

Investigating solid forms

Using motif searching, packing feature searching and packing similarity in Mercury

May 2022

Learning outcomes

- Learn how informatics and data-driven approaches can be used to understand solid form design and risk assessment.
- Learn how to use Motif searching.
- Learn how to perform crystal packing feature searches.
- Learn how to perform crystal packing similarity searches.
- Familiarise yourself with what other tools are available in the CSD-Materials suite and what they can be used to do.

What we do at the CCDC

Charitable Objective: Advancement of chemistry and crystallography for the public benefit through providing high quality information services and software

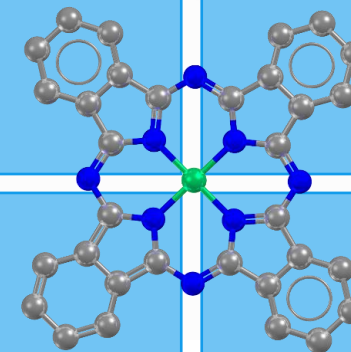
International repository of 3D curated structures

Collaborative research and knowledge-based services

Scientific software

Education and Outreach

CCDC



Structural databases



PDB
>175,000
polypeptides,
nucleotides
& saccharides



CSD
>1.1 million
organic and
metal-organic

ICSD
>230,000
(no C-H and C-C
bonds)
Elements,
minerals,
metals

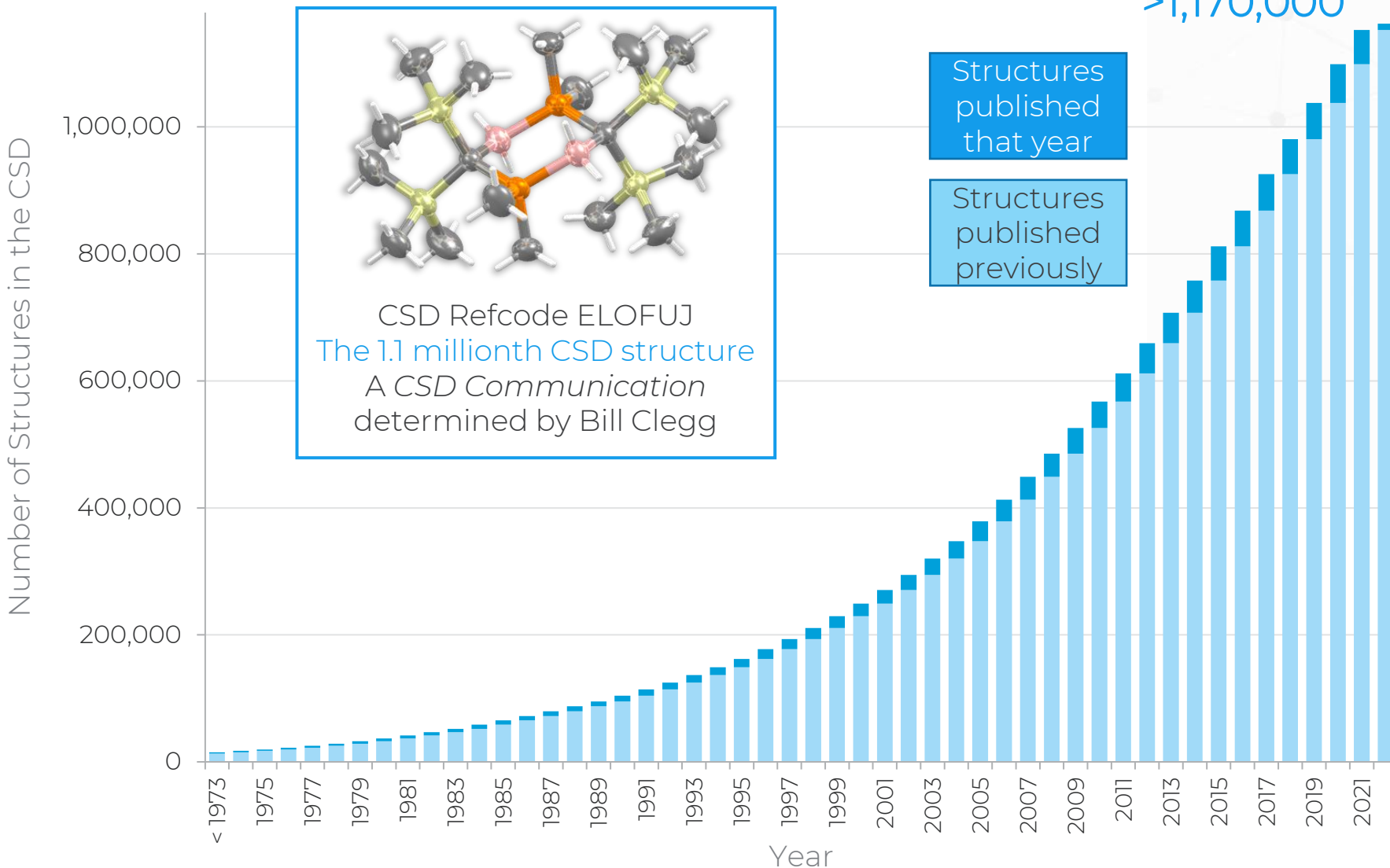
ICDD
Powder
diffraction
files



CCDC

 **FIZ Karlsruhe**
Leibniz Institute for Information Infrastructure

The Cambridge Structural Database



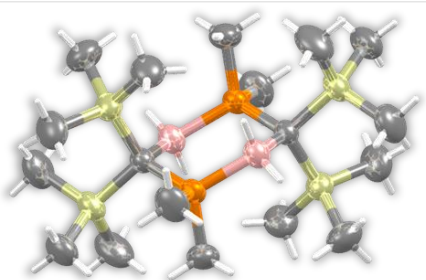
- Every published structure
 - ASAP & early view
 - CSD Communications
 - Patents
 - University repositories
 - Theses
- Every entry enriched and annotated by experts
- Discoverability of data and knowledge
- Sustainable for over 56 years
- A CoreTrustSeal repository



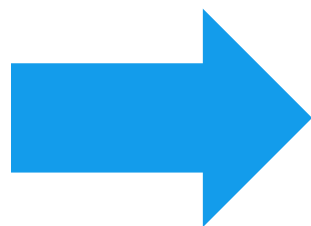
Certified as Trustworthy
by CoreTrustSeal

CCDC

CSD Refcodes



CSD Refcode -
ELOFUJ



What is ELOFUJ?

- A CSD Refcode
- A database reference code
- Containing 6-8 characters
- Used to identify entries in the CSD

Refcode families

- The same substances are assigned the *same* 6 letter code plus an additional 2 numbers
 - Polymorphs
 - New determinations or re-refinements of the same substance
 - Determinations at different temperatures/pressures
- Stereoisomers or different solvates, co-crystals, etc are assigned *different* refcode families

Inside the Cambridge Structural Database

The CSD is a database of all the published organic and metal-organic experimental crystal structures

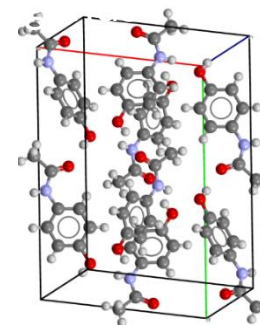
Organic
43%

Metal-Organic
57%

At least one transition metal,
lanthanide, actinide or any of Al,
Ga, In, Tl, Ge, Sn, Pb, Sb, Bi, Po

Organic

- Drugs
- Agrochemicals
- Pigments
- Explosives
- Protein ligands



Additional data

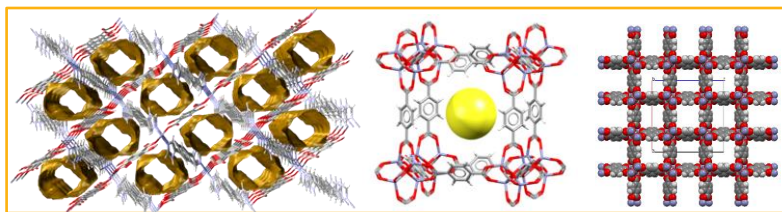
- 11,525 polymorph families
- 171,683 melting points
- 909,992 crystal colours
- 778,663 crystal shapes
- 24,916 bioactivity details
- 11,387 natural source data
- > 250,000 oxidation states

Not Polymeric
89%

Polymeric: 11%

Metal-Organic

- Metal Organic Frameworks
- Models for new catalysts
- Porous frameworks for gas storage
- Fundamental chemical bonding

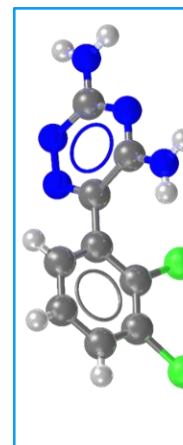


Single
Component
56%

Multi
Component
44%

Links and subsets

- DrugBank
- Druglike
- MOFs
- PDB ligands
- PubChem
- ChemSpider
- Pesticide PDB



A wealth of data in the CSD

Growth of co-crystals

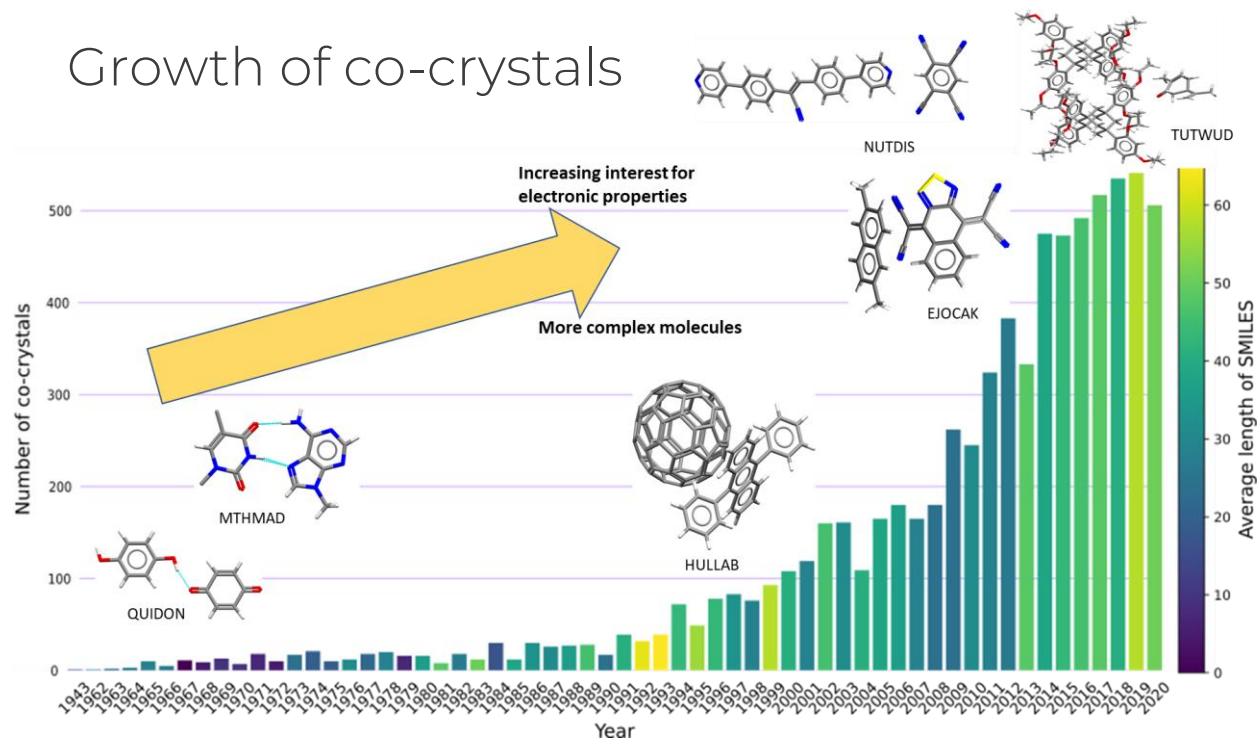
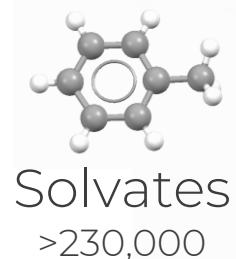
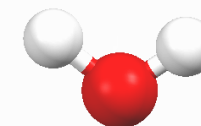


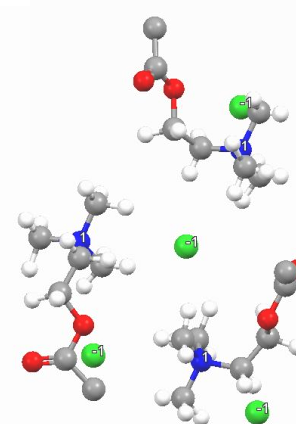
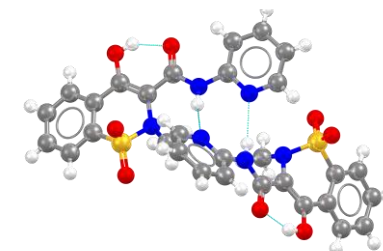
Chart showing the number of co-crystals in the CSD by year and colour coded by the average SMILES length. Image created by Katerina Vriza*, a CCDC sponsored PhD student.



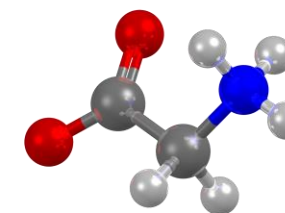
Hydrates
>140,000



Polymorphs
>11,000 polymorphic families



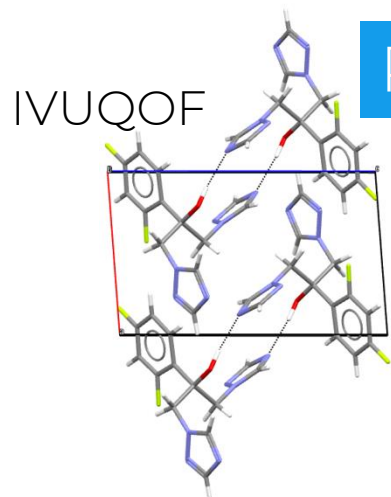
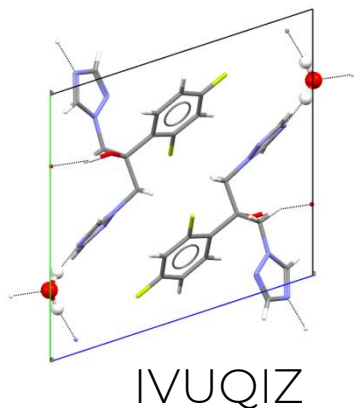
Salts



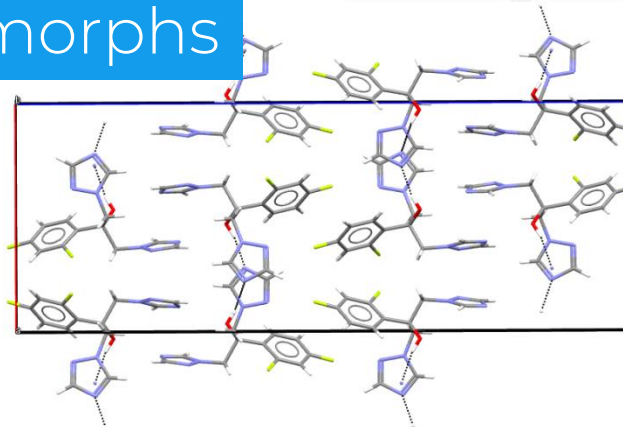
Refcode families
>1,000,000

*Katerina Vriza, University of Liverpool, PhD on Data driven discovery of functional molecular co-crystal

A solid form landscape

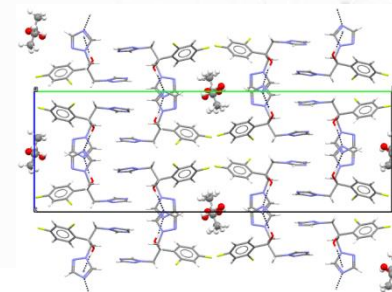
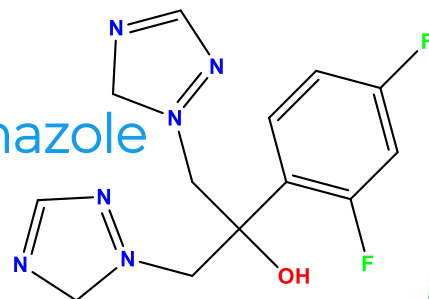


Polymorphs



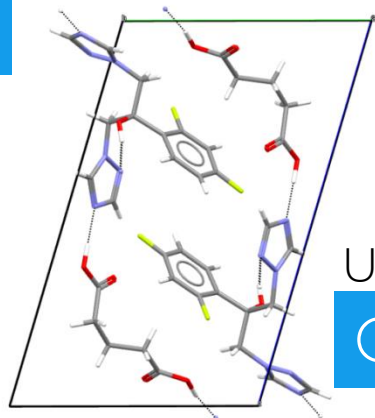
IVUQOF02

fluconazole



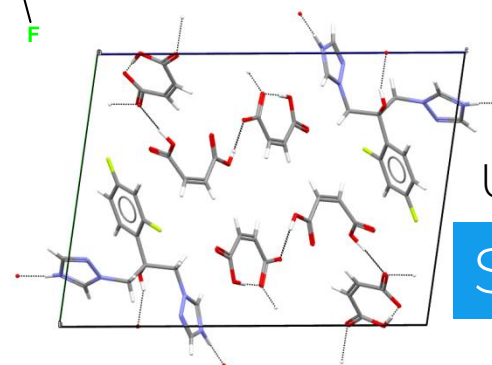
IVUQEV

Solvates



UPOQEW

Co-crystals



UPOQAS

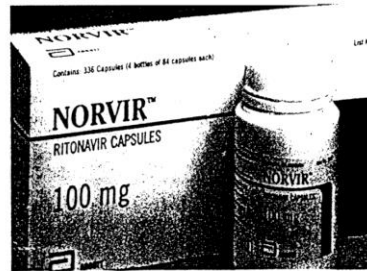
Salts

CCDC

Impact of Hydrogen Bonding on lattice stability -The Ritonavir story

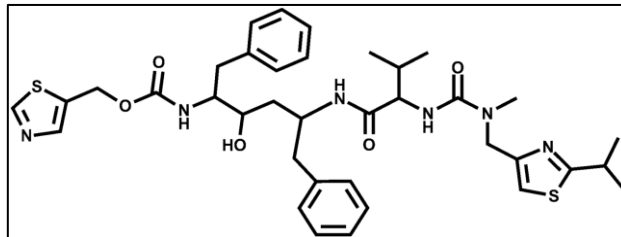
Manufacturing problems hit Abbott's HIV drug ritonavir

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.

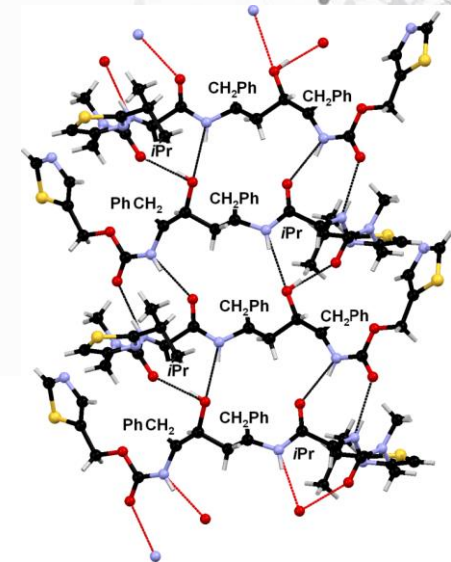
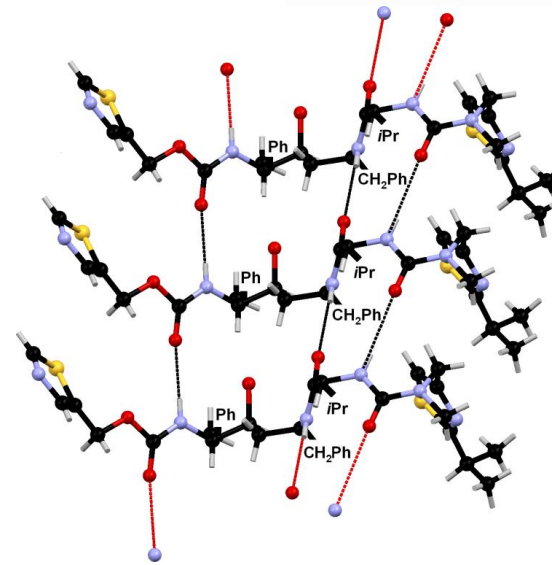


Capsules unlikely to be available from mid-August

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



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

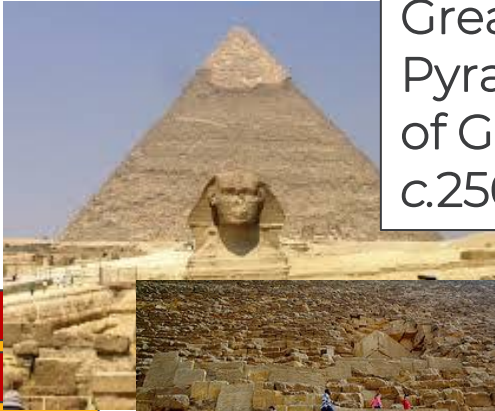
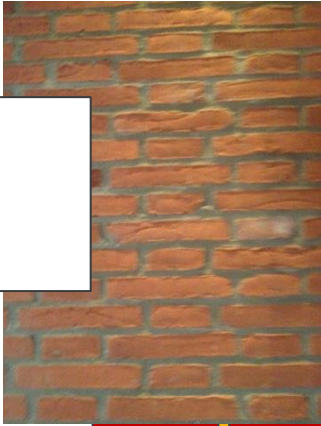


“Since the strength and completeness of the hydrogen bonding has attained the maximum possible in the Form II lattice, it is not thought possible that another undiscovered polymorph of ritonavir would exist with equivalent or lower solubility than that of Form II.”

Structural Informatics

Which is the stable wall?

