How to analyse small molecules interactions with Full Interaction Maps

REC

CCDC Virtual Workshop Summer 2021 – Session 2

Ilaria Gimondi, Suzanna Ward, Ioana Sovago, Khaled Takieddin, Eva Myers, Andy Maloney

July 2021

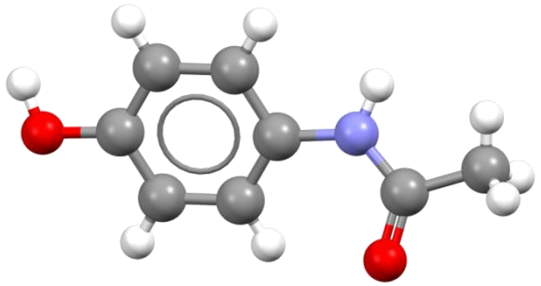
CCDC
advancing structural science

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

CCDC

Solid form selection in product development



Chemical & Physical Stability

Melting Point

Solubility

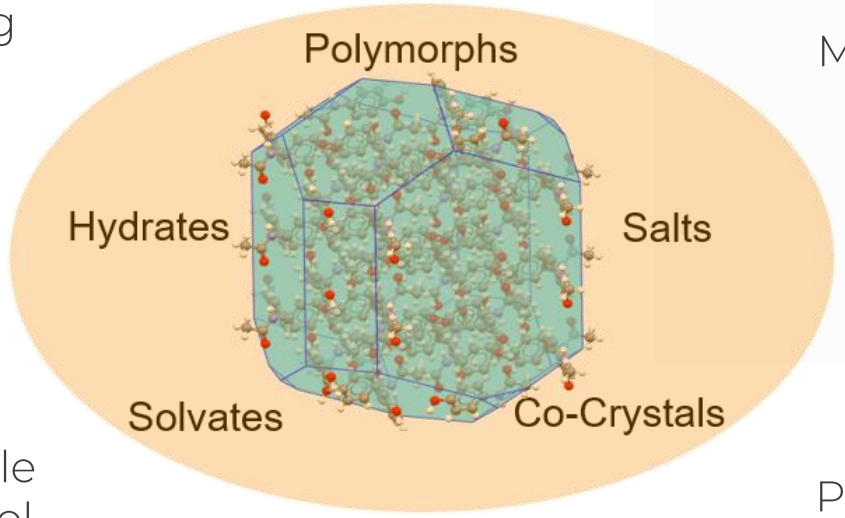
Particle Control

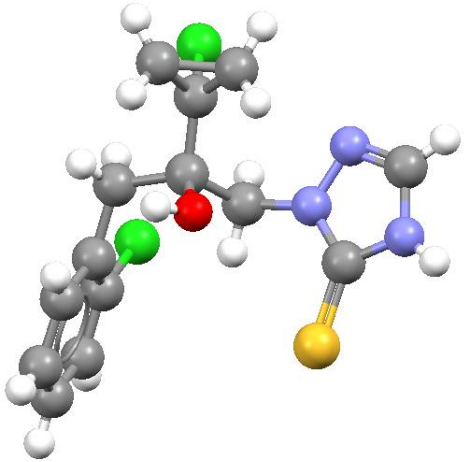
Product Process Control

Purification

Morphology

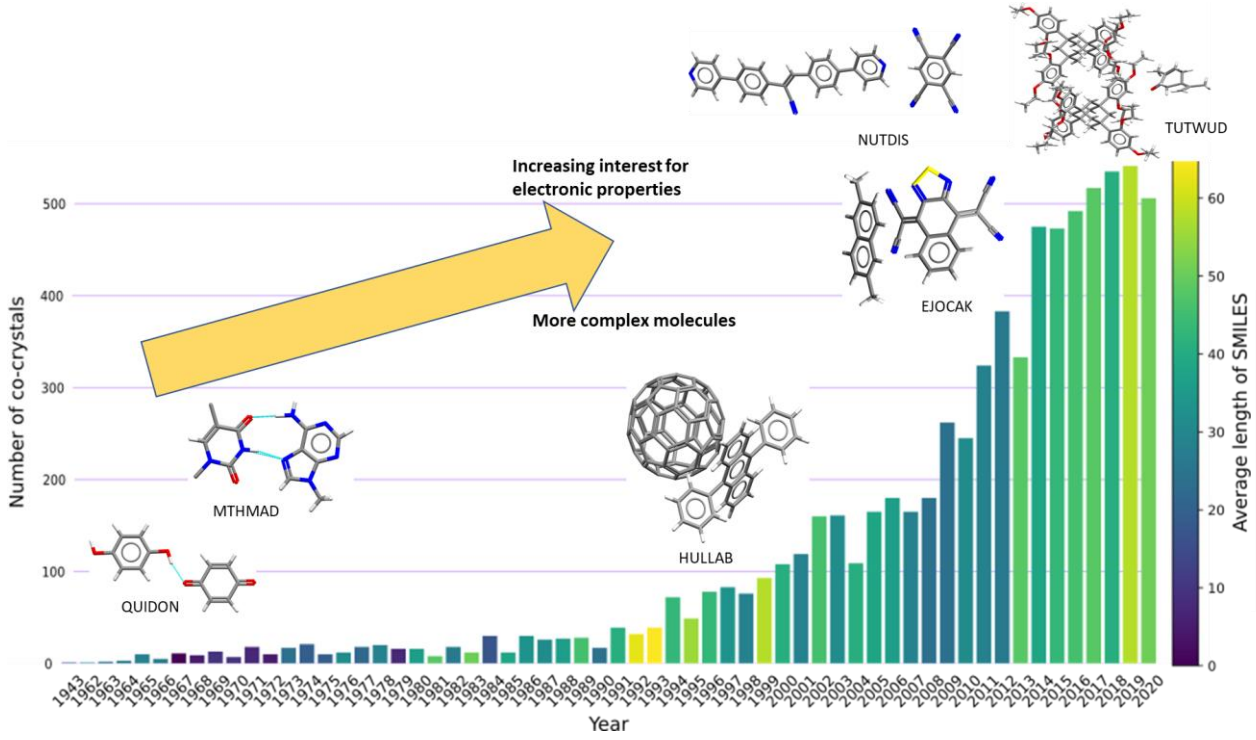
Mechanical Properties

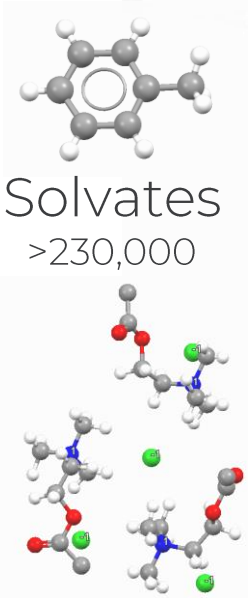




CCDC

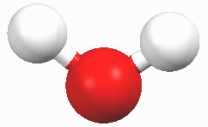
A wealth of data in the CSD



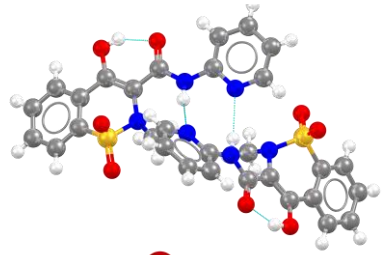


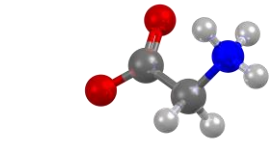
Solvates
>230,000

Hydrates
>140,000

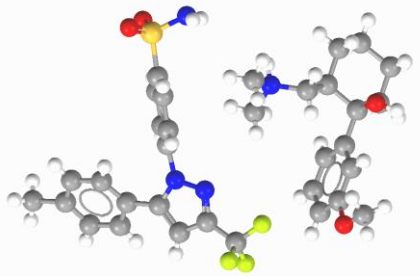


Polymorphs
>11,000 polymorphic families





Co-Crystals



Salts

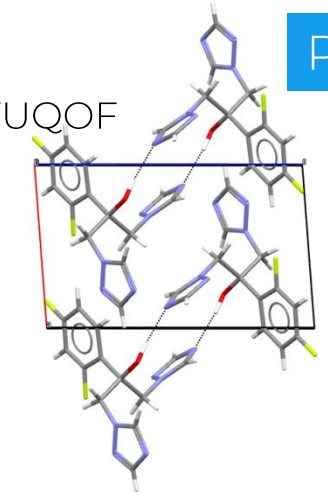
Refcode families
>1,000,000

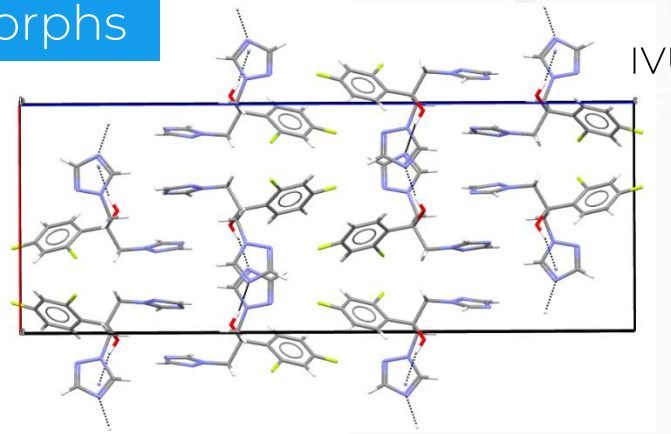
Katerina Vriza, University of Liverpool, PhD on Data driven discovery of functional molecular co-crystal

A solid form landscape

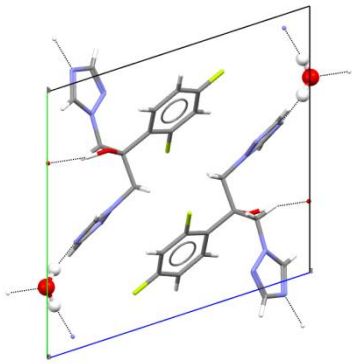
Polymorphs

IVUQOF



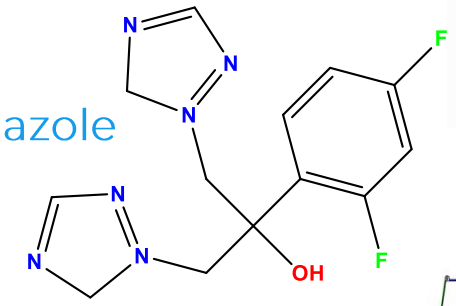


IVUQOF02

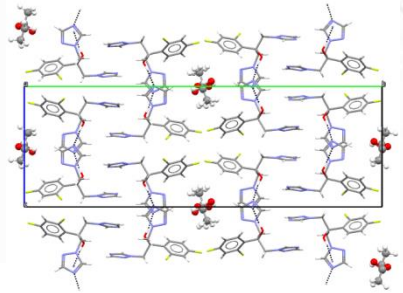


IVUQIZ

Hydrates

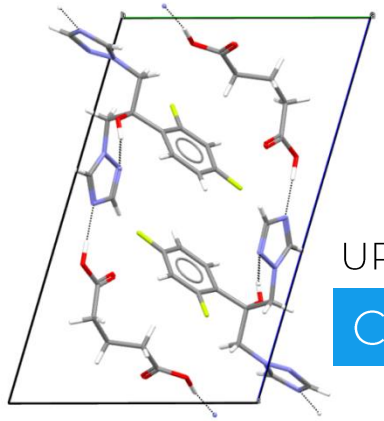


fluconazole



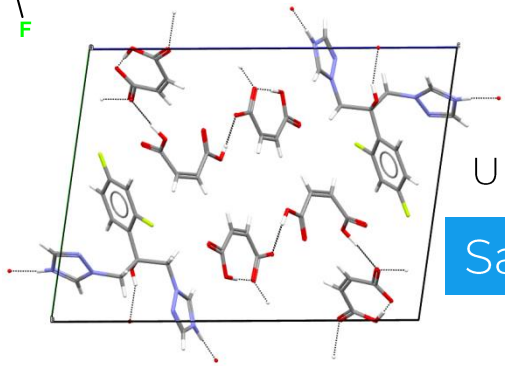
IVUQEV

Solvates



UPOQEW

Co-crystals



UPOQAS

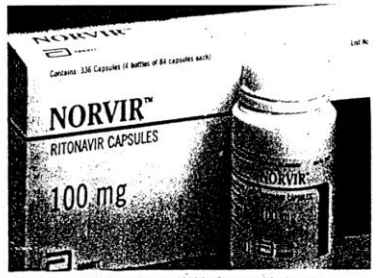
Salts

CCDC

Impact of Hydrogen Bonding on lattice stability -The Ritonavir story

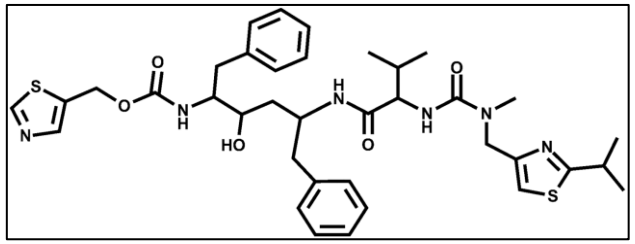
Manufacturing problems hit Abbott's HIV drug ritonavir

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.

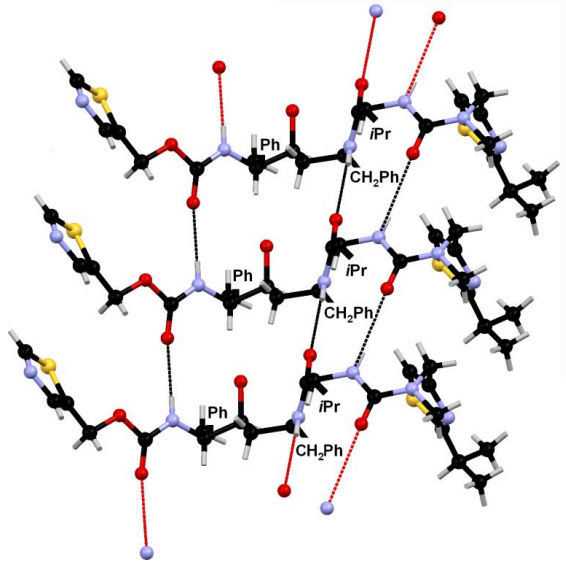


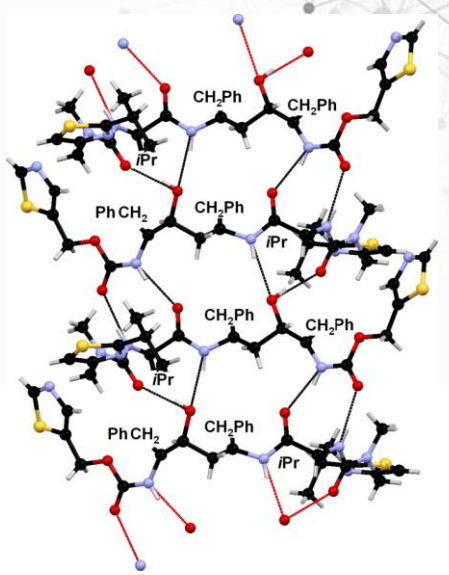
Capsules unlikely to be available from mid-August

The problem relates to "undesirable" crystal formation. Abbott says that a series of tests 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."

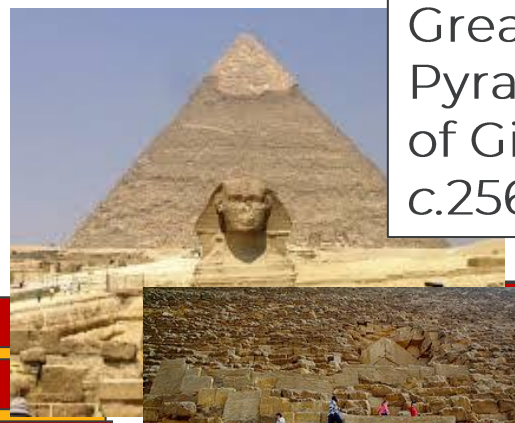
Org. Process Res. Dev. (2000), 4(5), 413-417. Pharmaceutical Research (2001), 18(6), 859-866.

CCDC

Structural Informatics

Which is the stable wall?

