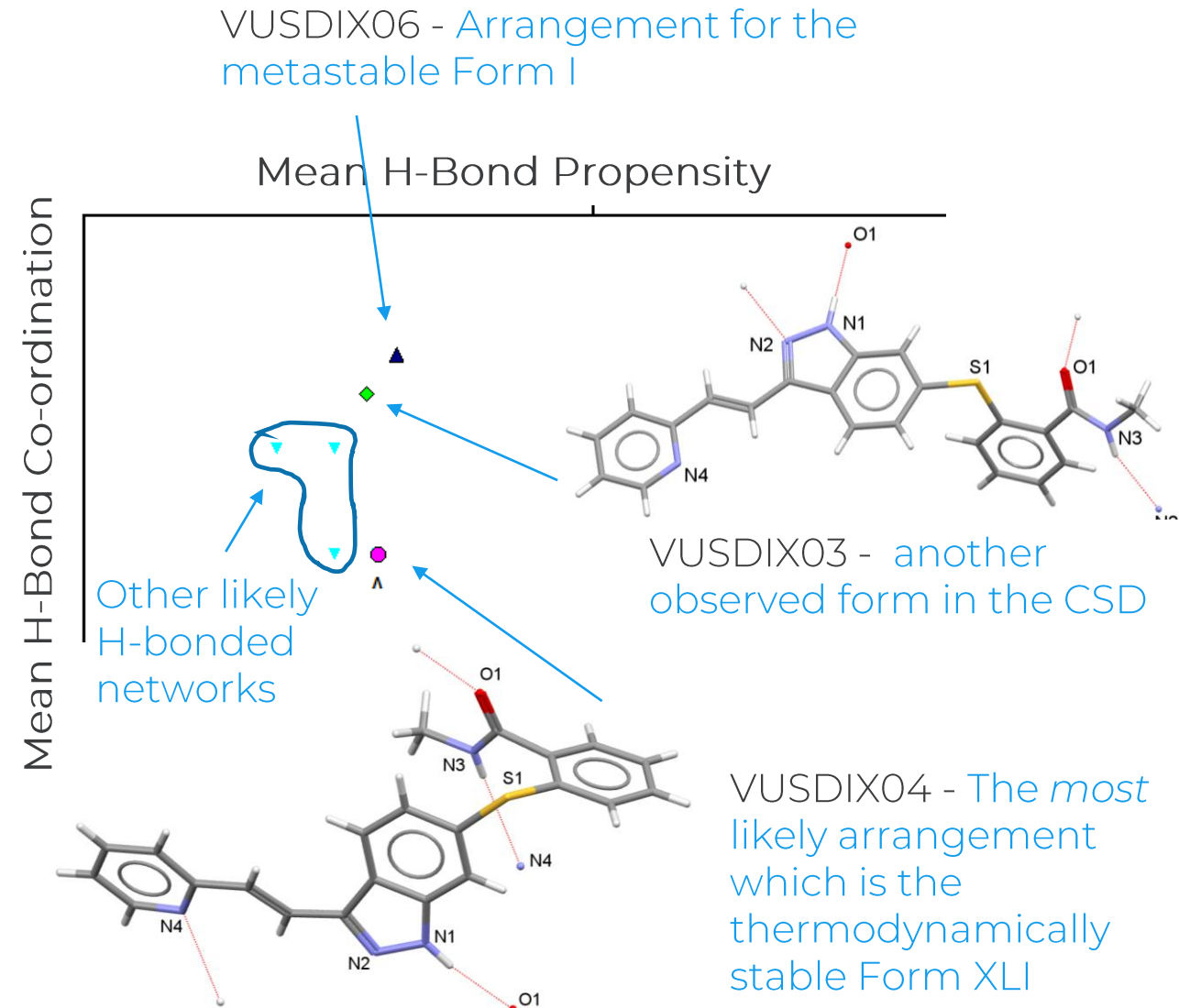
☒ Molecules which pass

☐ Molecules which fail

Working directory:

Hydrogen Bond Propensity

- 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



Calculating a Hydrogen Bond Propensity

CSD Refcode: JURZOO

JURZOO (C2) - Mercury

File Edit Selection Display Calculate CSD-Community CSD-Cgre CSD-Materials CSD-Discovery CSD Python API Help

Picking Mode: Lasso Atoms

Style: Ball and Stick Colour: by Element

Animate... Default view: b a b c a* b*

Search

Calculations

Polymorph Assessment

Co-Crystal Design

Full Interaction Maps...

Hydrate Analyser...

Solvate Analyser...

Aromatics Analyser...

Conformer Generation...

Launch DASH

Show Labels for All atoms with Atom Label

Atom selections:

Hydrogen Bond Propensities...

H-bond Coordination Quick-view

Propensity Prediction Wizard

Target Selection and Functional Group Definition

Working directory: C:/Users/ward Browse...

☒ Show advanced options

Functional group library: C:/Program Files/CCDC/CSD_2021/Mercury/functional_groups Browse...

Selected databases: CSD 5.42, Feb21 Select...

Hydrogen bond definition: Edit...

Use existing regression data: Load... Clear

Update Structure

Donors and acceptors

Donors: N2, N5

Acceptors: Cl1, Cl2, O1, N1, N2, N3, N5

Functional groups

Matched from libra...
acyclic_ar_et...
ar_cl
ar_N_NH2
pyrazoline_2
saturated_rin...

Add... Sketch... Load... Edit... Remove Remove All

✓ All donors and acceptors matched

Display Options

Display

☒ Packing

☐ Asymmetric Unit

☐ Auto centre

Reset

Short Contact < (sum of vdW radii)

H-Bond Default definition

Contacts... More Info Powder...