The
CCDC
c.1992



Great
Pyramid
of Giza
c.2560 BC



Hadrian's Wall
c.122



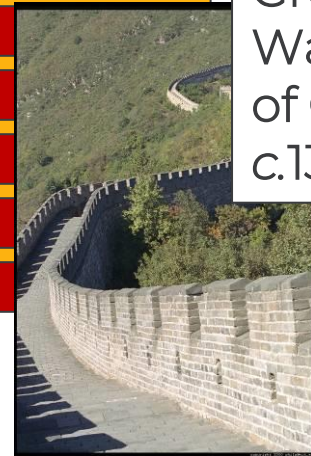
A

B

My
House
c.1967



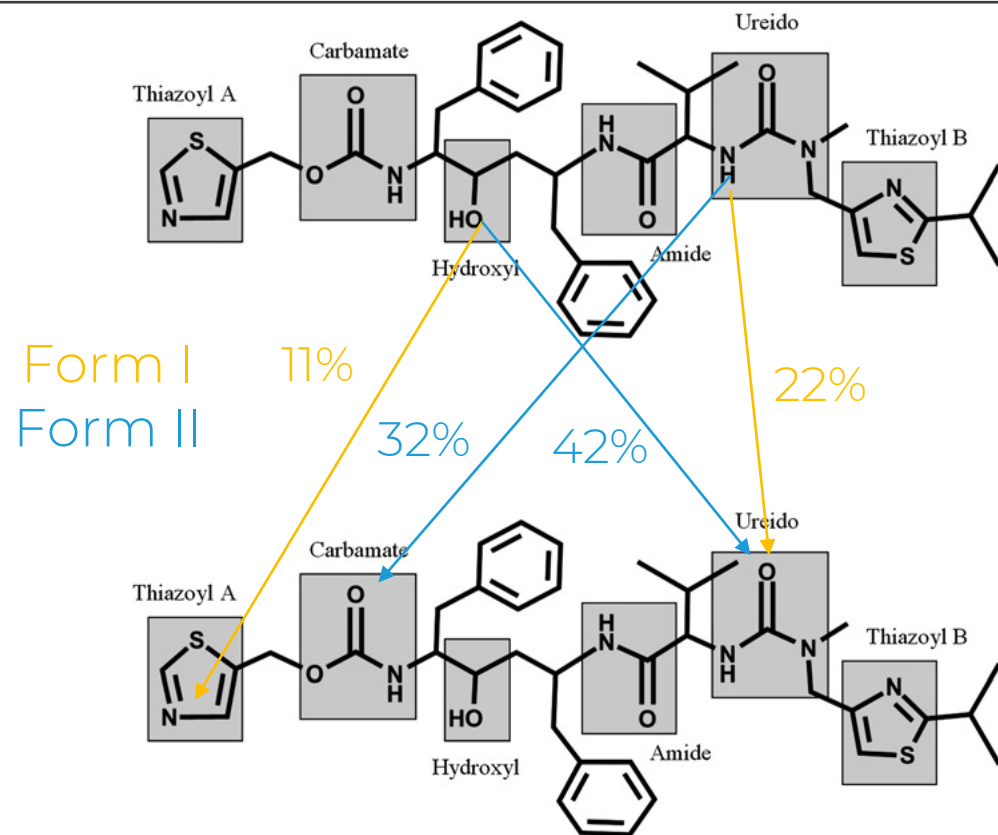
The database of walls indicates that A is the frequently observed arrangement and therefore we can predict it is the most stable form



Great
Wall
of China
c.1368

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 Fábán](#)^{ab} and [Neil Feeder](#)^c

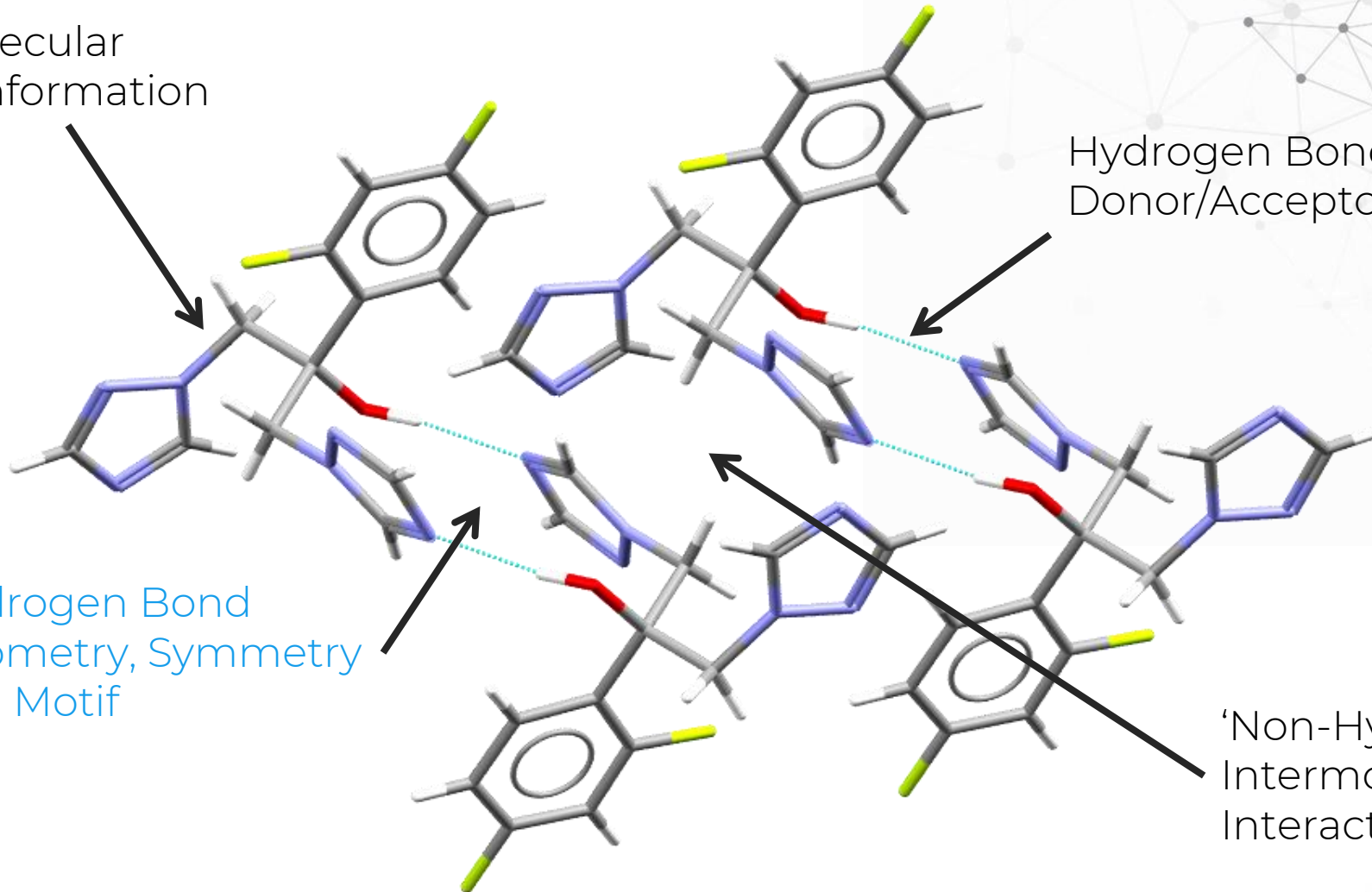
Characteristics that influence stability

Molecular
Conformation

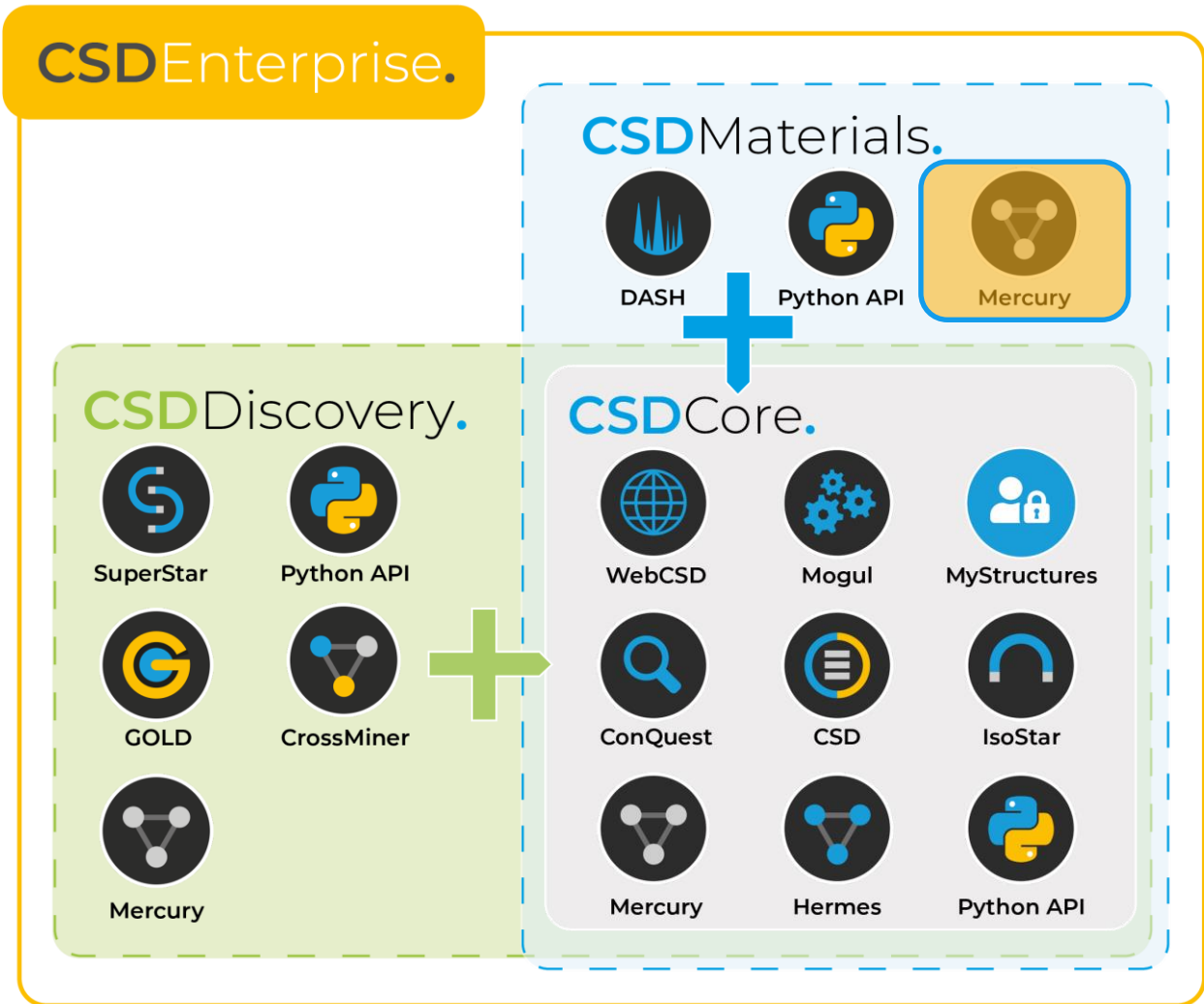
Hydrogen Bond
Donor/Acceptor Pairing

Hydrogen Bond
Geometry, Symmetry
and Motif

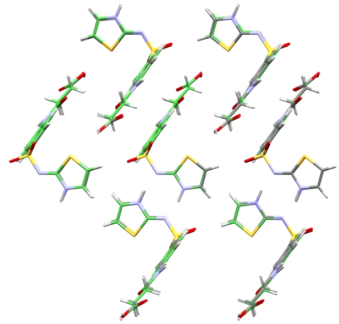
'Non-Hydrogen Bond'
Intermolecular
Interactions



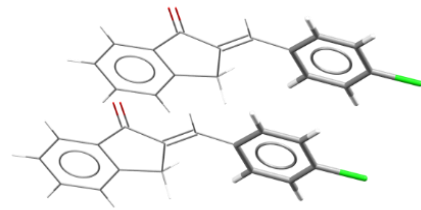
The CSD software



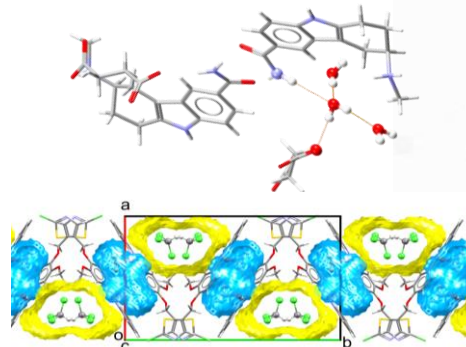
CSD-Materials overview



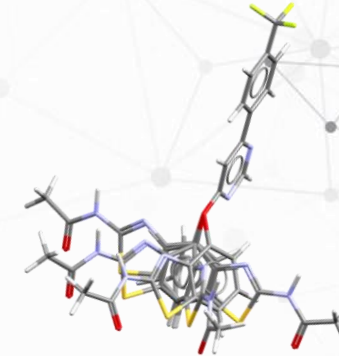
Crystal Packing Similarity



Motif Search & Packing Feature Search



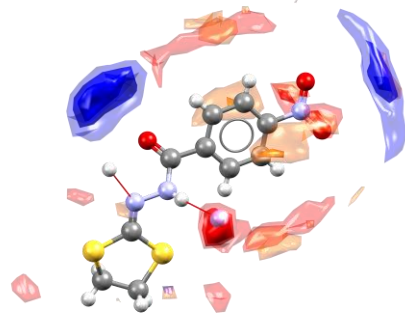
Hydrate Analyser & Solvate Analyser



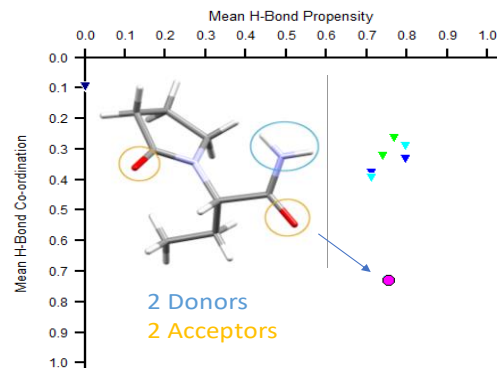
CSD Conformer Generator

Detailed Structural Analysis

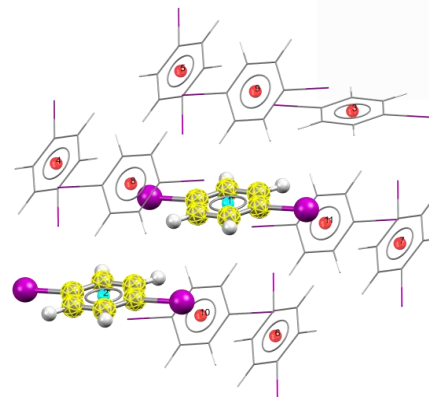
Solid Form Design



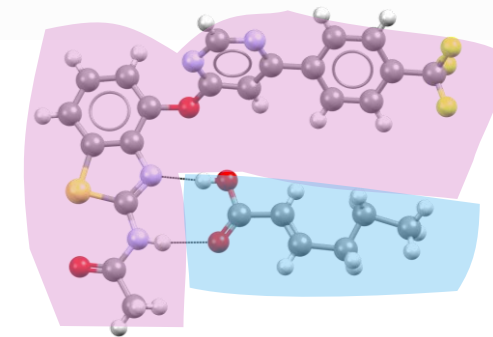
Full Interaction Maps



Hydrogen Bond Propensity



Aromatics Analyser

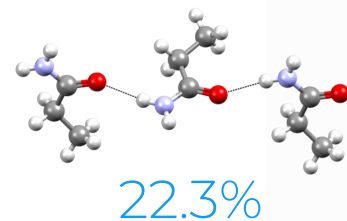
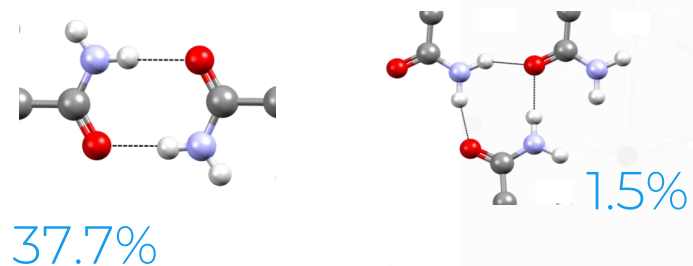
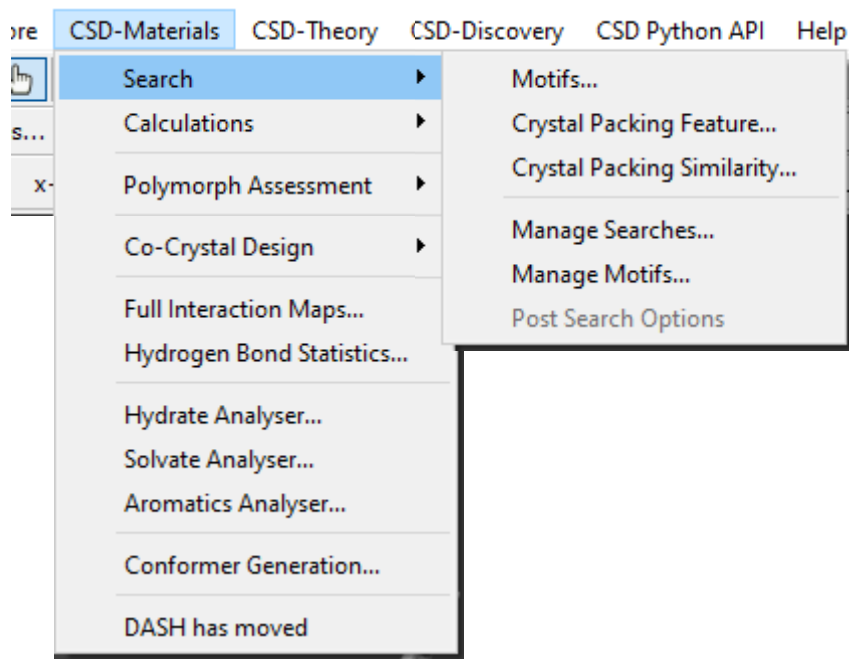


Molecular Complementarity

Solid Form Risk Assessment

Overview

- Allow the exploration of aspects of a structure to determine how usual a feature is, in context of the CSD.
- Searches are easy to set up and return results in a useful format.

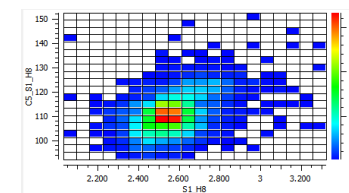
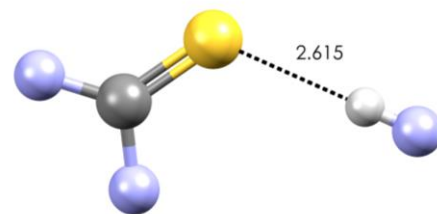
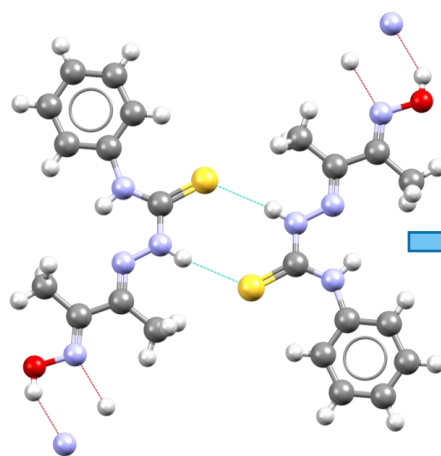


H-bond Motifs

Crystal Packing Feature

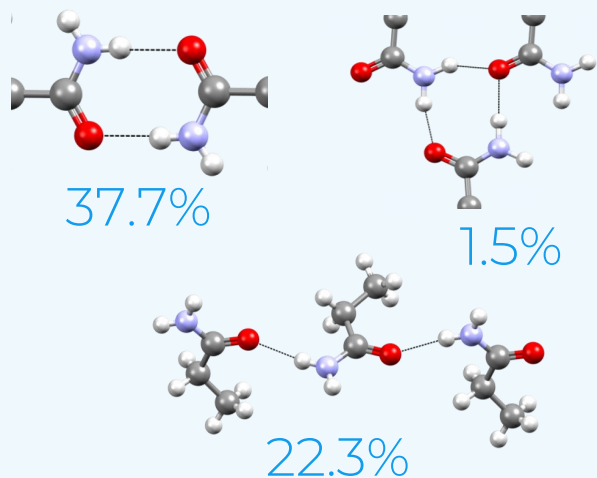
1.5%

Crystal Packing Similarity



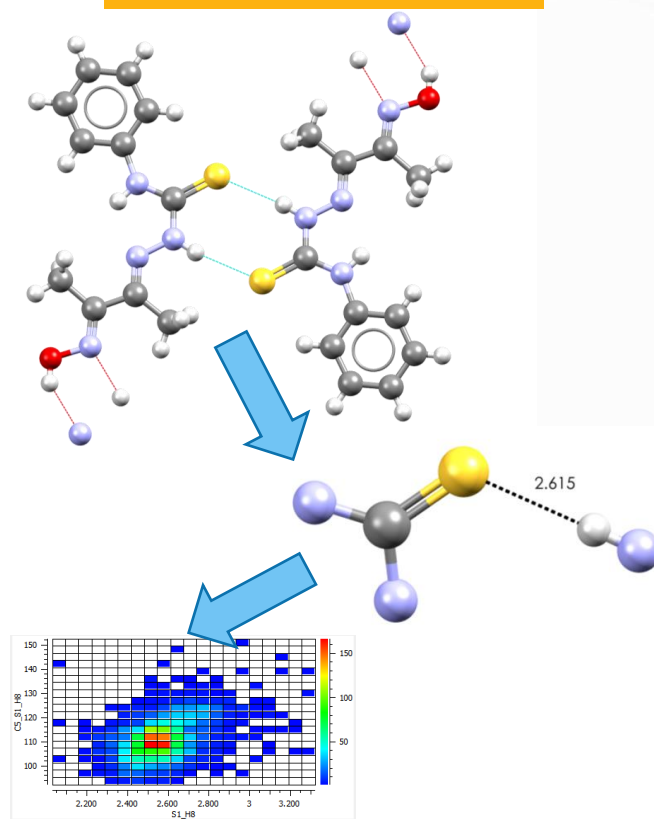
Searching motifs and crystal packing

Motifs

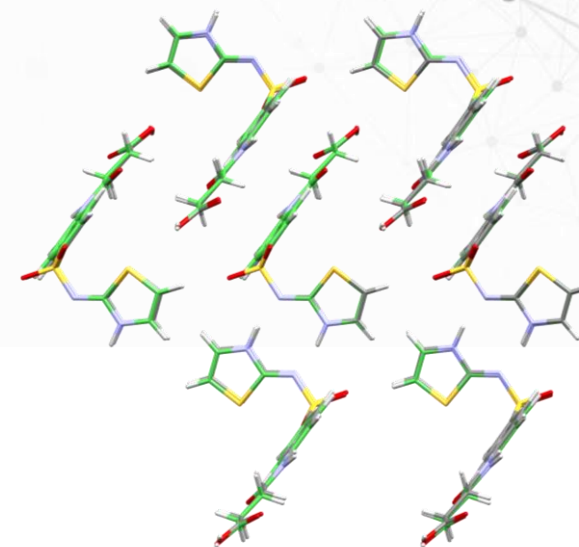


- H-bond motifs

Crystal Packing Feature

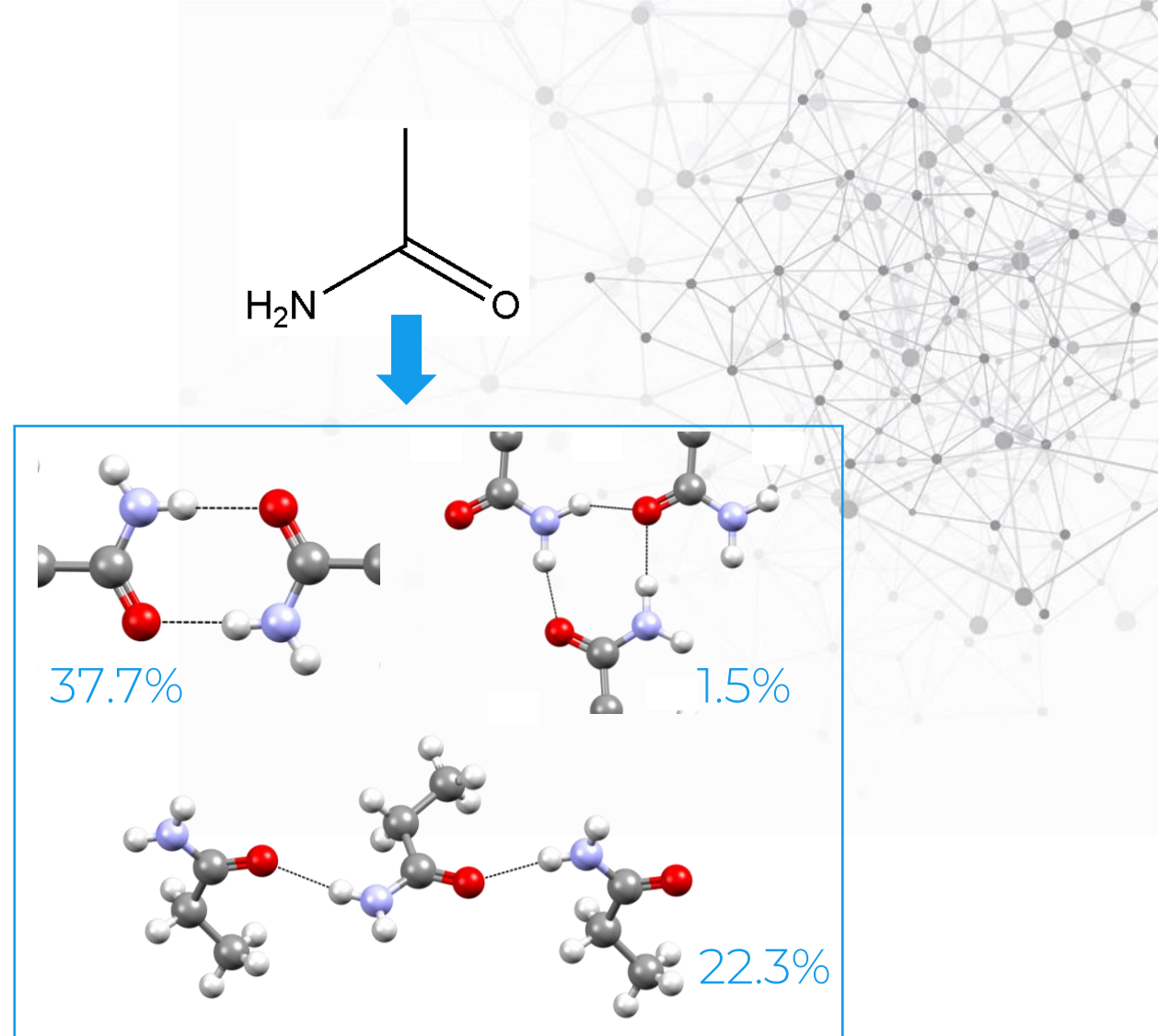


Crystal Packing Similarity



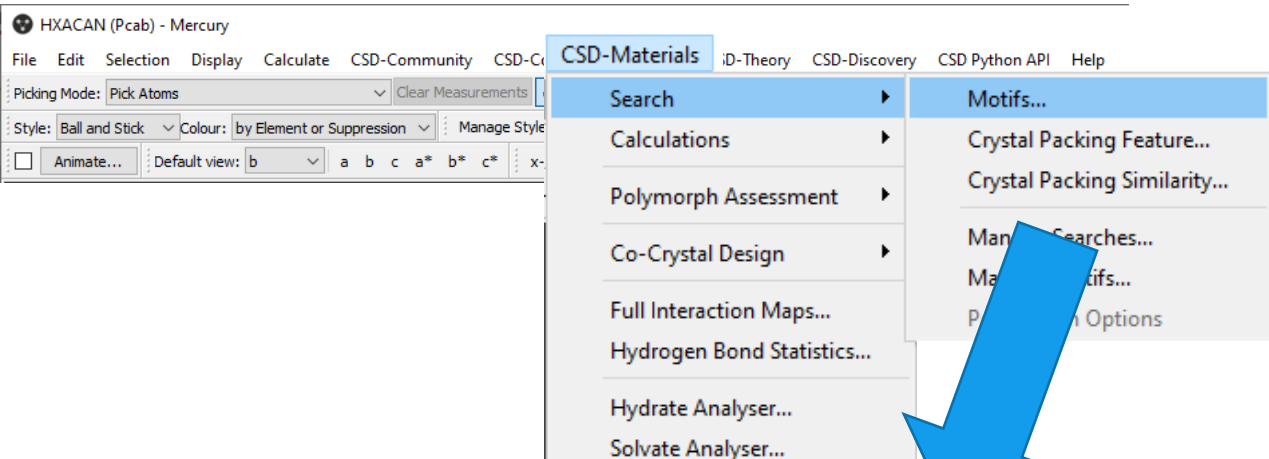
Motifs

- 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.