The CCDC c.1992



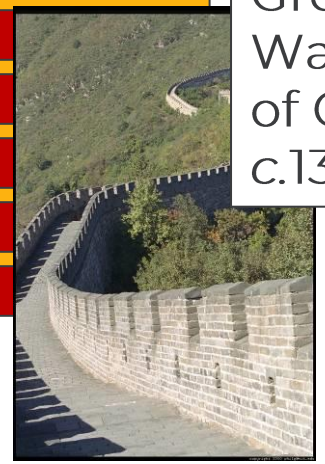
Great Pyramid of Giza c.2560 BC

Hadrian's Wall c.122

A

B

My House c.1967



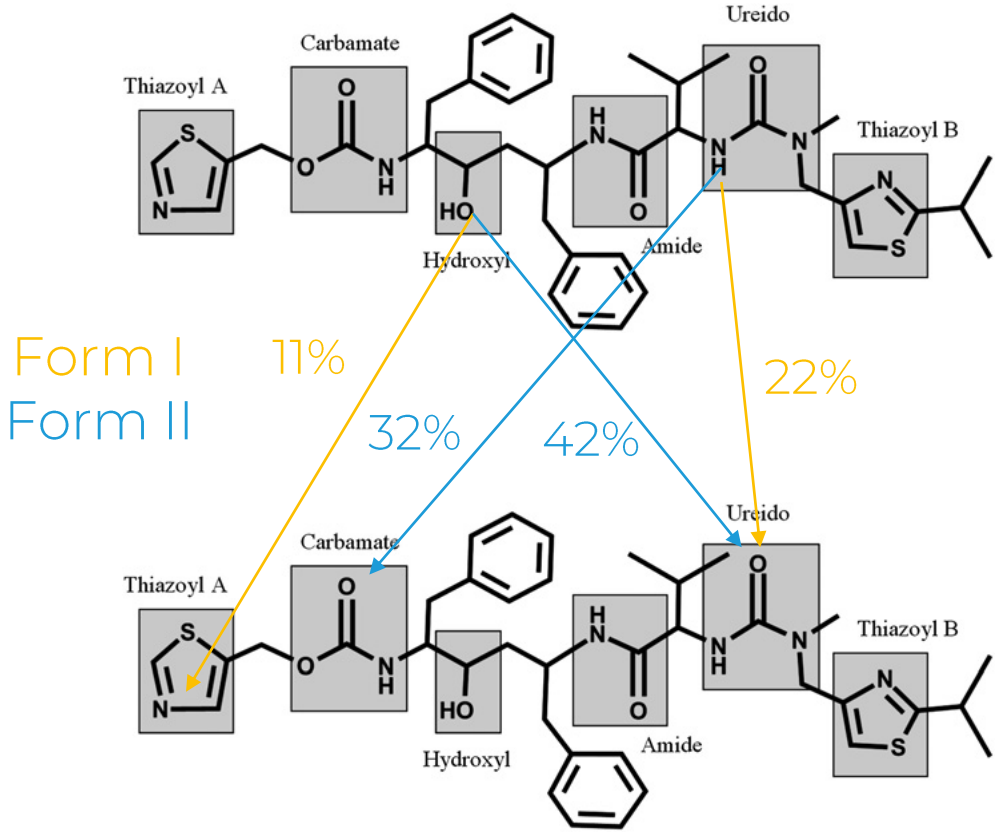
Great Wall of China c.1368

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

CCDC

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

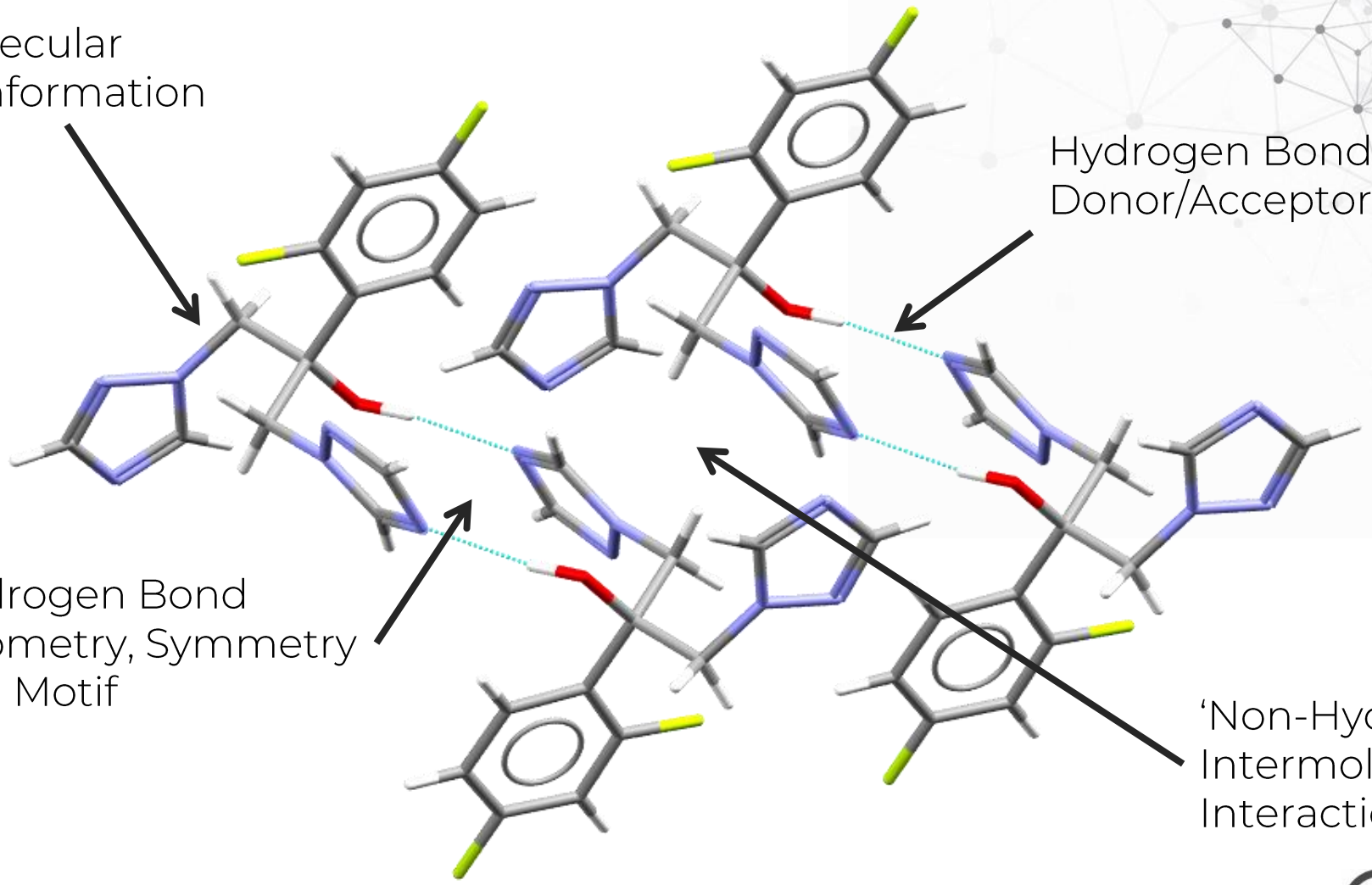
Knowledge-based H-bond prediction to aid experimental polymorph screening

Peter T. A. Galek,*[ab] Frank H. Allen,[a] László Fábián[ab] and Neil Feeder[c]

Galek *et al*, *CrystEngComm*, (2009), 11, 2634 - 2639

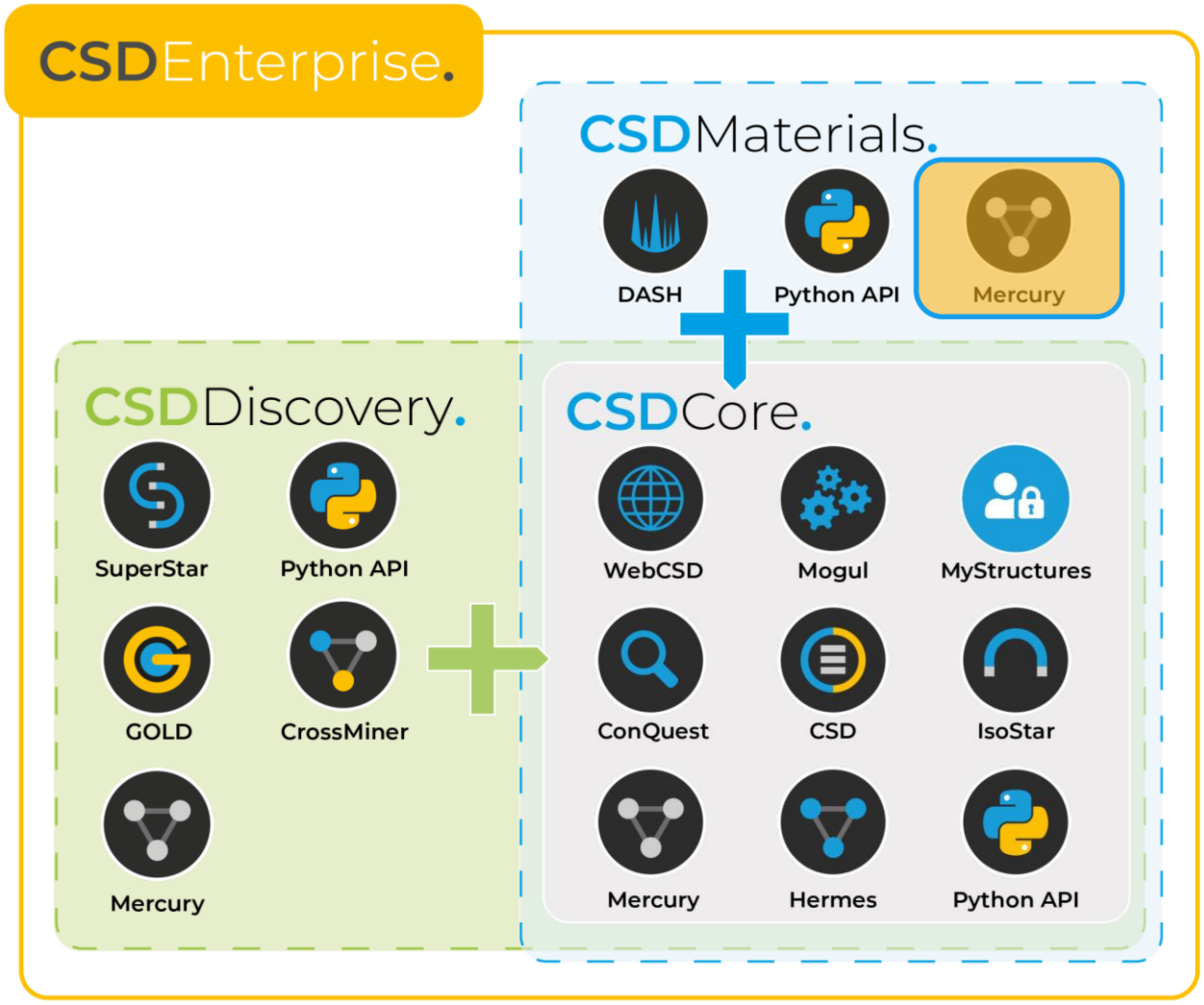
CCDC

Characteristics that influence stability



CCDC

The CSD software

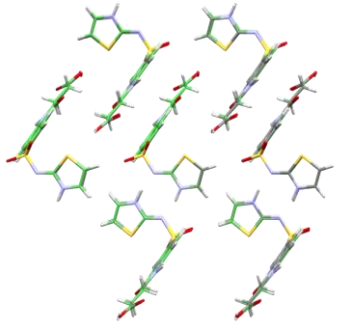


Professional Services

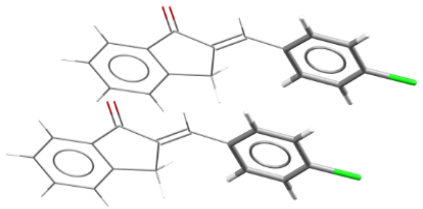
Research & Knowledge partnerships

CCDC

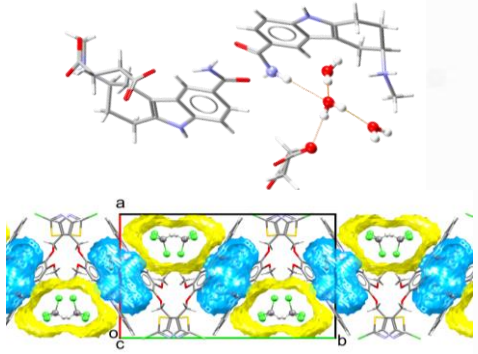
CSD-Materials overview



Crystal Packing Similarity

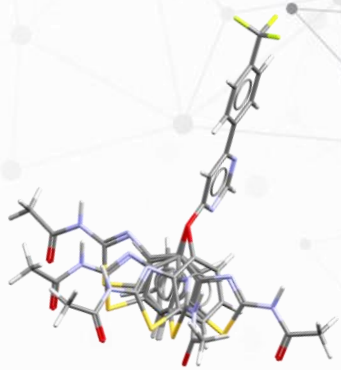


Motif Search & Packing Feature Search



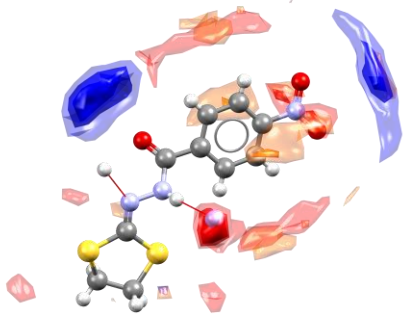
Hydrate Analyser & Solvate Analyser

Detailed Structural Analysis

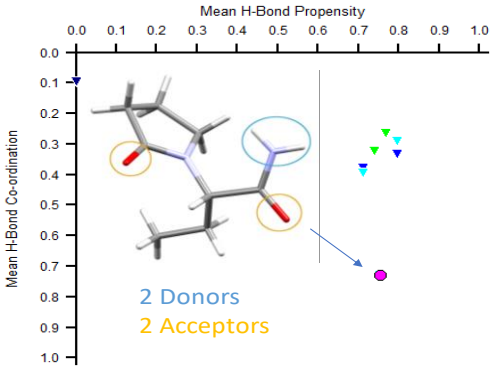


CSD Conformer Generator

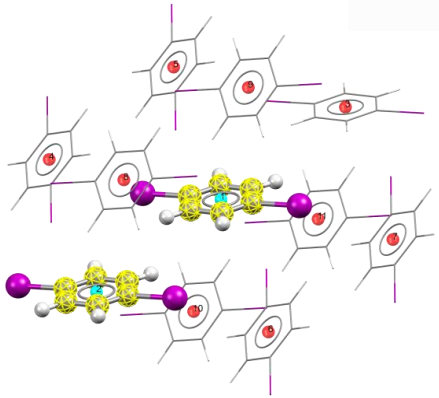
Solid Form Design



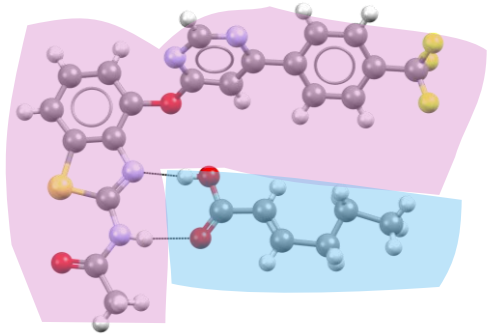
Full Interaction Maps



Hydrogen Bond Propensity



Aromatics Analyser



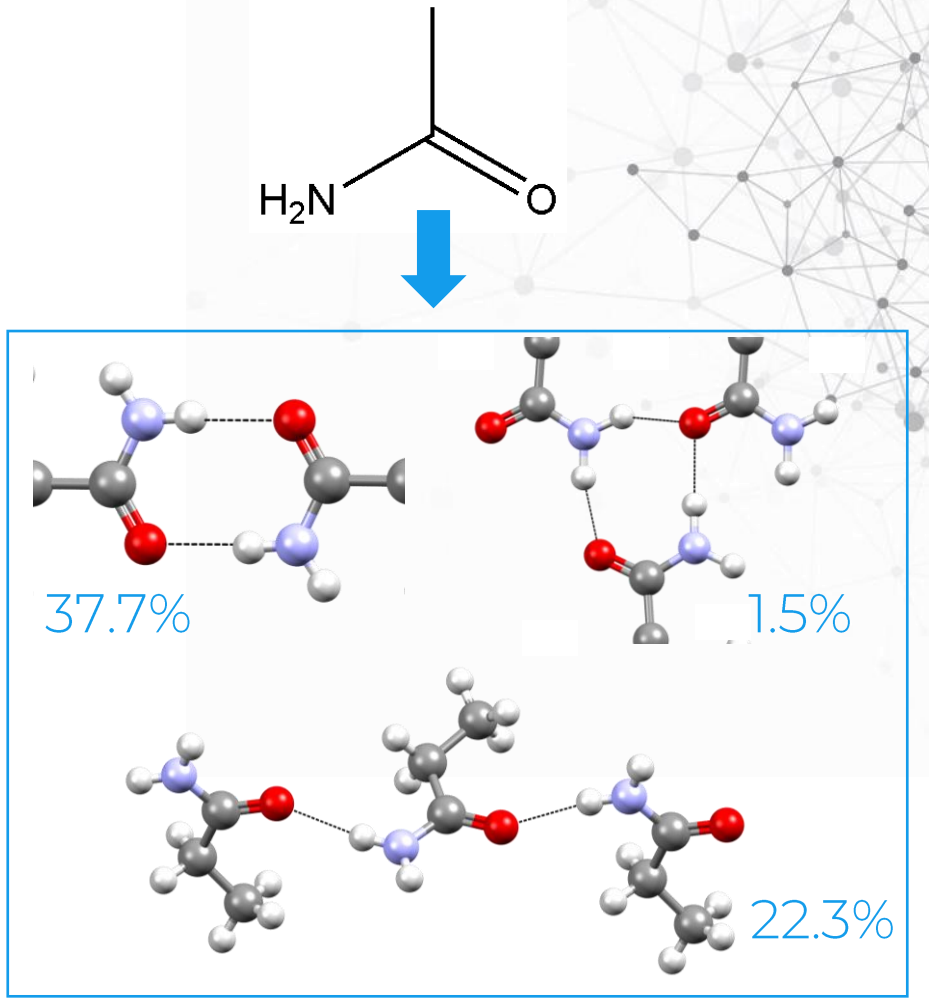
Molecular Complementarity

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

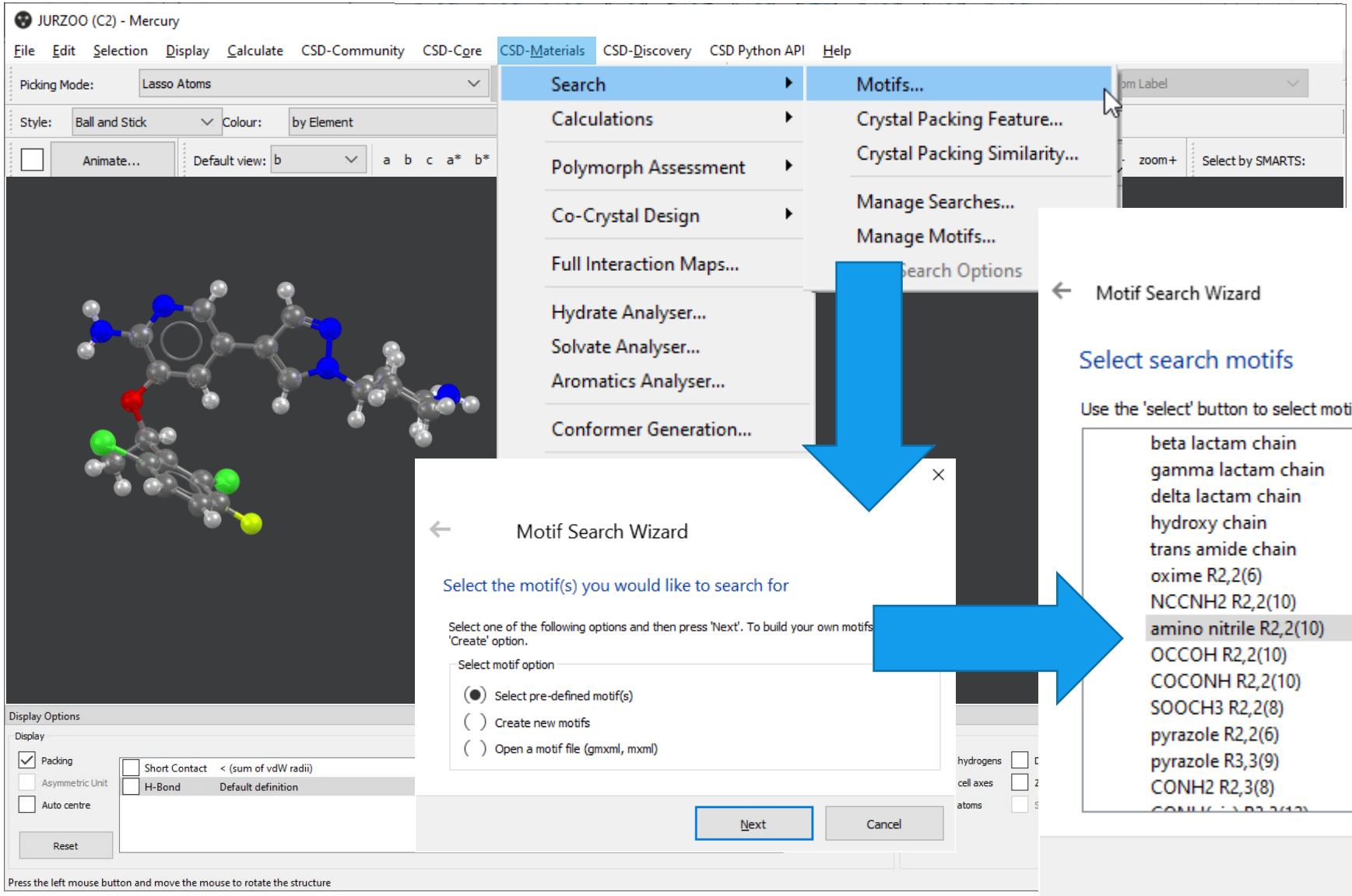


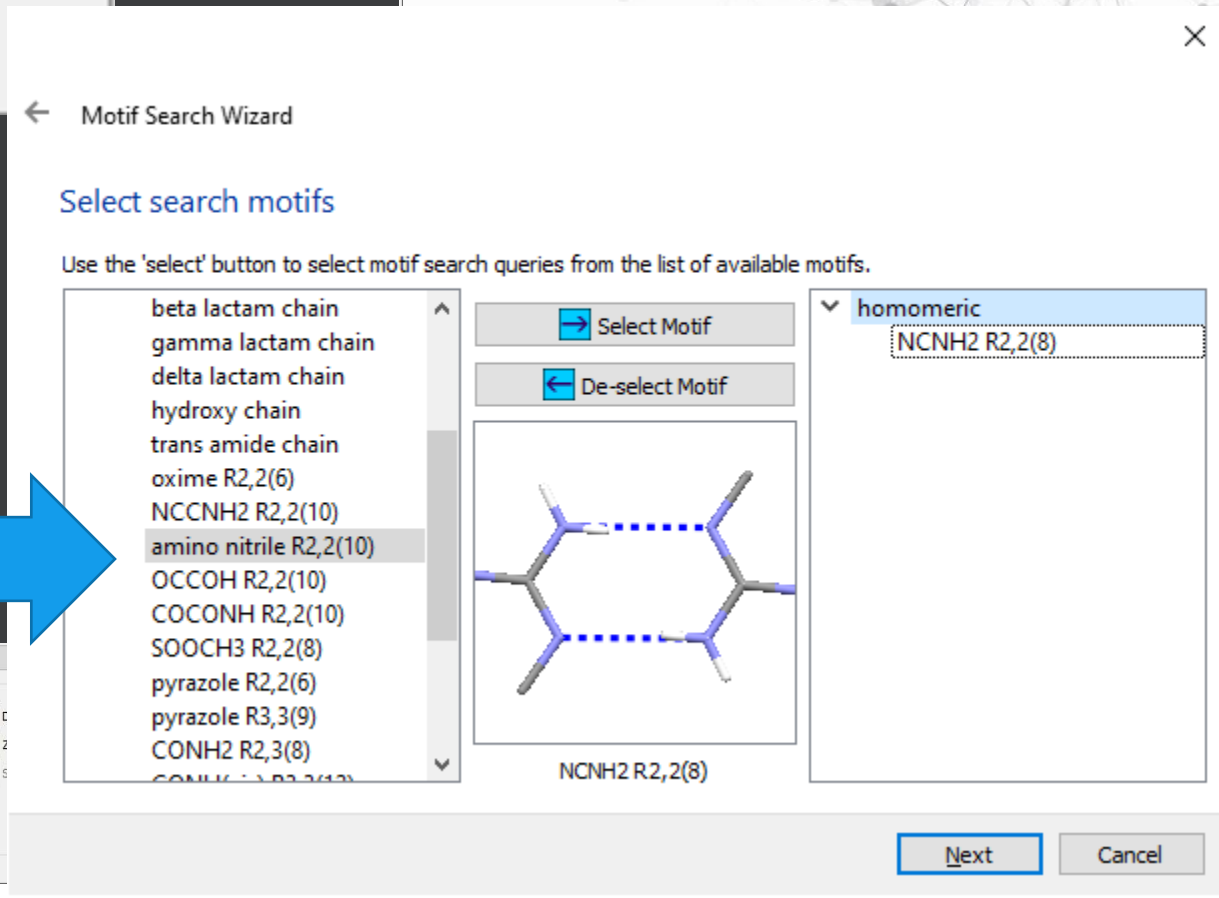
Frequency of occurrence of Primary Amide hydrogen bond motifs