Options

☒ Show hydrogens

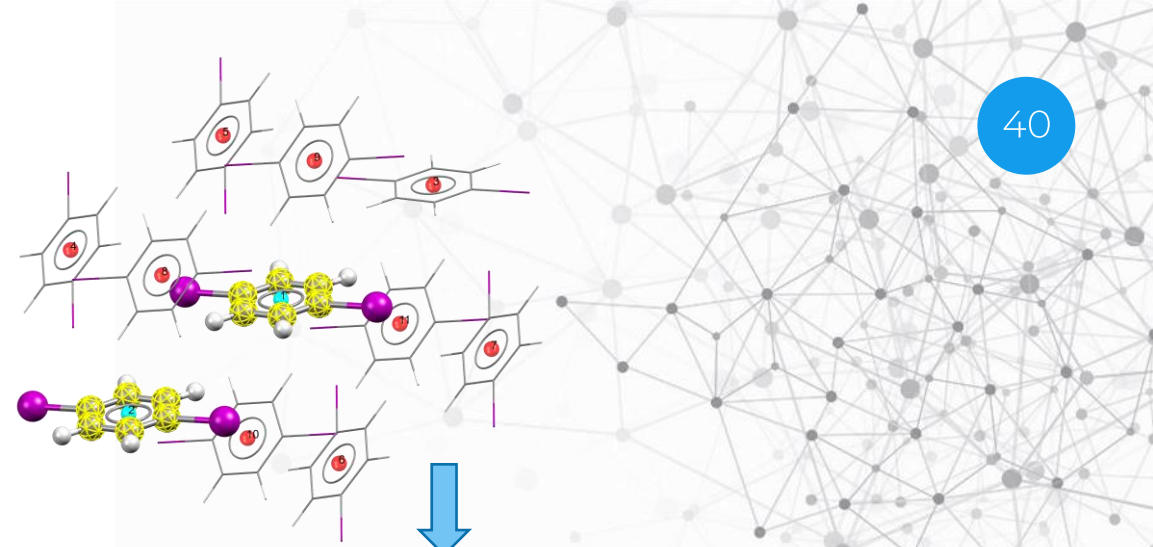
☒ Show cell axes

☐ Label atoms

Press the left mouse button and move the mouse to rotate the structure

Aromatics Analyser

- Intuitive visualisation & quantitative scoring of aromatic interactions
- Provides guidance on which geometries result in stabilising aromatic interactions
- Quantitative assessment provides score between 0 (no stabilising contribution) and 10 (an ideal aromatic interaction)
- Based on an Artificial Neural Network trained against DFT calculations



Aromatics Analyser... ZZZPRO03

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

	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecu	Score	Assessment
1	1	8	4.79	46.23	Yes	8.3	Strong
2	1	9	4.79	46.23	Yes	8.3	Strong
3	1	10	4.79	46.23	Yes	8.3	Strong
4	1	11	4.79	46.23	Yes	8.3	Strong
5	1	2	6.17	0	Yes	5.2	Moderate
6	1	3	6.17	0	Yes	5.2	Moderate
7	1	4	9.04	43.74	Yes	0.5	Weak
8	1	5	9.04	43.74	Yes	0.5	Weak

☐ Include Intramolecular pairs
 ☐ Exclude symmetry equivalent interactions
 Calculate
Export
Atom info

Close

Using the Aromatics Analyser

The screenshot displays the HXACAN (Pcab) - Mercury software interface. The main window shows a 3D molecular model of a complex organic structure with atoms labeled 1 through 13. A blue arrow points from the 'Aromatics Analyser...' option in the 'CSD-Materials' menu to the 'Aromatics Analyser... HXACAN' window.

The 'Aromatics Analyser... HXACAN' window displays a table of results for selected atoms in just one molecule. The table includes columns for Centroid 1, Centroid 2, Distance, Relative Orientation, Inter-molecular, Score, and Assessment.

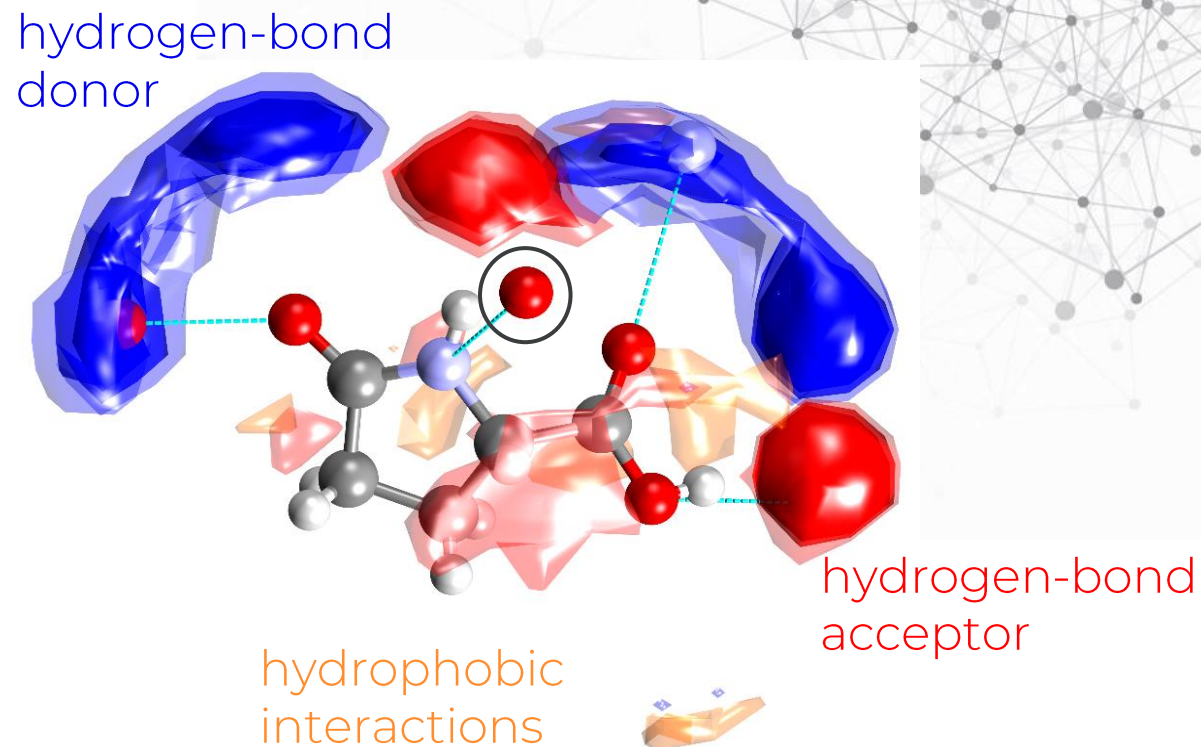
	Centroid 1	Centroid 2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	1	2	4.65	58.43	Yes	8.9	Strong
2	1	10	4.87	50.79	Yes	8	Strong
3	1	12	5.94	26.95	Yes	5.9	Moderate
4	1	7	8.93	0	Yes	0.6	Weak
5	1	8	8.6	58.43	Yes	0.6	Weak
6	1	6	9.38	0	Yes	0.4	Weak
7	1	4	9.88	50.79	Yes	0.2	Weak