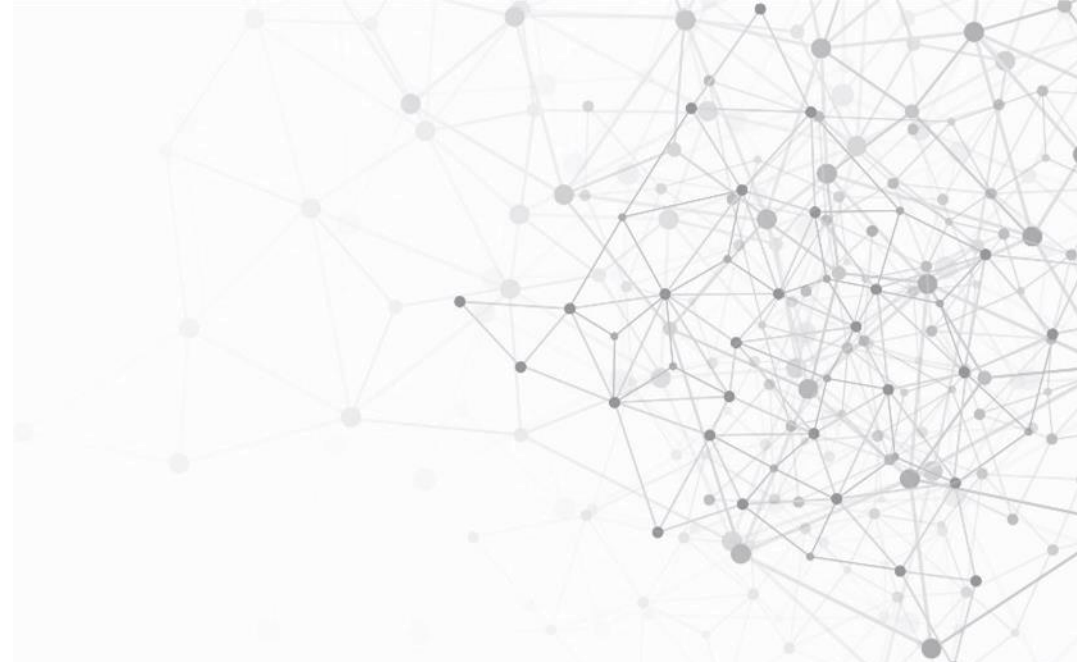
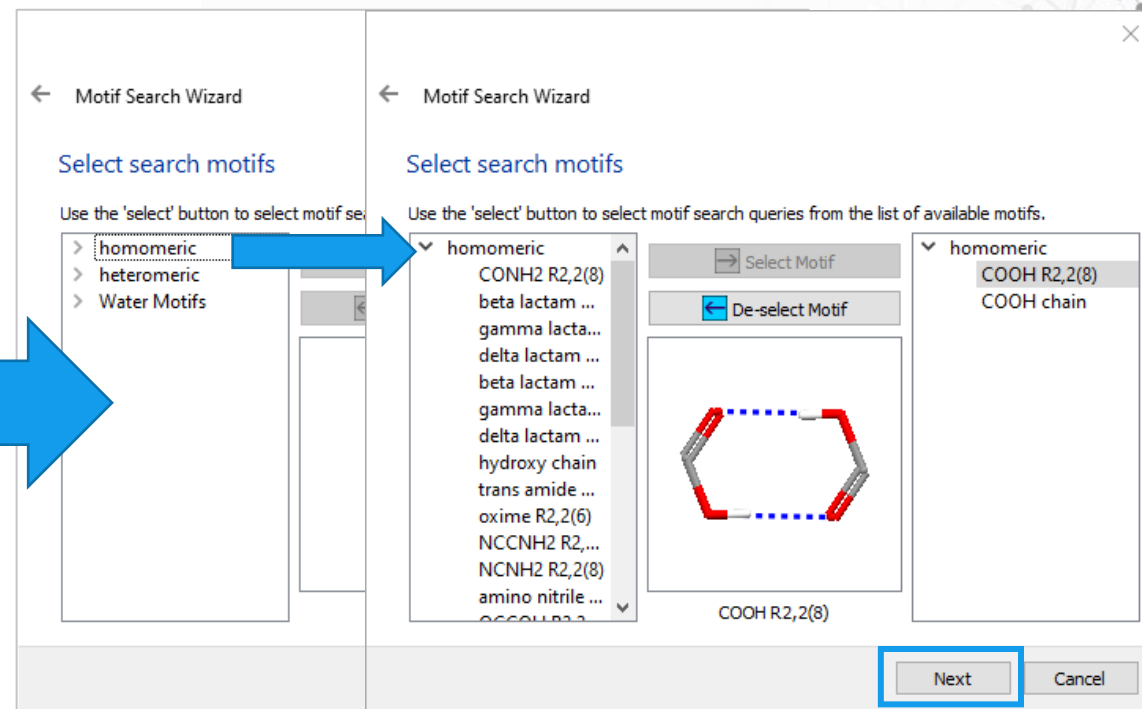
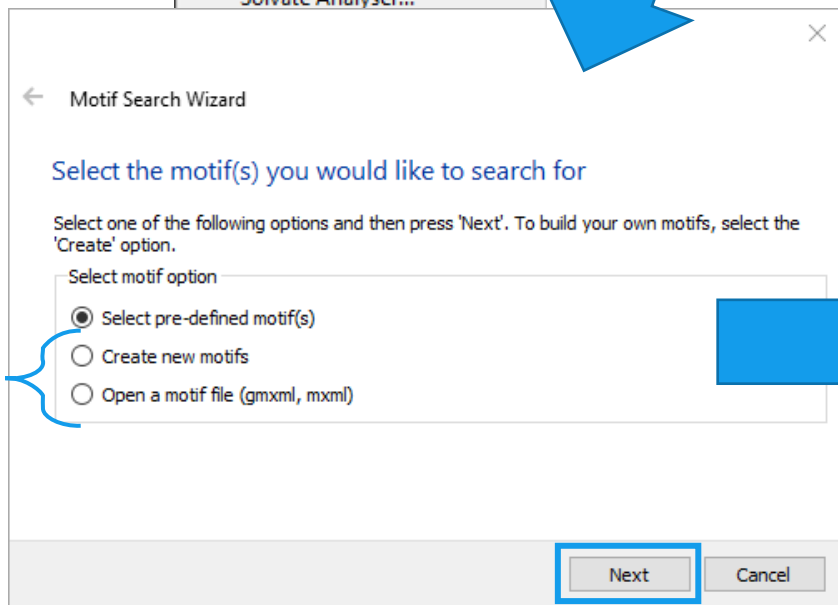


Frequency of occurrence of Primary Amide hydrogen bond motifs

Searching for motifs



bespoke motifs



← Motif Search Wizard

Select search motifs

Use the 'select' button to select motif search queries from the list below.

- homomeric
 - CONH2 R2,2(8)
 - beta lactam ...
 - gamma lacta...
 - delta lactam ...
 - beta lactam ...
 - gamma lacta...
 - delta lactam ...
 - hydroxy chain
 - trans amide ...
 - oxime R2,2(6)
 - NCCNH2 R2,...
 - NCNH2 R2,2(8)
 - amino nitrile ...

COOH R2,2(8)

Next

← Motif Search Wizard

Select search structures

Use the buttons to select/deselect items you wish to use

Available Structures

- Databases
 - Mar22

Selected Structures

- Databases
 - CSD 5.43

Next

← Motif Search Wizard

Enter a name for this search

Enter Search Name

motif_search_1

Start Search

Cancel

Searches

motif	# structures	% frequency
> COOH R2,2(8)	3608	20.5
▼ COOH chain	217	1.23
ACEDAC11		
ACEDAC12		
ACEDAC13		
ACEDAC14		
ACEDAC15		
ACEDAC16		
ACEDAC17		
ACEDAC18		
ACEDAC19		
ACEDAC20		
ACETAC01		
ACETAC02		
ACETAC03		
ACETAC07		
ACETAC09		
ADAGIY		
AFOREU		
ALILIS		
AMALUW		
AMBZGU10		
AQONNOJ		
ARUVAK		
ASUSAL		
ATAXIE		
AVUVOO		

View Options

View results: by motif

List all matches Multi-view mode

Show negative results

MOXDOT01 51% Pause

Structure Navigator Searches

Options

Show hydrogens Depth cue

Show cell axes Z-Clipping

Label atoms Stereo

Contacts... More Info... Powder...

motif_search_2 Options

motif	# structures	% frequency
> COOH R2,2(8)	7286	20.7
> COOH chain	403	1.15

View Options

View results: by motif

List all matches Multi-view mode

Show negative results

Structure Navigator Searches

Post Search Options

motif_search_1 complete

Would you like to:

Save Results...

Edit Search...

Filter Results...

These options are also available via the **options** button located at the top right of the searches window



Searching for a bespoke motif

- If a motif is not in the pre-defined list you can **create** it.
- Additional steps:

1. Specify groups involved

← Motif Search Wizard

Specify groups that will make up the motif search queries

Functional groups

Add... Sketch... Load... Remove Remove All Next Cancel

Select substructure

Substructure: ar_al_trans_amide

Elements

- All
- N

amine_Sring_1
amino
ar_al_amine
ar_al_ester
ar_al_ether_1
ar_al_ether_2
ar_al_sulfone
ar_al_trans_amide
ar_ar_amide_1
ar_ar_ether

OK Cancel

Select substructure

Substructure: ar_hydroxy

Elements

- All
- C
- H
- O
- N
- Si
- P
- S

OH₁

OK Cancel

2. Define contacts

← Motif Search Wizard

Specify contacts that will make up the motif search queries

Contacts

Add... Edit... Remove

Contact picker

Make a contact by selecting a group and an atom from both the "from" and "to" lists.

From	To
Group: ar_hydroxy	Group: ar_al_trans_amide
Atom: O	Atom: O

Contact Definition (between O atom and O atom)

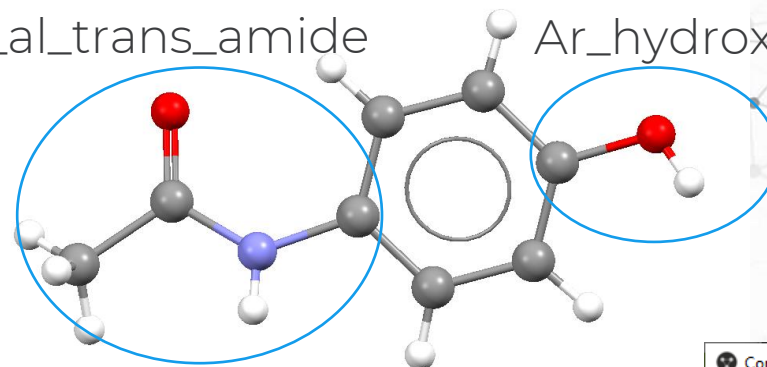
Distance < sum of vdW radii +0.1 Angstroms

h-bond angle unspecified

Modify... OK Cancel

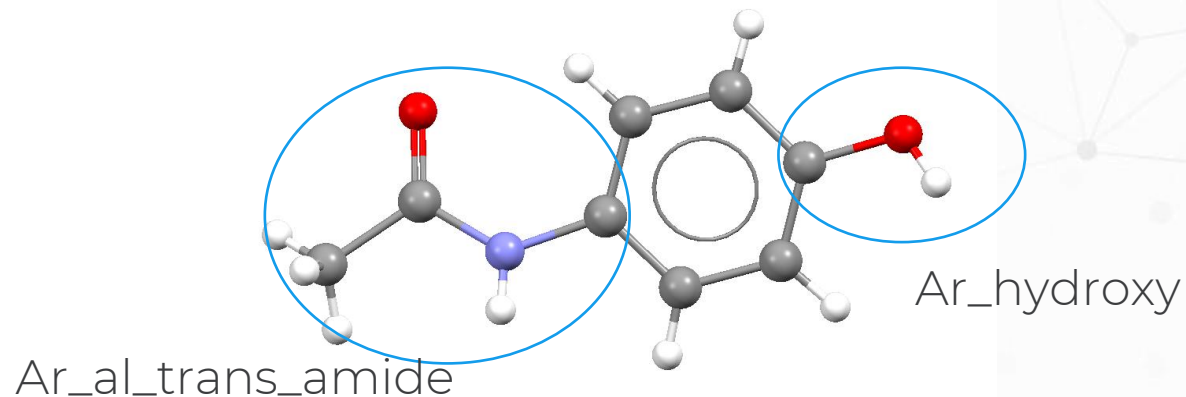
Ar_al_trans_amide

Ar_hydroxy

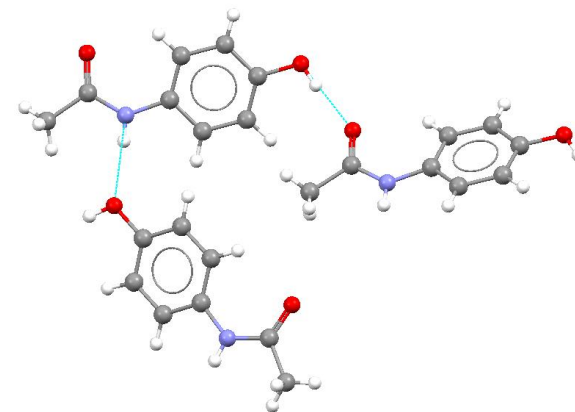


Investigating intermolecular interactions

- HXACAN



Donor	Acceptor	Hits	Frequency of Occurrence
Ar_hydroxy	Ar_al_trans_amide	79	41.6
Ar_hydroxy	Ar_hydroxy	3413	12.3
Ar_al_trans_amide	Ar_hydroxy	37	19.5
Ar_al_trans_amide	Ar_al_trans_amide	1131	32.8



*Searched best representative list

Investigating possible co-formers

For the *pure* form, the frequency of occurrence of interactions:

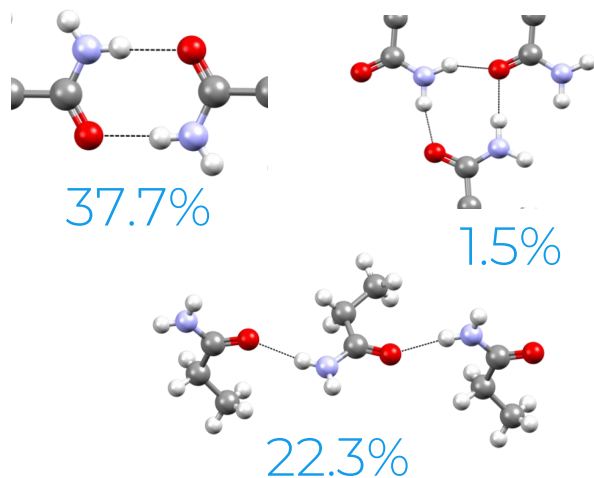
NH of trans amide to OH	20%	Trans-amide to trans-amide	33%
OH to C=O trans amide	42%	OH to OH	12%

Look at possible co-former groups: COOH, aromatic_nitrogen, saturated ring NH

motif	# structure	% frequency	Observed cocrystals
> inter_A-B- (A=NH1 of ar_al_trans_amide B=O of al_cooch_1)	60	35.7	0
> inter_A-B- (A=NH1 of ar_al_trans_amide B=N of aromatic_nitrogen)	46	27.4	2
> inter_A-B- (A=NH1 of ar_al_trans_amide B=NH1 of saturated_ring_NH)	3	9.09	2
> inter_A-B- (A=O of al_cooch_1 B=OH1 of ar_hydroxy)	135	25.1	1
> inter_A-B- (A=N of aromatic_nitrogen B=OH1 of ar_hydroxy)	1252	63.8	12
> inter_A-B- (A=NH1 of saturated_ring_NH B=OH1 of ar_hydroxy)	93	44.1	4