CCDC

Searching for motifs

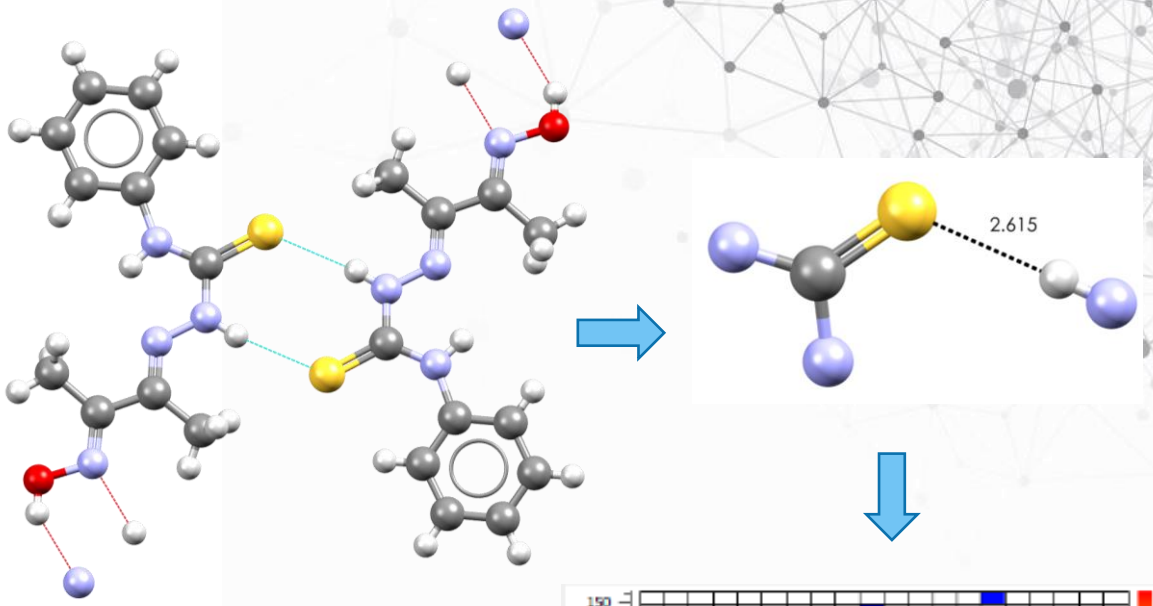
CSD Refcode: JURZOO



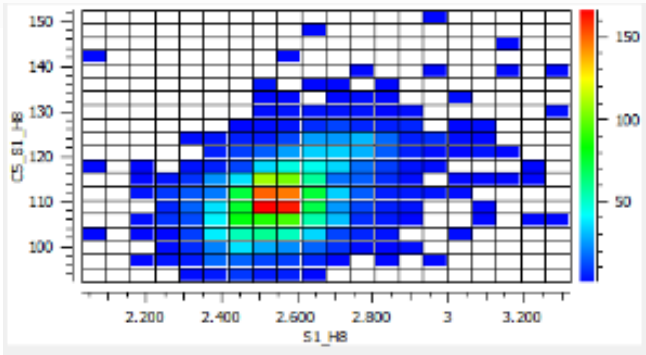


Crystal Packing Feature Search

- 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



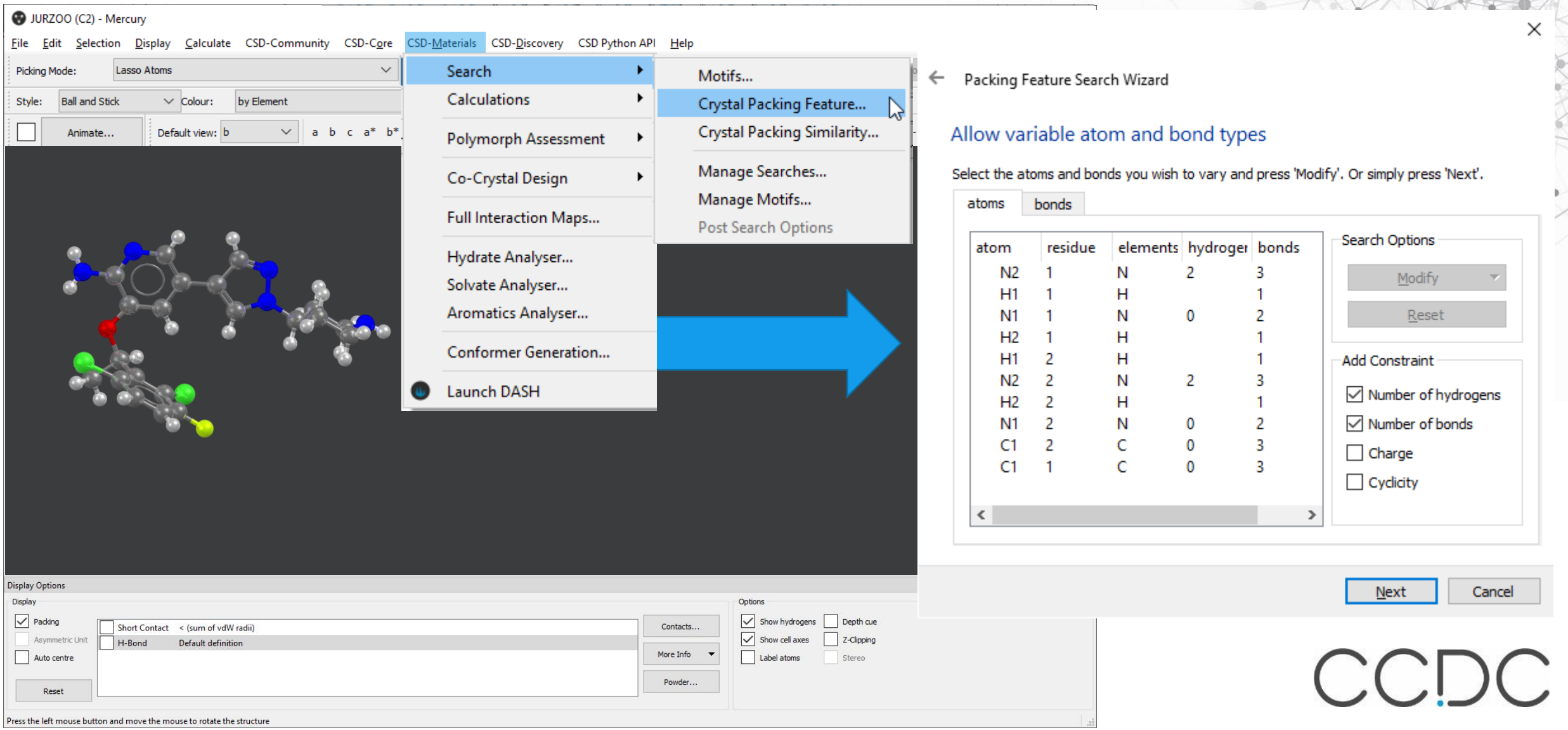
Query for S...H-N interaction as found in a thioamide derivative (DUXXOJ01)



CCDC

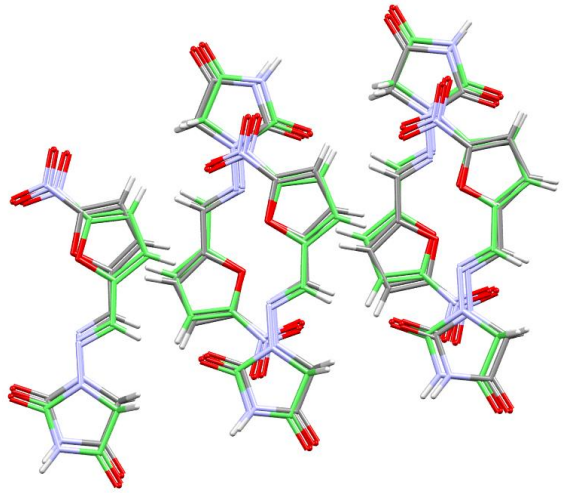
Searching for packing features

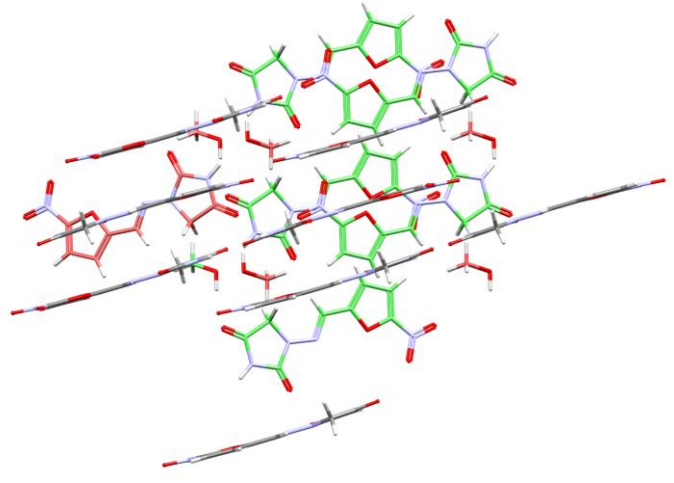
CSD Refcode: JURZOO



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 it's hydrated structure (Refcode: ULECAQ)

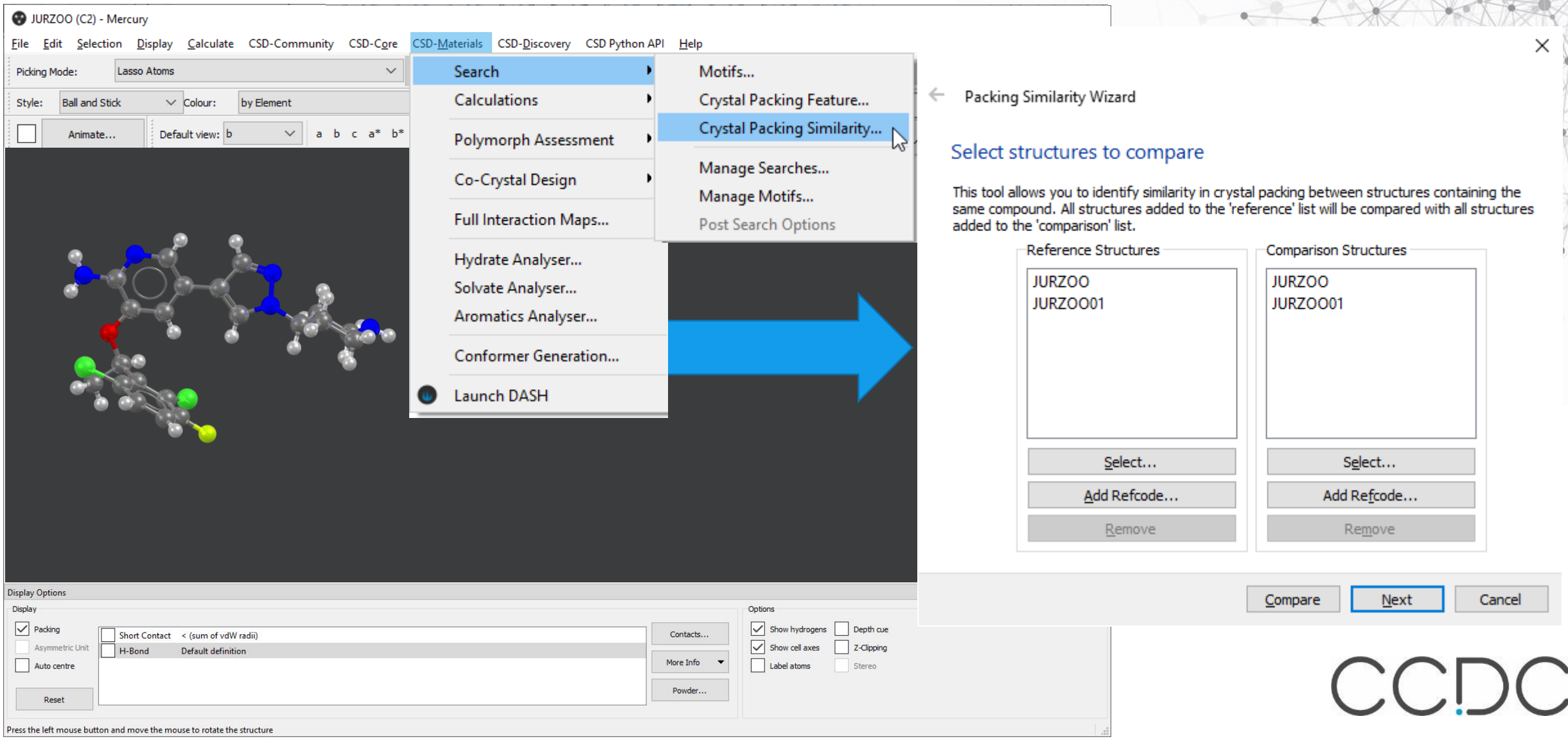
Molecules depicted in:

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

CCDC

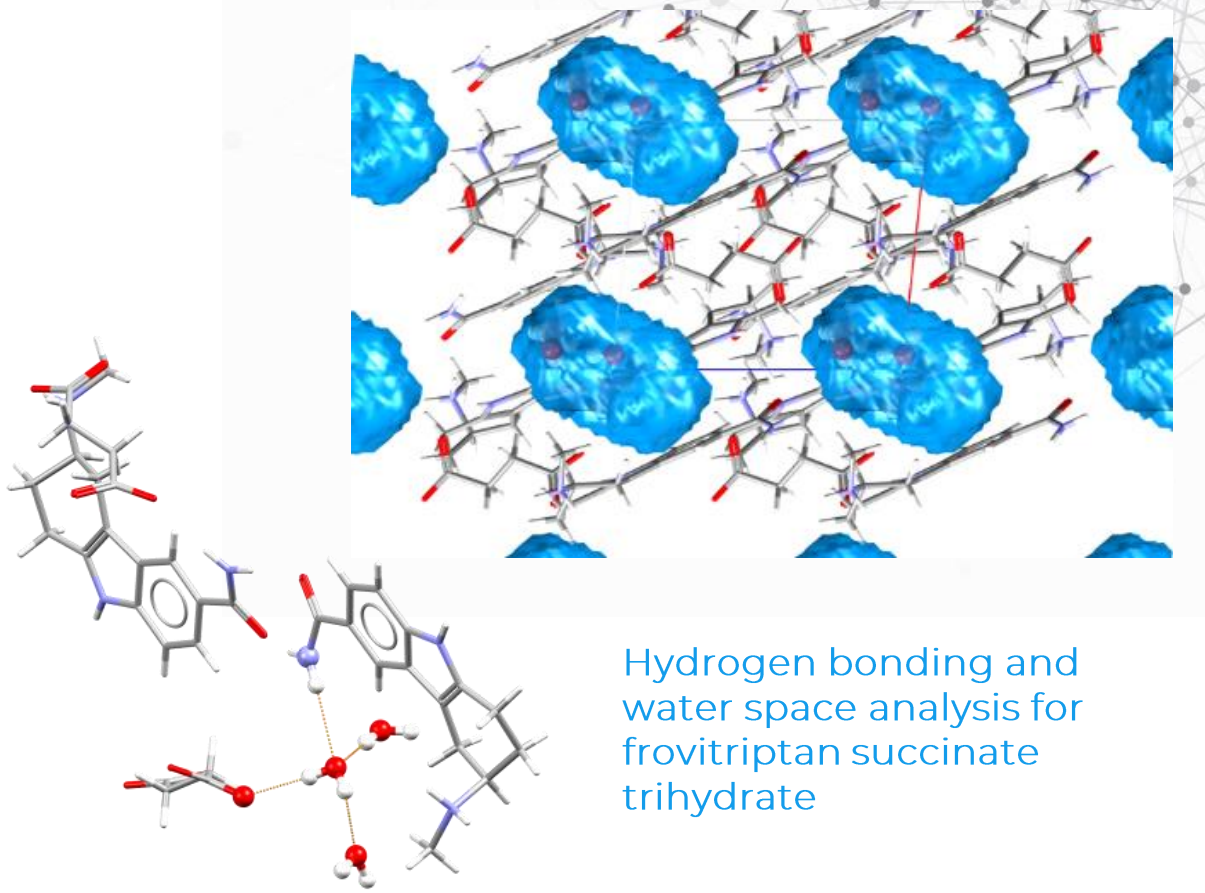
Searching for packing similarity

CSD Refcodes: JURZOO
JURZOO01



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

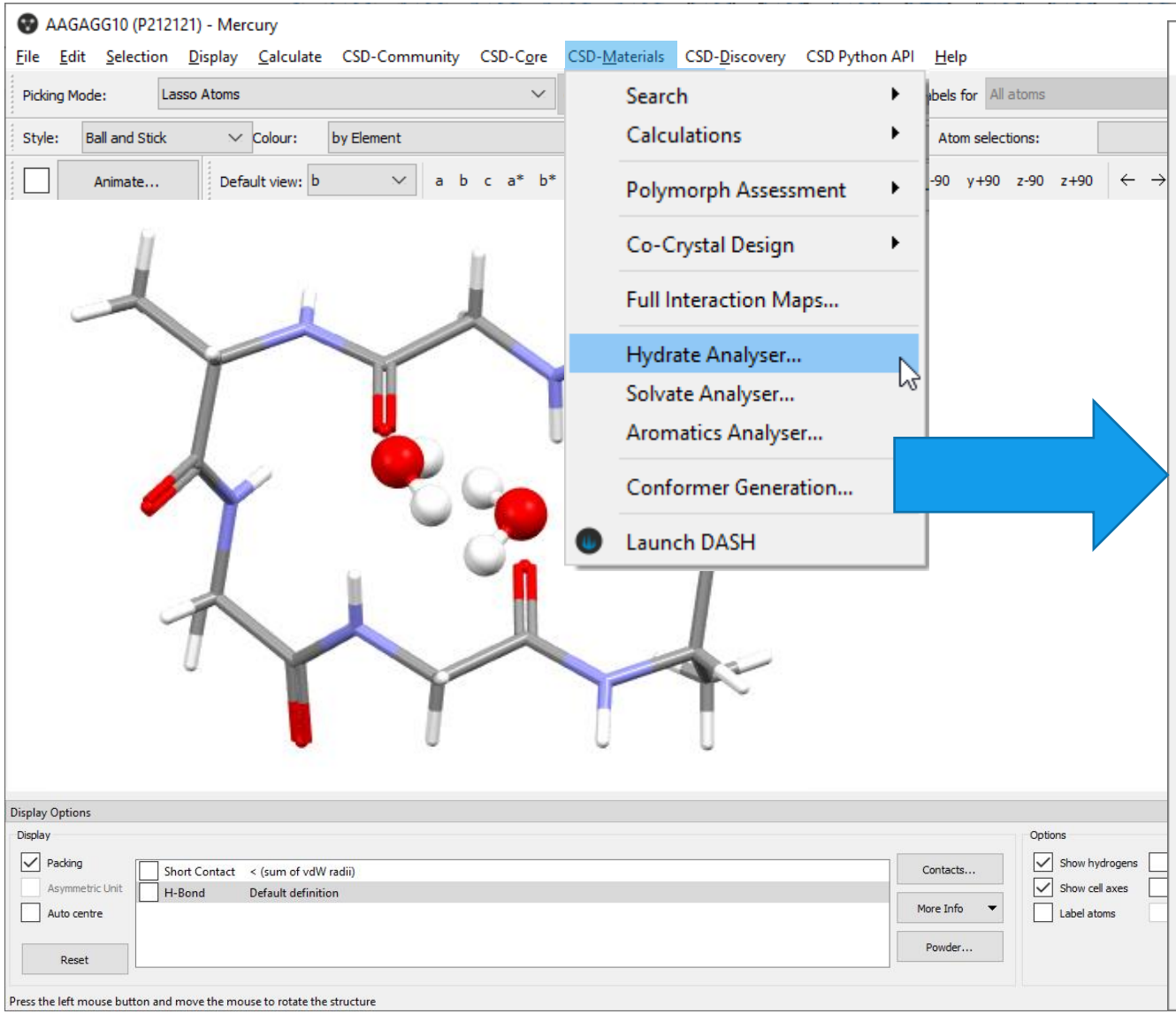


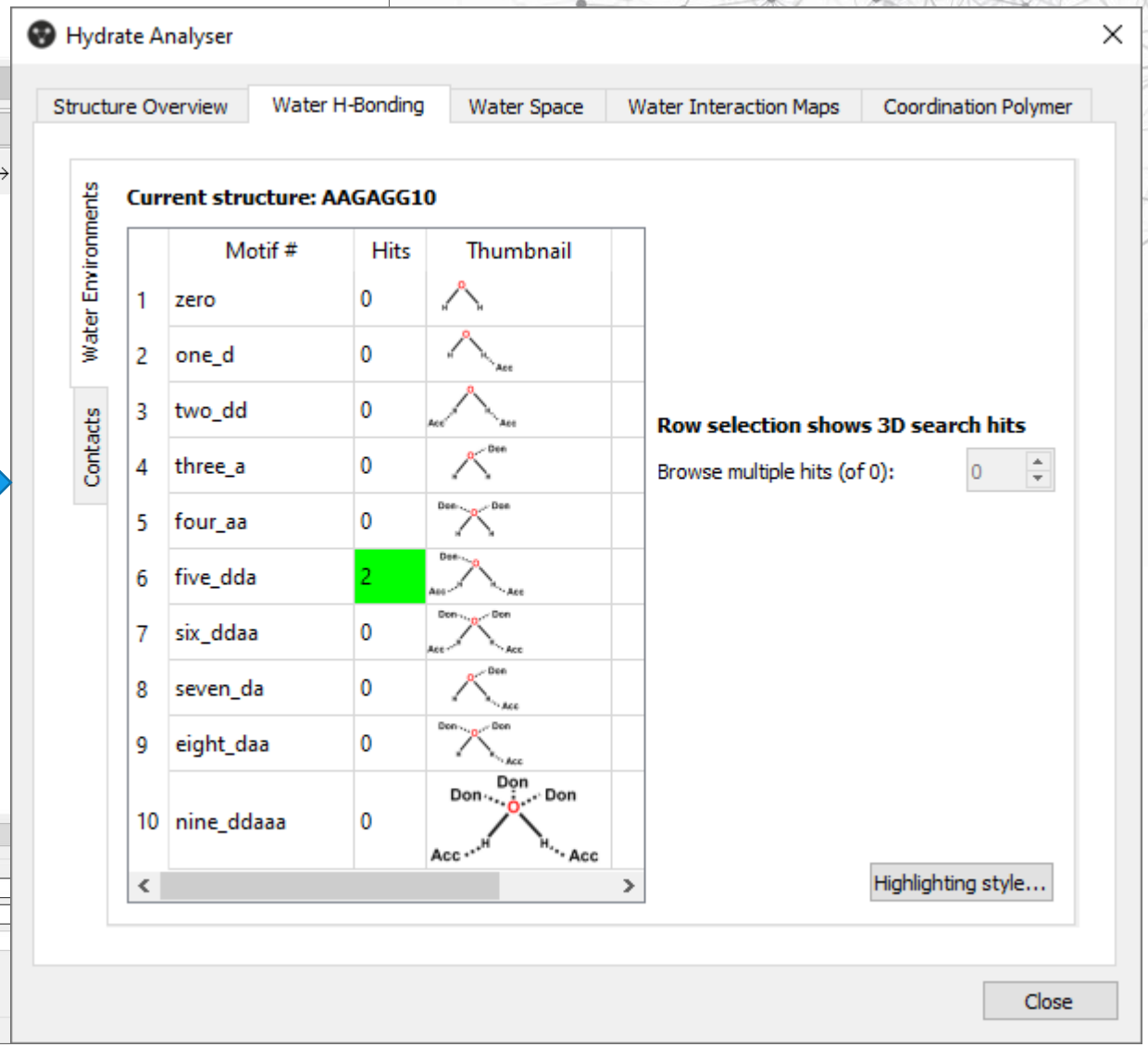
Hydrogen bonding and water space analysis for frovitriptan succinate trihydrate

CCDC

Using the Hydrate Analyser

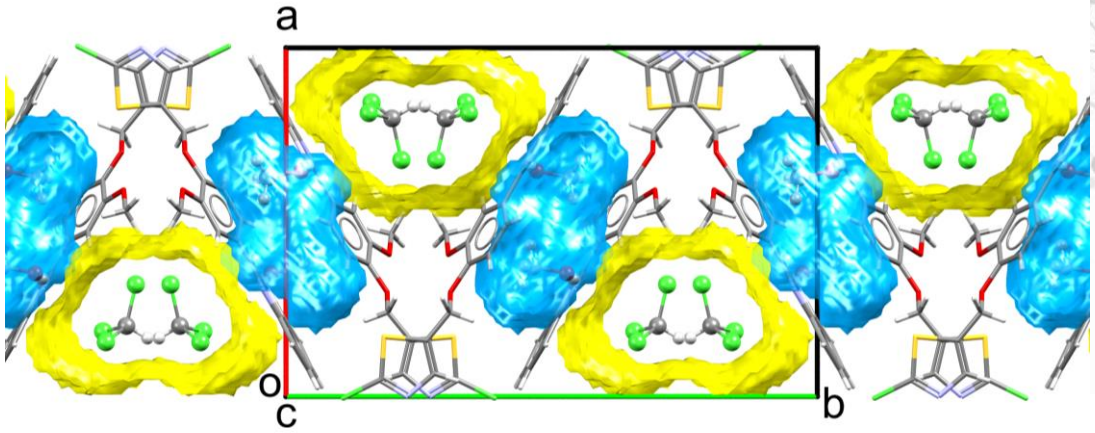
CSD Refcode: AAGAGG10





Solvate Analyser

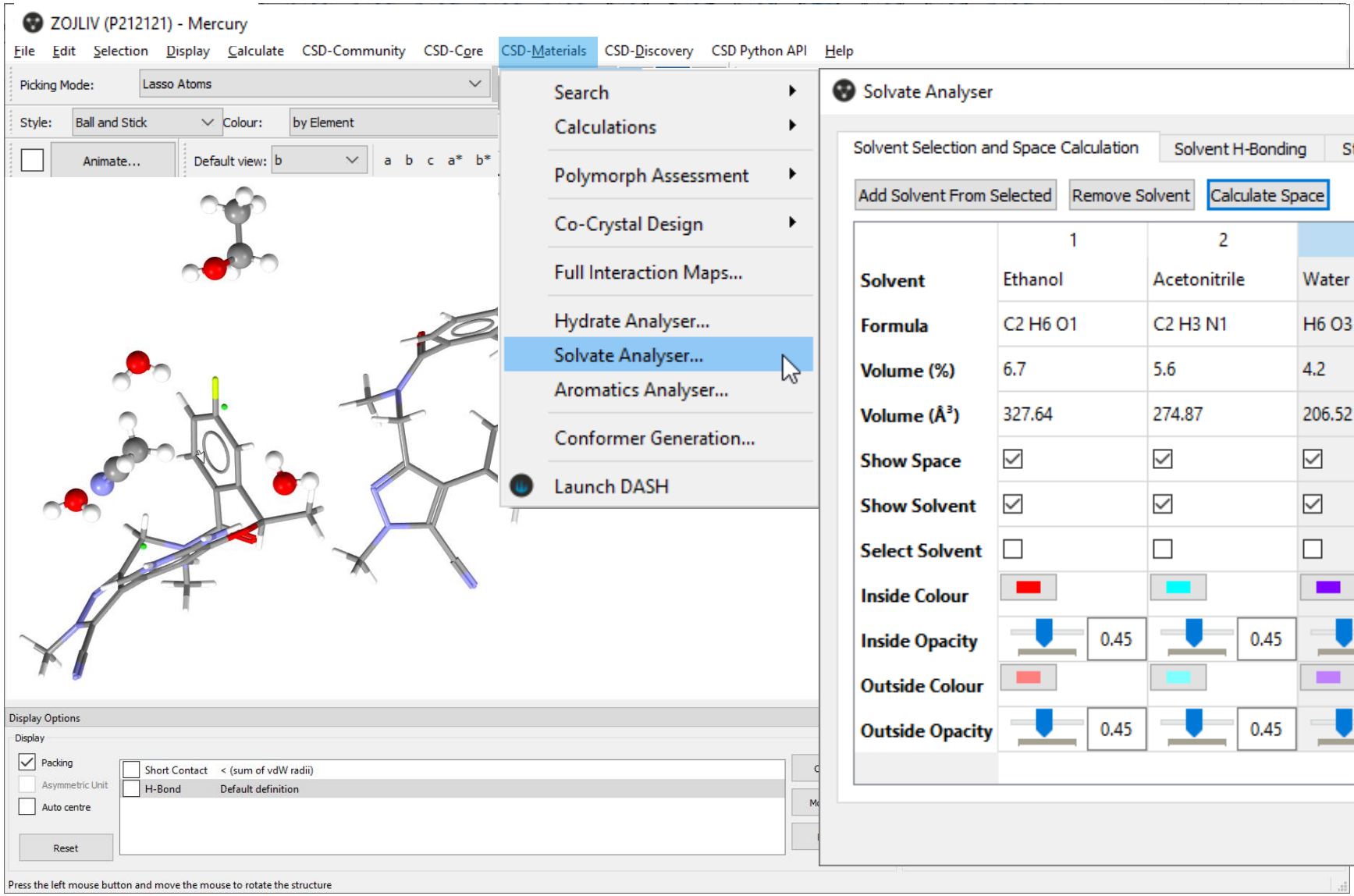
- Quick analysis of the structures containing one or more solvent molecules
- Easy selection of solvent molecule(s)
- Assessment of any hydrogen bonding motifs to/from the solvents
- Calculation and display of the space occupied by each of the different solvent molecules
- Obtain reports on the assessments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

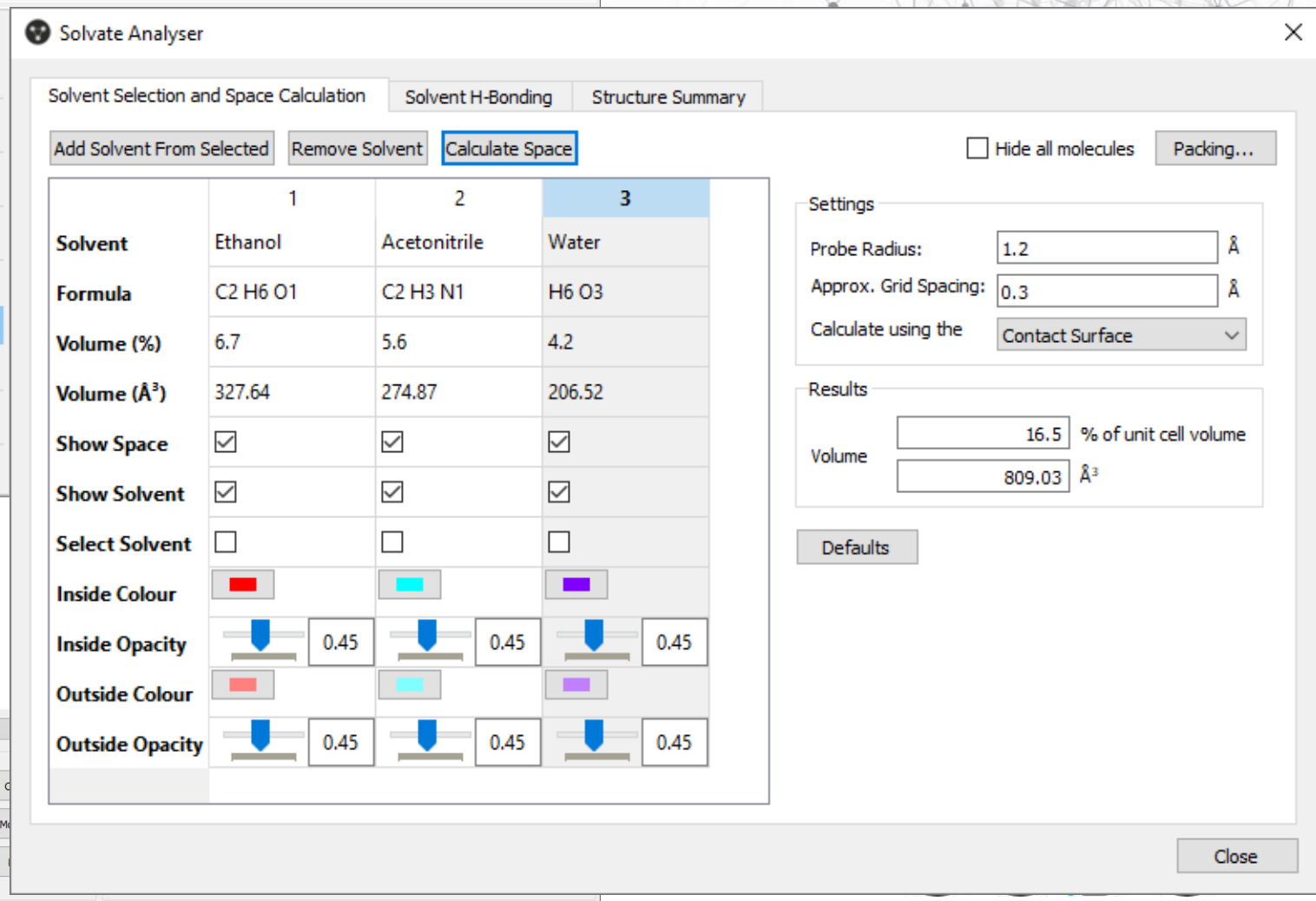


CCDC

CSD Refcode: ZOJLIV

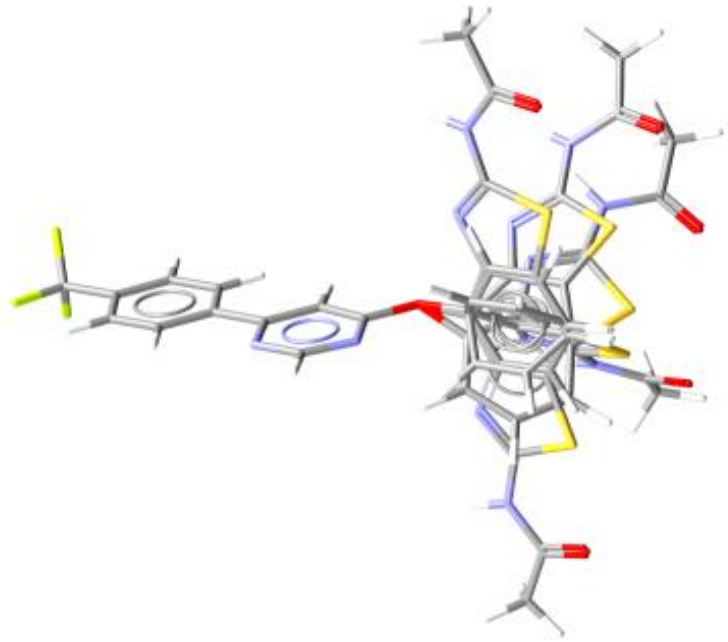
Using the Solvate Analyser





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

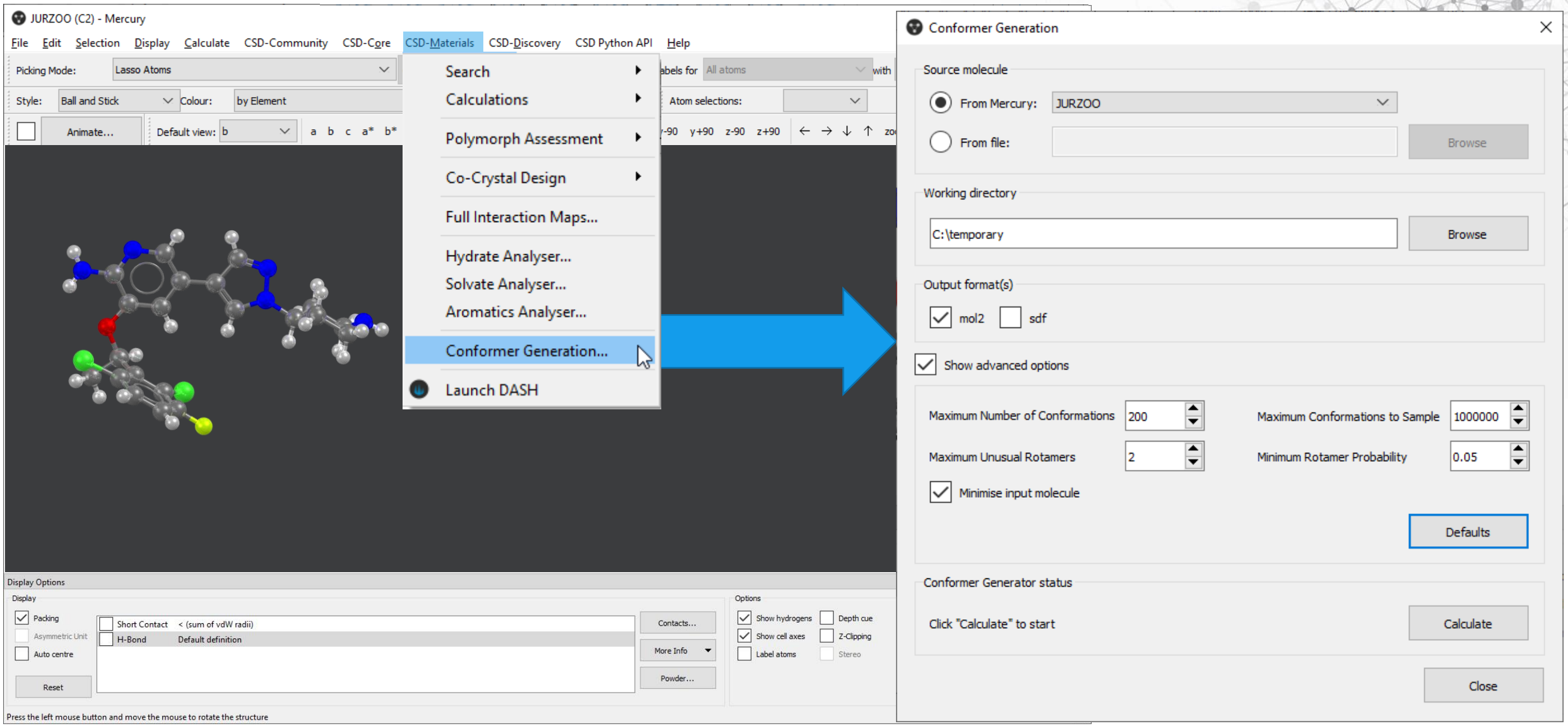


Ensemble of diverse conformations of AMG517 generated by the CSD conformer generator.