Below the table, there are checkboxes for 'Include Intramolecular pairs' (unchecked) and 'Exclude symmetry equivalent interactions' (checked). Buttons for 'Calculate', 'Export', 'Atom info', and 'Close' are visible at the bottom of the window.

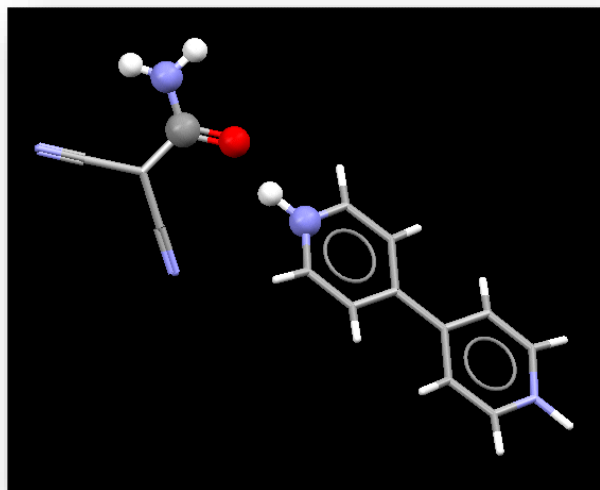
An orange box with white text states: "A previous CCDC virtual workshop covered our Aromatic Analyser in full".

Full Interaction Maps (FIMs)

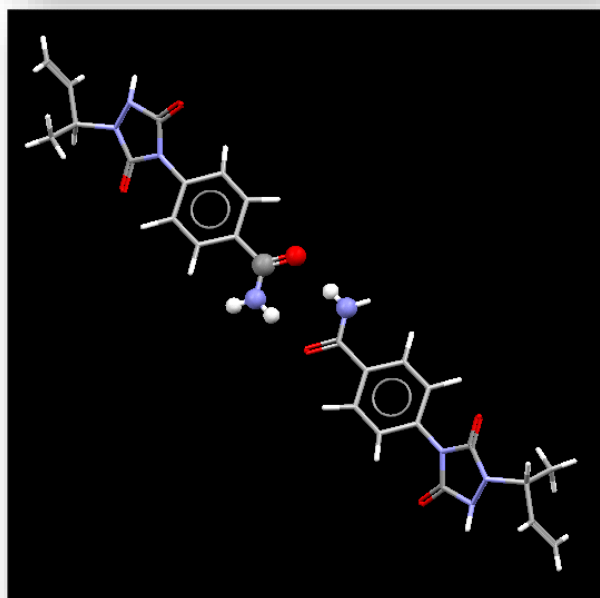
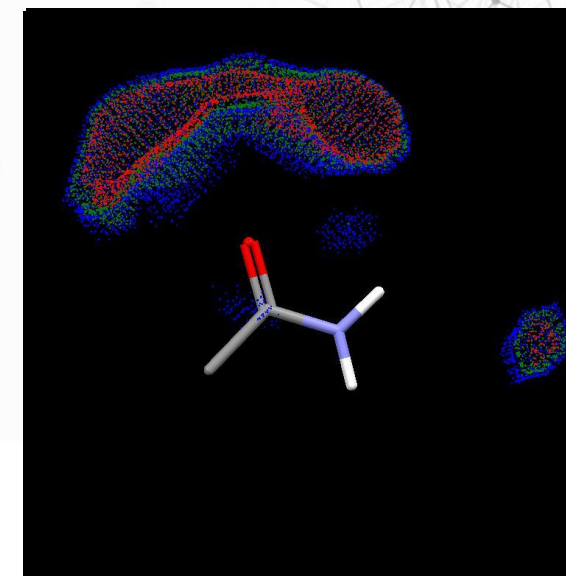
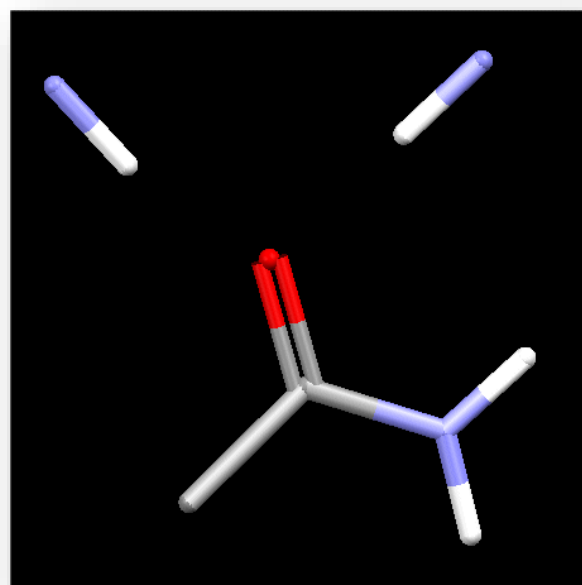
- Map interaction preferences around complete molecules in a crystal structure
- Visualise observed atom-atom contacts with respect to likely geometries in 3D space
- Identify interaction hot-spots around chemical groups