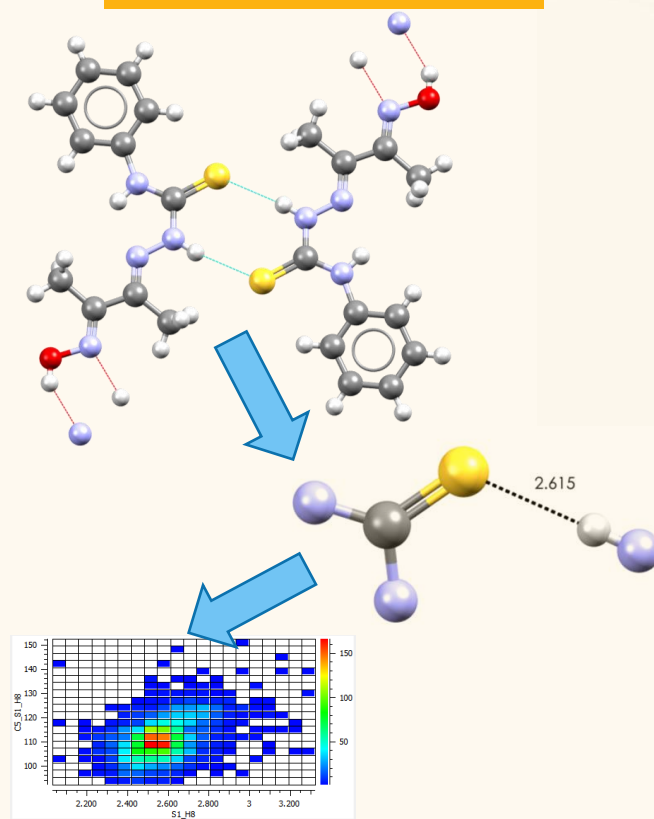
Searching motifs and crystal packing

Motifs

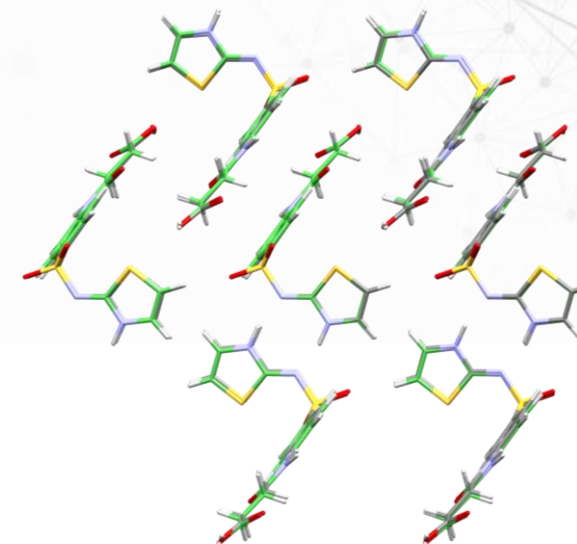


- H-bond motifs

Crystal Packing Feature

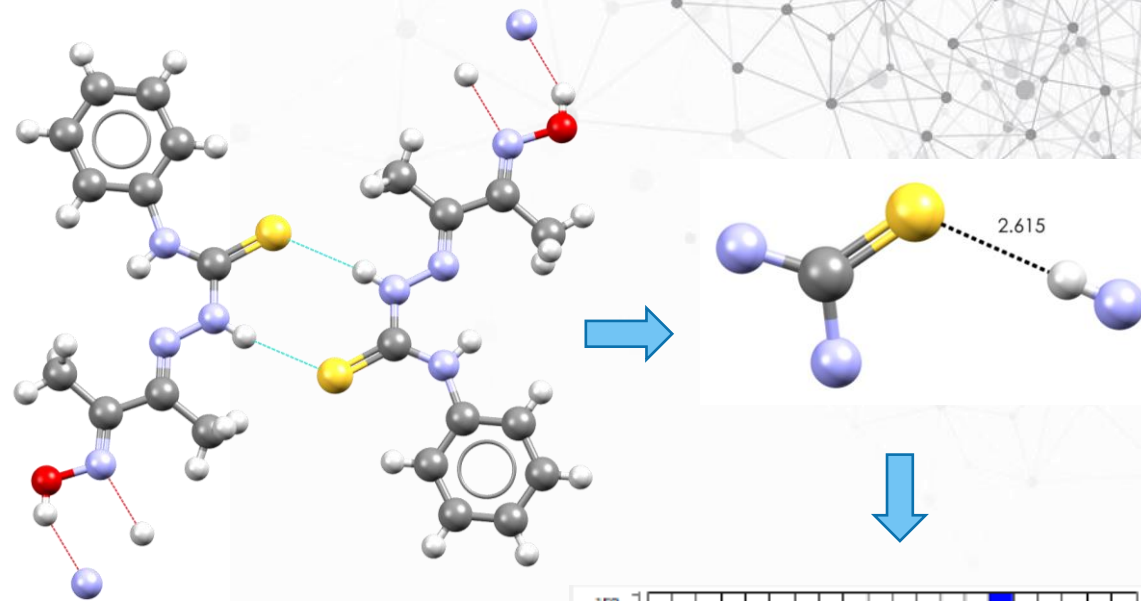


Crystal Packing Similarity

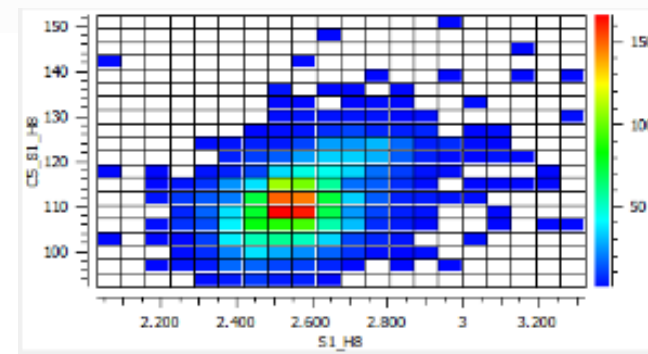


Crystal Packing Feature Search

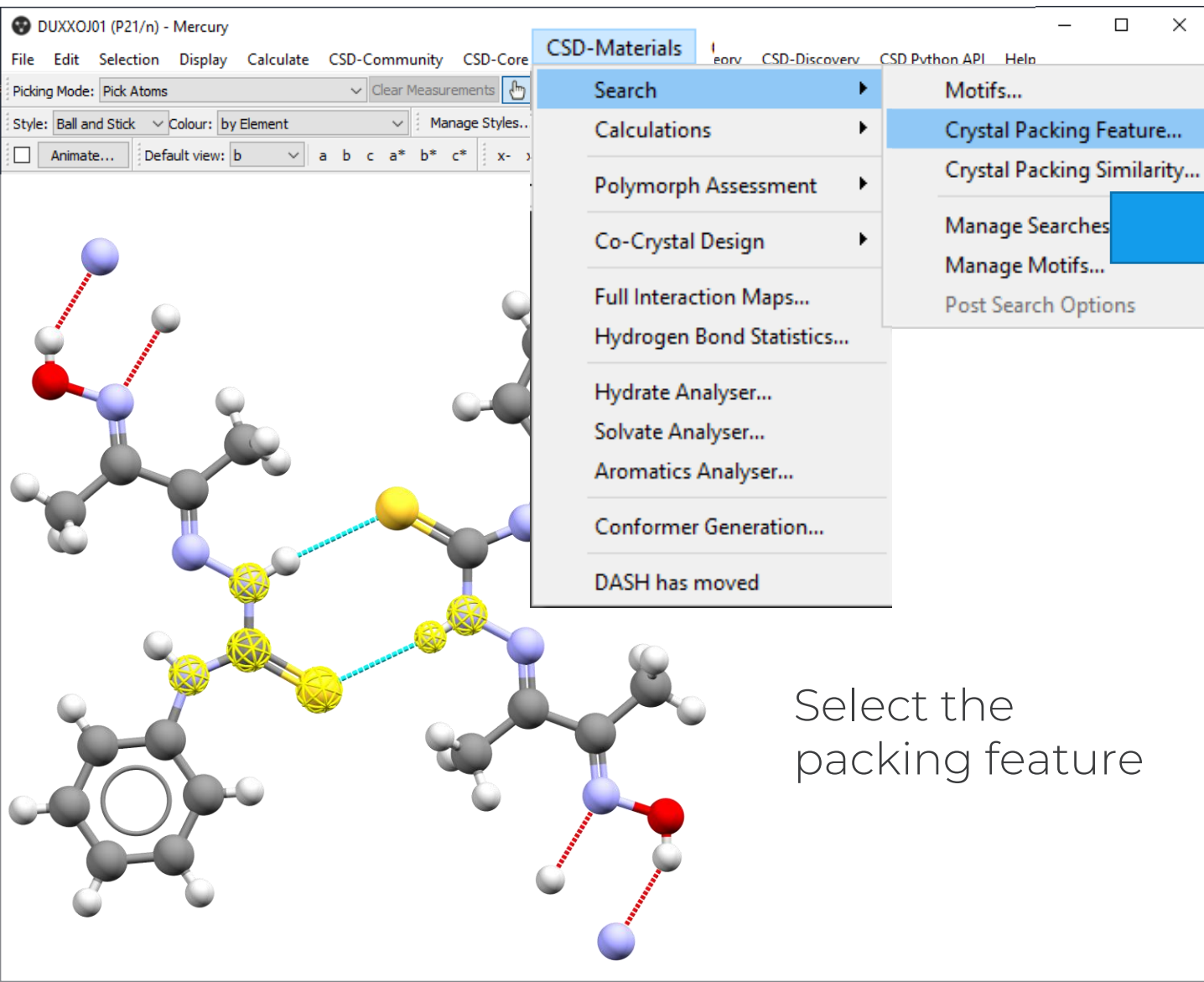
- Perform a substructure search
- Investigate conformations of molecules or bonded fragments
- Search for non-covalent interactions such as π - π or hydrogen bond interactions
- Search for particular spatial arrangements of functional groups
- Search for particular spatial arrangements of molecules



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



Searching for packing features



The screenshot shows the Mercury software interface. The main window displays a ball-and-stick model of a crystal structure with atoms represented by spheres and bonds by sticks. A menu is open over the 'CSD-Materials' tab, with the 'Search' option selected. The 'Search' submenu is also open, showing 'Crystal Packing Feature...' as the selected option. A blue arrow points from this menu item towards the 'Packing Feature Search Wizard' dialog box on the right.

DUXXOJ01 (P21/n) - Mercury

File Edit Selection Display Calculate CSD-Community CSD-Core

Picking Mode: Pick Atoms Clear Measurements

Style: Ball and Stick Colour: by Element Manage Styles...

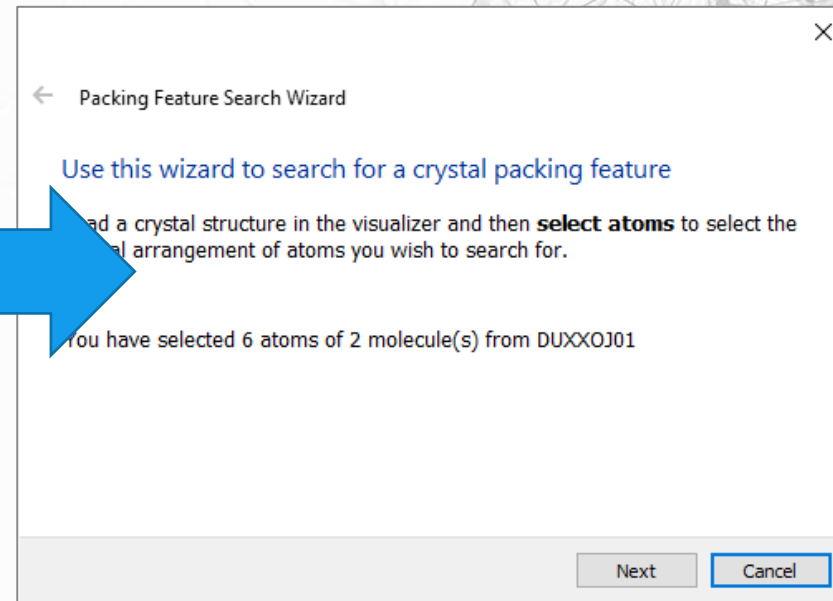
Animate... Default view: b a b c a* b* c* x-

CSD-Materials

- Search
- Calculations
- Polymorph Assessment
- Co-Crystal Design
- Full Interaction Maps...
- Hydrogen Bond Statistics...
- Hydrate Analyser...
- Solvate Analyser...
- Aromatics Analyser...
- Conformer Generation...
- DASH has moved

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

Select the packing feature



The screenshot shows the 'Packing Feature Search Wizard' dialog box. It contains instructions for using the wizard to search for a crystal packing feature. A blue arrow points from the 'Crystal Packing Feature...' menu item to the 'Next' button.

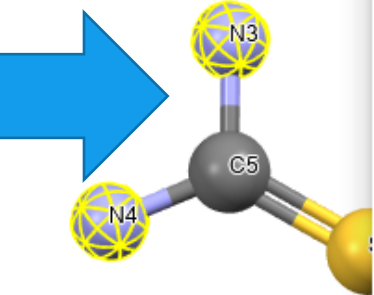
Packing Feature Search Wizard

Use this wizard to search for a crystal packing feature

Load a crystal structure in the visualizer and then **select atoms** to select the arrangement of atoms you wish to search for.

You have selected 6 atoms of 2 molecule(s) from DUXXOJ01

Next Cancel



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	hydroger	bonds
N4	1	N	1	3
N3	1	N	1	3
C5	1	C	0	3
H8	2	H		1
N3	2	N	1	3
S1	1	S	0	1

Search Options

- Modify
- Element
- Hydrogens
- Charge
- Number of bonded atoms
- Cyclicity
- Charge
- Cyclicity

Next Cancel



Packing Feature Search Wizard

Allow tolerances on the geometry of the packing feature

Level of Geometric Similarity Required

Very high High Medium Low Custom

Custom Tolerances

Distances must match those of selected feature to within + or - 30 %

Angles must match those of selected feature to within + or - 20 degrees

Match Options

All matched fragments must belong to same molecule

Show distances Show angles

Next Cancel

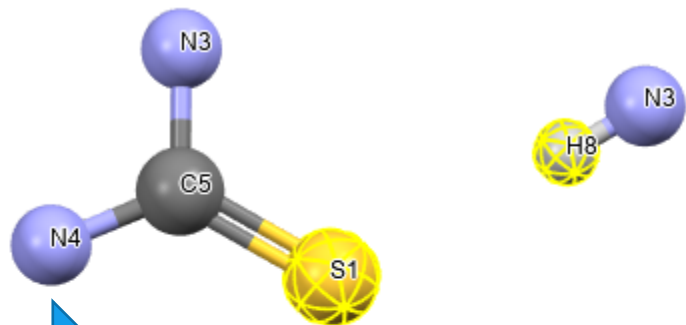
Element

- C
- H
- O
- N
- S
- P
- F
- Cl
- Any
- More
- Other Elements...

More

- Any Halogen
- Any Metal
- Any Non Metal
- Any Transition Metal
- C or H
- C or N
- Not Hydrogen
- O or S
- Other Elements...

You may set some atoms or bonds to be variable. E.g., the selected ones could be either a C or an N



You may set to monitor some parameters such as distances, angles and torsions

Packing Feature Search Wizard

Select Parameters

Select atoms in the visualiser to select **distance**, **angle** or **torsion** parameters. Or simply press 'Next'.

Current Selection:
S1 H8
Add Distance >

Parameter List

Delete
Rename

Next

Packing Feature Search Wizard

Select search structures

Use the buttons to select/deselect items you wish to use

Available Structures

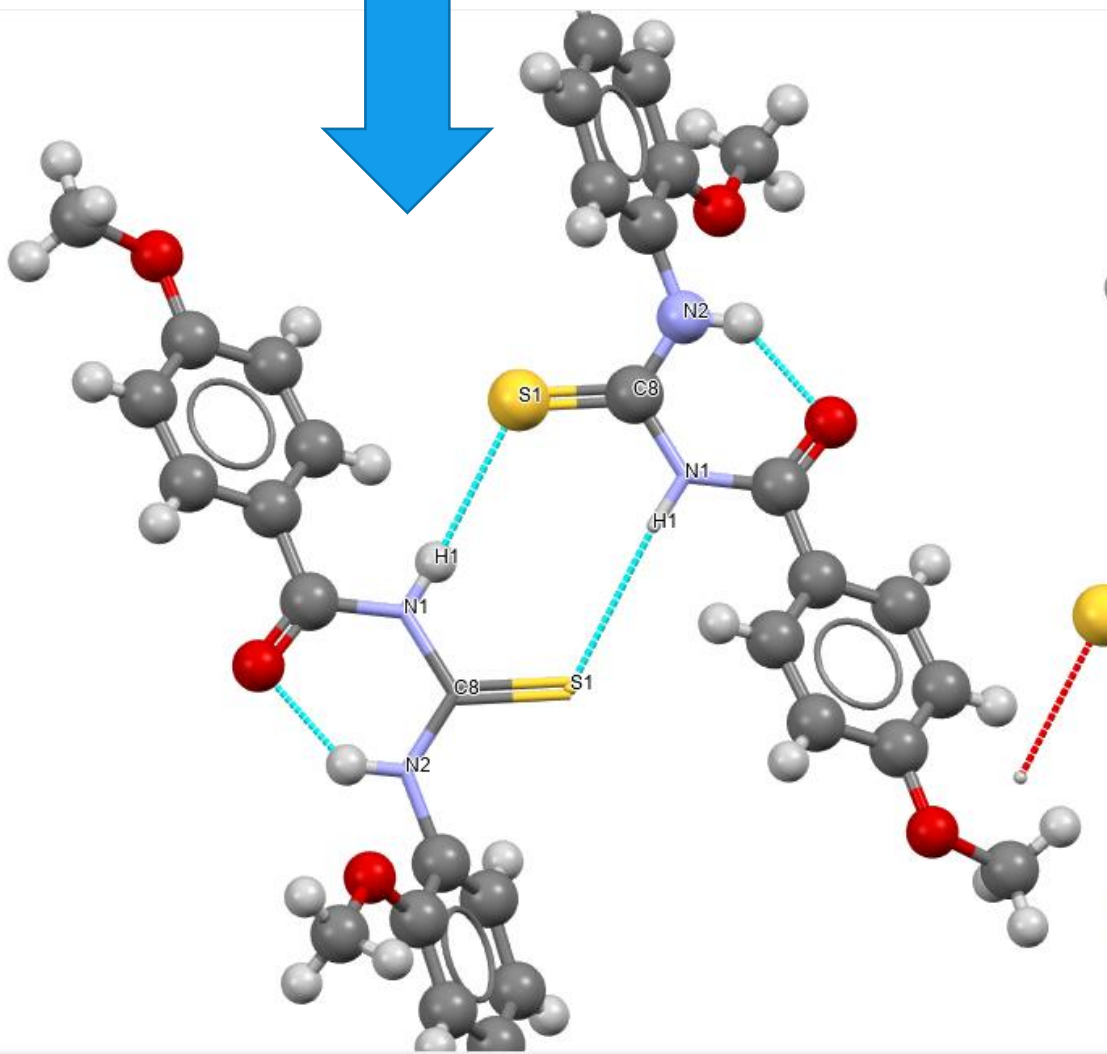
- ▼ Databases
 - Mar22

Selected Structures (1161919)

- ▼ Databases
 - CSD 5.43

Next Cancel

Select filters and name the run and start the search!



Searches

Packing Feature_feature_search

1762 hits	RMS	S1_H8
ABEFAP	0.048	2.70176
ABESUW	0.148	2.51547
ABOVEW	0.118	2.58532
ABOVOG	0.133	2.56231
ACAFEQ	0.253	2.47826
ACAFEQ01	0.156	2.54067
ACAFIU	0.245	2.50152
ACAFUG	0.24	2.64227
ACESOR	0.231	2.50905
ACEXIQ	0.181	2.69929
ACIZAP	0.146	2.65814
ADAHET	0.192	2.64739
ADAVOR	0.147	2.61819
ADEZAL	0.187	2.54114
ADEZAL02	0.198	2.52302
ADISIR	0.077	2.77197
AFUGOZ	0.236	2.59472
AFULOE	0.1	2.60527
AGAVIP	0.209	2.57117

View Options

- Show packing feature
- Show negative results
- List all matches

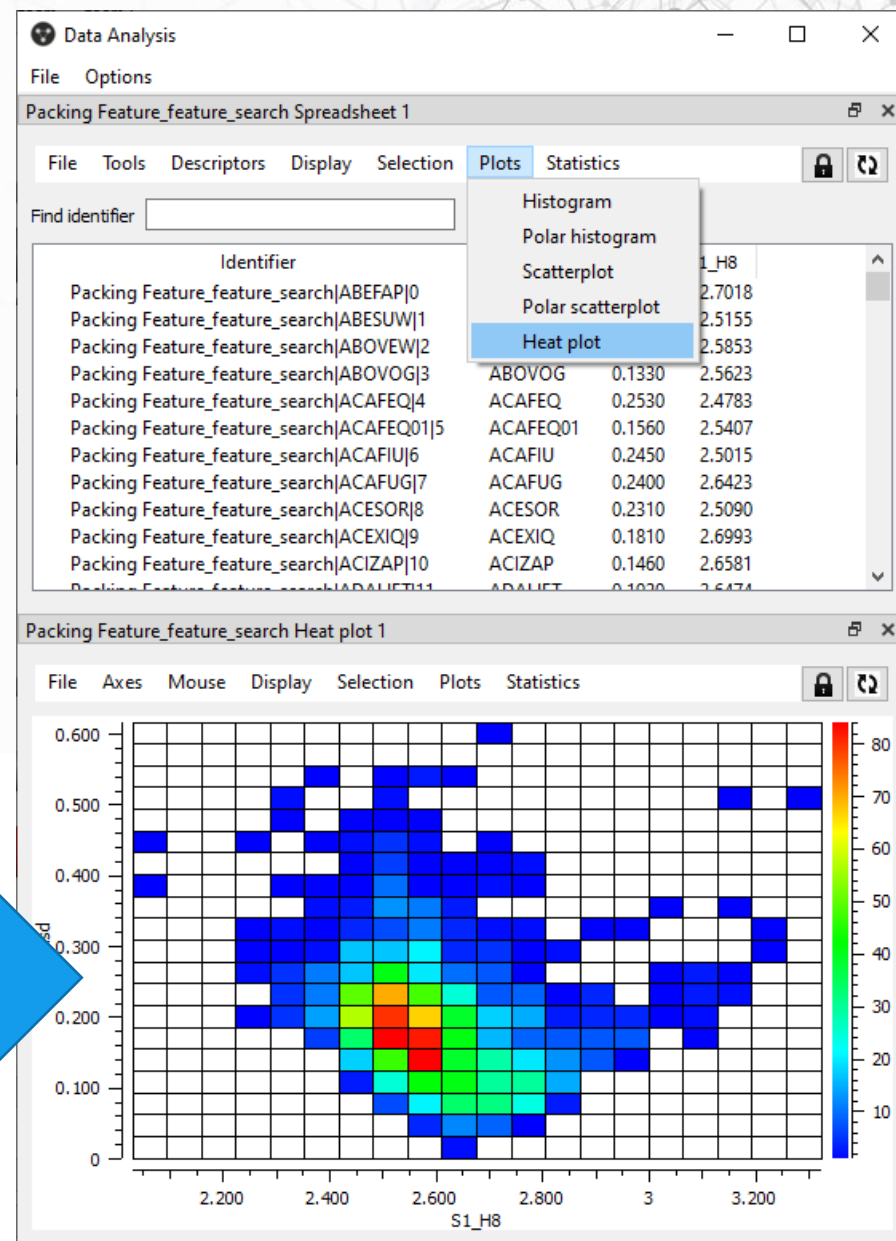
Spreadsheet...

Structure Navigator Searches

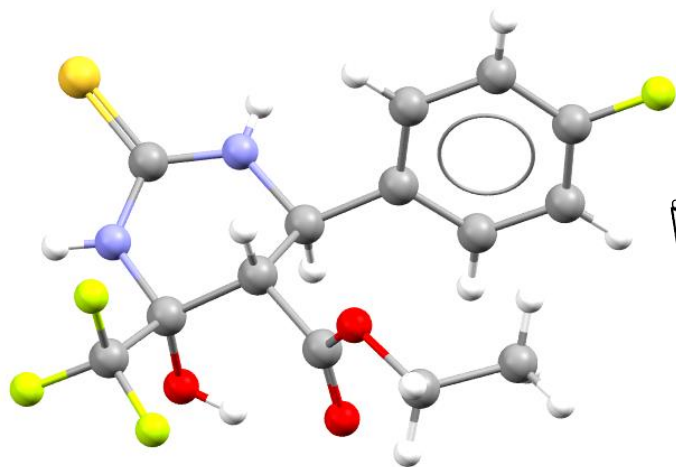
Post Search Options

Packing Feature_feature_search complete
Would you like to:

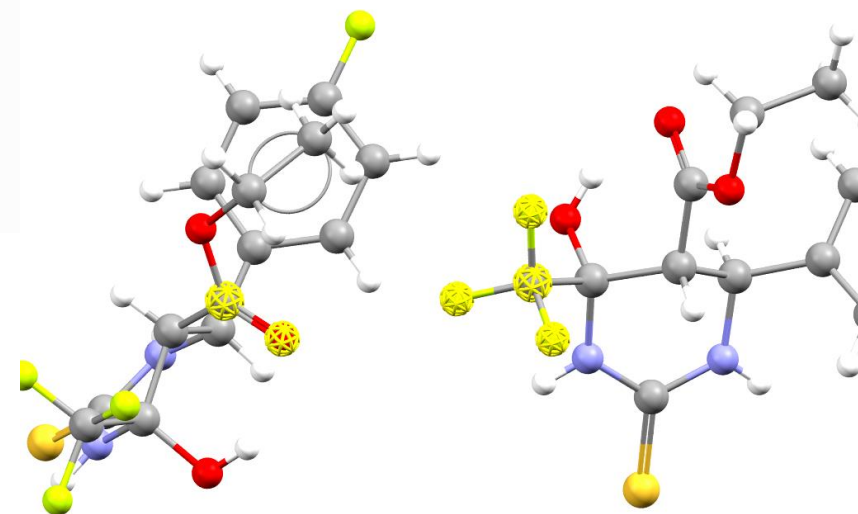
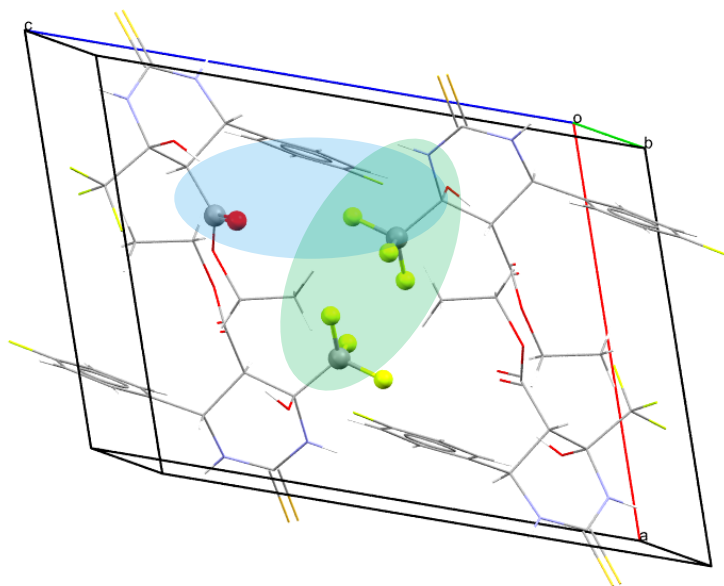
Analyse the results