CCDC

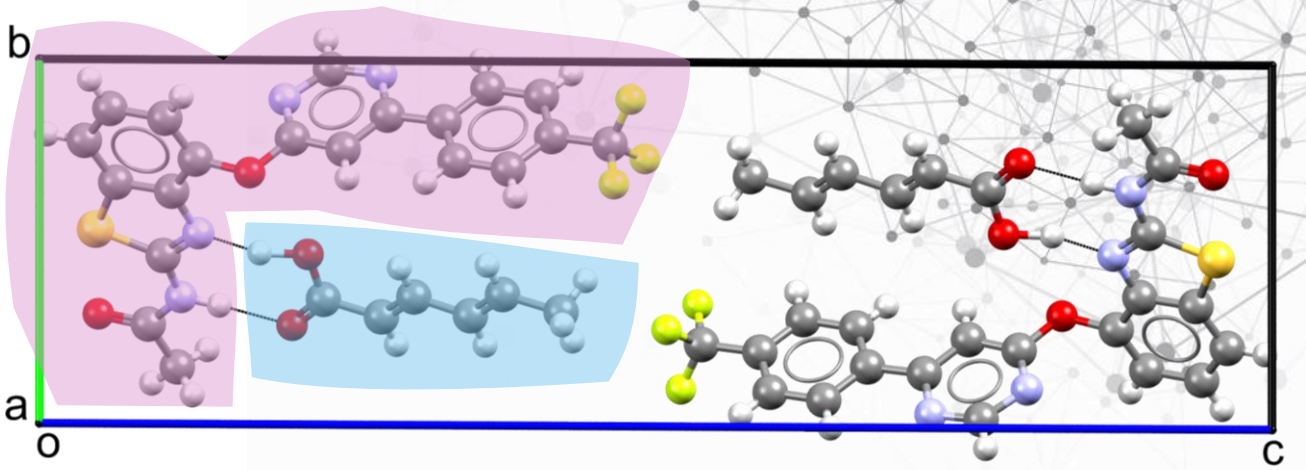
Generating conformers

CSD Refcode: JURZOO



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

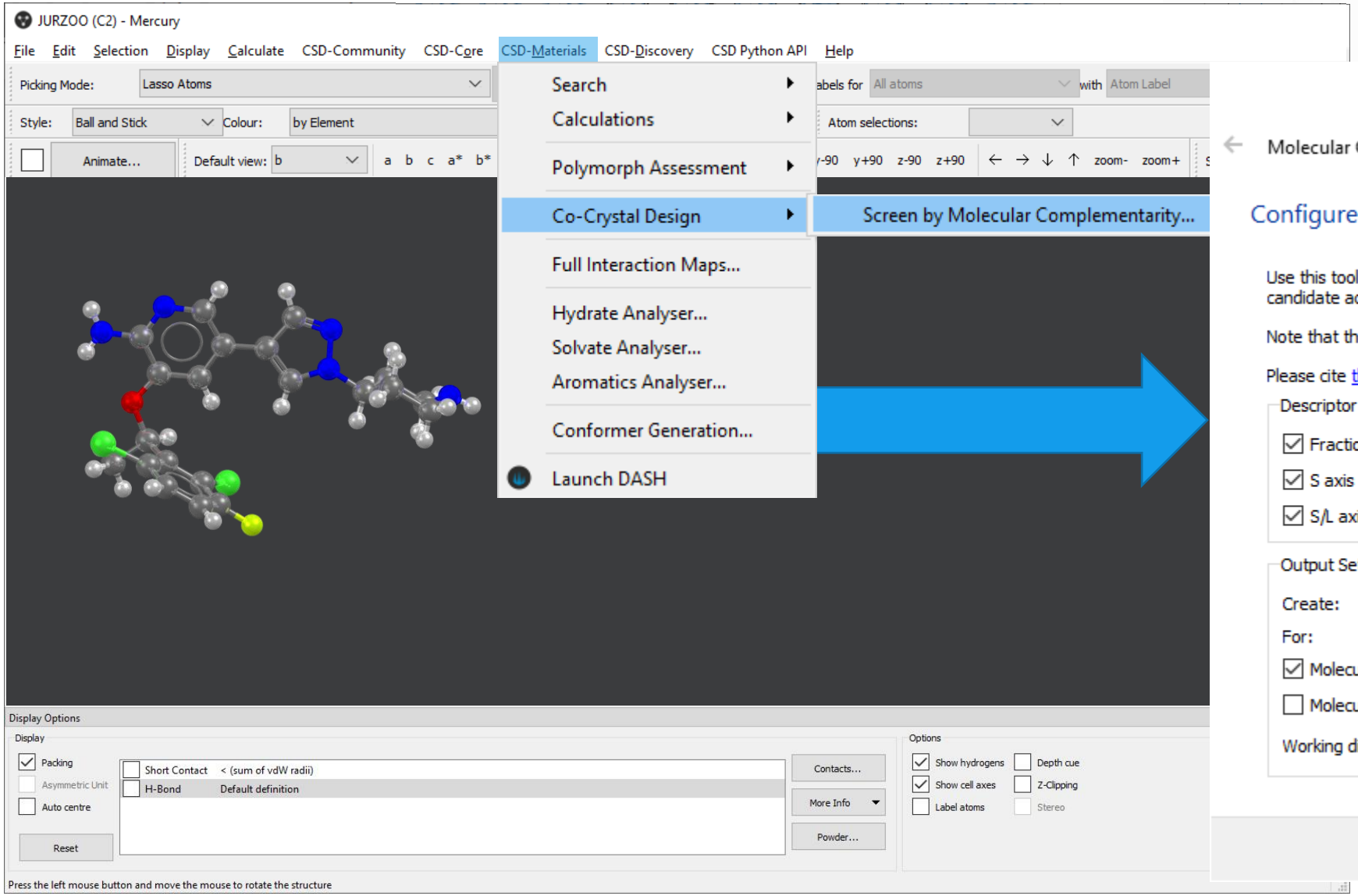


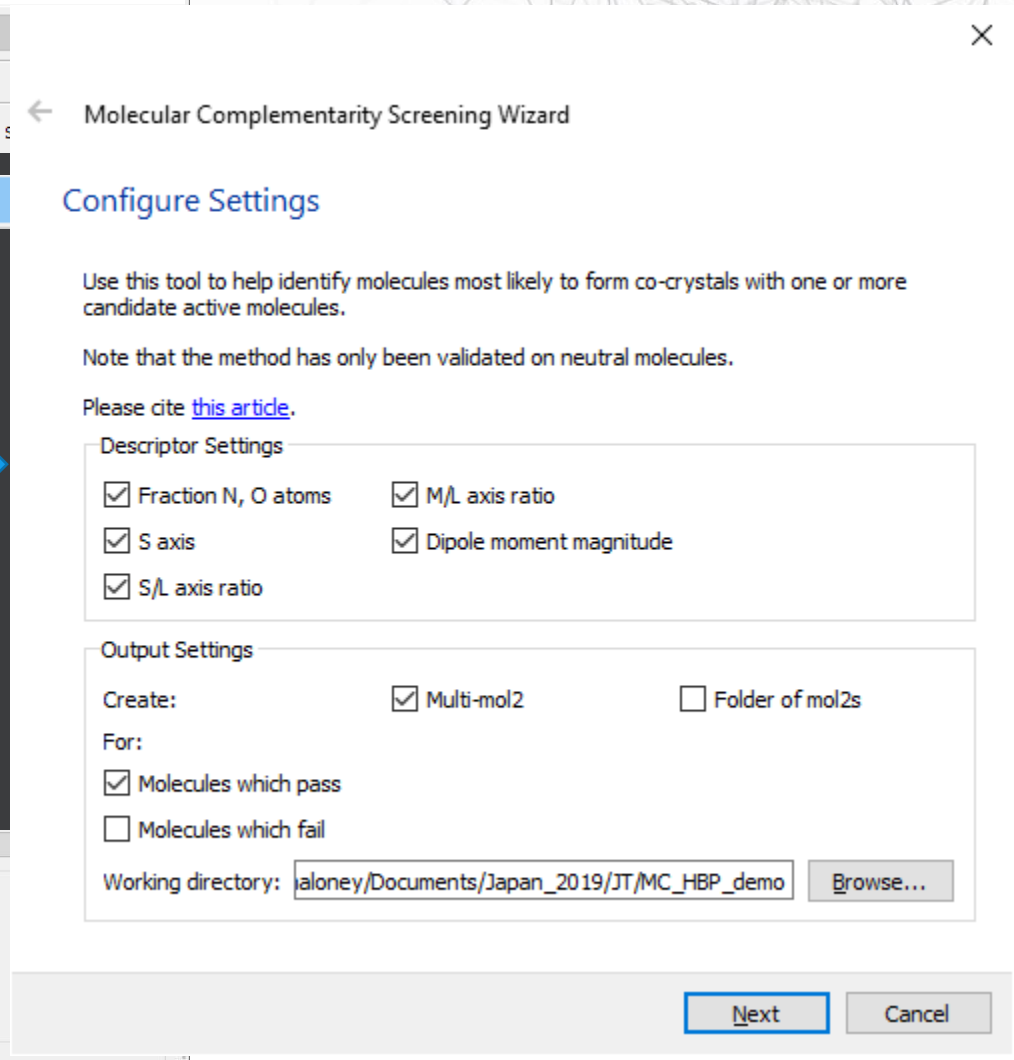
	ML axis ratio	S axis (/Å)	SL axis ratio	Dipole Moment (/Debye)	Fraction of NO
Sorbic Acid	0.50	4.17	0.38	1.03	0.25
AMG 517	0.66	6.46	0.35	1.65	0.20
AMG 517:Sorbic Acid |Delta|	0.16	2.29	0.03	0.62	0.05
|Delta|Pass Criteria	<0.32	<3.2	<0.28	<5.8	<0.29
AMG 517:Sorbic Acid |Delta| Meets Criteria	Yes	Yes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

L. Fabian, Cryst. Growth Des., 2009, 9 1436-1443, DOI: 10.1021/cg800861m

CCDC

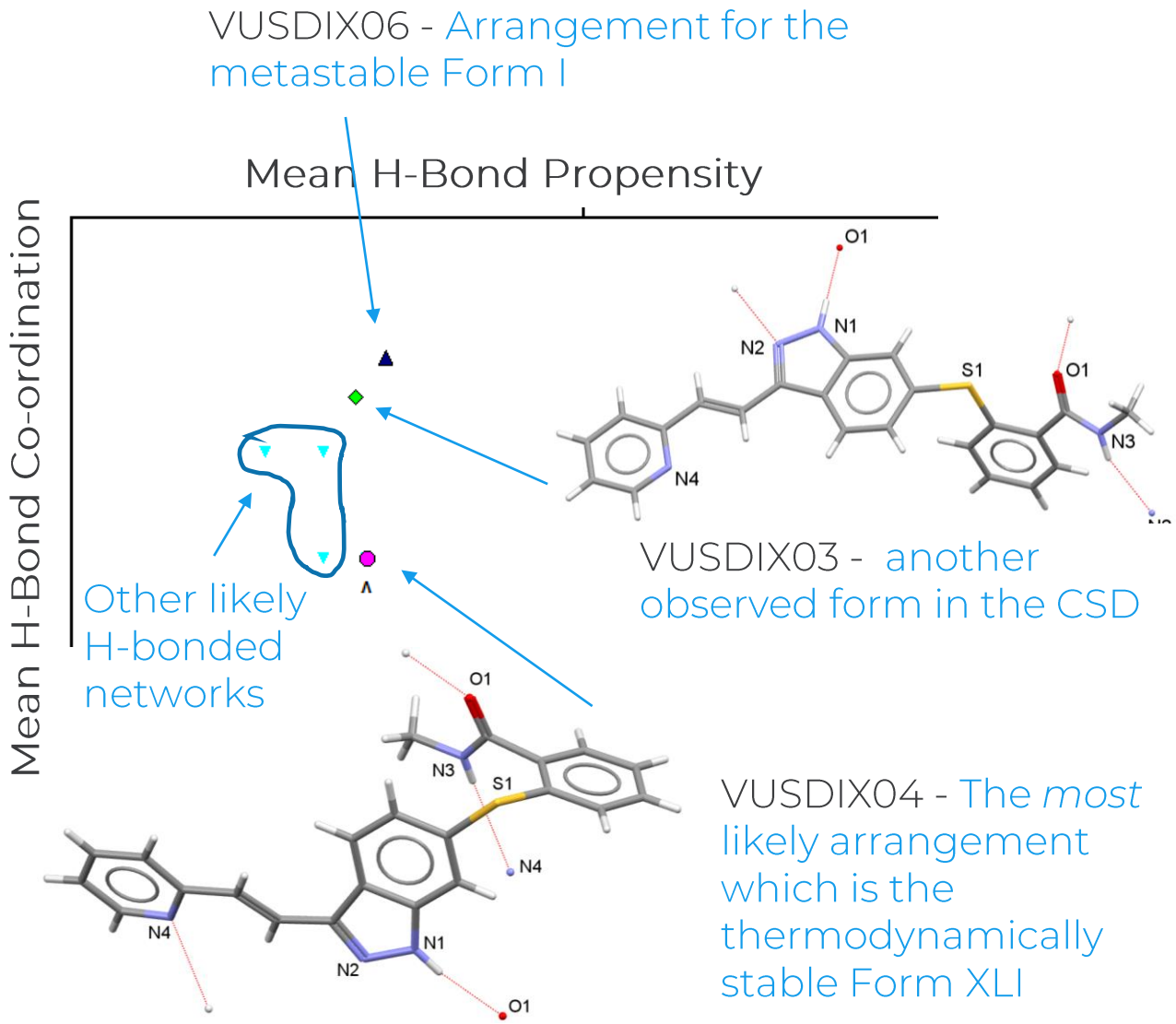
Performing molecular complementarity





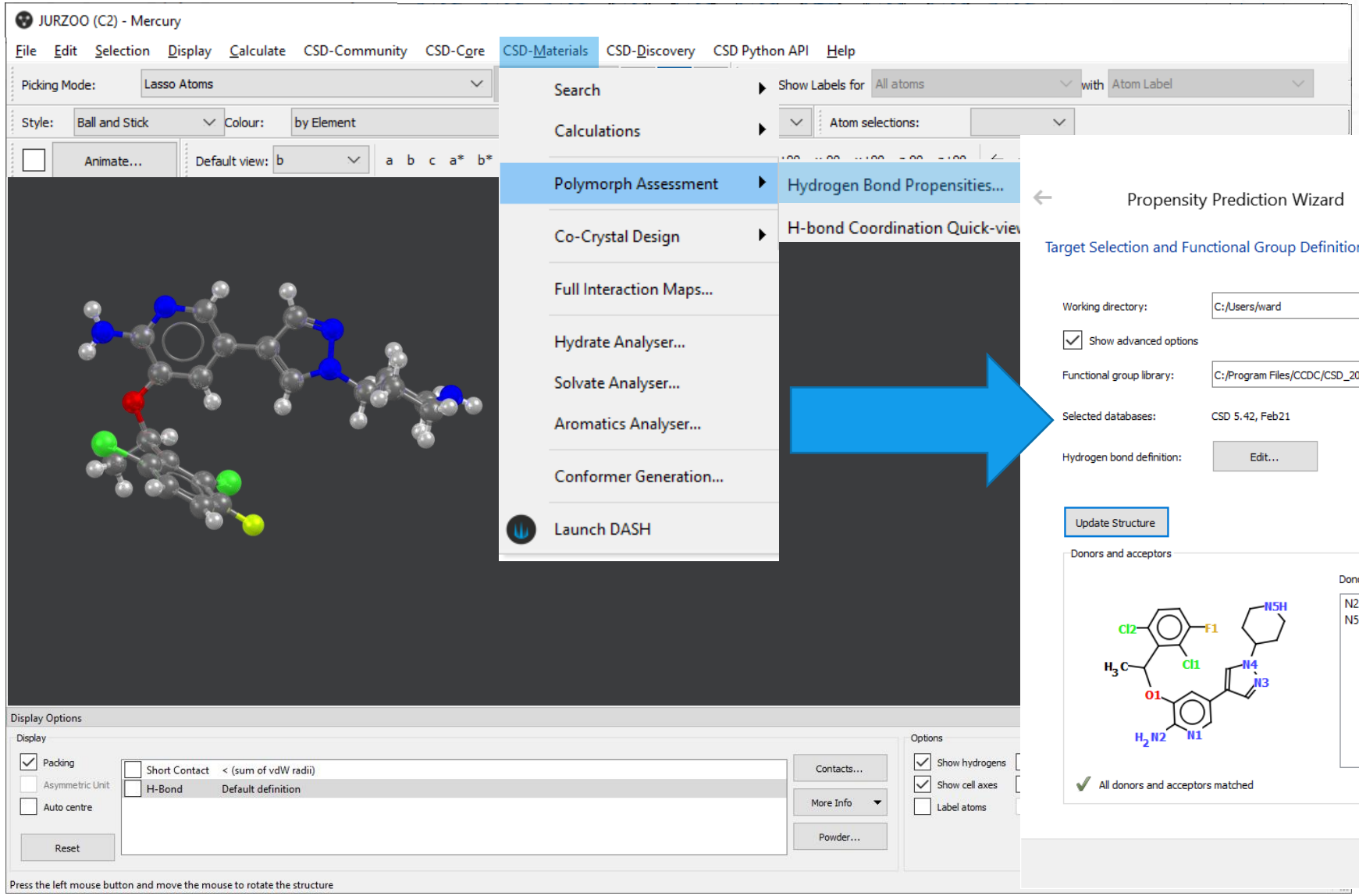
Hydrogen Bond Propensity

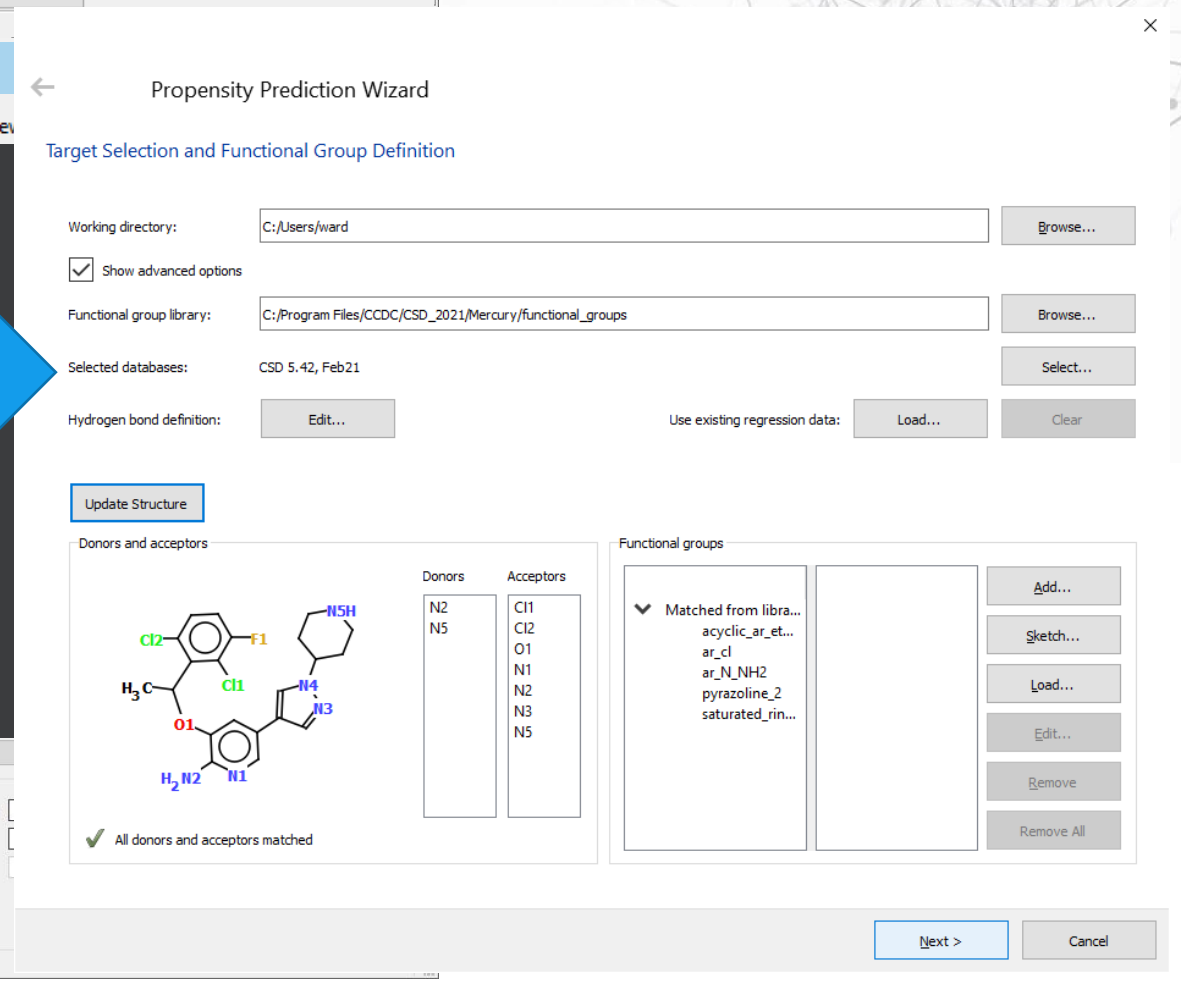
- Predict likely hydrogen bonds for a given molecule
- Assess crystal forms, e.g., by identifying sub-optimal hydrogen bonding
- Calculate hydrogen bond propensities for individual donor and acceptor groups
- Perform a comprehensive analysis of hydrogen bonding on a set of structures



