Welcome to CSDU

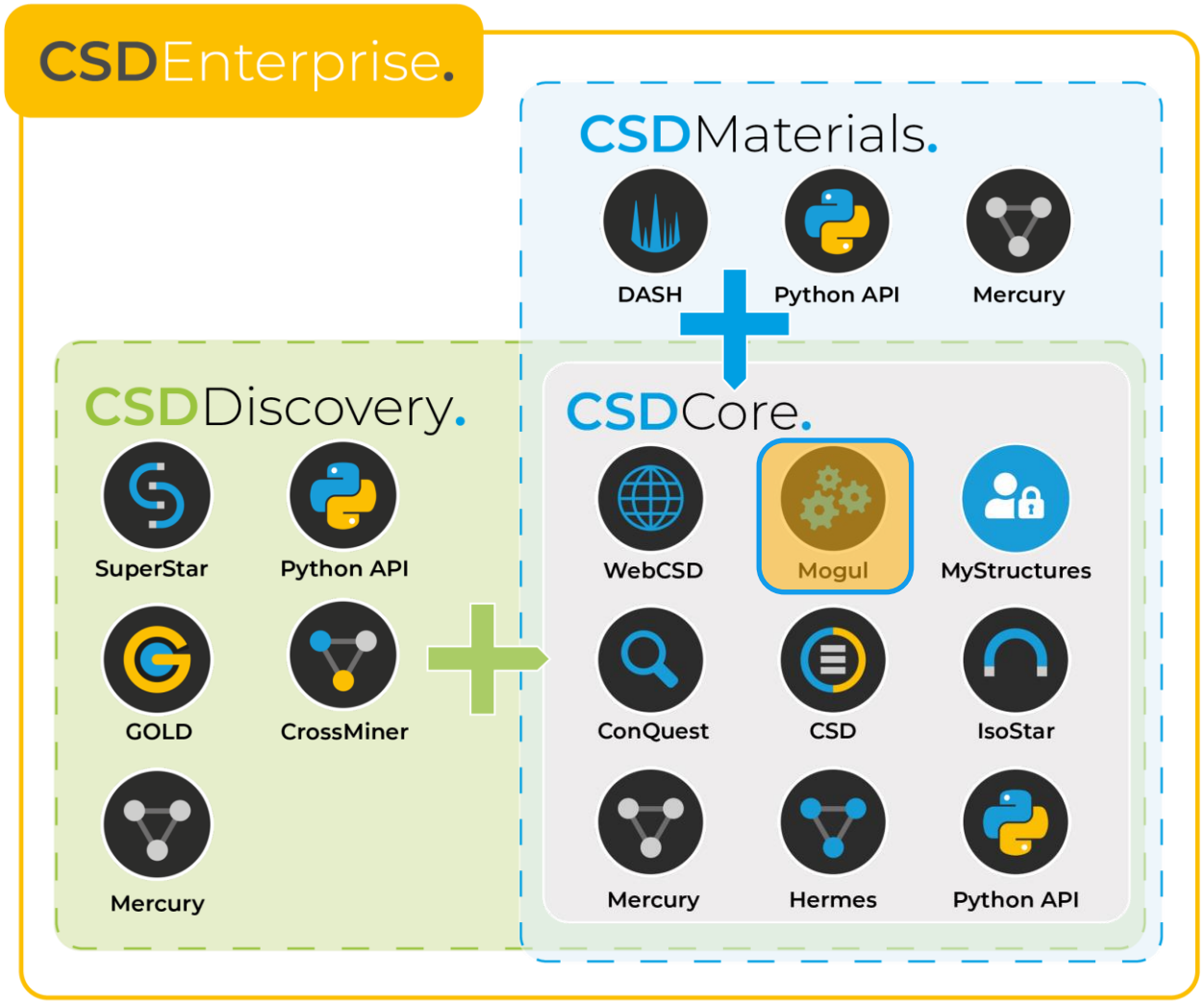
Analysing molecular geometries 101 - basics of Mogul

CCDC
advancing structural science

Learning outcomes

- How to use the Mogul geometry check from Mercury to assess the geometry of a molecule.
- How to run a geometry check on specific features (for example a torsional angle) of a molecule that you load.
- How to interpret the results obtained.

The CSD Software



Professional Services

Research & Knowledge partnerships

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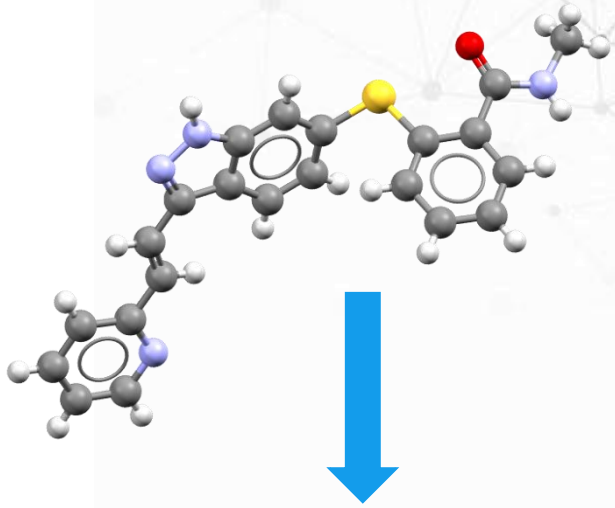
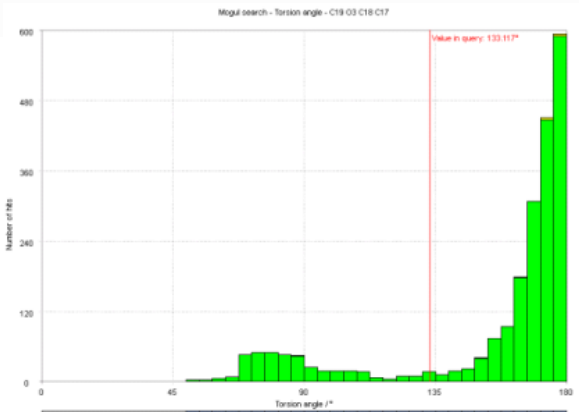
CSD-Core – Conformations

- Mogul provides precise information on preferred molecular geometries
- Validate molecular geometries rapidly using interactive plots & statistics
- Identify any unusual features of a given query structure
- Mine millions of chemically classified bond lengths, angles, torsion angles and ring conformations in the CSD





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Mogul

- Incorporates pre-computed libraries of bond lengths, valence angles, torsion angles and ring conformations derived entirely from the CSD
- Validate complete geometry: retrieve distributions, and figures of merit for all bonds, angles, torsions and rings in the molecule
- Fragment Generalisation: If fragment specified is rare, Mogul will include CSD results from the most similar fragments
- Hyperlinking to the CSD: View CSD entries in specific areas of histogram
- Integration with other software: Instruction file permits other programs to interact with Mogul

Bruno *et al., J. Chem. Inf. Comput. Sci.*, 44, 2133-2144, 2004

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When could we use Mogul?