Understanding intermolecular interactions



central group: $-\text{CONH}_2$
contact group: NH

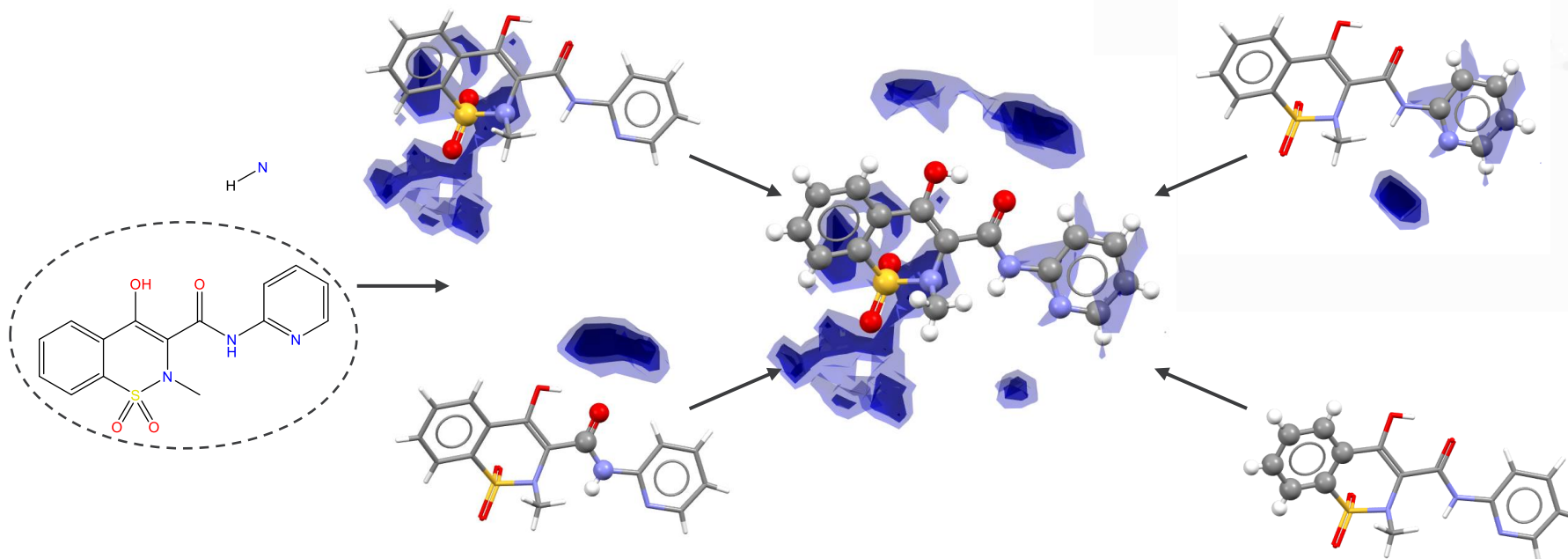


Search for structures containing desired contact

Superimpose hits and display as scatterplots or contour plots

Combining plots into Full Interaction Maps

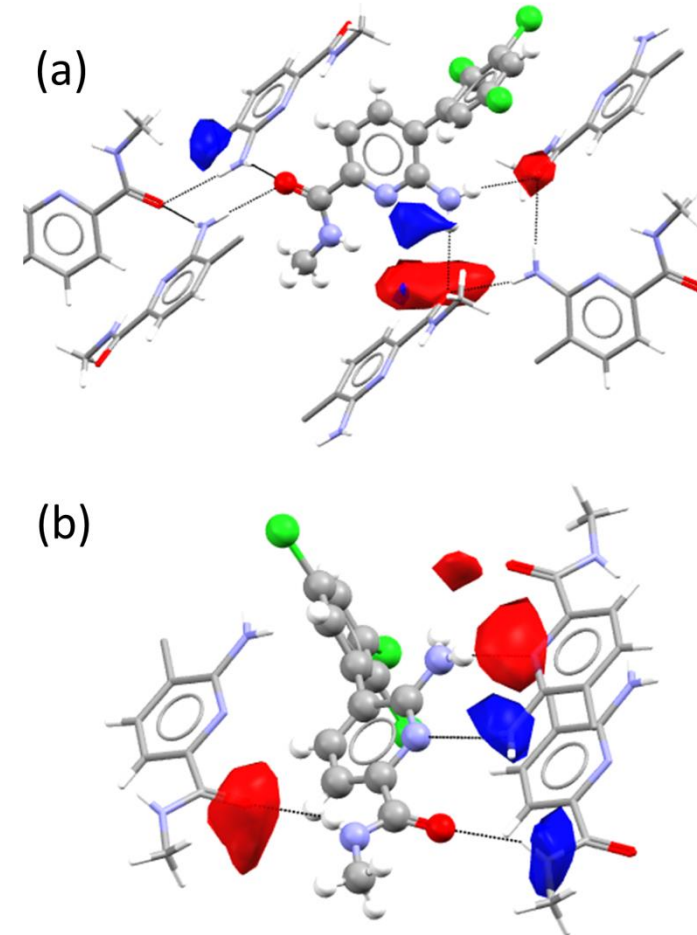
- Molecule is broken down into fragments
- IsoStar maps for each fragment are combined to give the Full Interaction Map



- Multiple maps can be generated for different probes

Predicting intermolecular interaction geometries

- “Early development candidate”
 - Two polymorphs, metastable (a) and stable (b)
 - Packing arrangement of stable form (b) satisfies Full Interaction Map particularly well
 - Packing arrangement of (a) does not



Creating a FIM

FIMs enable you to generate a 3D interaction map around a molecule representing regions of higher probability to find interactions with certain functional groups

Getting started with Full Interaction Maps

Ilaria Gimondi – February 15, 2021

Our collection of educational resources has been growing throughout 2020, welcoming new How to videos (on our YouTube and LabTube channels), new self-guided workshops and updates to our existing material. We also added a feedback survey for you to fill in at the end of each workshop to let us know how we are doing and how we can improve.

This month we include in our collections 2 new resources, both about Full Interaction Maps (FIMs, for short): an educational video and a self-guided workshop. Both are the right time to write a blog about FIMs, to help you get the most out of the first steps to FIMs.

How do FIMs work?

Full Interaction Maps (FIMs) are a powerful tool that represents the regions of higher probability to find interactions with certain functional groups. We made it available to you as a self-guided workshop.