Calculating a Hydrogen Bond Propensity

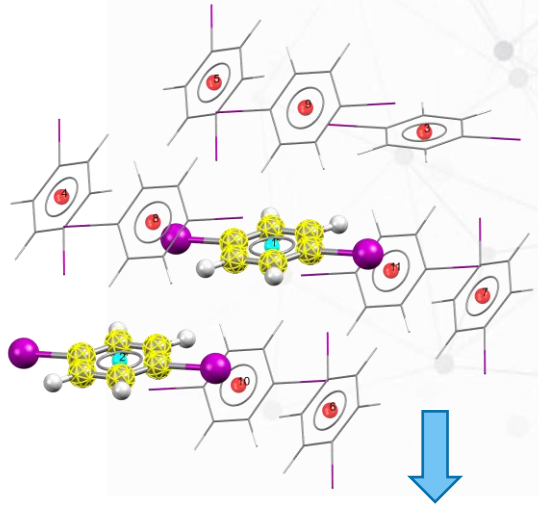
CSD Refcode: JURZOO





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

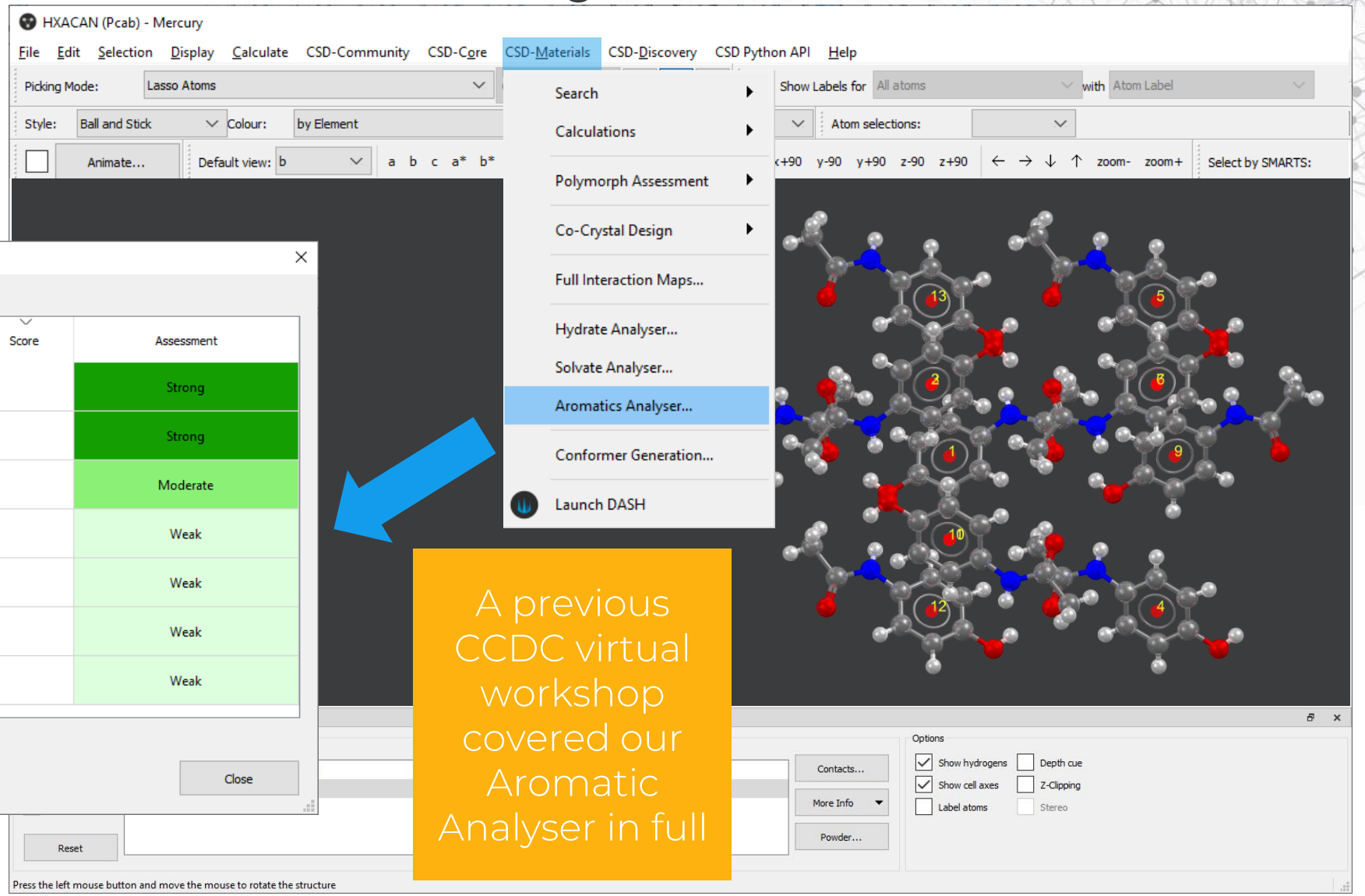
	Centroid1	Centroid2	Distance	Relative Orientation	Inter-olecula	Score	Assessment
1	1	8	4.79	46.23	Yes	8.3	Strong
2	1	9	4.79	46.23	Yes	8.3	Strong
3	1	10	4.79	46.23	Yes	8.3	Strong
4	1	11	4.79	46.23	Yes	8.3	Strong
5	1	2	6.17	0	Yes	5.2	Moderate
6	1	3	6.17	0	Yes	5.2	Moderate
7	1	4	9.04	43.74	Yes	0.5	Weak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

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

Close

CCDC

Using the Aromatics Analyser

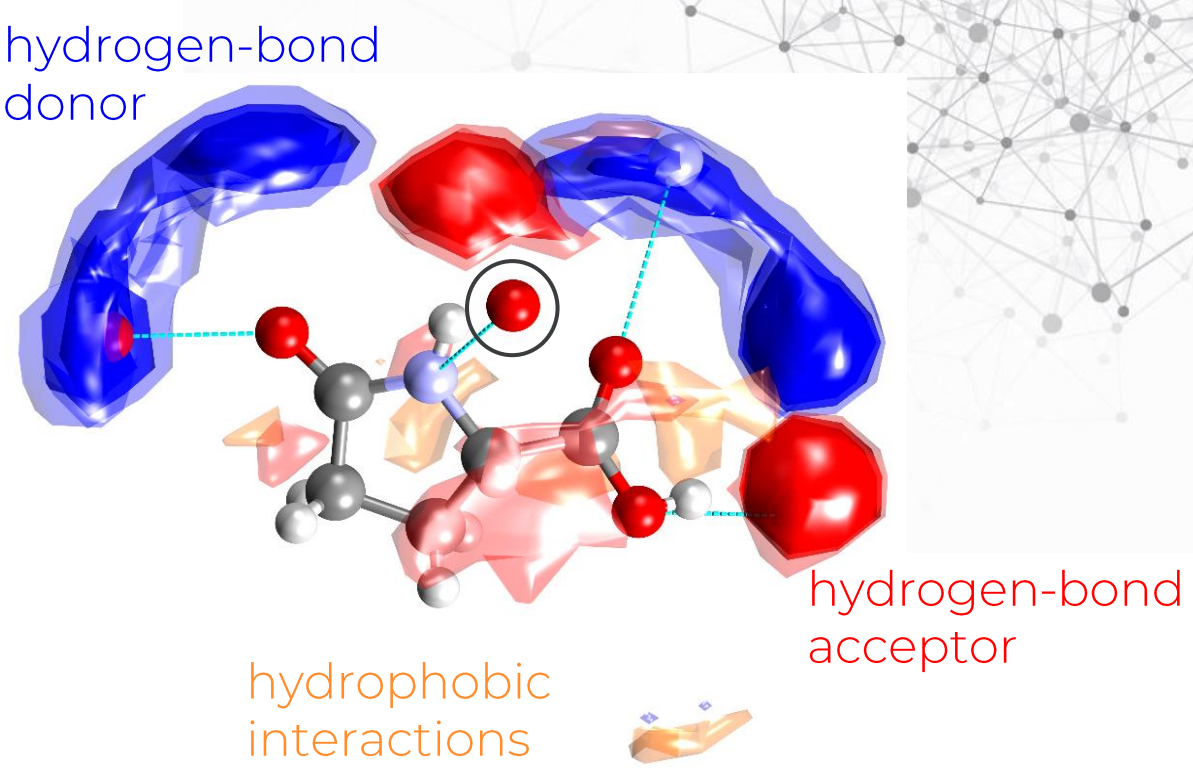


	Centroid1	Centroid2	Distance	Relative Orientation	Inter-molecular	Score	Assessment
1	1	2	4.65	58.43	Yes	8.9	Strong
2	1	10	4.87	50.79	Yes	8	Strong
3	1	12	5.94	26.95	Yes	5.9	Moderate
4	1	7	8.93	0	Yes	0.6	Weak
5	1	8	8.6	58.43	Yes	0.6	Weak
6	1	6	9.38	0	Yes	0.4	Weak
7	1	4	9.88	50.79	Yes	0.2	Weak

A previous CCDC virtual workshop covered our Aromatic Analyser in full

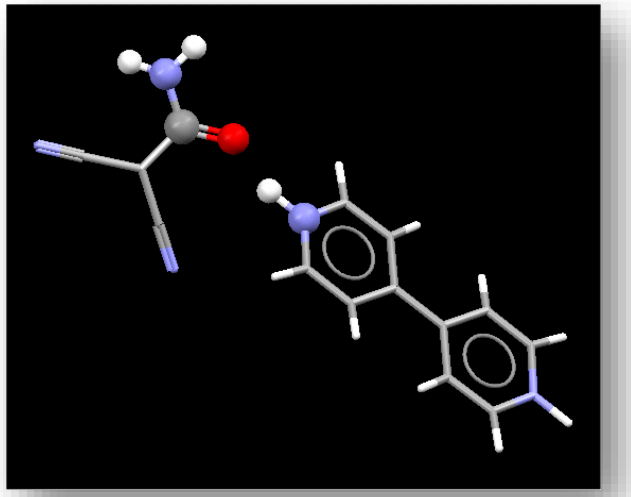
Full Interaction Maps (FIMs)

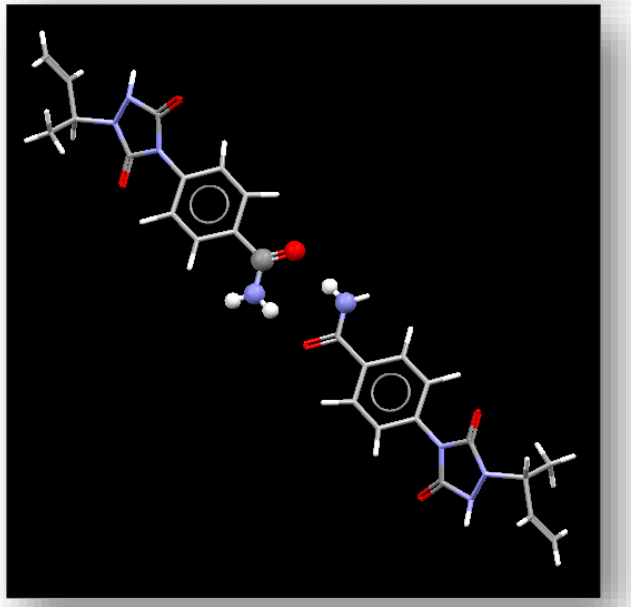
- Map interaction preferences around complete molecules in a crystal structure
- Visualise observed atom-atom contacts with respect to likely geometries in 3D space
- Identify interaction hot-spots around chemical groups



CCDC

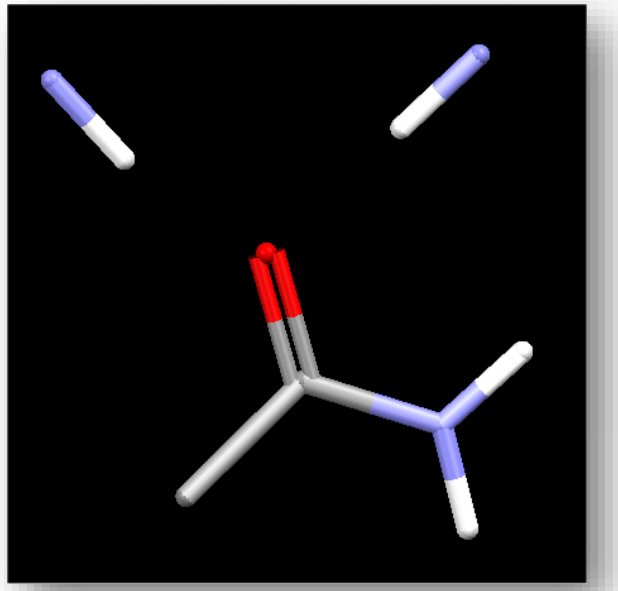
Understanding intermolecular interactions

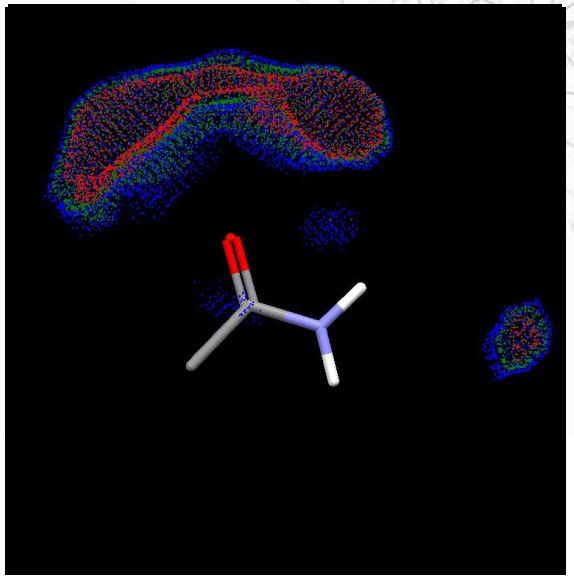




central group: -$CONH_2$

contact group: NH





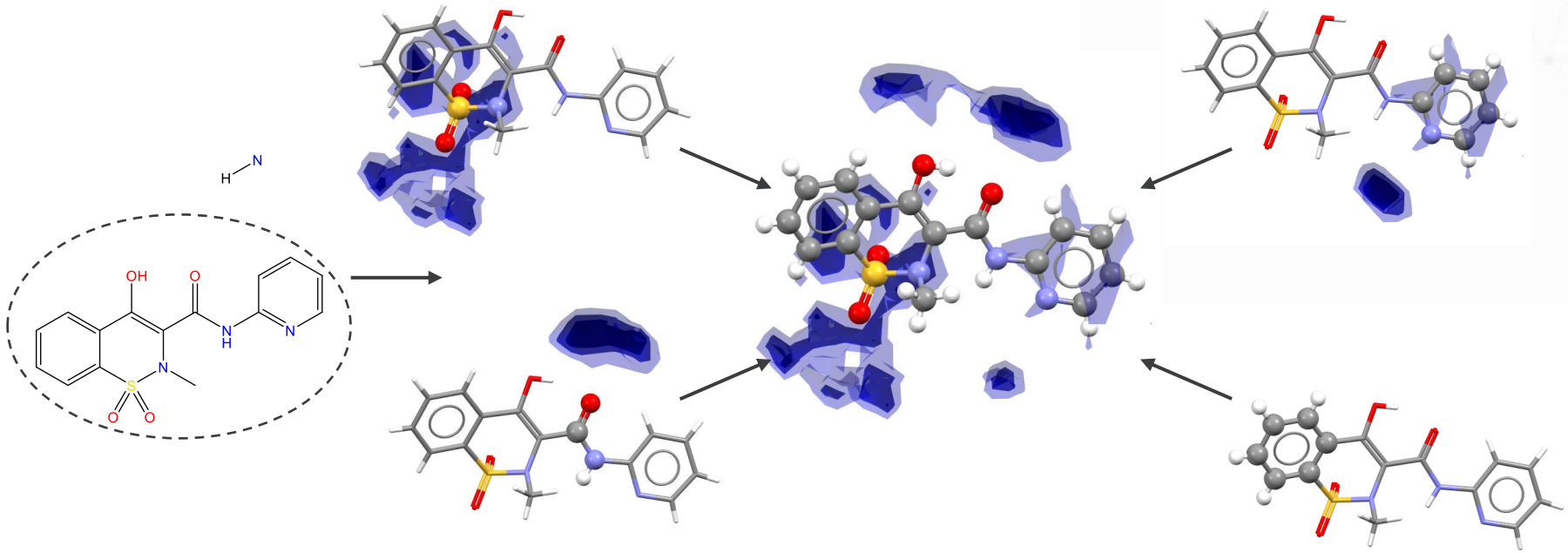
Search for structures containing desired contact