- In teaching to help us understand fundamental chemistry
- To help design and assess new materials such as drug molecules
- To validate conformations
  - To analyse calculated conformations
  - To filter out protein-ligand docking solutions with unlikely ligand conformations
- To validate geometries
  - To check molecular dimensions of new crystal structures
- To create restraint data/ligand dictionaries
  - For protein refinement
  - To guide small molecule structure solution from powder diffraction data

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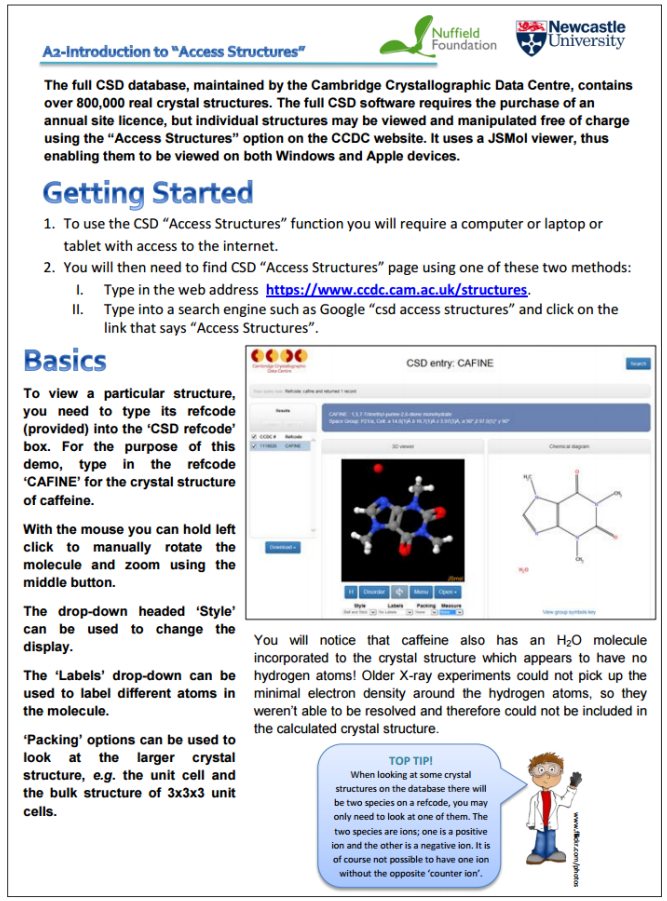
Using Mogul to teach chemistry



A2-Introduction to "Access Structures"

Nuffield Foundation | Newcastle University

The full CSD database, maintained by the Cambridge Crystallographic Data Centre, contains over 800,000 real crystal structures. The full CSD software requires the purchase of an annual site licence, but individual structures may be viewed and manipulated free of charge using the "Access Structures" option on the CCDC website. It uses a JSMol viewer, thus enabling them to be viewed on both Windows and Apple devices.

Getting Started

1. To use the CSD "Access Structures" function you will require a computer or laptop or tablet with access to the internet.
2. You will then need to find CSD "Access Structures" page using one of these two methods:
   I. Type in the web address https://www.ccdc.cam.ac.uk/structures.
   II. Type into a search engine such as Google "csd access structures" and click on the link that says "Access Structures".

Basics

To view a particular structure, you need to type its refcode (provided) into the 'CSD refcode' box. For the purpose of this demo, type in the refcode 'CAFINE' for the crystal structure of caffeine.

With the mouse you can hold left click to manually rotate the molecule and zoom using the middle button.

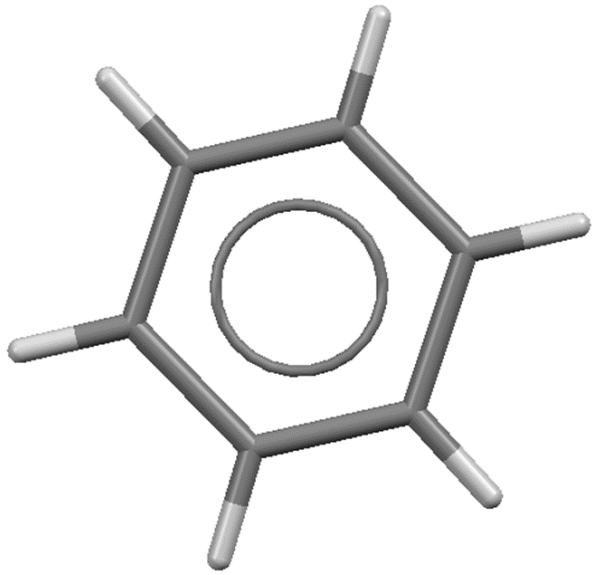
The drop-down headed 'Style' can be used to change the display.

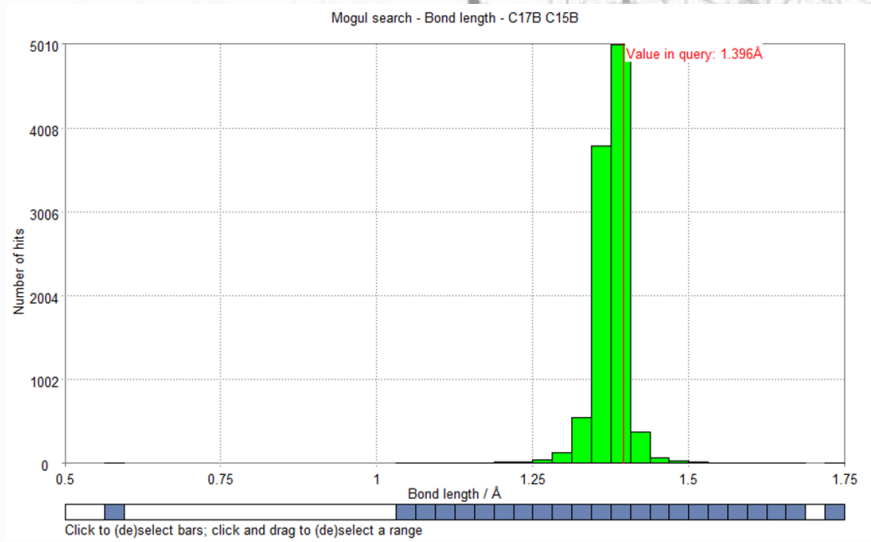
The 'Labels' drop-down can be used to label different atoms in the molecule.