Interactions that are not H-bonds

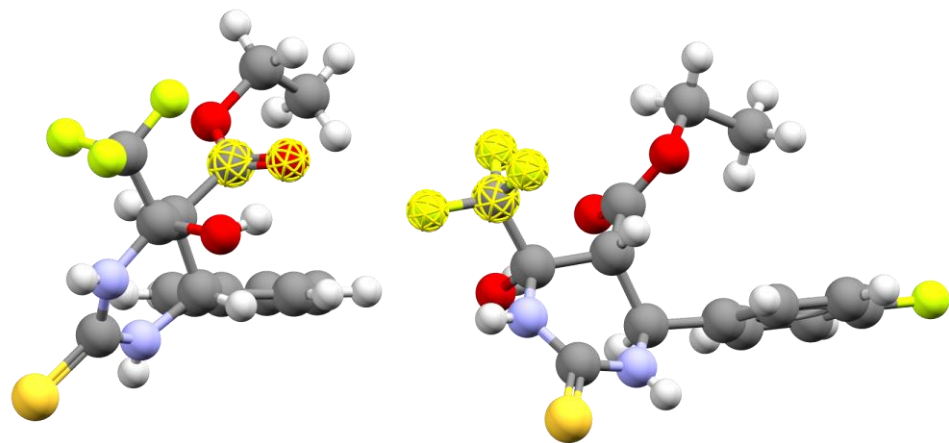


LAQKEV



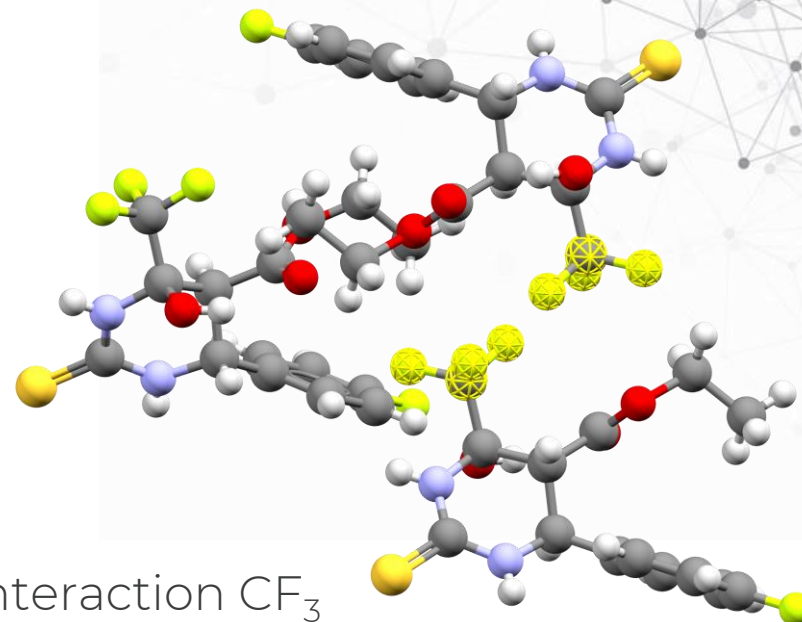
CCDC

Interactions that are not H-bonds



CF₃ interaction with carbonyl
Packing Feature search
367 hits (5735 structures searched) 6.4%

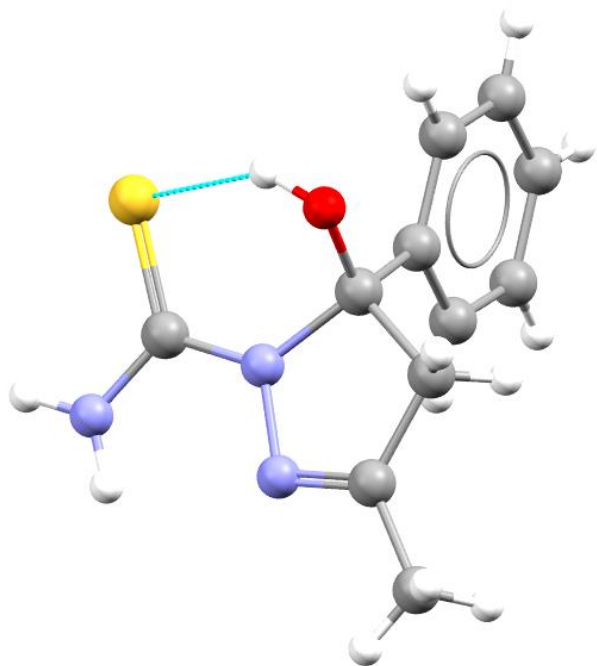
Rf values for F...O interactions ~0.3



CF₃ interaction CF₃
Packing Feature search
2114 hits (12406 structures searched) 17.0%

Rf value for CF₃-CF₃ up to 1.26

Intramolecular geometry



- Intramolecular bond
- How common is this?

ABACAJ

Intramolecular geometry

← Packing Feature Search Wizard

Use this wizard to search for a crystal packing feature

Load a crystal structure in the visualizer and then **select atoms** to select the spatial arrangement of atoms you wish to search for.

Or load a previously defined feature <select feature>

You have selected 6 atoms of 1 molecule(s) from ABACAJ

← 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'.

atom	residue	elements
S1	1	S
C1	1	C
O1	1	O
C5	1	C
N3	1	N
H6	1	H

Search Options

Modify

Reset

Add Constraint

Number of hydrogens

Number of bonds

Charge

Cyclicity

Next Cancel

← Packing Feature Search Wizard

Select Parameters

Select **atoms** in the visualiser to select **distance**, **angle** or **torsion** parameters. Or simply press 'Next'.

Current Selection:

Parameter List

- S1_O1
- O1_C5_N3_C1
- S1_C1_N3_C5

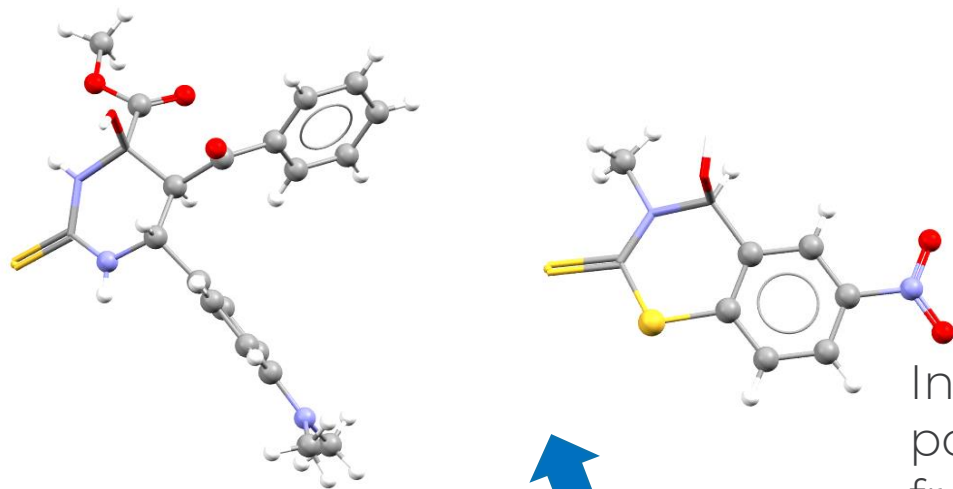
Delete

Rename

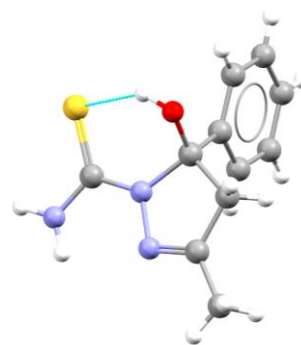
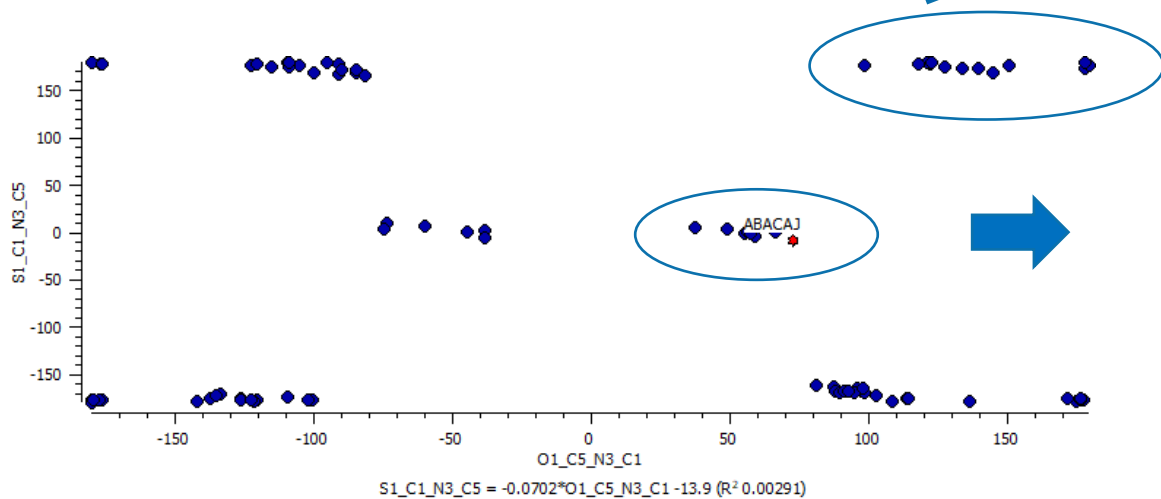
Add >

Next Cancel

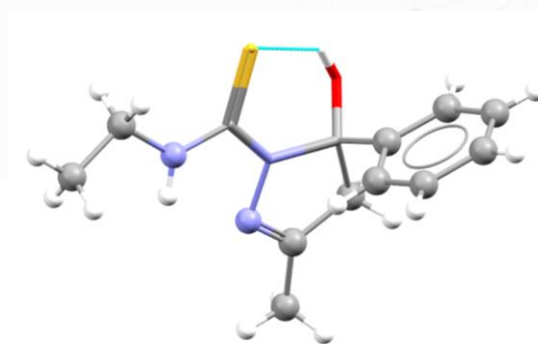
The image shows a sequence of three screenshots from a software interface. The first screenshot shows the initial wizard screen with instructions and a 3D molecular model where six atoms (S1, C1, O1, C5, N3, H6) are highlighted in yellow. A blue arrow points from this screen to the second screenshot. The second screenshot shows the 'Allow variable atom and bond types' step, featuring a table of selected atoms and a list of search options. A blue arrow points from the second screenshot to the third screenshot. The third screenshot shows the 'Select Parameters' step, where a parameter list is populated with 'S1_O1', 'O1_C5_N3_C1', and 'S1_C1_N3_C5'. The 3D model in this screenshot shows green dashed lines representing the selected parameters: a distance of 3.126 between S1 and O1, an angle of -0.79 between C1, N3, and O1, and a torsion angle of 55.4 between C1, N3, C5, and O1.



Intramolecular interaction not possible due to chemistry of fragment

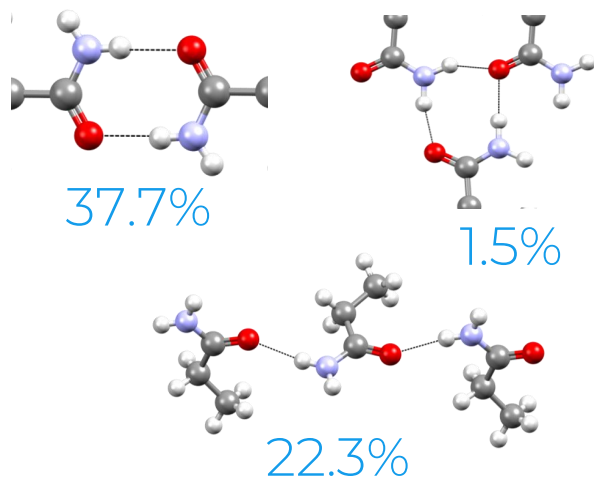


When physically allowed, intra H bond, observed frequently



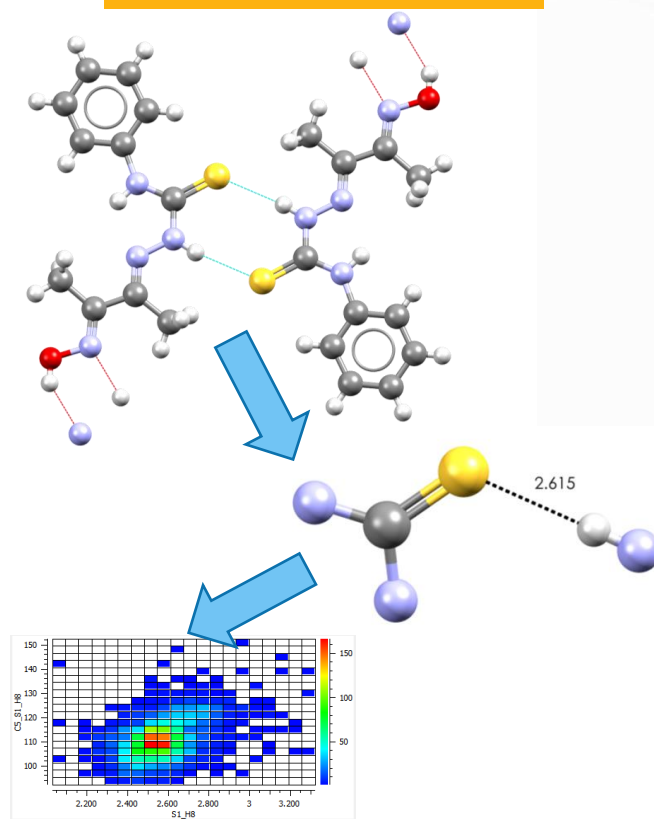
Searching motifs and crystal packing

Motifs

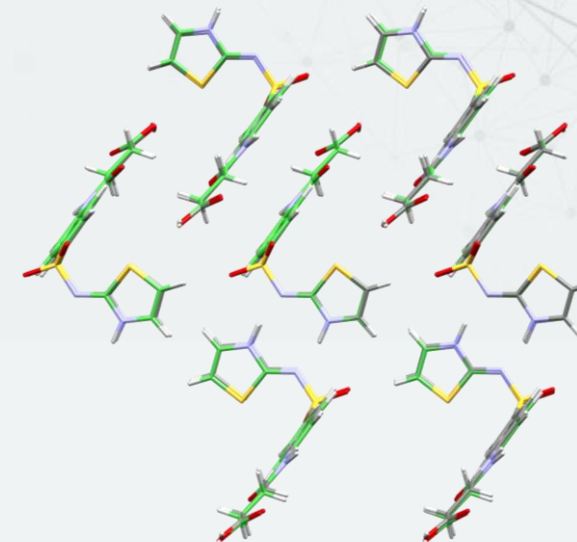


- H-bond motifs

Crystal Packing Feature

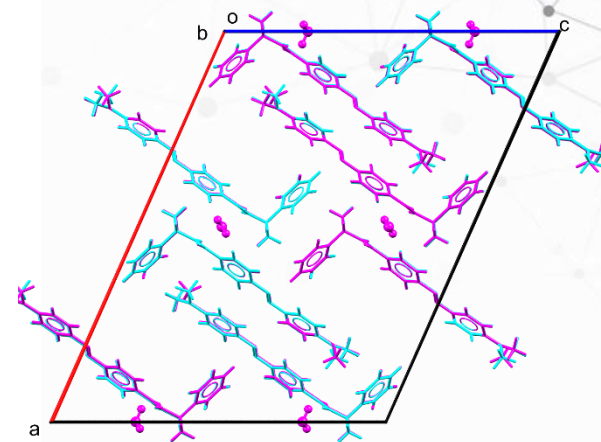


Crystal Packing Similarity



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:

- CN(C)c1ccc(cc1)/N=N/c2ccc(cc2)Nc3ccccc3 (Refcode: URUCAN)
- and its hydrated structure (Refcode: URUCEL)

Molecules depicted in:

- **magenta** show the hydrated structure
- **blue** show the anhydrous structure

Searching for packing similarity

The image shows a screenshot of the Mercury software interface. The main window displays a ball-and-stick model of a complex organic molecule. The 'CSD-Materials' menu is open, and the 'Crystal Packing Similarity...' option is highlighted with a blue arrow. Below the menu, the 'Select structures to compare' dialog box is open, showing the 'Reference Structures' list with 'URUCAN' and the 'Comparison Structures' list. A second dialog box, 'Enter Refcode', is also open, showing the refcode 'URUCER' and the 'Refcode Family' field.

URUCAN (C2/c) - 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

Select structures to compare

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

Reference Structures

URUCAN

Select... Add Refcode... Remove

Comparison Structures

Select... Add Refcode... Remove

Compare Next Cancel

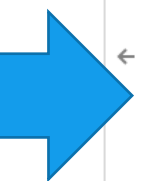
Enter Refcode

Refcode: URUCER

Refcode Family: URUCER

Enter refcode family

OK Cancel



Packing Similarity Wizard

Select Options

Packing shell size

Size of molecular cluster to compare: molecules

Filter comparisons that do not have all 30 molecules in common

Geometric tolerances

Distance tolerance: %

Angle tolerance: degrees

Default

Packing Similarity Wizard

Select Options

When comparing crystals

Allow molecular differences Allow structure inversion

Ignore hydrogen positions Ignore each atom's hydrogen count

Ignore bond types Ignore each atom's bond count

When comparing multi-component crystals

Ignore smallest molecular components

When comparing Z' > 1 crystals

Show only the highest similarity result

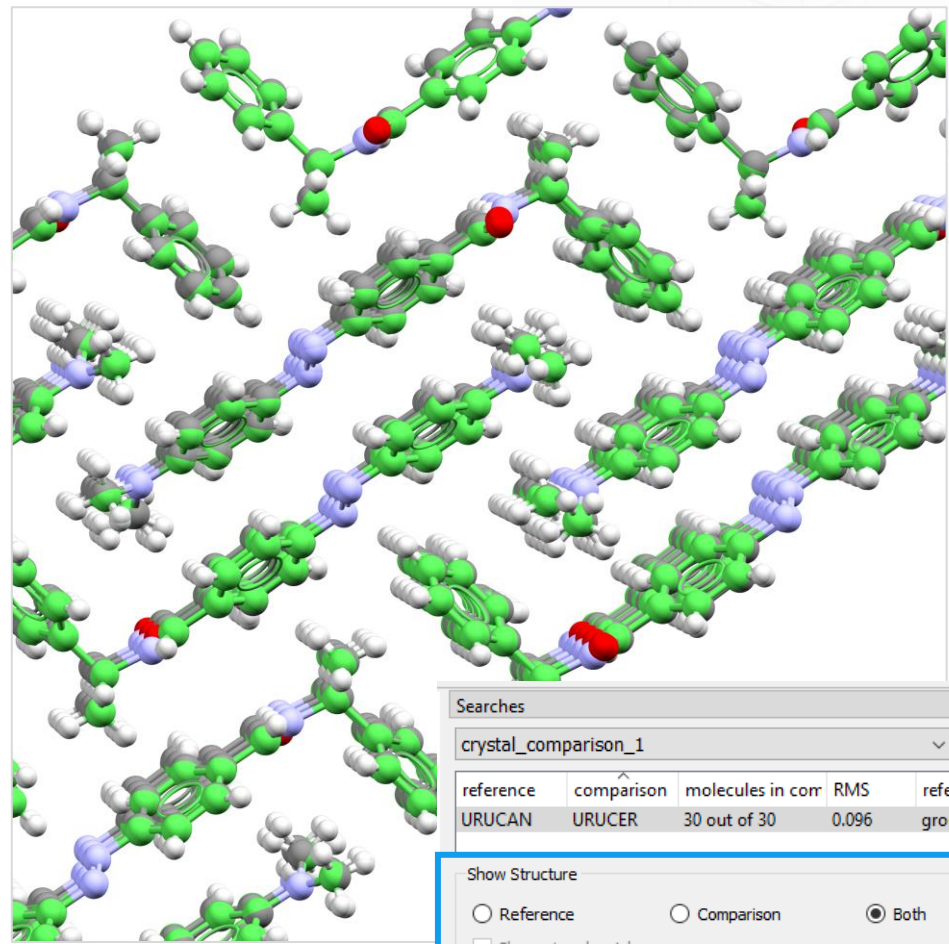
Default

Packing Similarity Wizard

Enter a name for the search

Enter Search Name

Compare Cancel



- Reference structure: **grey** carbon atoms.
- Comparison structure: **green** C if in matching molecules, **red** C if missed matches.

Searches

crystal_comparison_1 Options

reference	comparison	molecules in com	RMS	reference group
URUCAN	URUCER	30 out of 30	0.096	group1

Show Structure

Reference Comparison Both

Show missed matches

Group by similarity

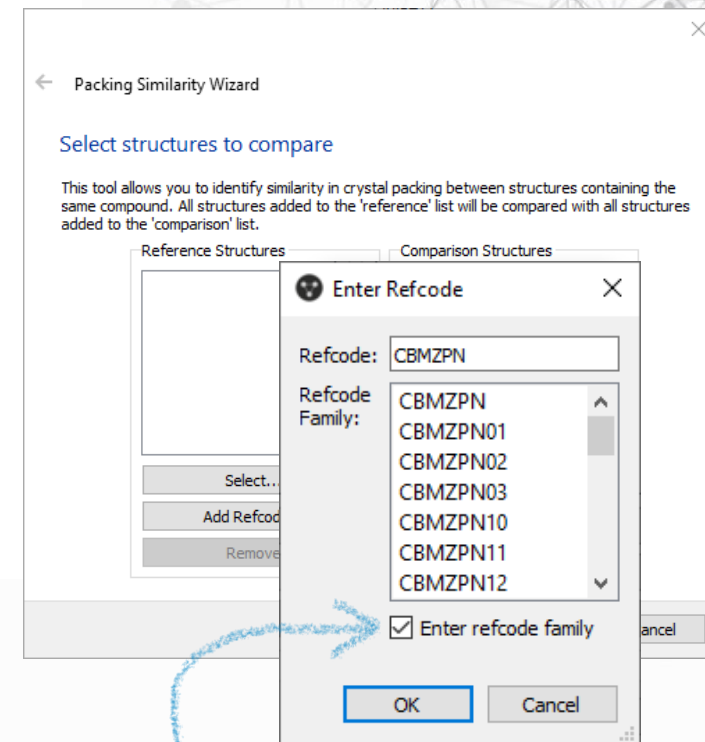
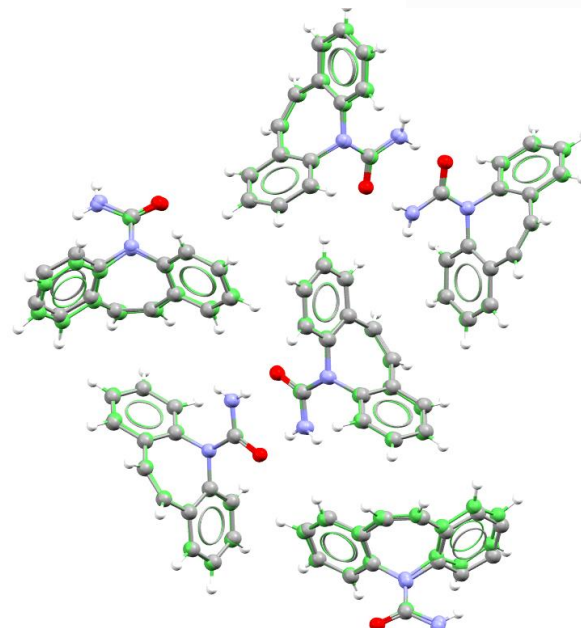
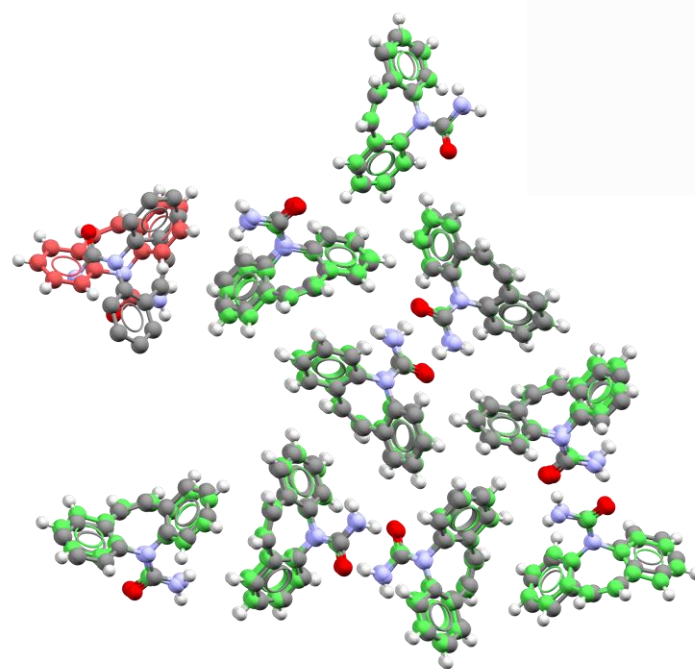
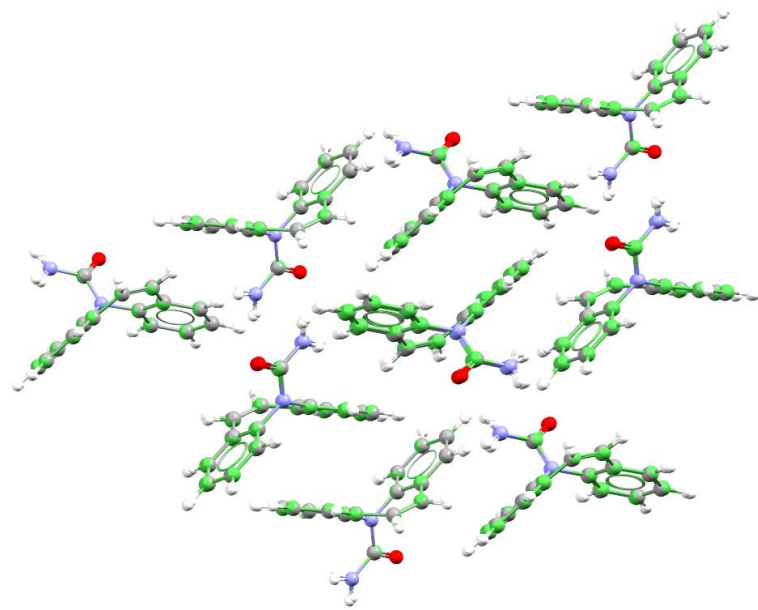
Structure Navigator Searches