A great way to get started with FIMs is to show you how FIMs work, together with new examples that will give you an idea about insightful information that FIMs can provide on your molecules, crystal structures, and ligand interactions. Our new educational video on FIMs aims exactly at this.

Full Interaction Maps (FIMs)



CCDC

Click on the image to watch the video on YouTube.

The screenshot shows the Mercury software interface. The 'Full Interaction Maps' dialog box is open, displaying options for map contour levels and hotspots. A blue arrow points to the 'Probe' section, which lists various functional groups for interaction mapping. The 'CSD-Materials' menu is also visible, with 'Full Interaction Maps...' highlighted.

Full Interaction Maps Options:

- Map Contour Levels:**
 - ☒ Display first contour with initial level of 2.0
 - ☒ Display second contour with initial level of 4.0
 - ☒ Display third contour with initial level of 6.0
- Hotspots:**
 - ☐ Generate hotspots in the map
- Probe:**
 - ☒ Uncharged NH Nitrogen
 - ☐ Charged NH Nitrogen
 - ☐ RNH3 Nitrogen
 - ☐ Alcohol Oxygen
 - ☒ Carbonyl Oxygen
 - ☐ Water Oxygen
 - ☐ Oxygen Atom
 - ☐ Methyl Carbon
 - ☒ Aromatic CH Carbon
 - ☐ C-F Fluorine

Buttons: Calculate Maps, Clear Maps & Hotspots, Load Maps..., Save Maps..., Close, Defaults, Reset.

<https://www.ccdc.cam.ac.uk/Community/blog/getting-started-with-FIMs/>

Press the left mouse button and move the mouse to rotate the structure

Creating a hotspot

1

2 Calculate Maps

3

Hotspots represent the positions of highest local density for each contour surface. Find this in our *Glossary*.

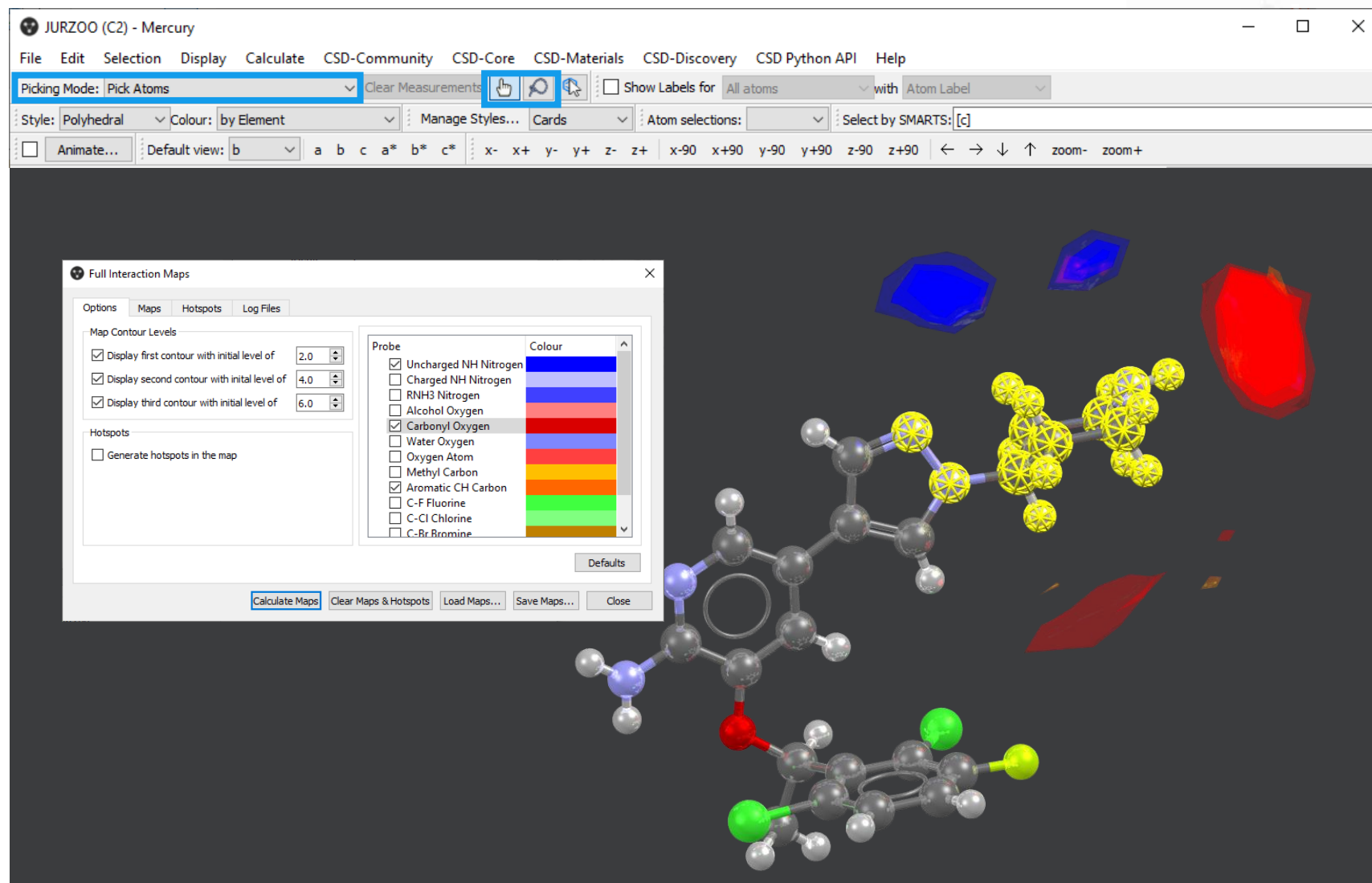
The screenshot shows the ADEZUF (Pna21) - Mercury software interface. The 'Full Interaction Maps' dialog box is open, showing 'Map Contour Levels' and 'Hotspots' options. The 'Hotspots' section has 'Generate hotspots in the map' checked. The 'Calculate Maps' button is highlighted. A blue arrow points from the 'Calculate Maps' button to the 'Edit Existing Contours' dialog box. The 'Edit Existing Contours' dialog box shows a table of contours with columns for Probe, Level, Level Range, Color, Visible, Display Type, and Opacity.