'Packing' options can be used to look at the larger crystal structure, *e.g.* the unit cell and the bulk structure of 3x3x3 unit cells.

You will notice that caffeine also has an H_2O molecule incorporated to the crystal structure which appears to have no hydrogen atoms! Older X-ray experiments could not pick up the minimal electron density around the hydrogen atoms, so they weren't able to be resolved and therefore could not be included in the calculated crystal structure.

TOP TIP!
When looking at some crystal structures on the database there will be two species on a refcode, you may only need to look at one of them. The two species are ions; one is a positive ion and the other is a negative ion. It is of course not possible to have one ion without the opposite 'counter ion'.





- Distance is about 1.38Å
- Taken from over 450,000 benzene rings in reported in the CSD

https://www.ccdc.cam.ac.uk/Community/educationalresources/teaching-modules/

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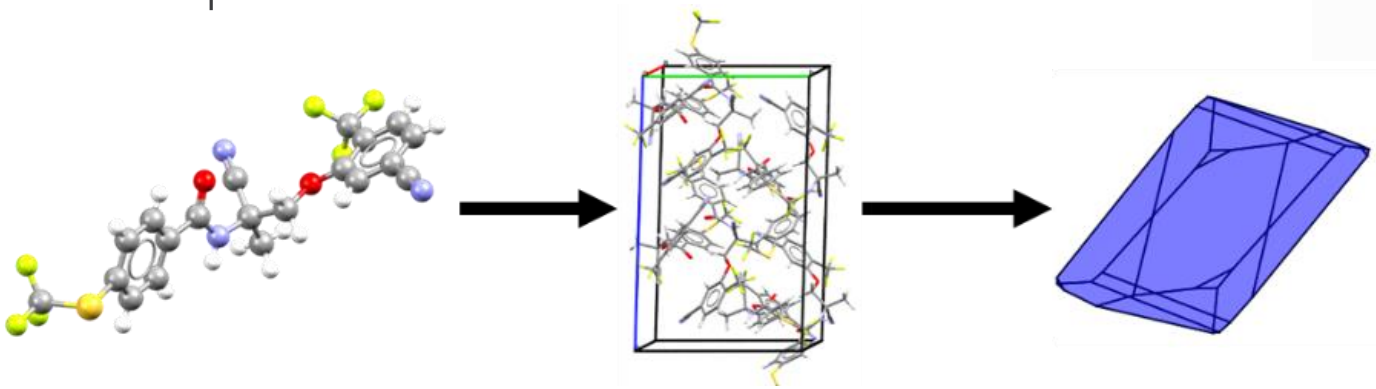
Using Mogul to inform key decisions

- The term "solid form informatics" was first introduced in mid-2000s
  - *Use of structural knowledge to inform key decisions in pharmaceutical development*
- Now a key part of the solid form development workflow at most major pharmaceutical companies



JPP Journal of Pharmacy and Pharmacology

Research Paper

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]

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Keywords
Cambridge Structural Database; quality-by-design; solid-form informatics; solid-form selection

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Abstract

Objectives To demonstrate how the use of structural informatics during drug development assists with the assessment of the risk of polymorphism and the selection of a commercial solid form.

Methods The application of structural chemistry knowledge derived from the hundreds of thousands of crystal structures contained in the Cambridge Struc-

CrystEngComm

PAPER View Article Online

Knowledge-based approaches to co-crystal design†

Peter A. Wood,* Neil Feeder, Matthew Furlow, Peter T. A. Galek, Colin R. Groom and Elna Pidcock

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www.rsc.org/crystengcomm

The use of knowledge-based methods has been intimately connected with the field of co-crystal design since the seminal papers of Etter and Desiraju in the 1990s. Here we explain and exemplify how rational co-crystal design has been carried out in the past using crystal structure knowledge as well as presenting emerging methodologies for knowledge-based co-former selection.

1. Introduction

The definition of a co-crystal,[1–4] whether this is the correct term to use[5] and even whether it should contain a hyphen has been debated at length in the literature. At the most basic level, a co-crystal is a crystalline form composed from two or more components with a particular stoichiometry. Generally, the definitions used in the Crystal Engineering field also place some or all of the following requirements on the solid forms in question:

1. All components are organic species (ruling out inorganics or organometallics).
2. None of the components are charged (otherwise classified as salts).
3. None of the components are water (otherwise classified as hydrates).

the structure of a synthetic β-*C*-arylglucoside published by Deshpande and co-workers in 2012.[7] This crystal structure contains water, ethanol, a zwitterionic component and a neutral API, so could be described as a co-crystal, hydrate, solvate, zwitterionic salt or all of the above. Practically, the definitions used will also vary based on the application of the resulting co-crystal and the approaches for co-crystal design. In this paper we focus mostly on systems where all the components are neutral, organic species and point out if any further assumptions or requirements are added through the use of a certain design method.

Co-crystals are of interest in both academic research and industrial application as they represent the opportunity to access new solid forms and therefore modified physical properties. This contrasts with polymorphism which, when observed, can be difficult to control and rarely represents an opportunity to

Robert Docherty *et al Journal of Pharmacy and Pharmacology*, (2015) 67, 857. doi: 10.1111/jphp.12394.
Taylor *et al. J. Chem. Inf. Model.*, (2014) 54 (9), 2500. Wood, P. A. *et al. CrystEngComm* (2013) 15, 65