Post Search Options

Select what to visualise

Carbamazepine

- CBMZPN
- Quickly identify similarly packed structures/
polymorph families

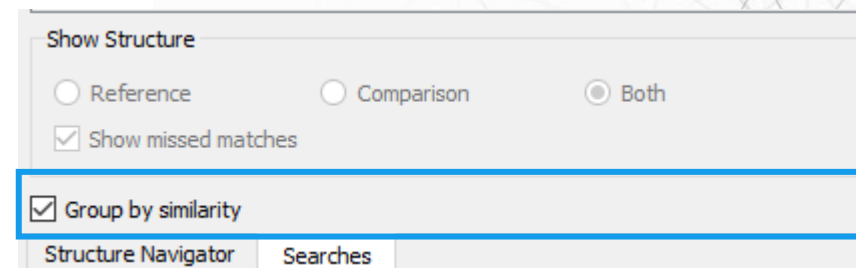


Tick Enter refcode family to add all the structures of carbamazepine

Carbamazepine

- Quickly identify similarly packed structures/ polymorph families

reference	comparison	molecules in com	RMS	reference	PXRD similarity	group	spacegroup	density	a	b	c	alpha	beta	gamma
CBMZPN01	CBMZPN02	15 out of 15	0.011	group2	1	group1								
CBMZPN01	CBMZPN03	2 out of 15	0.288	group2	0.803	group1								
CBMZPN01	CBMZPN10	15 out of 15	0.008	group2	1	CBMZPN13	P-1	1.335	5.1856	20.57...	22.24...	84.19...	87.97...	85.1053
CBMZPN01	CBMZPN11	2 out of 15	0.306	group2	0.889	CBMZPN03	R-3	1.235	35.454	35.454	5.253	90	90	120
CBMZPN01	CBMZPN12	2 out of 15	0.127	group2	0.919	CBMZPN11	P-1	1.339	5.1705	20.574	22.245	84.124	88.008	85.187
CBMZPN01	CBMZPN13	2 out of 15	0.274	group2	0.888	group2								
CBMZPN01	CBMZPN14	15 out of 15	0.028	group2	0.999	CBMZPN17	P21/n	1.38	7.4874	11.04...	13.77...	90	92.939	90
CBMZPN01	CBMZPN16	1 out of 15	0.074	group2	0.919	CBMZPN18	P21/n	0	7.4874	11.04...	13.77...	90	92.939	90
CBMZPN01	CBMZPN17	15 out of 15	0.084	group2	0.993	CBMZPN19	P21/n	1.38	7.487	11.041	13.775	90	92.9	90
CBMZPN01	CBMZPN18	15 out of 15	0.084	group2	0.993	CBMZPN20	P21	1.342	7.542	11.155	13.919	90	92.885	90
CBMZPN01	CBMZPN19	15 out of 15	0.084	group2	0.993	CBMZPN21	P21/n	1.374	7.498	11.058	13.789	90	92.838	90
CBMZPN01	CBMZPN20	15 out of 15	0.015	group2	0.993	CBMZPN22	P21/n	1.382	7.4893	11.03...	13.764	90	92.953	90
CBMZPN01	CBMZPN21	15 out of 15	0.078	group2	1	CBMZPN23	P21/n	1.382	7.4893	11.03...	13.764	90	92.953	90
CBMZPN01	CBMZPN22	15 out of 15	0.09	group2	0.994	CBMZPN27	P21/n	1.373	7.494...	11.06...	13.80...	90	92.91...	90
CBMZPN01	CBMZPN23	15 out of 15	0.09	group2	0.992	CBMZPN28	P21/n	1.326	7.578	11.176	13.991	90	93.08	90
CBMZPN01	CBMZPN27	15 out of 15	0.059	group2	0.995	CBMZPN29	P21/n	1.327	7.576	11.188	13.967	90	87.03	90
CBMZPN01	CBMZPN28	15 out of 15	0.073	group2	0.998	CBMZPN30	P21/n	1.283	7.68	11.44	13.92	90	91.22	90
CBMZPN01	CBMZPN29	15 out of 15	0.057	group2	0.998	CBMZPN31	P21/n	1.386	7.46	11.04	13.76	90	92.61	90
CBMZPN01	CBMZPN30	15 out of 15	0.229	group2	0.982	CBMZPN32	P21/n	1.344	7.534	11.15	13.917	90	92.94	90
CBMZPN01	CBMZPN31	15 out of 15	0.093	group2	0.993	CBMZPN33	P21/n	1.376	7.4907	11.058	13.78...	90	92.903	90
CBMZPN01	CBMZPN32	15 out of 15	0.161	group2	0.997	CBMZPN01	P21/c	1.347	7.529	11.148	15.47	90	116.17	90
CBMZPN01	CBMZPN33	15 out of 15	0.07	group2	0.994	CBMZPN02	P21/n	1.344	7.534	11.15	13.917	90	92.94	90
CBMZPN02	CBMZPN03	2 out of 15	0.291	group2	0.804	CBMZPN10	P21/n	1.343	7.537	11.156	13.912	90	92.86	90
CBMZPN02	CBMZPN10	15 out of 15	0.012	group2	1	CBMZPN14	P21/n	1.333	7.55	11.186	13.954	90	92.938	90
CBMZPN02	CBMZPN11	2 out of 15	0.309	group2	0.89	group3								
CBMZPN02	CBMZPN12	2 out of 15	0.13	group2	0.919	CBMZPN12	C2/c	1.296	26.609	6.9269	13.957	90	109.7...	90
						group4								
						CBMZPN16	Pbca	1.326	9.1245	10.45...	24.82...	90	90	90



- Show missed matches
- Ignore smallest component
- Allow molecular differences

Review of basics of Mercury



AABHTZ (P-1) - Mercury

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

Picking Mode: Pick Atoms Clear Measurements Show Labels for All atoms with Atom Label

Style: Ball and Stick Colour: by Element or Suppression Manage Styles... Work Atom selections:

Animate... Default view: b a b c a* b* c* x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 Select by SMARTS: [c]

Structure Navigator

AABHTZ Find

Crystal Structures	Spacegroup
AABHTZ	P-1
AACANI10	P21/c
AACANI11	P21/c
AACFAZ	Pbcn
AACFAZ10	Pbcn
AACMAL	P21/c
AACMHX10	Pbca
AACRHA	Pncm
AACRHC	P-1
AACRUB	Cc
AACRUB01	C2/c
AADAMC	P21/c
AADMPY	P-1
AADMPY10	P-1
AADRIB	P21
AAGAGG10	P212121
AAGGAG10	P21

Display Options

Display

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

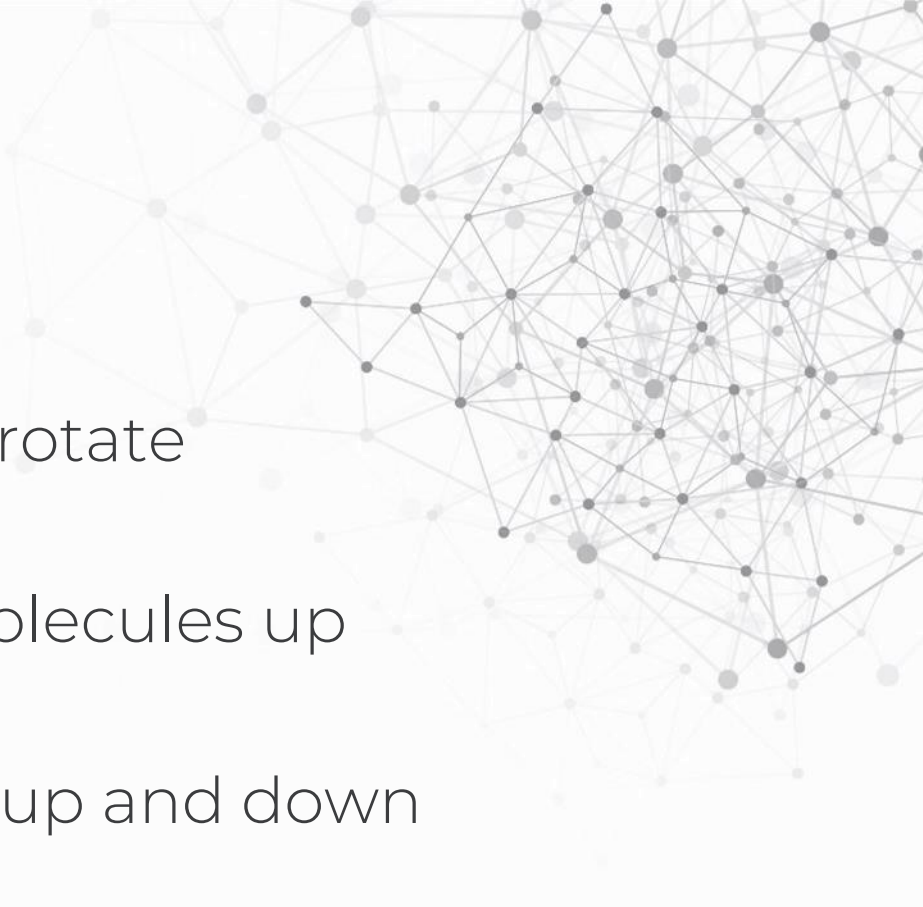





Options

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

Reset Contacts... More Info Powder... Multiple Structures Structures...

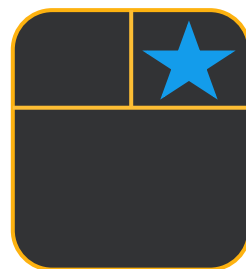
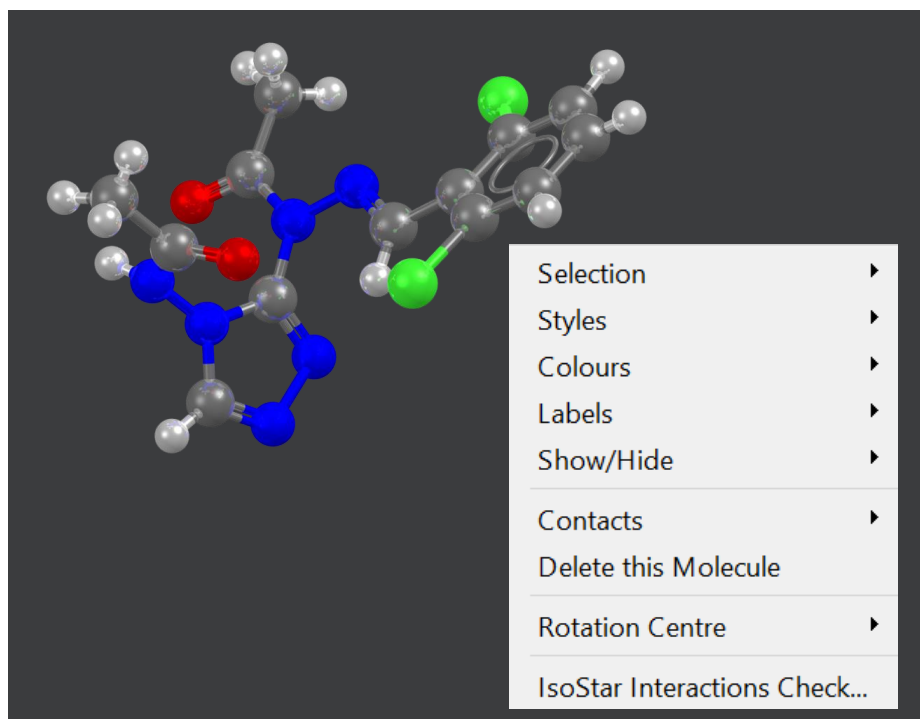
Press the left mouse button and move the mouse to rotate the structure

The 3D window basics

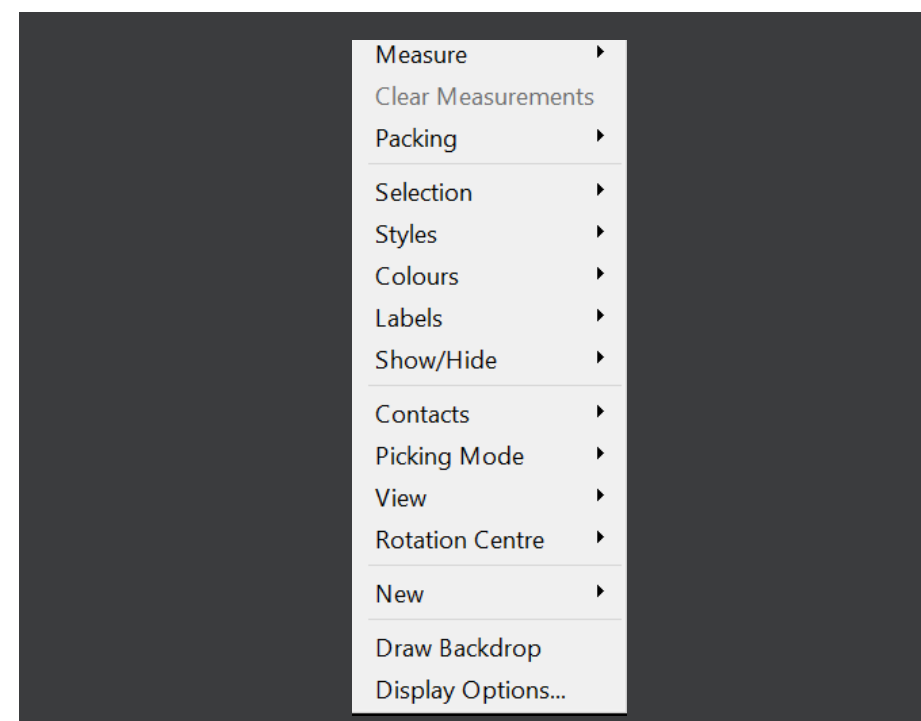
- 
-  • **Left mouse** button and move – rotate molecules
 -  • **Middle Mouse** wheel – move molecules up and down
 -  • **Right mouse** button and move up and down – zoom in and out of molecules
 -  • **Shift + Left mouse** button and move - rotate in the plane molecules
 -  • **Ctrl + Left mouse** button and move - translate molecules

Right mouse click

Near a molecule





Away from a molecule



Picking Mode: Pick Atom

Style: Capped Sticks

 Animate... De**Styles****Labels****Colours****Show/Hide****More Information****Symmetry Elements...****Voids...****Display Options...****Manage Styles...****View along****Dial box...** **Splash screen****Toolbars**Measurements    Show Labels for All atoms with Atom Label

Manage Styles... Work Atom selections:

b* c* x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 ← → ↓ ↑ zoom- >> Select by SMARTS: >>

- Display Options
- Graph Sets
- Intermolecular Potentials
- Searches
- Post Search Options
- Structure Navigator**
- Picking Toolbar
- Labels
- Display
- Style Manager Toolbar
- Atom Selection Toolbar
- Select by SMARTS
- Animation Toolbar
- Crystal Orientation Operations
- Alignment and Orientation Operations

Structure Navigator

Type in a refcode Find

Crystal Structures	Spacegroup
AABHTZ	P-1
AACANI10	P21/c
AACANI11	P21/c
AACFAZ	Pbcn
AACFAZ10	Pbcn
AACMAL	P21/c
AACMHX10	Pbca
AACRHA	Pncm
AACRHC	P-1
AACRUB	Cc
AACRUB01	C2/c
AADAMC	P21/c
AADMPY	P-1
AADMPY10	P-1
AADRIB	P21
AAGAGG10	P212121
AAGGAG10	P21
AALCFE	P21/c
AALPRO	P21/c
AAMAND	P212121
AAMTCO	P-1
AAMTCO10	P-1
AAMTXP	P21/n
AANHGX	Pna21
AANHGX01	Pna21
AANOPM	P21
AAPUNI	P21/a

Display Options

Display Packing Asymmetric Unit Auto centre

Reset

 Short Contact < (sum of vdW radii) H-Bond Default definition

Contacts...

More Info

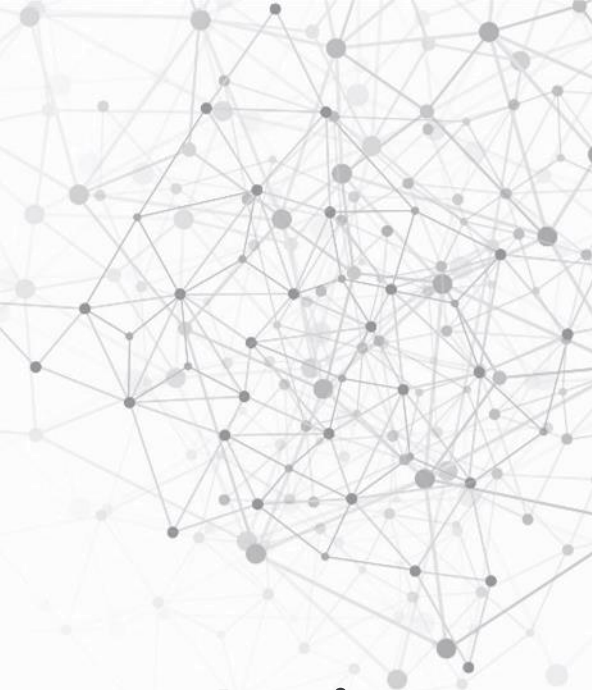
Powder...

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

<< >>

 Tree View Multiple Structures

Structures...

**Handy tips:**

- Recovering Toolbars
- Resetting view

Changing display - Style

Display Calculate CSD-Community CSD-System CSD-M

- Styles ▶
 - Wireframe
 - Stick
 - Ball and stick
 - Spacefill
 - Ellipsoid
 - Polyhedral
- Labels ▶
- Colours ▶
- Show/Hide ▶
- More Information ▶
- Symmetry Elements...
- Voids...
- Display Options...
- Manage Styles...
- View along ▶
- Dial box...
- Splash screen
- Toolbars ▶

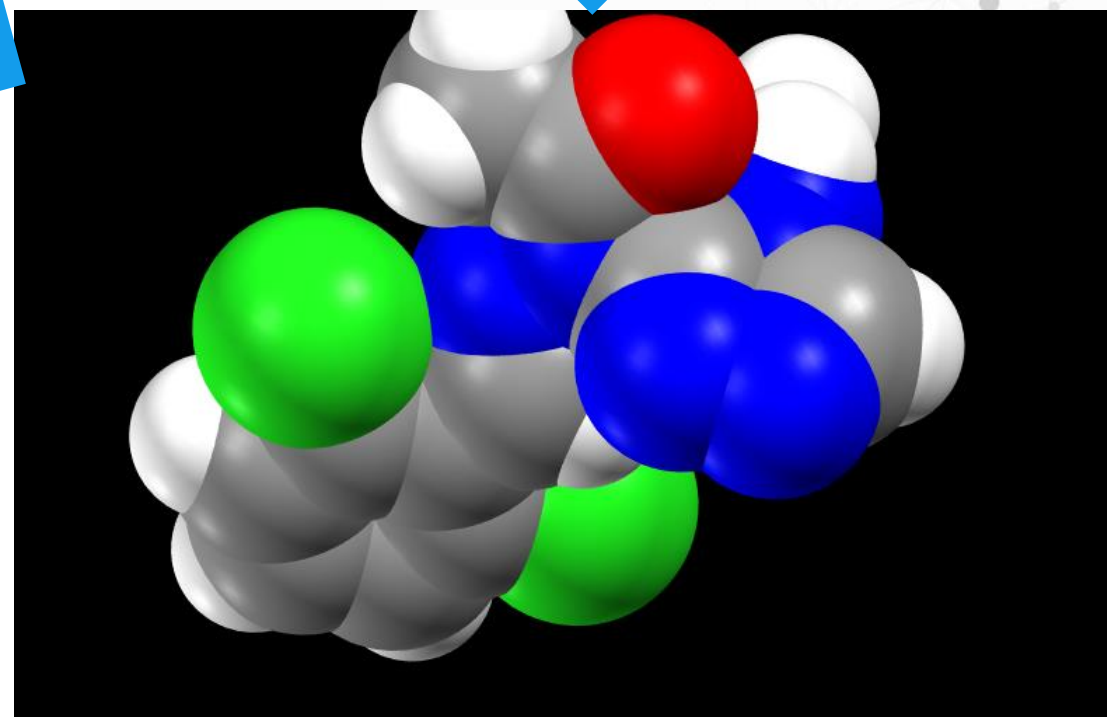
Stick settings...
Ball and Stick settings...
Spacefill settings...
Ellipsoid settings...
Polyhedral settings...
Contact settings...
Measurement settings...
Selected atoms

File Edit Selection Display Calculate C...

Picking Mode: Pick Atoms

Style: Spacefill ▼ Colour: by Element

Animate... Fault view: b ▼



AABHTZ (P-1) - Mercury

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

Picking Mode: Expand Contacts

Style: Ball and Stick Colour:

Animate... Default view

Measurements Show Labels for All atoms with Atom Label

Manage Styles... Publication Atom selections:

x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 ← → ↓ ↑ zoom- zoom+ Select by SMARTS: >>

Structure Navigator

AABHTZ Find

Crystal Structures

AABHTZ	P-1
AACANI10	P21/c
AACANI11	P21/c
AACFAZ	Pbcn
AACFAZ10	Pbcn
AACMAL	P21/c
AACMHX10	Pbca
AACRHA	Pnccm
AACRHC	P-1
AACRUB	Cc
AACRUB01	C2/c
AADAMC	P21/c
AADMPY	P-1
AADMPY10	P-1
AADRIIB	P21
AAGAGG10	P212121
AAGGAG10	P21

Packing and Slicing

Packing

Show cell axes

Label cell axes

Pack

a: 0.0 1.0 +0.5

b: 0.0 1.0 +0.5

c: 0.0 1.0 +0.5

2x2x2

Reset 3x3x3

Include atoms

... that fit

... in molecules whose Centroids fit

... in molecules where Any atom fits

... in molecules where All atoms fit

Display Options

Display

Packing

Asymmetric Unit

Auto centre

Short Contact < (sum of vdW radii)

H-Bond Default definition

Reset

Options

Show hydrogens Depth cue

Show cell axes Z-Clipping

Label atoms Stereo

Contacts... More Info Powder...