	Probe	Level	Level Range [min., max.]	Color	Visible	Display Type	Opacity
1	Uncharged NH Nitrogen	2.00	[0.00, 10.45]	Blue	<input type="checkbox"/>	triangle	0.2
2	Uncharged NH Nitrogen	4.00	[0.00, 10.45]	Blue	<input type="checkbox"/>	triangle	0.5
3	Uncharged NH Nitrogen	6.00	[0.00, 10.45]	Blue	<input type="checkbox"/>	triangle	0.8
4	Carbonyl Oxygen	2.00	[0.00, 61.87]	Red	<input type="checkbox"/>	triangle	0.2
5	Carbonyl Oxygen	4.00	[0.00, 61.87]	Red	<input type="checkbox"/>	triangle	0.5

Explore More: More advanced uses

- Not enough time to explore all the insights that you can get from Full Interaction Maps.
- But here are a selection of more advanced tips and tricks

Generate FIMs for selected atoms



You can generate FIMs for a portion of a molecule.

Select the relevant atoms before calculating the maps.

Reminder: To select atoms you can:

- Change the picking mode to Pick Atoms or Lasso Atoms
- Use the Lasso button
- Go to Selection > Select Atoms or
- Right click for visualiser menu > Selection > select atoms

Change the colour of probes

The screenshot displays the Mercury software interface for JURZOO (C2). The main window shows a molecular model with various colored probes (red, green, yellow, orange) overlaid on a grey ball-and-stick model. Two dialog boxes are open:

- Select Color**: This dialog allows users to choose a color for a probe. It features a grid of basic colors, a color wheel, and a color bar. The selected color is shown in a preview box, and its HTML color code is displayed as #00aa7f. An orange arrow points from the 'Uncharged NH Nitrogen' probe in the 'Full Interaction Maps' dialog to this color selection dialog.
- Full Interaction Maps**: This dialog has tabs for Options, Maps, Hotspots, and Log Files. The 'Maps' tab is active, showing options for map contour levels and hotspots. The 'Probe' list includes various chemical features, with 'Uncharged NH Nitrogen' selected. A color bar next to the probe list shows the color mapping for each probe type.

You can change the colour for each probe by clicking on the Colour in the Full Interaction Maps Options tab

Access FIMs through CSD-Discovery

You can also access FIMs in the CSD-Discovery menu

The screenshot displays the Mercury software interface (IJUMEG (C2/c) - Mercury). The 'CSD-Discovery' menu is open, showing options: Search, Calculation, Polymorph, Co-Crystal, Full Interaction Maps..., Conformer Generation..., Launch GOLD Docking, Launch Protein Interactions, and Launch Ligand Overlay. The 'Full Interaction Maps...' option is highlighted. Below the menu, the 'Full Interaction Maps' dialog box is open, showing the 'Options' tab. The 'Map Contour Levels' section has three checked options: 'Display first contour with initial level of 2.0', 'Display second contour with initial level of 4.0', and 'Display third contour with initial level of 6.0'. The 'Hotspots' section has 'Generate hotspots in the map' unchecked. The 'Probe' section has 'Uncharged NH Nitrogen' checked, 'Charged NH Nitrogen' unchecked, 'RNH3 Nitrogen' unchecked, 'Alcohol Oxygen' unchecked, 'Carbonyl Oxygen' checked, and 'Water Oxygen' unchecked. The 'Colour' section shows a color scale from blue to red. The 'Calculate Maps' button is highlighted. The background shows a 3D molecular model with interaction maps.

Full Interaction Maps

Options Maps Hotspots Log Files

Map Contour Levels

- ☒ Display first contour with initial level of 2.0
- ☒ Display second contour with initial level of 4.0
- ☒ Display third contour with initial level of 6.0

Hotspots

- ☐ Generate hotspots in the map

Probe

- ☒ Uncharged NH Nitrogen
- ☐ Charged NH Nitrogen
- ☐ RNH3 Nitrogen
- ☐ Alcohol Oxygen
- ☒ Carbonyl Oxygen
- ☐ Water Oxygen

Colour

Defaults

Calculate Maps Clear Maps & Hotspots Load Maps... Save Maps... Close

Display Options

Display

- ☐ Packing
- ☐ Asymmetric Unit
- ☐ Auto centre

Reset

Short Contact < (sum of vdW radii + 0.1Å)

- ☒ H-Bond User defined

Contacts... More Info Powder...

Options

- ☒ Show hydrogens
- ☐ Show cell axes
- ☐ Label atoms
- ☐ Depth cue
- ☐ Z-Clipping
- ☐ Stereo

Save FIMs

FEMPIY (Pbcn) - Mercury

File Edit Selection Display Calculate CSD-Community CSD-Core CSD-Materials CSD-Discovery CSD Python API Help

Picking Mode: Pick Atoms

Style: Ball and Stick

Animate... Default

Full Interaction Maps

Options Maps Hotspots Log Files

Map Contour Levels

- ☒ Display first contour with initial level of 2.0
- ☒ Display second contour with initial level of 4.0
- ☒ Display third contour with initial level of 6.0

Hotspots

- ☐ Generate hotspots in the map

Probe

- ☒ Uncharged NH Nitrogen
- ☐ Charged NH Nitrogen
- ☐ RNH3 Nitrogen
- ☐ Alcohol Oxygen
- ☒ Carbonyl Oxygen
- ☐ Water Oxygen
- ☐ Oxygen Atom
- ☐ Methyl Carbon
- ☒ Aromatic CH Carbon

Colour

Defaults

Calculate Maps Clear Maps & Hotspots Load Maps... Save Maps... Close

Atom Label

by SMARTS: [c]