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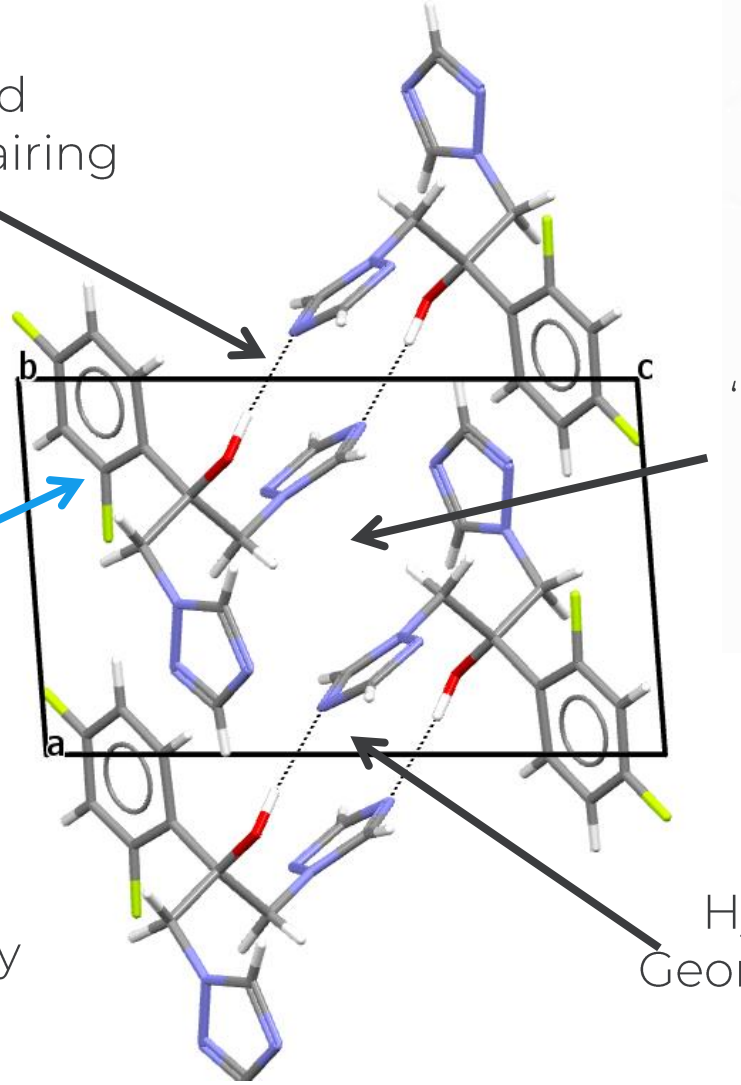
10

Characteristics that influence stability

Hydrogen Bond
Donor/Acceptor Pairing



'Non-Hydrogen Bond'
Intermolecular
Interactions

Molecular
Conformation

Hydrogen Bond
Geometry, Symmetry
and Motif

We can mine the CSD to identify these intra and intermolecular geometric preferences.

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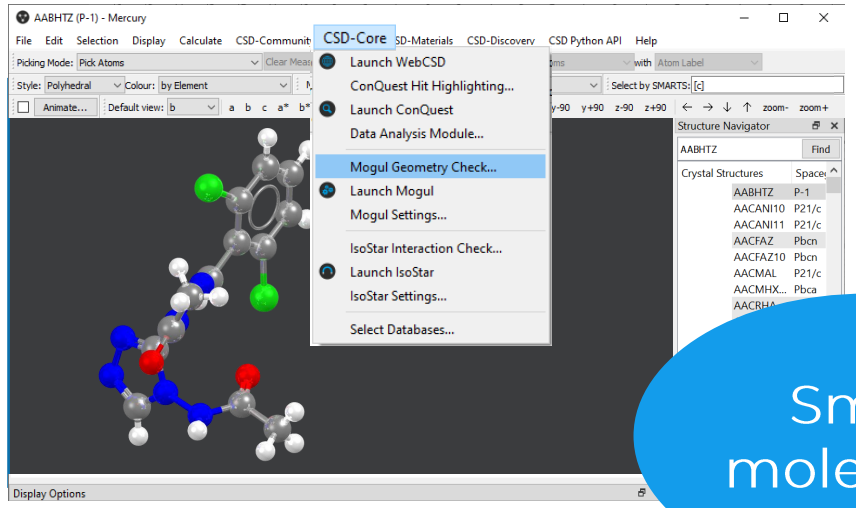
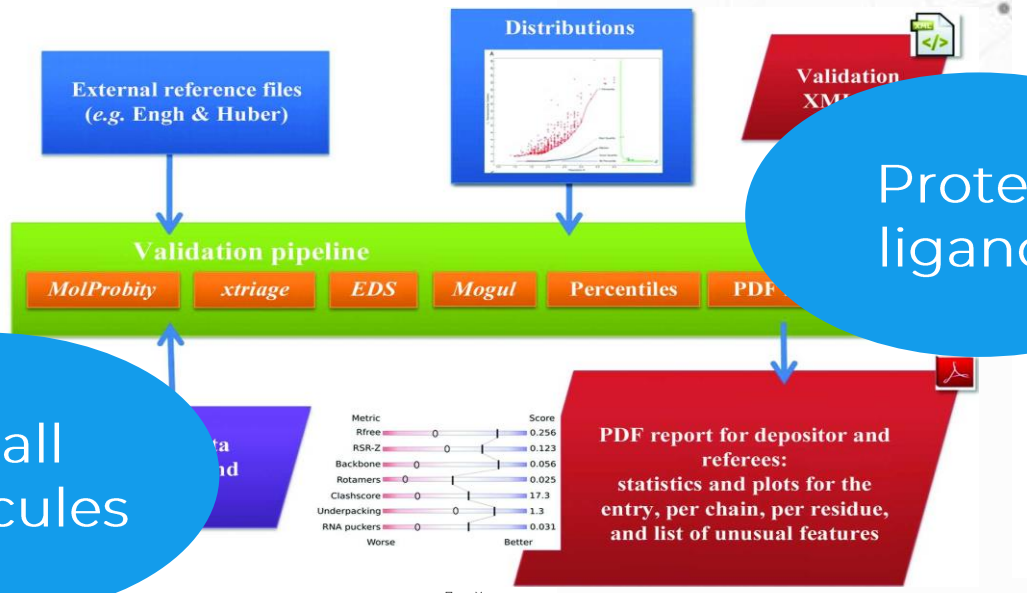
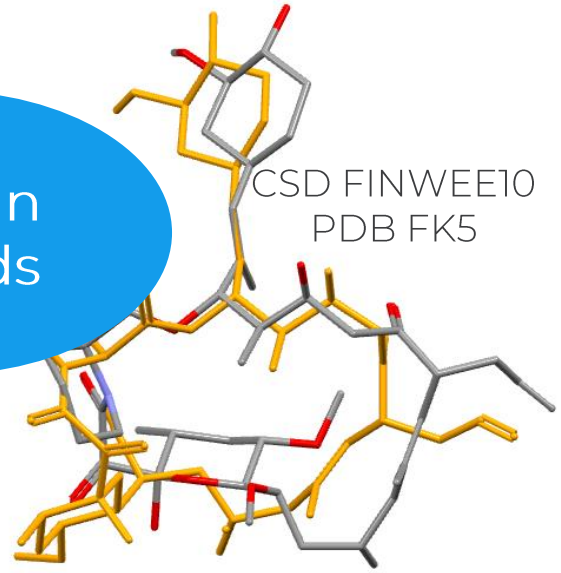
Using Mogul to check new structural data