Reset button: a friend!

Click on a red contact to see the whole molecule

HXACAN (Pcab) - Mercury

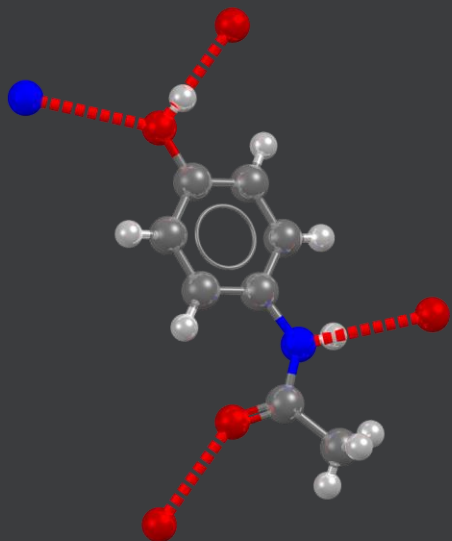
File Edit Selection Display Calculate CSD-Community CSD-Core CSD-Materials CSD-Discovery CSD Python API Help

Picking Mode: Expand Contacts Clear Measurements Show Labels for All atoms with Atom Label

Style: Ball and Stick Colour: by Element Manage Styles... Publication Atom selections:

Animate... Default view: b a b c a* b* c* x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 Select by SMARTS:

Visualising hydrogen bonds



Structure Navigator

HXACAN Find

Crystal Structures

Define H-bonds

Select options and click OK or Apply when done

Require hydrogen atom to be present

D-H...A angle >= 120.0 degrees

Donor atom types:

- all donors
- nitrogen
 - metal bound N
 - imine N
 - aromatic (6-ring) N
 - amide or thioamide N

Acceptor atom types:

- all acceptors
- nitrogen
 - metal bound N
 - terminal N (cyano, etc.)
 - aromatic (6-ring) N
 - other 2-coordinate N
 - 3-coordinate N
 - unclassified N

Distance: 5.00

Donor separated by > 3 bonds

Default Cancel Apply OK

Click on "Default definition" to change the default H-bond definition

Display Options

Display

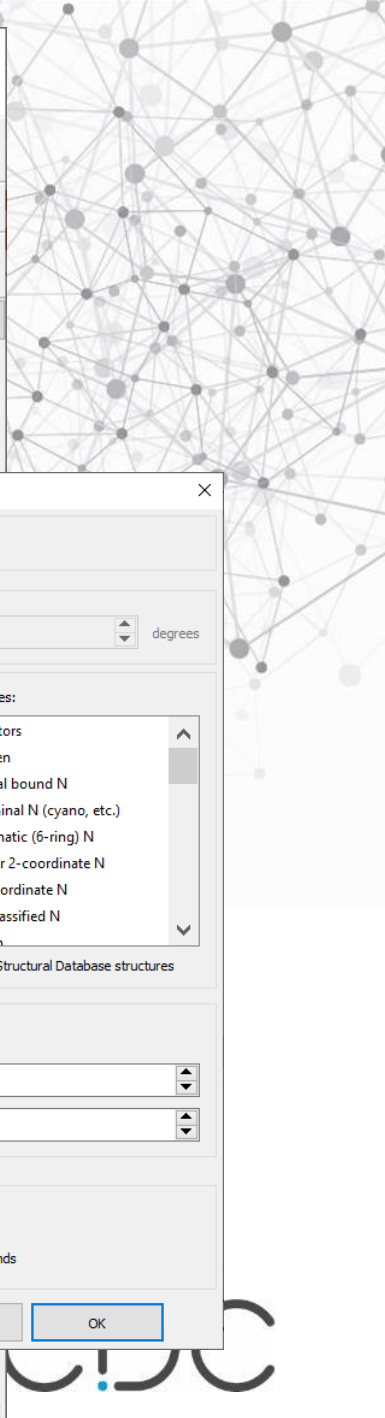
- Packing
- Asymmetric Unit
- Auto centre
- Short Contact < (sum of vdW radii)
- H-Bond Default definition

Options

- Show hydrogens
- Show cell axes
- Label atoms

Reset Contacts... More Info Powder...

Click on a red contact to see the whole molecule



HXACAN (Pcab) - Mercury

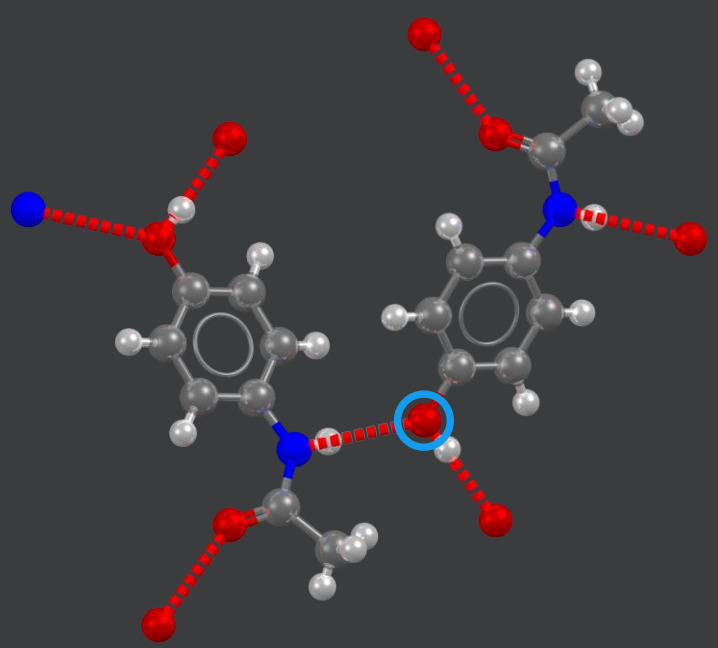
File Edit Selection Display Calculate CSD-Community CSD-Core CSD-Materials CSD-Discovery CSD Python API Help

Picking Mode: Expand Contacts Clear Measurements Show Labels for All atoms with Atom Label

Style: Ball and Stick Colour: by Element Manage Styles... Publication Atom selections:

Animate... Default view: b a b c a* b* c* x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 Select by SMARTS:

Left click on the atoms at the end of the dashed lines (known as hanging contacts) to expand the network



- Selection
- Styles
- Colours
- Labels
- Show/Hide
- Contacts**
- Delete this Molecule
- Rotation Centre
- IsoStar Interactions Check...

Right click on hanging contacts to see more advanced options including delete hanging contacts

Structure Navigator

HXACAN Find

Crystal Structures

- Expand All
- Expand Contact
- Expand Contacts from this Atom
- Expand Contacts from this Molecule**
- Find Contacts from this Atom
- Find Contacts from this Molecule
- Delete Hanging Contacts
- Delete Contact
- Delete Contacts from this Atom
- Delete Contacts from this Molecule
- Delete this Molecule
- Reset Contacts

Display Options

Tip - Change H-bond thickness by Display>Styles>Contact settings...

Tip - Change H-bond colours by Display>Colours>Contacts...>colour by distance>All contacts

Click on a red contact to see the whole molecule



Graph Sets

Calculate CSD-Community

Centroids...

Planes...

Packing/Slicing...

Contacts...

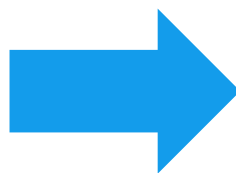
Molecular Shell...

Graph Sets...

Powder Pattern...

Structure Overlay...

Molecule Overlay...



Graph Sets describe the H-bonds pattern.

Learn more in the *Glossary* on the handout.

HXACAN (Pcab) - Mercury

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

Picking Mode: Expand Contacts Clear Measurements Show Labels for All atoms with >>

Style: Ball and Stick Colour: by Element Manage Styles... Publication Atom selections:

Animate... Default view: b a b c a* b* c* x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 Select by SMARTS: >>

Graph Sets

descriptor ^	level	period	# molecules
C1,1(7) a	1	1	2
C1,1(9) b	1	1	2
C2,2(6) >a>b	2	2	3
C2,2(16) >a<b	2	2	3
C4,4(22) >a>b<a<b	2	4	5
R4,4(22) >a>b<a>b	2	4	4
R6,6(36) >a>a>b<a<a<b	2	6	6
R6,6(40) >a>b>b<a>b>b	2	6	6

Options

Display Options

Display

Packing Short Contact < (sum of vdW radii) Contacts...

Asymmetric Unit H-Bond Default definition More Info

Auto centre Reset Powder...

Options

Show hydrogens Depth cue

Show cell axes Z-Clipping

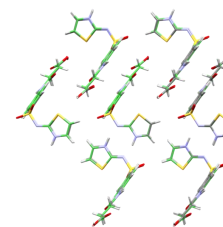
Label atoms Stereo

Click on a red contact to see the whole molecule

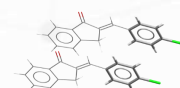
Click through the graph set descriptors to see the different H-bond patterns

Explore More: Tips and tricks

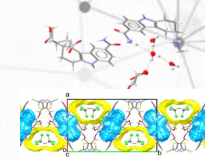
- What else can you do with CSD-Materials to investigate your solid form?
- What else can we learn from the 1.1 million structures in the CSD to guide solid form design and risk assessment?



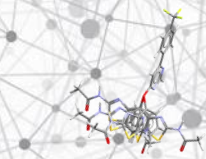
Crystal Packing Similarity



Motif Search & Packing Feature Search

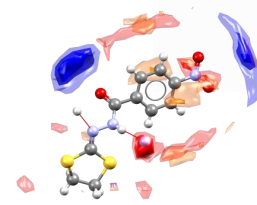


Hydrate Analyser & Solvate Analyser

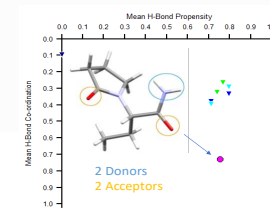


CSD Conformer Generator

Detailed Structural Analysis

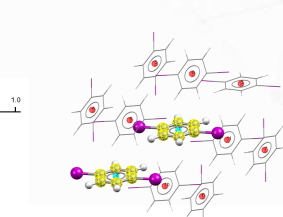


Full Interaction Maps

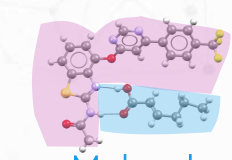


Hydrogen Bond Propensity

Solid Form Design



Aromatics Analyser

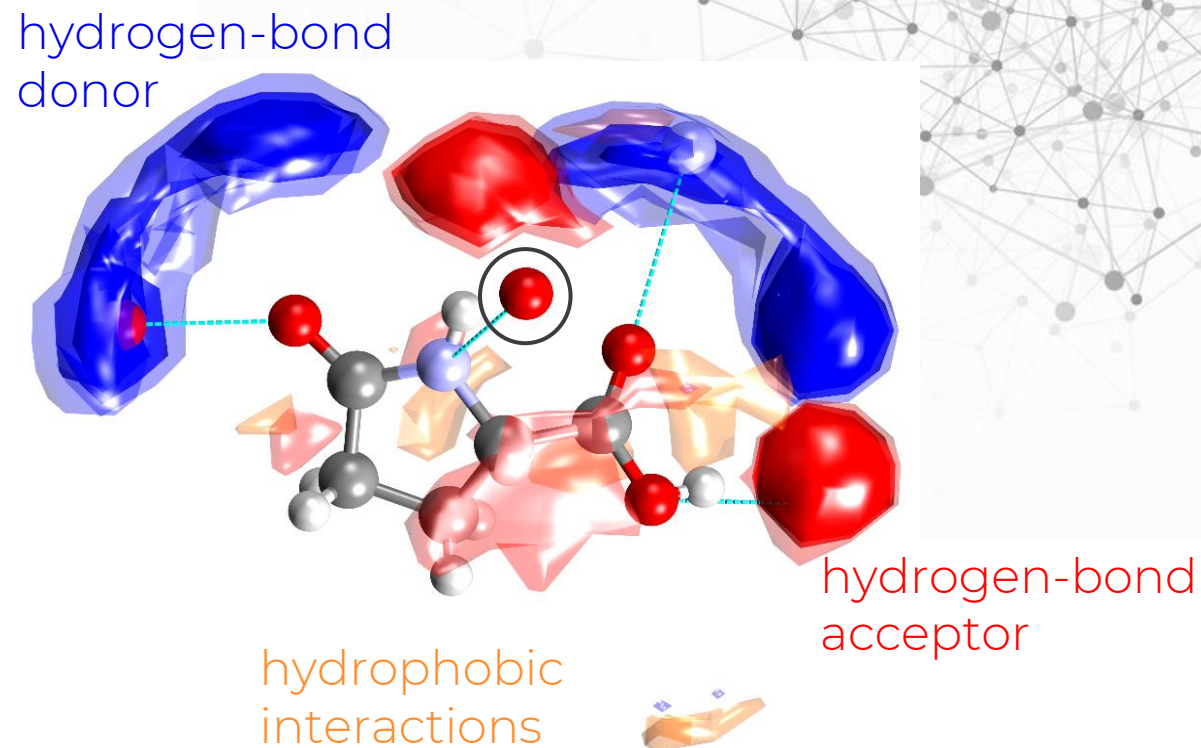


Molecular Complementarity

Solid Form Risk Assessment

Full Interaction Maps (FIMs)

- FIMs enable you to generate a 3D interaction map around a molecule representing regions of higher probability to find interactions with certain functional groups.
- Visualise observed atom-atom contacts with respect to likely geometries in 3D space.
- Identify interaction hot-spots around chemical groups.



Creating a FIM

The screenshot displays the Mercury software interface for creating Full Interaction Maps (FIM). The main window shows a ball-and-stick model of a molecule with interaction maps overlaid in various colors (red, orange, yellow, green, blue). The 'CSD-Materials' menu is open, highlighting the 'Full Interaction Maps...' option. A blue arrow points from this menu item to the 'Full Interaction Maps' dialog box.

Full Interaction Maps Dialog Box:

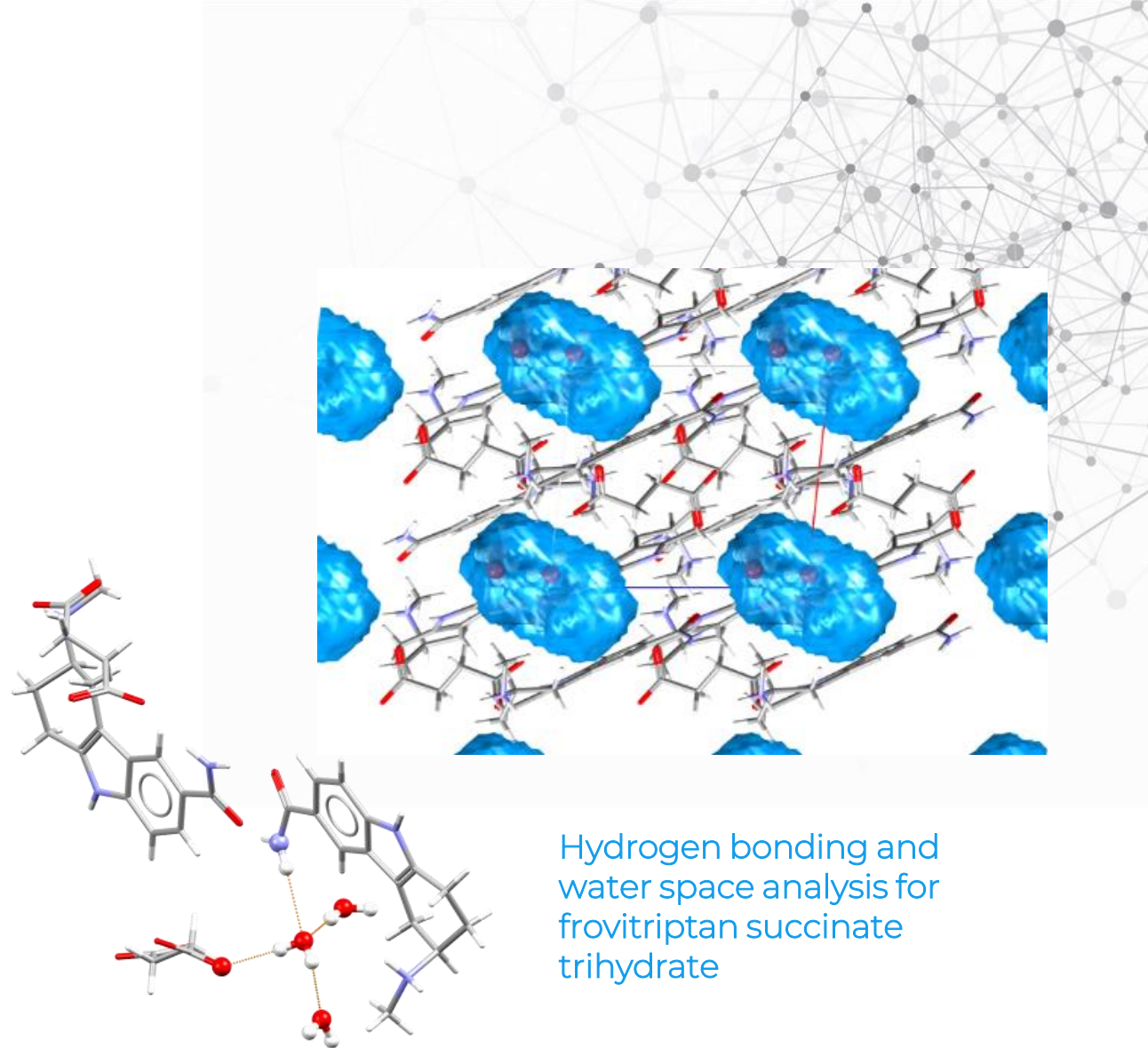
- Options:** Maps, Hotspots, Log Files
- Map Contour Levels:**
 - Display first contour with initial level of 2.0
 - Display second contour with initial level of 4.0
 - Display third contour with initial level of 6.0
- Hotspots:**
 - Generate hotspots in the map
- Probe:**
 - Uncharged NH Nitrogen
 - Charged NH Nitrogen
 - RNH3 Nitrogen
 - Alcohol Oxygen
 - Carbonyl Oxygen
 - Water Oxygen
 - Oxygen Atom
 - Methyl Carbon
 - Aromatic CH Carbon
 - C-F Fluorine
- Color Scale:** A vertical color bar with a 'Col' label and a 'v' icon, showing a gradient from blue to red to yellow to green.
- Buttons:** Calculate Maps, Clear Maps & Hotspots, Load Maps..., Save Maps..., Close, Defaults, Reset

Main Window Options:

- 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
- Default view: b a b c a* b*
- Search: Labels for All atoms with Atom Label
- Atom selections: [Dropdown]
- Navigation: y-90 y+90 z-90 z+90 [Left] [Right] [Down] [Up] zoom- zoom+ Select by SMARTS:
- Launch DASH
- Options: Show hydrogens Depth cue Show cell axes Z-Clipping Label atoms Stereo
- Buttons: Contacts..., More Info, Powder...

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 frovitriptan succinate trihydrate

CSD Refcode: AAGAGG10

Using the Hydrate Analyser

Mercury (AAGAGG10 (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*

Labels for: All atoms

Atom selections: -90 y+90 z-90 z+90 ← →

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

Hydrate Analyser

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

Current structure: AAGAGG10

Water Environments	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	

Contacts

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

Options

Show hydrogens

Show cell axes

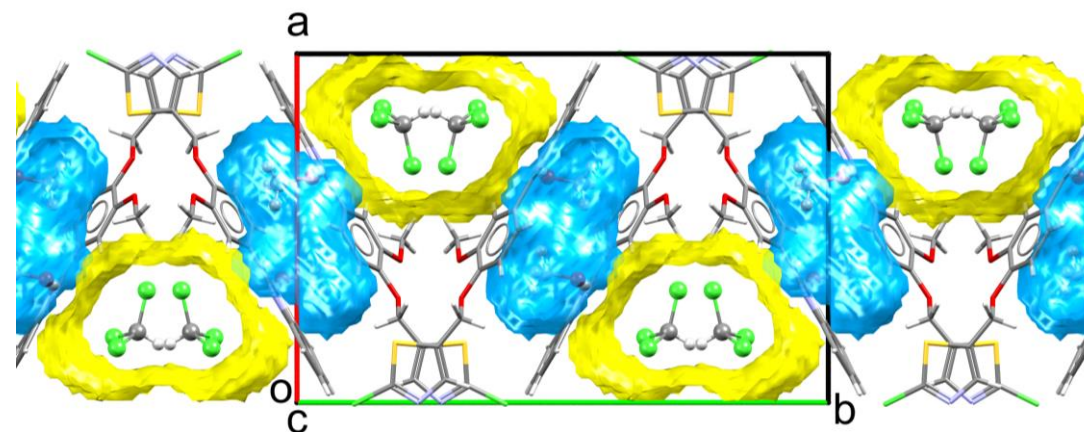
Label atoms

Contacts... More Info Powder... Reset

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
Polymorph Assessment
Co-Crystal Design
Full Interaction Maps...
Hydrate Analyser...
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	C2 H6 O1	C2 H3 N1	H6 O3
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	<input type="color" value="#FF0000"/>	<input type="color" value="#00FFFF"/>	<input type="color" value="#800080"/>
Inside Opacity	<input type="range" value="0.45"/>	<input type="range" value="0.45"/>	<input type="range" value="0.45"/>
Outside Colour	<input type="color" value="#FF0000"/>	<input type="color" value="#00FFFF"/>	<input type="color" value="#800080"/>
Outside Opacity	<input type="range" value="0.45"/>	<input type="range" value="0.45"/>	<input type="range" value="0.45"/>

Hide all molecules Packing...

Settings

Probe Radius: Å

Approx. Grid Spacing: Å

Calculate using the

Results

Volume % of unit cell volume

Volume Å³

Defaults

Close

Display Options

Display

Packing Short Contact < (sum of vdW radii)

Asymmetric Unit H-Bond Default definition

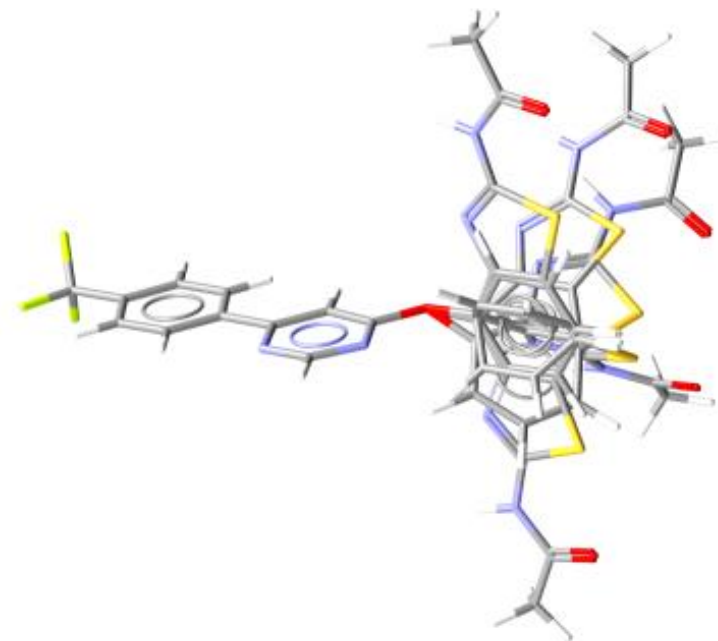
Auto centre

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

CSD Refcode: JURZOO

The image shows the Mercury software interface with the 'Conformer Generation' dialog box open. The main window displays a ball-and-stick model of a complex organic molecule. The 'CSD-Materials' menu is open, and the 'Conformer Generation...' option is highlighted. A large blue arrow points from this menu item to the dialog box.