Superimpose hits and display as scatterplots or contour plots

CCDC

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



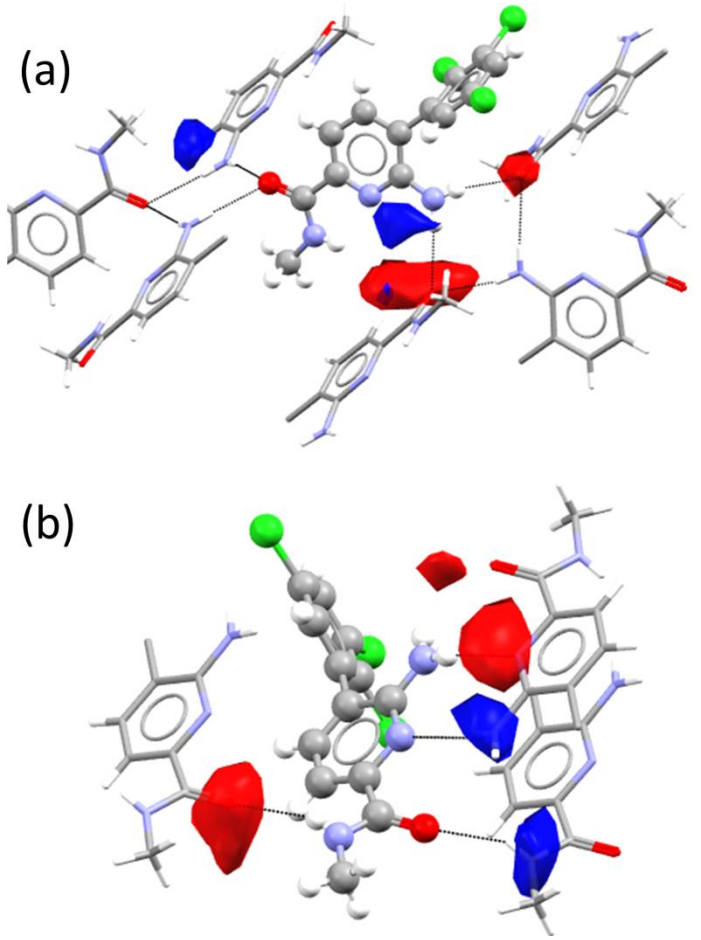
- Multiple maps can be generated for different probes

P. A. Wood *et al.*, *CrystEngComm* (2013), **15**, 65–72

CCDC

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

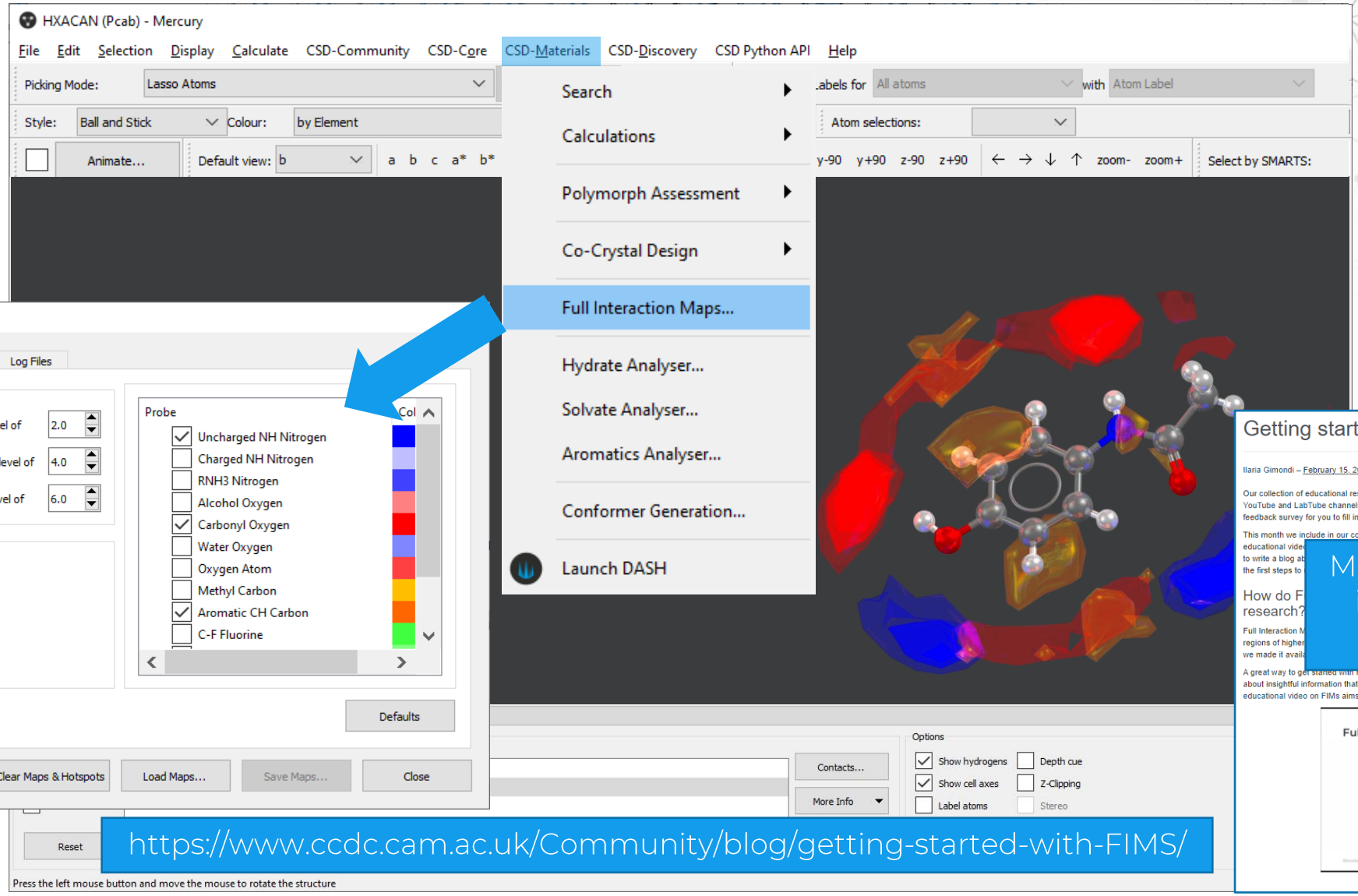


N. Feeder *et al.*, *J. Pharm. Pharmacol.* (2015), **67**(6), 857-868

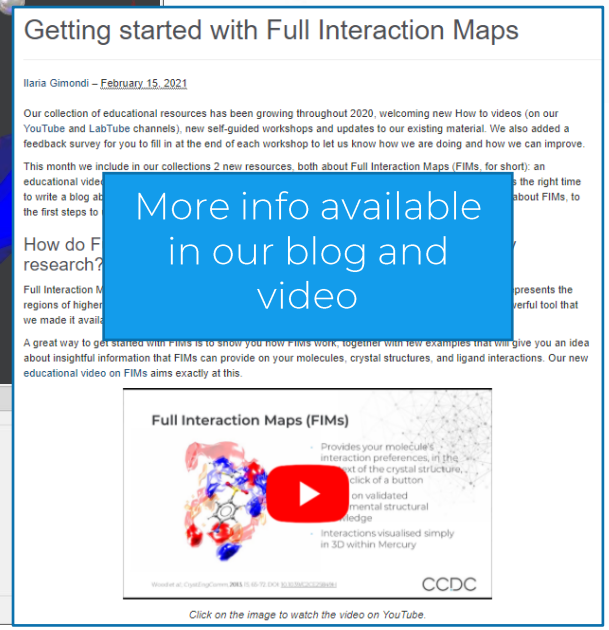
CCDC

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

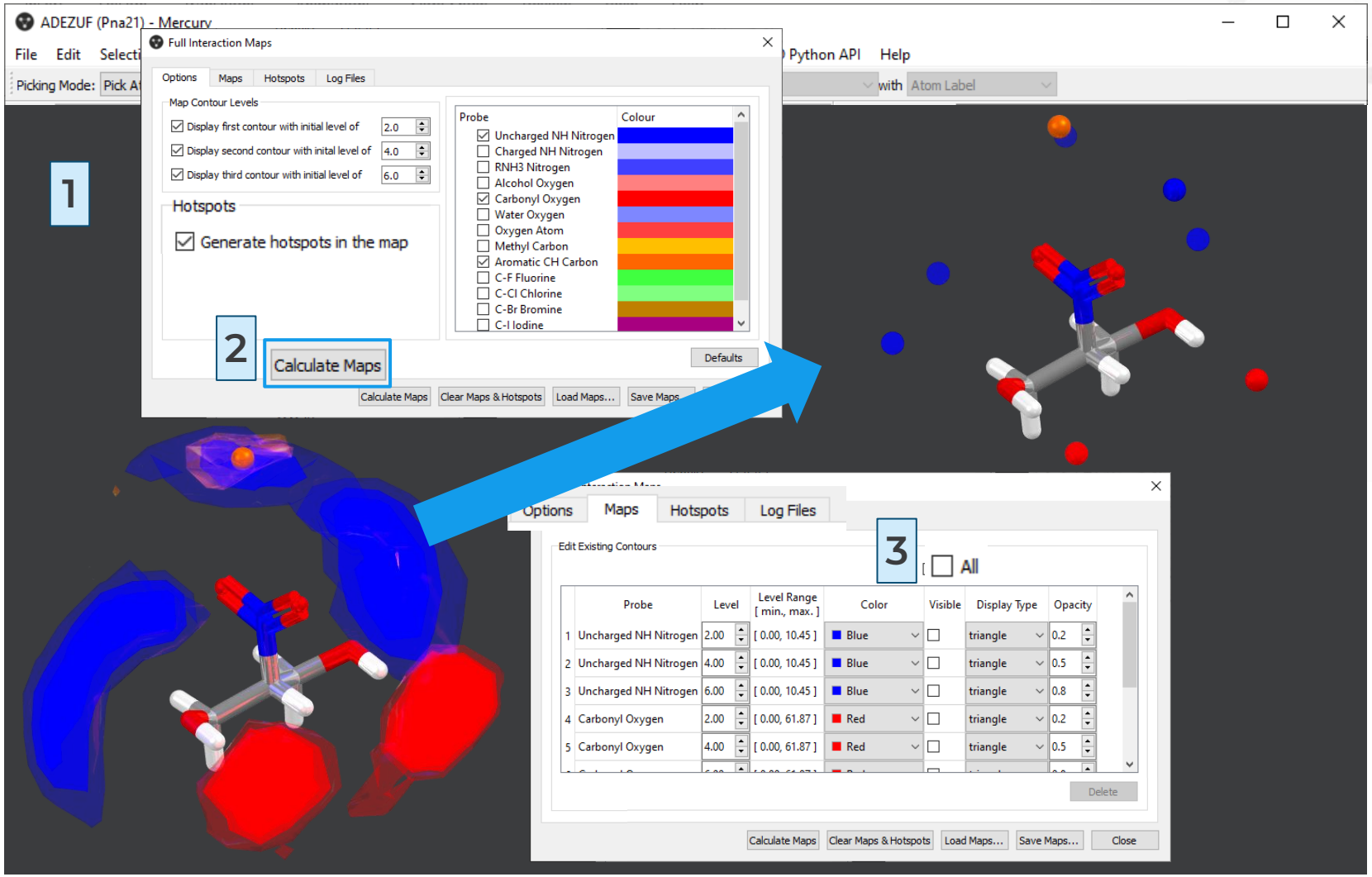


More info available in our blog and video



https://www.ccdc.cam.ac.uk/Community/blog/getting-started-with-FIMS/

Creating a hotspot



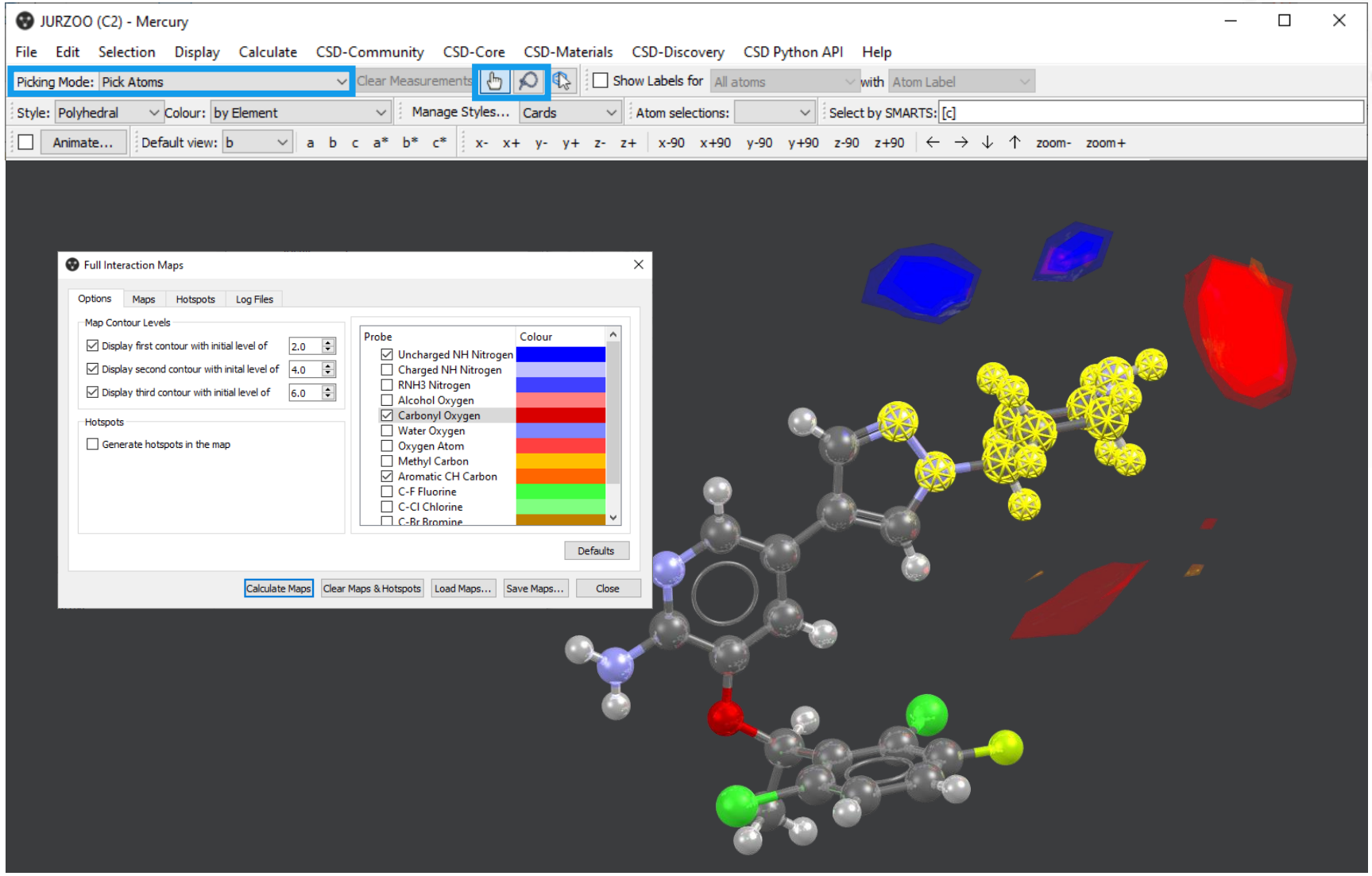
Hotspots represent the positions of highest local density for each contour Surface. Find this in our *Glossary*.

CCDC

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



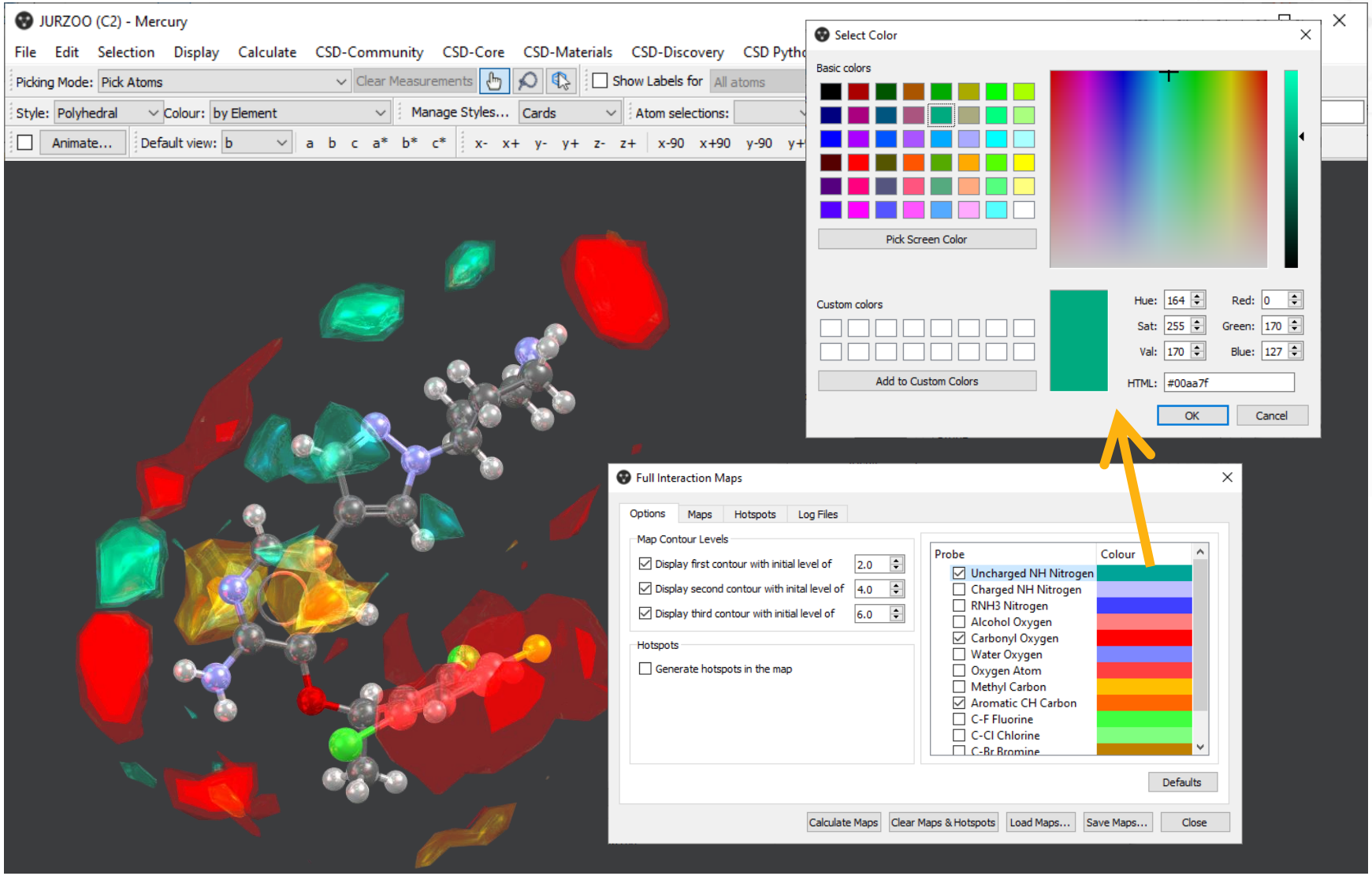
You can generate FIMs for a portion of a molecule.