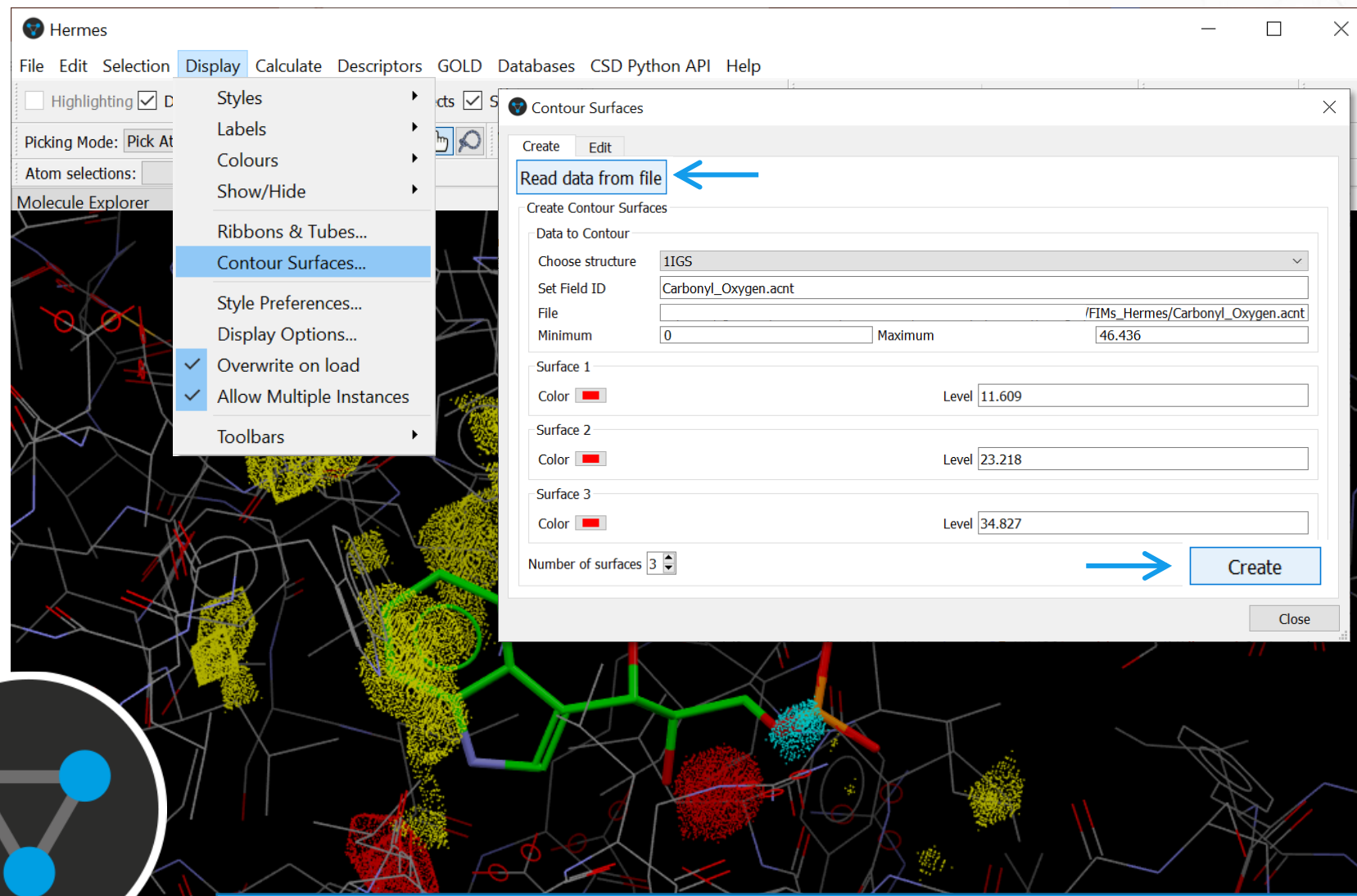
+90 ← → ↓ ↑ zoom- zoom+

FEMPIY-FIMs

- Aromatic_CH_Carbon.acnt
- Aromatic_CH_Carbon.err
- Aromatic_CH_Carbon.ins
- Aromatic_CH_Carbon
- Carbonyl_Oxygen.acnt
- Carbonyl_Oxygen.err
- Carbonyl_Oxygen.ins
- Carbonyl_Oxygen
- FEMPIY_fim.mol2
- Uncharged_NH_Nitrogen.acnt
- Uncharged_NH_Nitrogen.err
- Uncharged_NH_Nitrogen.ins
- Uncharged_NH_Nitrogen

You can save a FIM in the Full Interaction Maps Options tab by clicking Save Maps...

Visualise FIMs in Hermes



You can generate FIMs for a ligand in Mercury and save the Maps as seen in the previous slide.

Load the Maps in Hermes to visualise the contour of the FIMs in the environment.

Getting started with Full Interaction Maps

Ilaria Gimondi - February 15, 2021

Our collection of educational resources has been growing throughout 2020, welcoming new How to videos (on our YouTube and LabTube channels), new self-guided workshops and updates to our existing material. We also added a feedback survey for you to fill in at the end of each workshop to let us know how we are doing and how we can improve.

This month we released an educational video about FIMs, the right time to write a blog about them. It's the first steps to understanding FIMs, to support an educational video.

How do FIMs work? Full Interaction Maps enables you to generate a 3D interaction map that wraps around a molecule and represents the regions of higher probability to find interactions with certain functional groups. We believe it is such a powerful tool that we made it available in Mercury with both the CSD-Materials and the CSD-Discovery licenses.

A great way to get started with FIMs is to show you how FIMs work, together with few examples that will give you an idea about insightful information that FIMs can provide on your molecules, crystal structures, and ligand interactions. Our new educational video on FIMs aims exactly at this.

More info available
in our blog

<https://www.ccdc.cam.ac.uk/Community/blog/getting-started-with-FIMs/>

Programmatic access to FIMs in our API

For API documentation
in Mercury go to CSD
Python API > CSD
Python API
Documentation the
navigate to Interaction
Maps

CSD Python API Help

Analysis

Reports

Searches

user_support.py

welcome.py

calculate_CSD_diversity_score.py

Options...

CSD Python API Documentation

CSD Python API Forum



CSD Python API 3.0.4 documentation » Descriptive documentation »



Table of Contents

- Interaction Maps
 - Introduction
 - Use Cases
 - Analyse Crystal and Small Molecule
 - Analyse Protein Binding Site
 - Other Settings

Previous topic

Analysing molecular interactions preferences

Next topic

Crystal packing similarity

Quick search



Interaction Maps

Note: the `ccdc.interaction.InteractionMapAnalysis` is available only to CSD-Discovery, CSD-Materials and CSD-Enterprise users.