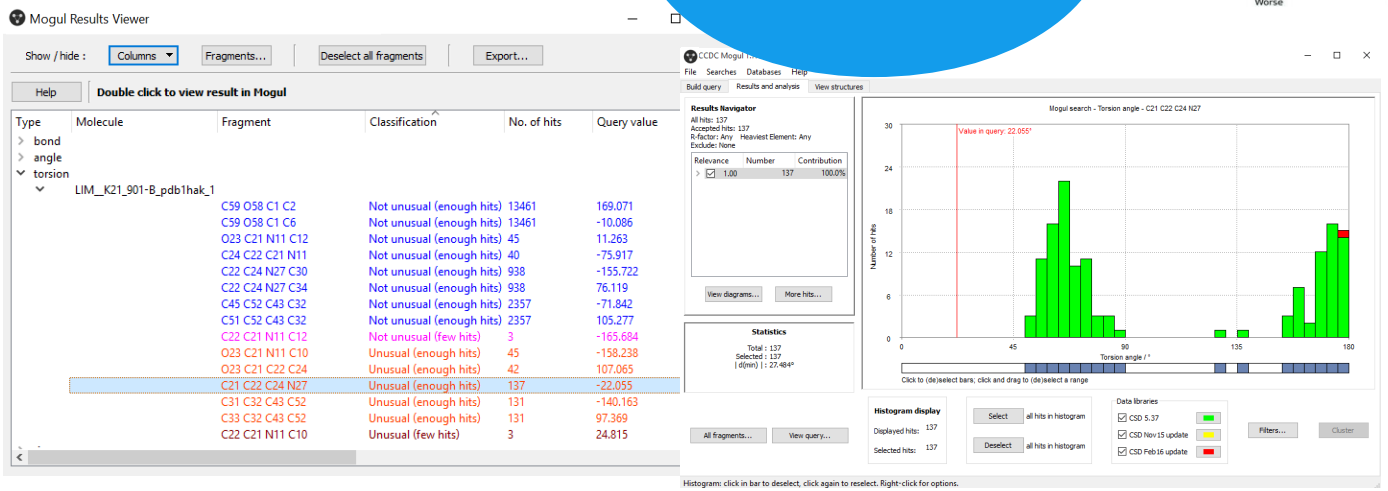


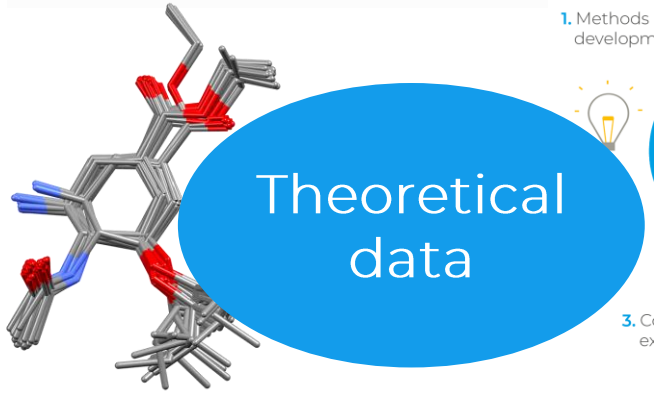


Small molecules

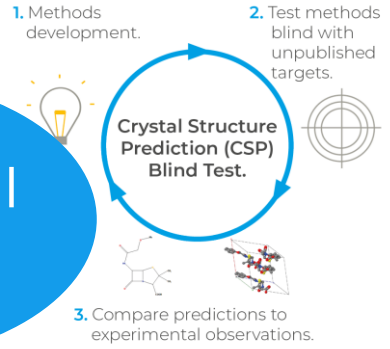
Protein ligands







Theoretical data



I.J.Bruno, G.P.Shields, R.Taylor, *Acta Cryst.* (2011). B67, 333-349 DOI: 10.1107/S0108768111024608

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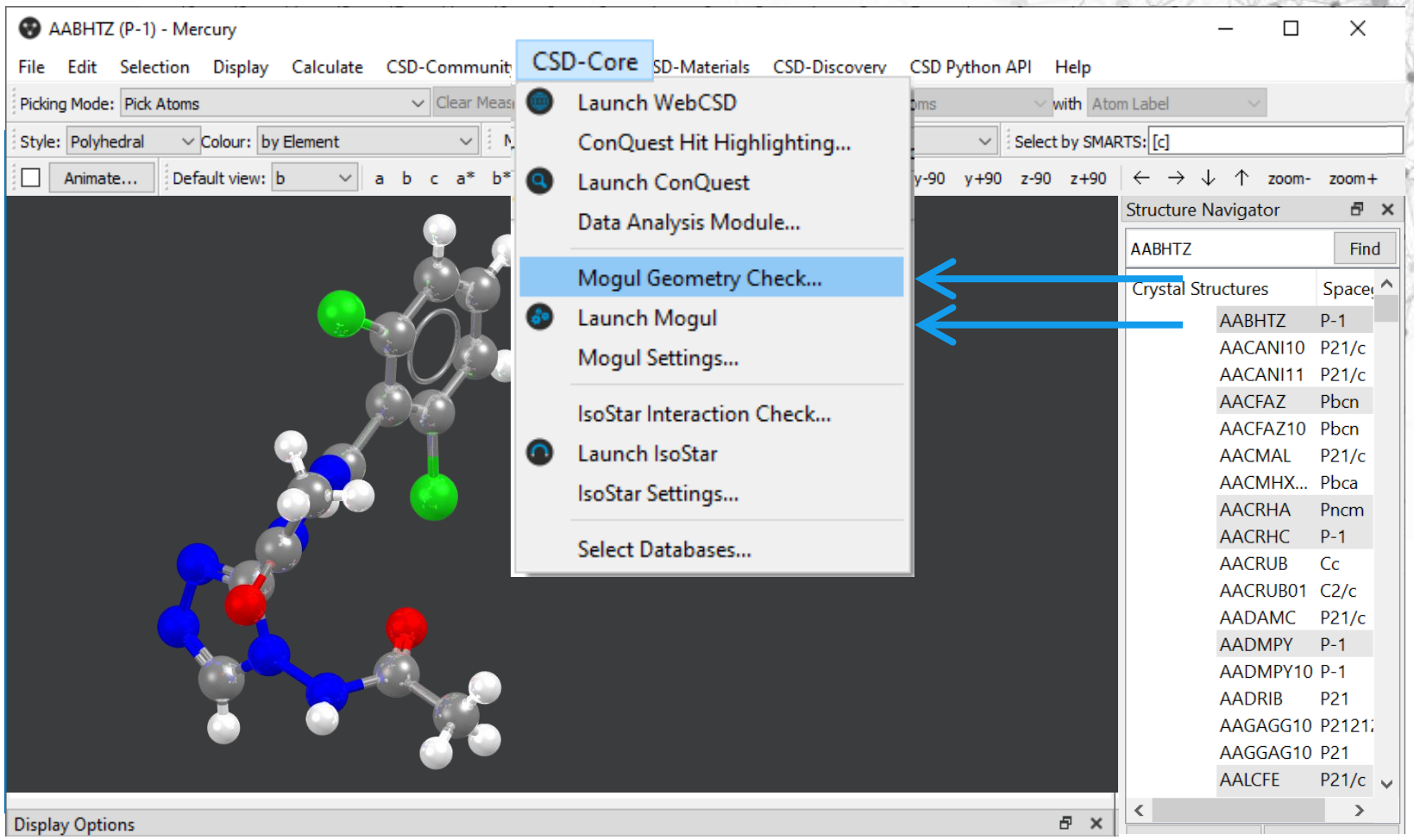
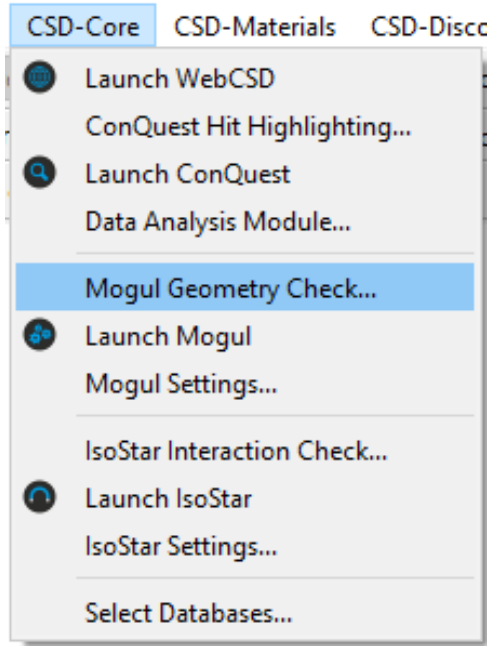
Chemical coverage - the details....