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

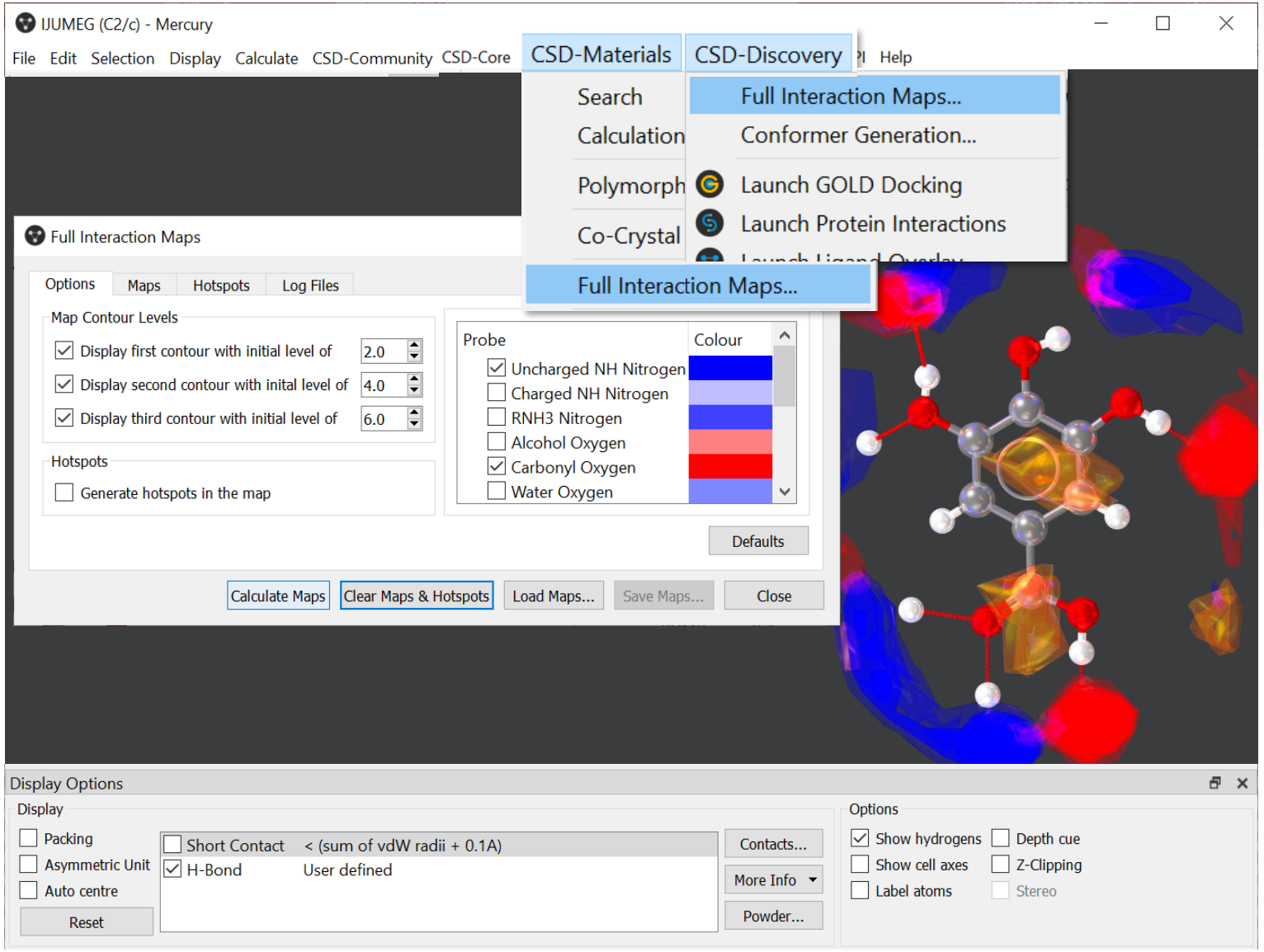
Change the colour of probes



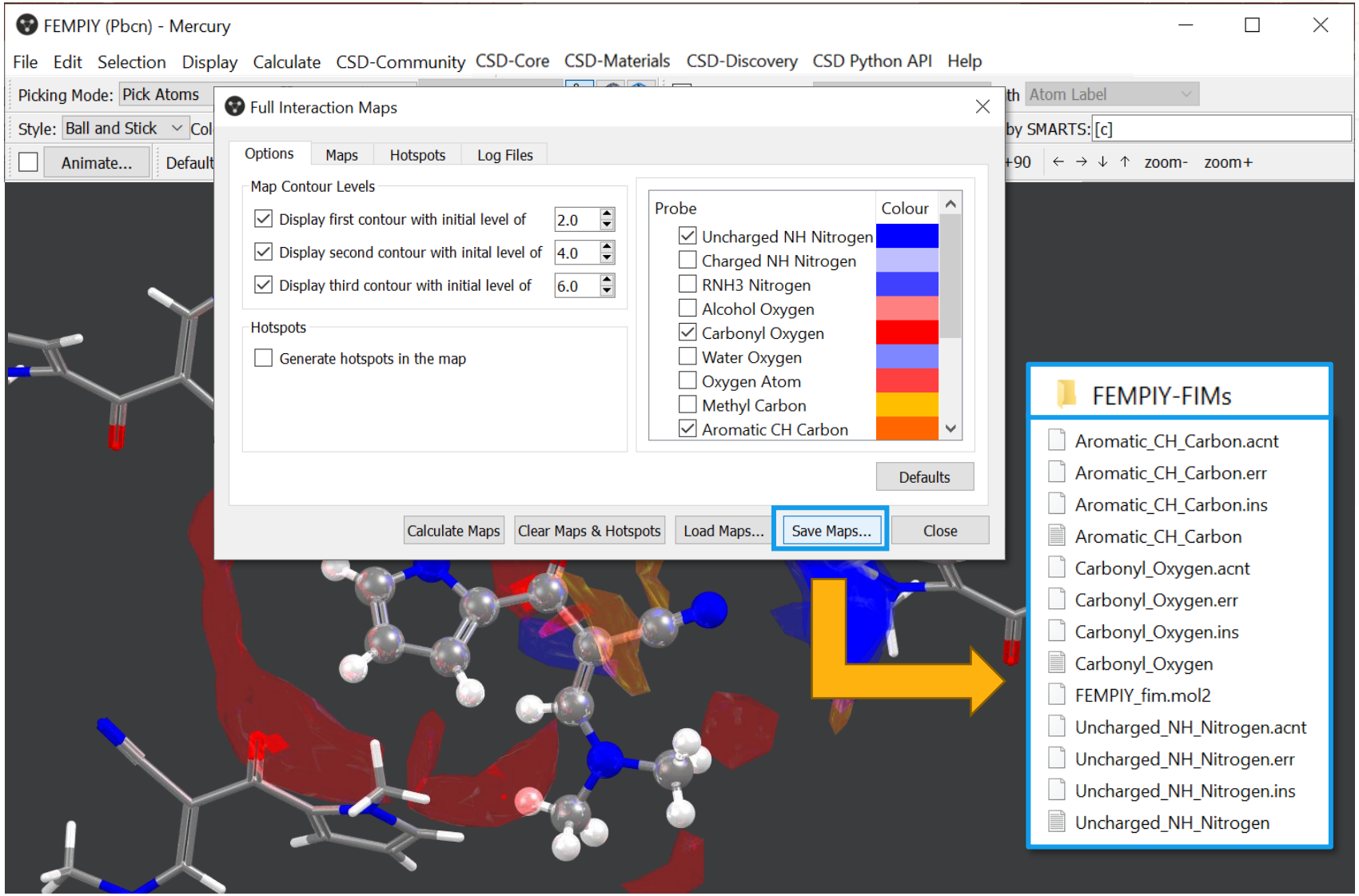
You can change the colour for each probe by clicking on the Colour in the Full Interaction Maps Options tab

Access FIMs through CSD-Discovery

You can also access FIMs in the CSD-Discovery menu

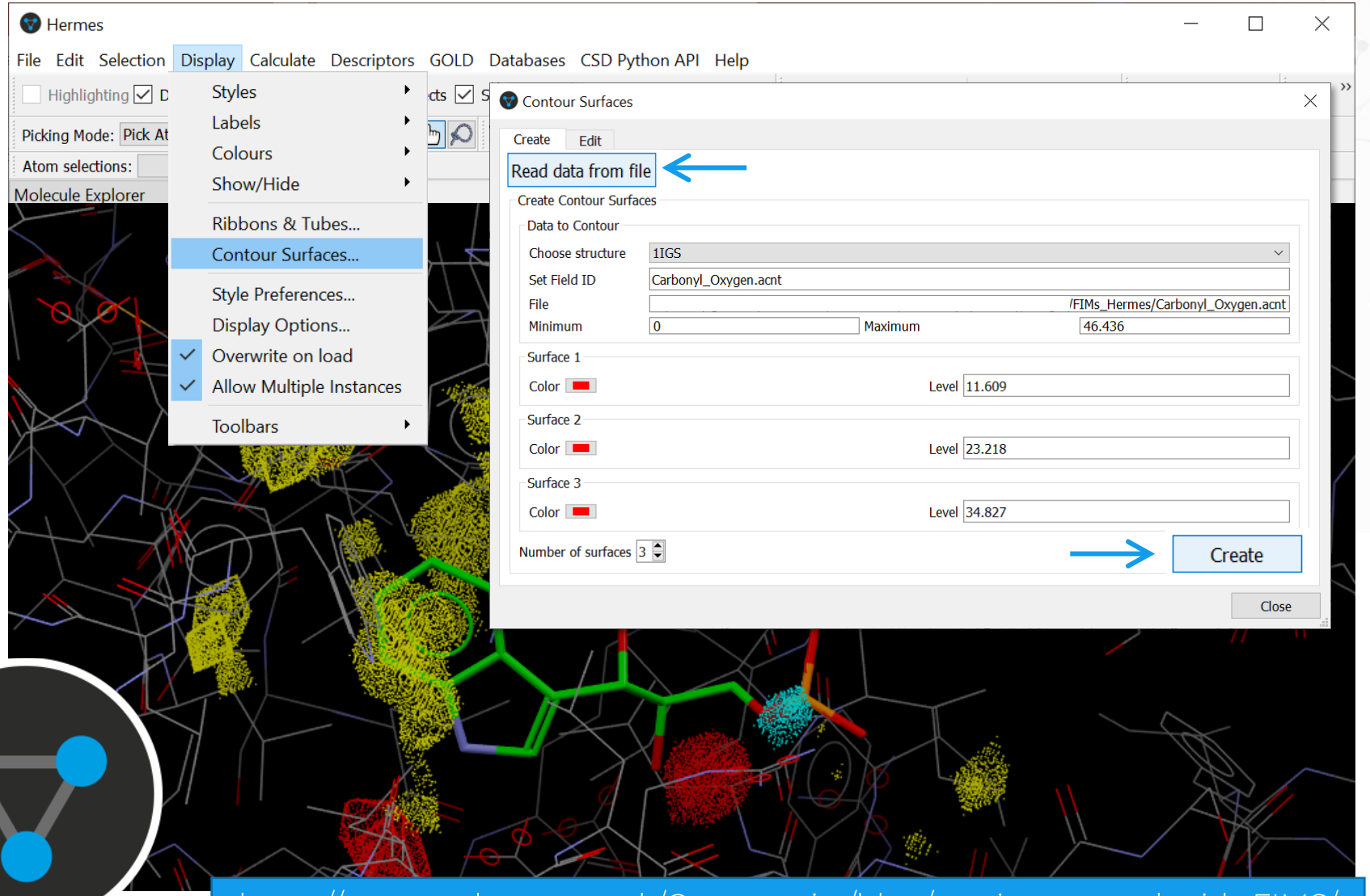


Save FIMs



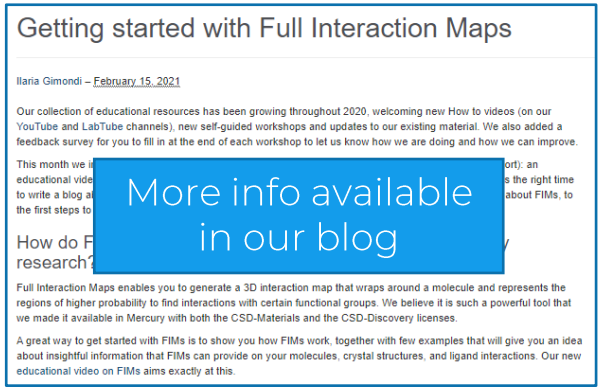
You can save a FIM in the Full Interaction Maps Options tab by clicking Save Maps...

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.

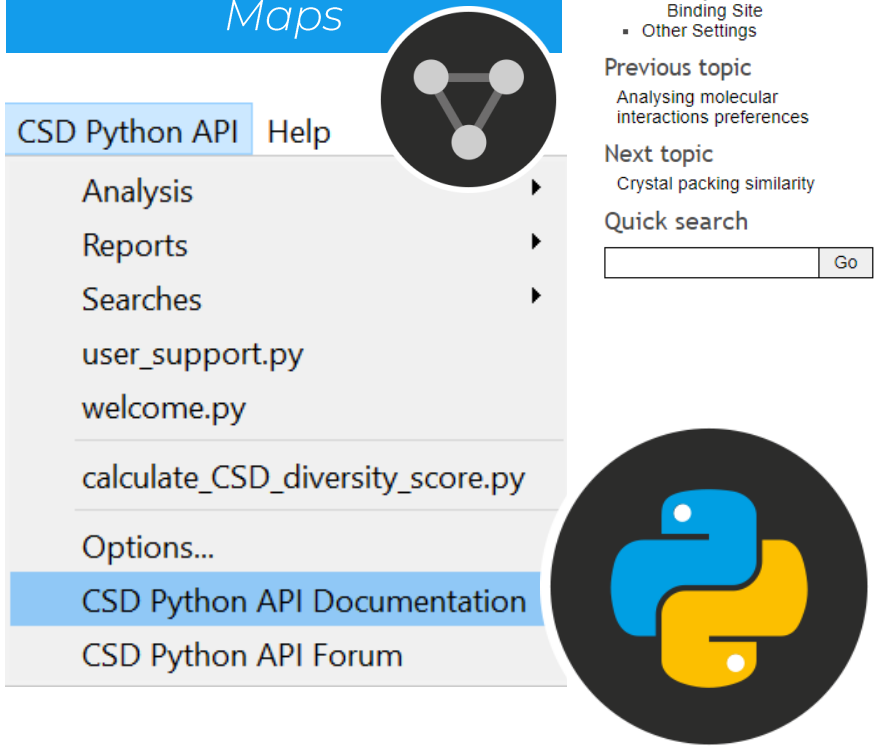


More info available in our blog

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



CCDC
advancing structural science

Table of Contents

Previous topic
Analysing molecular interactions preferences

Next topic
Crystal packing similarity

Quick search
Go

Interaction Maps

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

ccdc.interaction.InteractionMapAnalysis

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, 65?72, 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
```

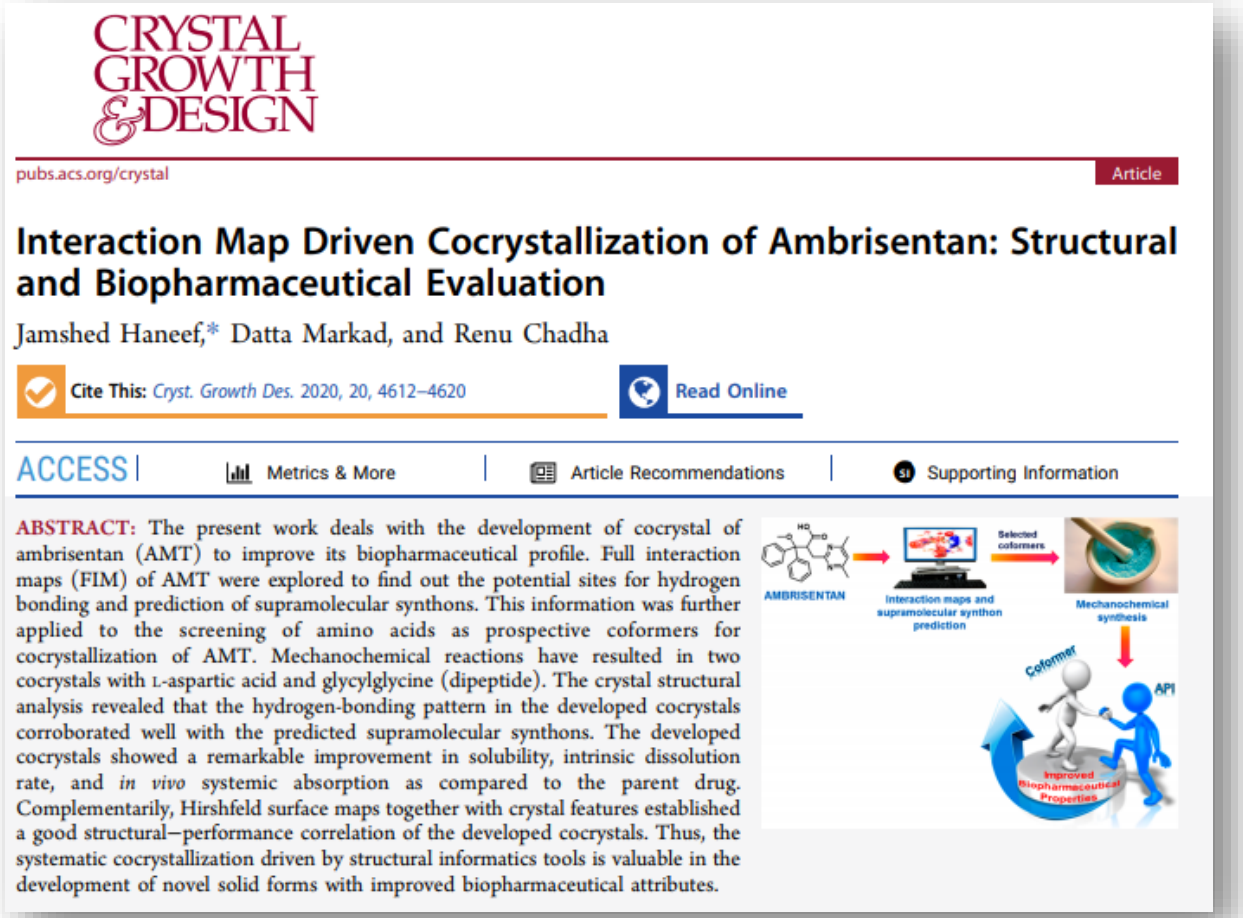
Then we will load a crystal structure for paracetamol:

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

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 Read Online

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

Jamshed Haneef, Datta Markad, and Renu Chadha, *Crystal Growth & Design* **2020** *20* (7), 4612-4620.
DOI: 10.1021/acs.cgd.0c0042

CCDC

Get a certificate and help us improve

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

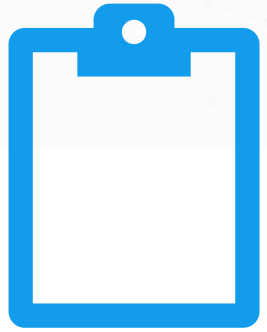
1. Complete the test
2. Score 10/10
3. Receive your certificate

- 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

https://www.ccdc.cam.ac.uk/Community/educationalresources/

Want to explore more?

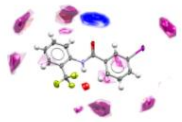
Training and Educational Resources

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 e, our database of over one million entries are available for free through our Access Structures portal.

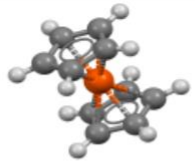
are an educator looking for supplementary teaching materials, find out more about the Teaching Database **here**. If you have developed your own modules using the CSD and like to share them with the broader community, please contact us at education@ccdc.cam.ac.uk.

ep up to date with the latest news from education and outreach at the CCDC, sign up for the Education and Outreach Newsletter **here**.

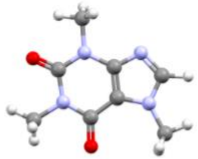


CSD-Materials

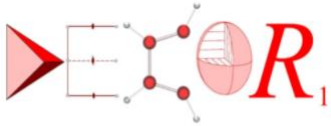
Tools to help you to understand your material's behaviours and refine its properties.



Information on the Teaching Subset



Access a series of teaching modules for use in the classroom

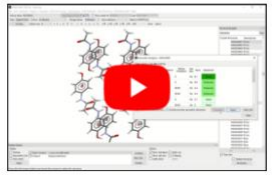


DECOR: Educational Resources for Teaching Crystallography

Register for E&O newsletter

Self-guided workshops

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

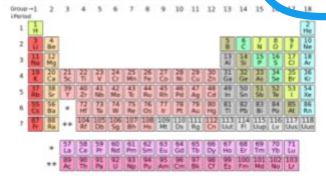


Watch software training and support videos

CSD University modules

On-demand modules with completion certificate

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



Explore the Periodic Table through Crystal Structures

YouTube and LabTube channels

CCDC