Introduction

The `ccdc.interaction.InteractionMapAnalysis` uses crystallographic information about non-bonded interactions to generate interaction maps around small molecules or within protein binding site. Depending on the settings used, the calculated maps provide the interaction preferences for your molecule as a whole in the context of the crystal structure, or the interaction preferences for all or selected cavities in a protein.

Note: For more information on the details of the fundamental methodology please see:

"SuperStar: A knowledge-based approach for identifying interaction sites in proteins.", M. L. Verdonk, J. C. Cole and R. Taylor, J. Mol. Biol., 289, 1093-1108, 1999, DOI: 10.1006/jmbi.1999.2809.

"Evaluation of molecular crystal structures using Full Interaction Maps", P. A. Wood, T. S. G. Olsson, J. C. Cole, S. J. Cottrell, N. Feeder, P. T. A. Galek, C. R. Groom, E. Pidcock, CrystEngComm, 15, 65772, 2013, DOI: 10.1039/C2CE25849H.

See also: API documentation for the interaction module

Use Cases

Analyse Crystal and Small Molecule

One common use for `ccdc.interaction.InteractionMapAnalysis` is to analyse a crystal to determine the preferred binding sites of particular functional groups. We will exemplify this by considering paracetamol. Firstly, let us import the relevant modules and classes:

```
>>> from ccdc import io
>>> from ccdc.interaction import InteractionMapAnalysis
```

Then we will load a crystal structure for paracetamol:

```
>>> csd = io.EntryReader('csd')
>>> paracetamol = csd.crystal('HXACAN')
```

ccdc.interaction.InteractionMapAnalysis

Find out more:
The basics of our
CSD Python API
were covered in
our last series of
CCDC Virtual
workshops!

CCDC

Using FIMs to help develop new forms

CRYSTAL GROWTH & DESIGN
pubs.acs.org/crystal

Article

Interaction Map Driven CocrySTALLIZATION of Ambrisentan: Structural and Biopharmaceutical Evaluation

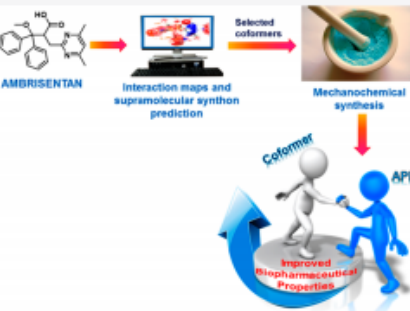
Jamshed Haneef,* Datta Markad, and Renu Chadha

Cite This: *Cryst. Growth Des.* 2020, 20, 4612–4620

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ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The present work deals with the development of cocrystal of ambrisentan (AMT) to improve its biopharmaceutical profile. Full interaction maps (FIM) of AMT were explored to find out the potential sites for hydrogen bonding and prediction of supramolecular synthons. This information was further applied to the screening of amino acids as prospective coformers for cocrystallization of AMT. Mechanochemical reactions have resulted in two cocrystals with L-aspartic acid and glycylglycine (dipeptide). The crystal structural analysis revealed that the hydrogen-bonding pattern in the developed cocrystals corroborated well with the predicted supramolecular synthons. The developed cocrystals showed a remarkable improvement in solubility, intrinsic dissolution rate, and *in vivo* systemic absorption as compared to the parent drug. Complementarily, Hirshfeld surface maps together with crystal features established a good structural–performance correlation of the developed cocrystals. Thus, the systematic cocrystallization driven by structural informatics tools is valuable in the development of novel solid forms with improved biopharmaceutical attributes.



Full Interaction Maps



Systematic cocrystallization



Novel solid forms with improved biopharmaceutical attributes

Get a certificate and help us improve

Do you want to earn a completion certificate for this session?

1. Complete the test
2. Score 10/10
3. Receive your certificate

- Test available until Friday at 2:00 pm BST!



How did it go today?

What do you want to learn next?

- Let us know in our short post-workshop survey



Find the links for both survey in the chat box or in tomorrow's email



CCDC

Want to explore more?

Training and Educational Resources

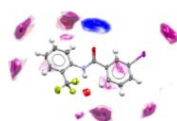
The wealth of information contained within the Cambridge Structural Database (CSD) extends far beyond a collection of crystal structures. Knowledge derived from these materials informs much of chemistry, biochemistry, and biology. Chemical and structural concepts are often difficult to grasp without real world, interactive examples for students to explore.

The CCDC and our colleagues continually produce educational materials for use in classroom and computer lab settings, or as independent study modules. Many of these materials make use of the Teaching Subset - a freely available set of over 750 structures that can be investigated with the free version of our Mercury visualisation and analysis program. Of course, our database of over one million entries are available for free through our Access Structures portal.

If you are an educator looking for supplementary teaching materials, find out more about the Teaching Database [here](#). If you have developed your own modules using the CSD and would like to share them with the broader community, please contact us at education@ccdc.cam.ac.uk.

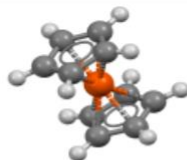
To keep up to date with the latest news from education and outreach at the CCDC, sign up for the Education and Outreach Newsletter [here](#).

Register for
E&O newsletter



CSD-Materials

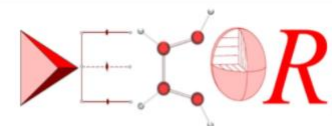
Tools to help you to understand your material's behaviours and refine its properties.



Information on the Teaching Subset



Access a series of teaching modules for use in the classroom



DECOR: Educational Resources for Teaching Crystallography

Self-guided workshops



Download a series of self-guided workshop materials for CCDC tools and features



Watch software training and support videos

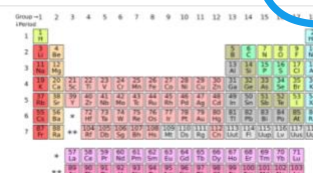


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On-demand
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