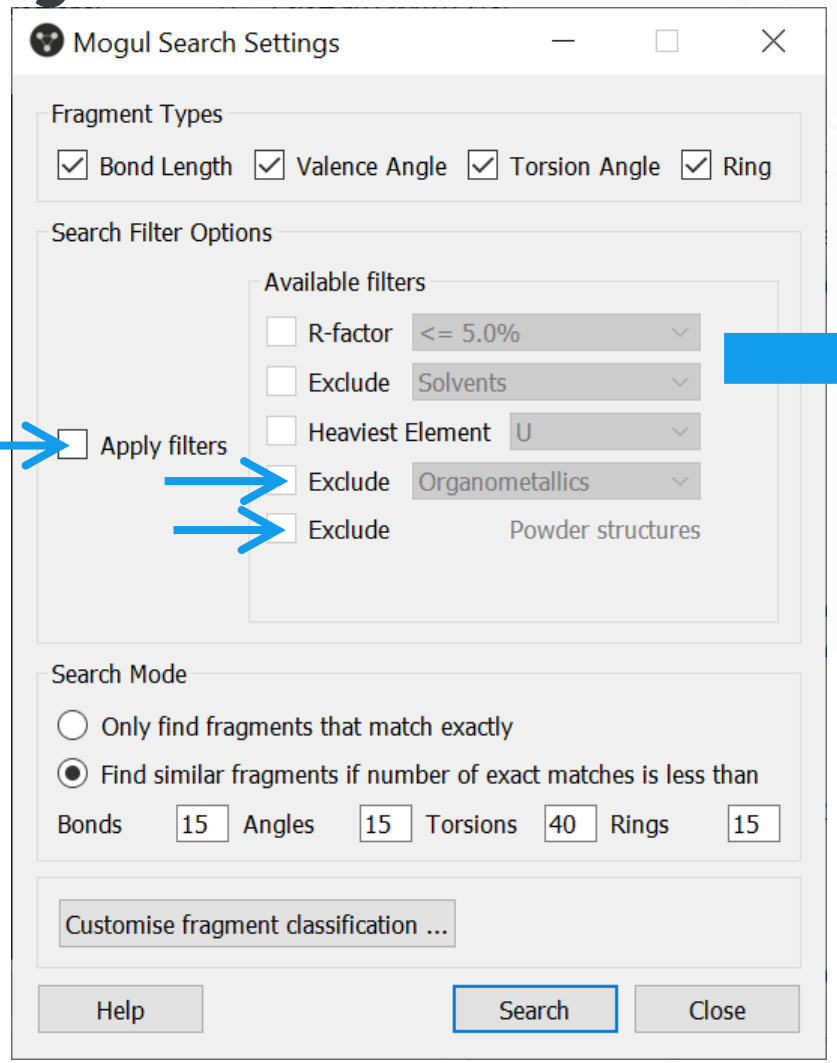
- Based on data in the CSD - organic and metal-organic experimental structures
  - Bond Lengths
  - Valance angles
  - Torsion angles
  - Rings
- Large distributions are reduced by random selection
- Bond fragments and rings involving metals are characterised in exactly the same way as organic fragments
- The following are not included:
  - Bonds, angles & torsions involving H atoms
  - Valence angles & torsions involving metals
  - Cyclic torsions of rings less than 8 atoms
  - Rings containing less than 5 atoms (fused and bridged rings are included)