Conformer Generation

Source molecule

- From Mercury: JURZOO
- From file: [Browse]

Working directory

C:\temporary [Browse]

Output format(s)

- mol2
- sdf

Show advanced options

Maximum Number of Conformations: 200

Maximum Conformations to Sample: 1000000

Maximum Unusual Rotamers: 2

Minimum Rotamer Probability: 0.05

Minimise input molecule

[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

[Reset]

Options

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

[Contacts...]

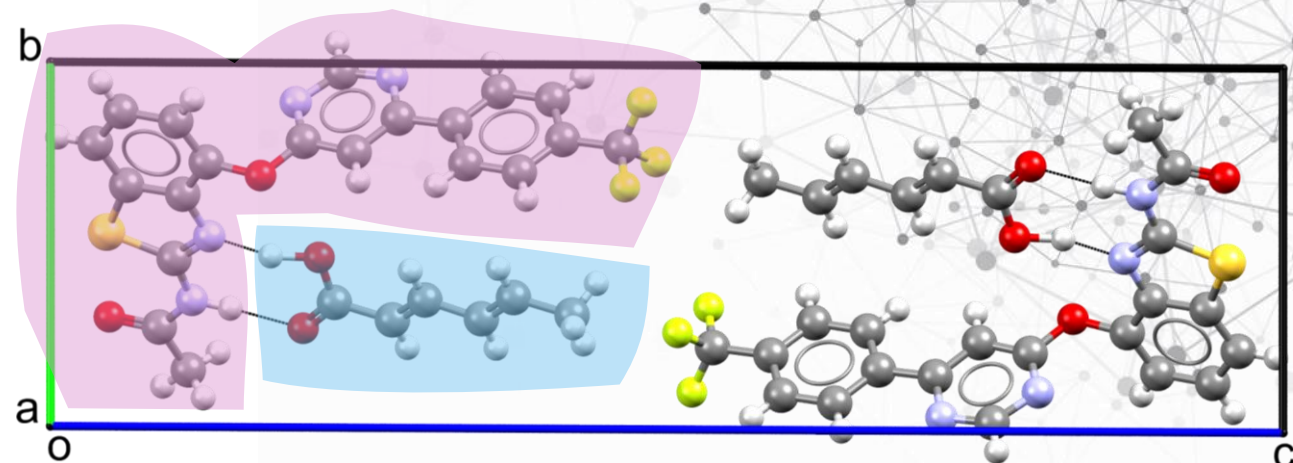
[More Info]

[Powder...]

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

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:

y-90 y+90 z-90 z+90 ← → ↓ ↑ zoom- zoom+

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:

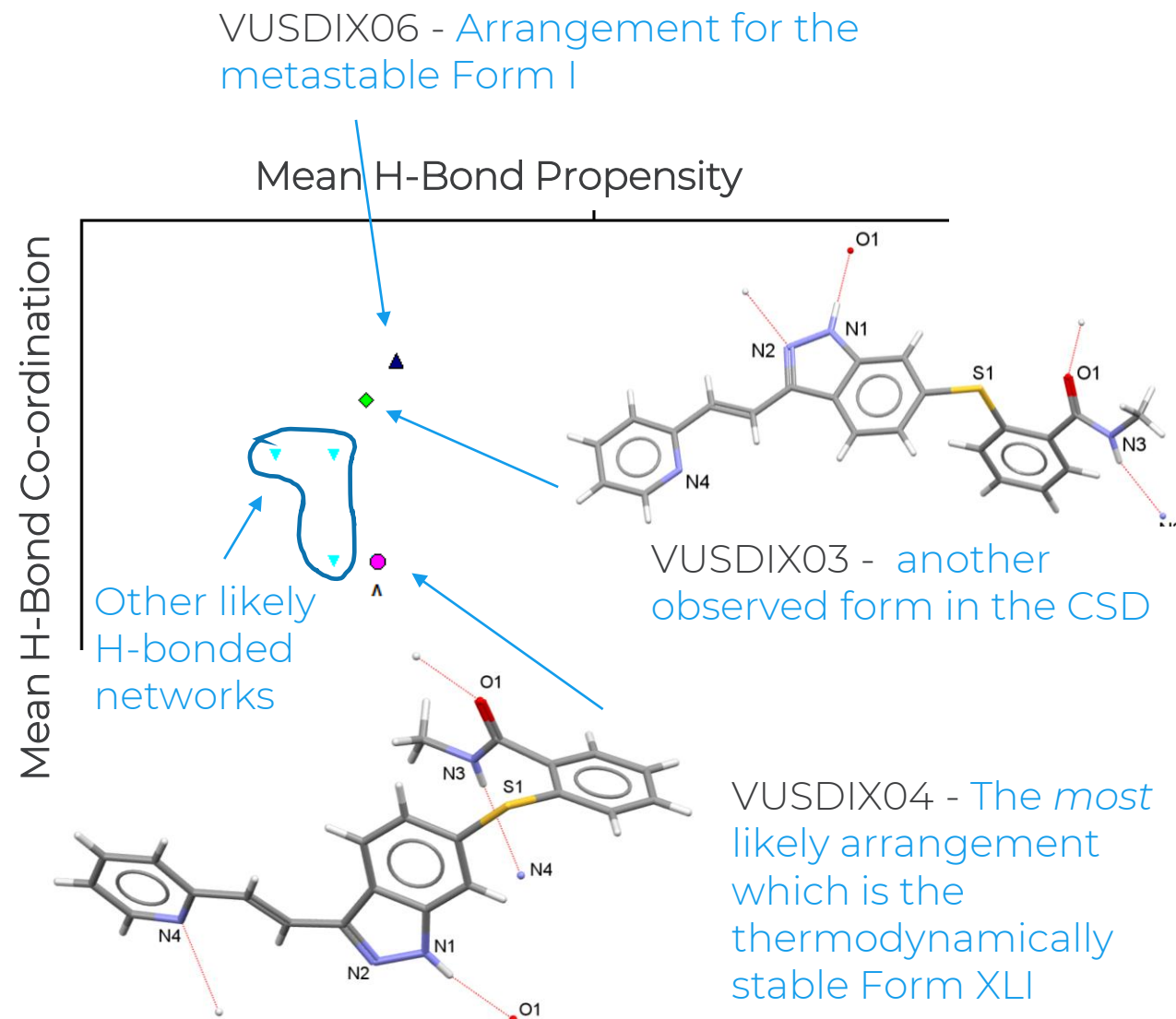
Molecules which pass

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 Show Labels for All atoms with Atom Label

Calculations Atom selections:

Polymorph Assessment Hydrogen Bond Propensities... H-bond Coordination Quick-view

Co-Crystal Design

Full Interaction Maps...

Hydrate Analyser...

Solvate Analyser...

Aromatics Analyser...

Conformer Generation...

Launch DASH

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: C11, C12, O1, N1, N2, N3, N5

Functional groups: Matched from libra... acyclic_ar_et..., ar_cl, ar_NH2, pyrazoline_2, saturated_rin...

✓ All donors and acceptors matched

Display Options

Display

Packing Short Contact < (sum of vdW radii)

Asymmetric Unit H-Bond Default definition

Auto centre

Reset

Options

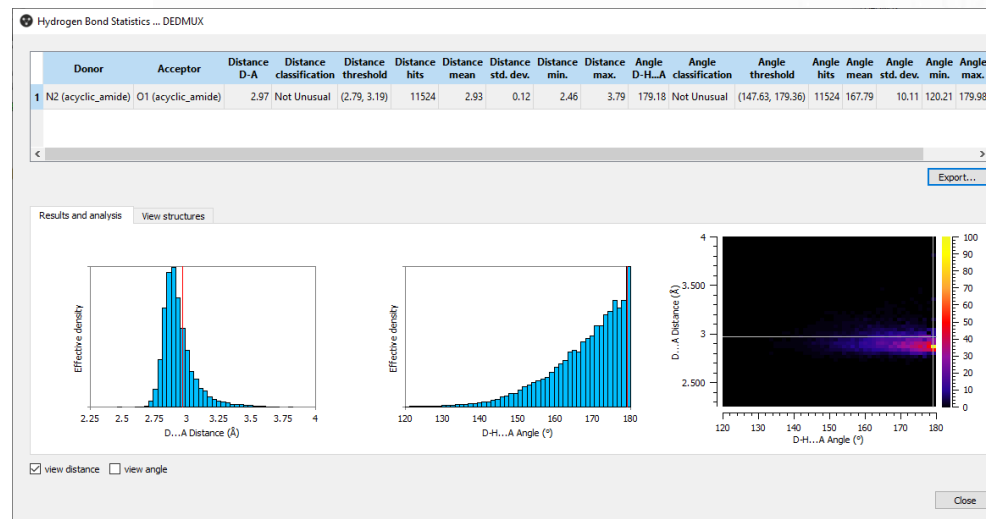
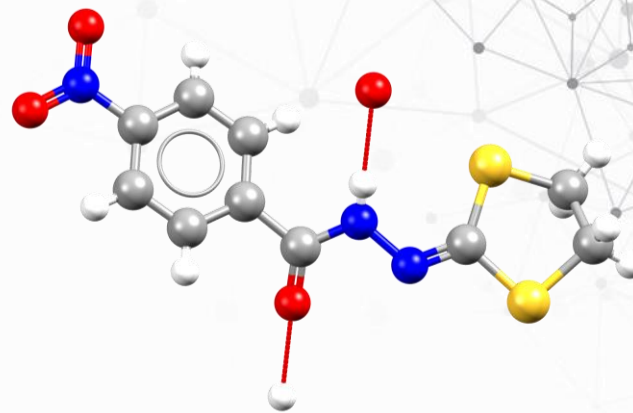
Show hydrogens Show cell axes Label atoms

Contacts... More Info Powder...

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

Hydrogen Bond Statistics

- Hydrogen Bond Statistics allows analysis of the usual- or unusual-ness of observed hydrogen bonds in a crystal structure.
- The interaction geometries are put in the context of the million+ crystal structures in the CSD.
- Contribute to assess the **stability of a given crystal structure**.



Calculating Hydrogen Bond Statistics

The screenshot displays the Mercury software interface for calculating hydrogen bond statistics. The main window shows a 3D ball-and-stick model of a molecule. A menu is open, highlighting 'Hydrogen Bond Statistics...'. A dialog box titled 'Hydrogen Bond Definition' is visible, showing the following settings:

Hydrogen Bond Definition

Quantile settings

Classify as unusual if:

Distance < 0.05 or distance > 0.95 quantiles

Angle < 0.05 or angle > 0.95 quantiles

Buttons: Search, Cancel, Reset, Edit

The 'Structure Navigator' window shows a list of crystal structures:

Crystal Structures	Spacegroup
DEDMUX	P21/c
DEDMUX01	P-1
DEDMUX02	P21/c
DEDNAB	P21/a
DEDNAC	P21/n
DEDNAD	P-1
DEDNEF	Pbca
DEDNEF01	Pbca
DEDNEG	Cmca
DEDNU	P21/c
DEDNIK	P-1
DEDNIM	P21/n
DEDNOP	P-1
DEDNOP01	P-1
DEDNOQ	C2/c
DEDNOS	P21

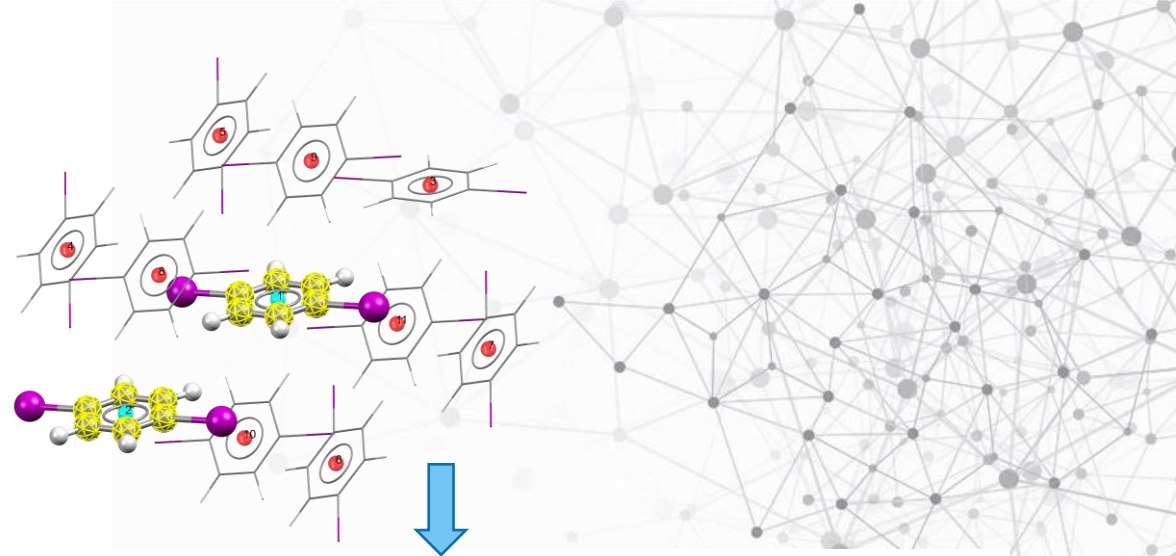
The 'Hydrogen Bond Statistics ... DEDMUX' window displays a table of results:

Donor	Acceptor	Distance D-A	Distance classification	Distance threshold	Distance hits	Distance mean	Distance std. dev.	Distance min.	Distance max.	Angle D-H...A	Angle classification	Angle threshold	Angle hits	Angle mean	Angle std. dev.	Angle min.	Angle max.
1 N2 (acyclic_amide)	O1 (acyclic_amide)	2.97	Not Unusual	(2.79, 3.19)	11524	2.93	0.12	2.46	3.79	179.18	Not Unusual	(147.63, 179.36)	11524	167.79	10.11	120.21	179.98

Below the table are three plots: 'Effective density' vs 'D...A Distance (Å)', 'Effective density' vs 'D-H...A Angle (°)', and a heatmap of 'D...A Distance (Å)' vs 'D-H...A Angle (°)'. The 'Search' and 'Cancel' buttons in the dialog box are highlighted with blue boxes and arrows.

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-molec:	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 Aromatics Analyser software interface. The main window shows a 3D ball-and-stick model of a complex organic molecule with several atoms highlighted in red and blue. A menu is open over the model, with 'Aromatics Analyser...' selected. A blue arrow points from this menu item to a separate window titled 'Aromatics Analyser... HXACAN'. This window contains a table with the following data:

	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

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. A yellow text box in the foreground contains the text: 'A previous CCDC virtual workshop covered our Aromatic Analyser in full'. The background shows the main software window with a menu open, including options like 'Search', 'Calculations', 'Polymorph Assessment', 'Co-Crystal Design', 'Full Interaction Maps...', 'Hydrate Analyser...', 'Solvate Analyser...', 'Conformer Generation...', and 'Launch DASH'. The 3D model has atoms labeled with numbers 1 through 13.

Scientific research using CSD-Materials



Figure 2. Flowchart for the CSD Motif Search.

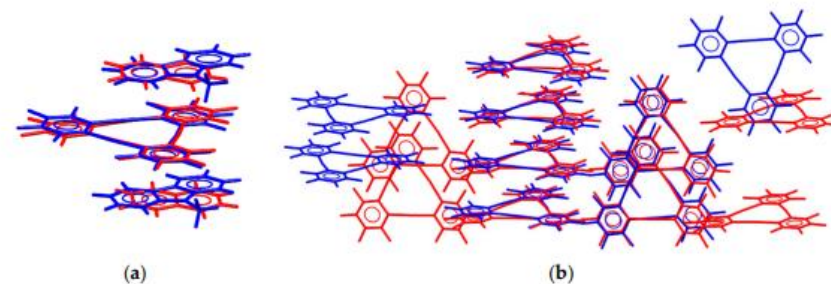


Figure 3. Examples of the (a) Packing Feature and (b) Packing Similarity search hits. A sandwich of a TPPM with two aromatic C_6 rings was constructed as the Packing Feature from a reference (red) [MOXMIV]^a molecule and was also found in (blue) [QATTAH]. The Packing Similarity comparison of an orthorhombic polymorph of TPPM (blue) [MOXMAN02] with its' three monoclinic polymorphs gives the best similarity with (red) [MOXMAN03]. ^a Here and below a six-letter CSD-Refcode of a compound is given in Figure braces.

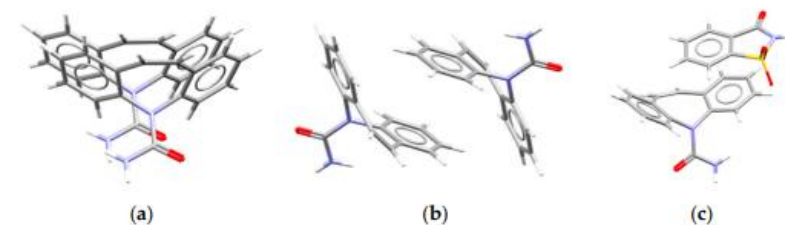


Figure 4. Carbamazepin molecules packed in (a) "translation stacks" in [CBMZPN11], (b) "inversion cups" in [CBMZPN01] and (c) "co-former pairs" in [UNEZAO].

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Pharmaceuticals | Hot Paper |

Insights into the Crystallisation Process from Anhydrous, Hydrated and Solvated Crystal Forms of Diatrizoic Acid

Katharina Fucke,^a Garry J. McIntyre,^{b, c} Marie-Hélène Lemée-Cailleau,^d Clive Wilkinson,^{b, d} Alison J. Edwards,^c Judith A. K. Howard,^b and Jonathan W. Steed^{a, b}

Abstract: Diatrizoic acid (DTA), a clinically used X-ray contrast agent, crystallises in two hydrated, three anhydrous and nine solvated solid forms, all of which have been characterised by X-ray crystallography. Single-crystal neutron structures of DTA dihydrate and monosodium DTA tetrahydrate have been determined. All of the solid-state structures have been analysed using partial atomic charges and hardness algorithm (PACHA) calculations. Even though in general all DTA crystal forms reveal similar intermolecular interactions, the overall crystal packing differs considerably from form to form. The water of the dihydrate is encapsulated between a pair of host molecules, which calculations reveal to be functional and whilst used in all the hydrate a hydrogen water squa formation i solvates inv hypothesis broken du process.

Introduction

Pharmaceutically relevant small organic molecules tend to exist in more than one crystal form.¹ These materials can represent different crystalline arrangements of the compound itself leading to polymorphs, which differ by the conformation of the molecule, by the overall packing, or by a combination of both.² In addition, solvent molecules from the crystallisation process can be included into the crystal lattice, leading to hydrates in the case of incorporated water and solvates for any other solvent.³ Both hydrates and solvates are a special case of co-crystal formation.⁴ Different crystal forms can exhibit quite varied physico-chemical characteristics, ranging from physico-chemical dissolution, ceutical co body fluids reach the i rectly affect drug formu Polymorp studied,⁵ in order accessible.⁶ However, it does not

crystals

Review

Intermolecular Interactions in Functional Crystalline Materials: From Data to Knowledge

Anna V. Vologzhanina

September 2019; Published: 13 September 2019

of organic, inorganic, and organometallic compounds are the end structure–property networks. In this review, some of these Cambridge Crystallographic Data Center (CCDC) to analyze red properties are described. The potential of studies supported e (CSD-Materials tools for investigation of dynamic processes ly active, high energy, optical, (electro)conductive, and other or the prediction of novel solid forms (polymorphs, co-crystals, e unusual applications, the potential for further development e are reported.

database; crystal structures; knowledge-based analysis; -property relations; supramolecular chemistry

ted to the analysis of networks between chemical composition, d numerous properties of compounds dates back to 1960s. tion technique and computational routines allowed to collect plenty of inorganic, organic, organometallic, and macromolecular of composition–structure–properties networks of these solids ecular geometry [1,2], steric, and electronic effects of functional packing [5], role and energetic of numerous intermolecular of the crystallographic community to present crystallographic

CRYSTAL GROWTH & DESIGN

Packing Polymorphism Affecting the Optoelectronic Properties of a π -Conjugated Organic Compound

Gilles H. Roche, David Flot, Joël J. E. Moreau, Olivier J. Dautel, Jean-Sébastien Filhol, and Arie van der Lee^{*}

ABSTRACT: [1]Benzothieno[3,2-*b*]benzothiophene (BTBT) derivatives are widely employed as hole transport materials in organic field-effect transistors. The electronic properties of these materials depend critically on the crystal packing, which in turn depends on the choice of the attached functional group. With symmetrically attached alcohol chains, the structure may display different packing modes depending on the number of CH_2 groups in the alkyl chain. The dipentanol BTBT derivative has two polymorphs I and II, crystallizing from different solvents, with distinct packing modes and consequently different electronic properties. Whereas the conformational changes are very small between I and II and the hydrogen bonding networks in the structures are identical, the adjacent BTBT cores are differently shifted and oriented with respect to each other. It is shown by density functional theory that polymorph I having unfavorable electronic properties is slightly more stable than polymorph II. This is caused by the much more attractive cross stacking between BTBT cores and CSHO chains in I than in II. The stacking in II originates rather from electrostatic interactions between the BTBT cores. The differences and similarities with the packing modes of the dibutanol and dihexanol derivatives are discussed. Both polymorphic forms I and II display negative uniaxial thermal expansion, but in different directions with respect to the packing of the molecules. Different scanning calorimetry measurements suggest that more than two polymorphs exist.

1. INTRODUCTION

Polymorphism is a widely occurring phenomenon in crystalline materials.^{1–7} Physicochemical properties of polymorphs can be very different and thus have implications on how they interact with their environment.^{8–10} Especially in pharmaceutical compounds the occurrence of polymorphism has been recognized as an inevitable process, which needs to be screened at an early stage of the development of new compounds being discovered and deposited in the CSD. This confirms in some sense McCrone's thesis¹¹ that the discovery of polymorphs is positively correlated with the energy and time put into the study of the compound, or in other words most single crystalline compounds are not investigated in depth anymore whenever the growth of single crystals suitable for X-ray diffraction analysis appears to be

<https://pubs.acs.org/doi/abs/10.1021/acs.cgd.1c00177>

<https://chemistry-europe.onlinelibrary.wiley.com/doi/abs/10.1002/chem.201404693>

<https://www.mdpi.com/2073-4352/9/9/478>

CCDC

What have we learnt?

- How informatics and data-driven approaches can be used to understand solid form design and risk assessment.
- How to use Motif searching to investigate motifs frequency in the CSD.
 - Using a pre-defined motif or a bespoke one.
- How to set up and run crystal packing feature searches.
 - How to analyse the results generating plots.
- How to perform crystal packing similarity searches.
 - On a pair of structures (e.g., anhydrous-hydrate).
 - Within a refcode family to identify polymorphs.
- What other tools available in the CSD-Materials suite can be used to do.

Want to explore more?

Training and Educational Resources

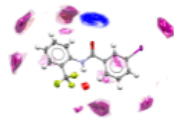
Register for
E&O newsletter

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](#).



CSD-Materials

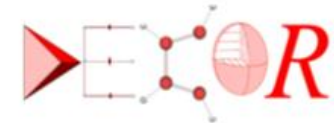
Tools to help you to understand your material's behaviours and refine its properties.



Information on the Teaching Subset



Access a series of teaching modules for use in the classroom



DECOR: Educational Resources for Teaching Crystallography



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



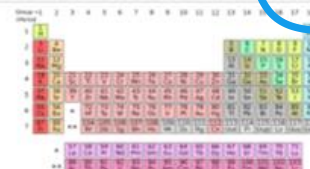
Watch software training and support videos



CSDU modules



Access fun science activities for kids through the CCDC Home learning page



Explore the Periodic Table through Crystal Structures

Self-guided workshops

On-demand modules with completion certificate

YouTube and LabTube channels

CCDC