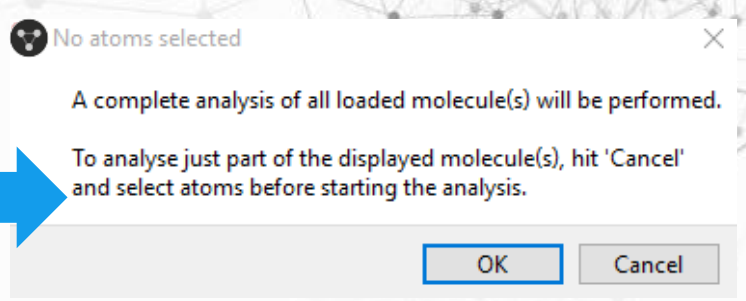
Show One: Mogul – Launch from Mercury

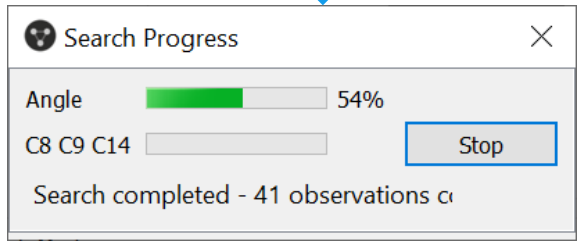


Mogul Geometry Check

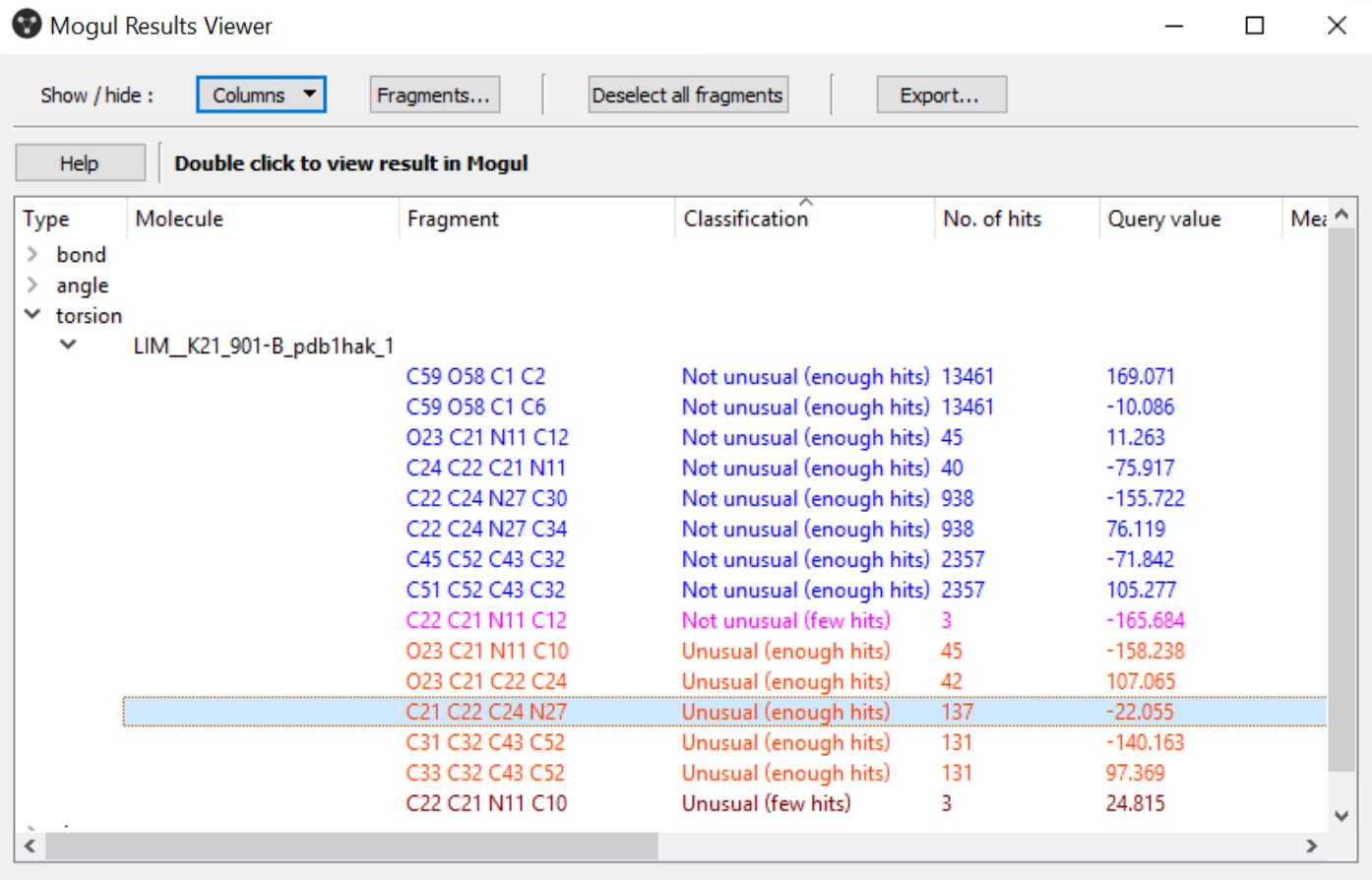








Mogul Geometry Check - Results



Type	Molecule	Fragment	Classification	No. of hits	Query value
bond					
angle					
torsion					
	LIM_K21_901-B_pdb1hak_1				
		C59 O58 C1 C2	Not unusual (enough hits)	13461	169.071
		C59 O58 C1 C6	Not unusual (enough hits)	13461	-10.086
		O23 C21 N11 C12	Not unusual (enough hits)	45	11.263
		C24 C22 C21 N11	Not unusual (enough hits)	40	-75.917
		C22 C24 N27 C30	Not unusual (enough hits)	938	-155.722
		C22 C24 N27 C34	Not unusual (enough hits)	938	76.119
		C45 C52 C43 C32	Not unusual (enough hits)	2357	-71.842
		C51 C52 C43 C32	Not unusual (enough hits)	2357	105.277
		C22 C21 N11 C12	Not unusual (few hits)	3	-165.684
		O23 C21 N11 C10	Unusual (enough hits)	45	-158.238
		O23 C21 C22 C24	Unusual (enough hits)	42	107.065
		C21 C22 C24 N27	Unusual (enough hits)	137	-22.055
		C31 C32 C43 C52	Unusual (enough hits)	131	-140.163
		C33 C32 C43 C52	Unusual (enough hits)	131	97.369
		C22 C21 N11 C10	Unusual (few hits)	3	24.815

Colour code:

- **Blue**: It is **not unusual** value in the CSD and there are **enough data** in the CSD for comparison.
- **Pink**: It is **not unusual** value in the CSD, but there are only **few data** in the CSD for comparison.
- **Orange**: It is an **unusual** value in the CSD and there are **enough data** in the CSD for comparison.
- **Brown**: It is an **unusual** value in the CSD, but there are only **few data** in the CSD for comparison.

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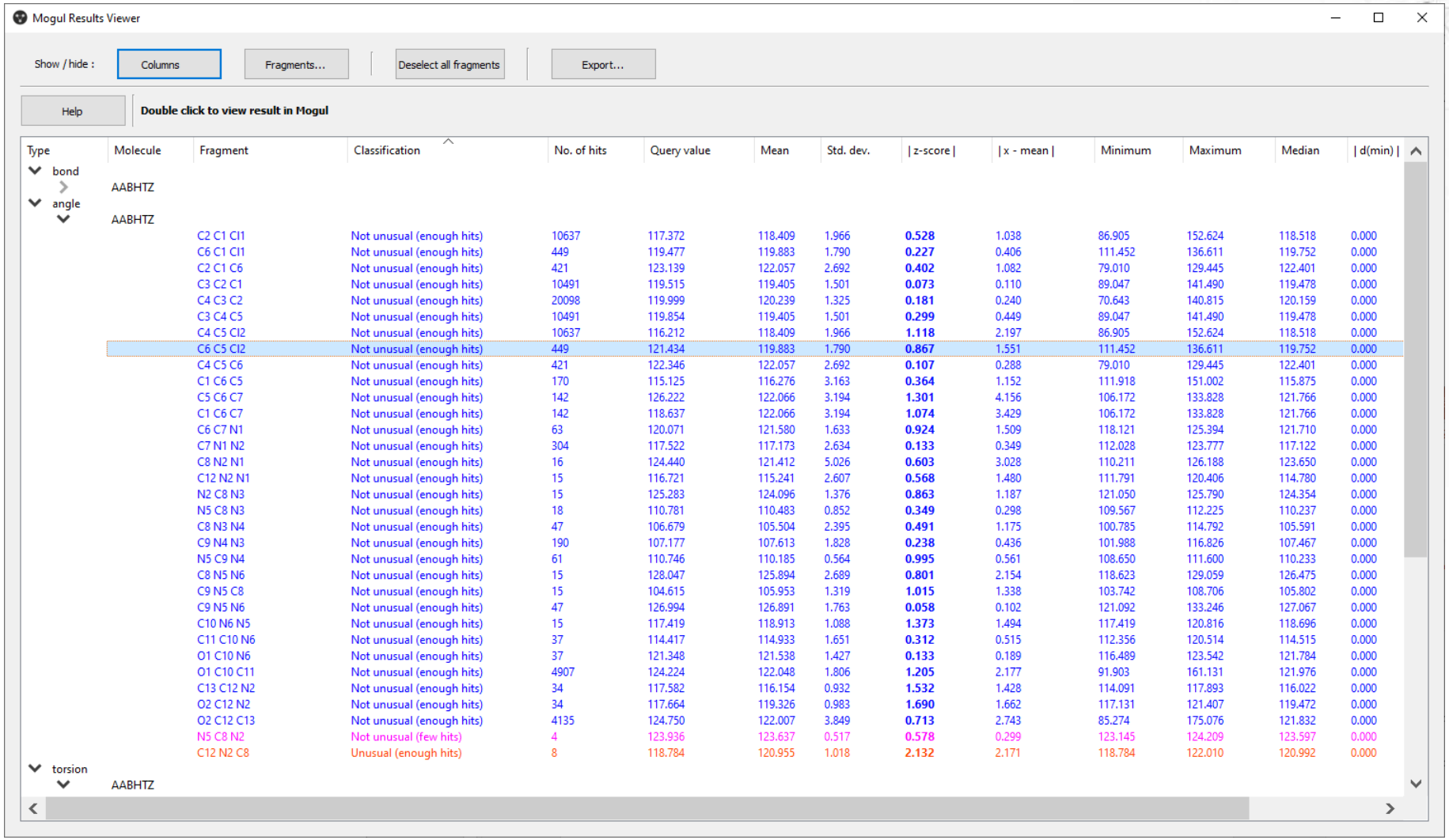
Mogul Geometry Check - Results



Type	Molecule	Fragment	Classification	No. of hits	Query value	Mean	Std. dev.	| z-score |	| x - mean |	Minimum	Maximum	Median	| d(min) |
bond													
	AABHTZ												
angle													
	AABHTZ												
		C2 C1 Cl1	Not unusual (enough hits)	10637	117.372	118.409	1.966	**0.528**	1.038	86.905	152.624	118.518	0.000
		C6 C1 Cl1	Not unusual (enough hits)	449	119.477	119.883	1.790	**0.227**	0.406	111.452	136.611	119.752	0.000
		C2 C1 C6	Not unusual (enough hits)	421	123.139	122.057	2.692	**0.402**	1.082	79.010	129.445	122.401	0.000
		C3 C2 C1	Not unusual (enough hits)	10491	119.515	119.405	1.501	**0.073**	0.110	89.047	141.490	119.478	0.000
		C4 C3 C2	Not unusual (enough hits)	20098	119.999	120.239	1.325	**0.181**	0.240	70.643	140.815	120.159	0.000
		C3 C4 C5	Not unusual (enough hits)	10491	119.854	119.405	1.501	**0.299**	0.449	89.047	141.490	119.478	0.000
		C4 C5 Cl2	Not unusual (enough hits)	10637	116.212	118.409	1.966	**1.118**	2.197	86.905	152.624	118.518	0.000
		C6 C5 Cl2	Not unusual (enough hits)	449	121.434	119.883	1.790	**0.867**	1.551	111.452	136.611	119.752	0.000
		C4 C5 C6	Not unusual (enough hits)	421	122.346	122.057	2.692	**0.107**	0.288	79.010	129.445	122.401	0.000
		C1 C6 C5	Not unusual (enough hits)	170	115.125	116.276	3.163	**0.364**	1.152	111.918	151.002	115.875	0.000
		C5 C6 C7	Not unusual (enough hits)	142	126.222	122.066	3.194	**1.301**	4.156	106.172	133.828	121.766	0.000
		C1 C6 C7	Not unusual (enough hits)	142	118.637	122.066	3.194	**1.074**	3.429	106.172	133.828	121.766	0.000
		C6 C7 N1	Not unusual (enough hits)	63	120.071	121.580	1.633	**0.924**	1.509	118.121	125.394	121.710	0.000
		C7 N1 N2	Not unusual (enough hits)	304	117.522	117.173	2.634	**0.133**	0.349	112.028	123.777	117.122	0.000
		C8 N2 N1	Not unusual (enough hits)	16	124.440	121.412	5.026	**0.603**	3.028	110.211	126.188	123.650	0.000
		C12 N2 N1	Not unusual (enough hits)	15	116.721	115.241	2.607	**0.568**	1.480	111.791	120.406	114.780	0.000
		N2 C8 N3	Not unusual (enough hits)	15	125.283	124.096	1.376	**0.863**	1.187	121.050	125.790	124.354	0.000
		N5 C8 N3	Not unusual (enough hits)	18	110.781	110.483	0.852	**0.349**	0.298	109.567	112.225	110.237	0.000
		C8 N3 N4	Not unusual (enough hits)	47	106.679	105.504	2.395	**0.491**	1.175	100.785	114.792	105.591	0.000
		C9 N4 N3	Not unusual (enough hits)	190	107.177	107.613	1.828	**0.238**	0.436	101.988	116.826	107.467	0.000
		N5 C9 N4	Not unusual (enough hits)	61	110.746	110.185	0.564	**0.995**	0.561	108.650	111.600	110.233	0.000
		C8 N5 N6	Not unusual (enough hits)	15	128.047	125.894	2.689	**0.801**	2.154	118.623	129.059	126.475	0.000
		C9 N5 C8	Not unusual (enough hits)	15	104.615	105.953	1.319	**1.015**	1.338	103.742	108.706	105.802	0.000
		C9 N5 N6	Not unusual (enough hits)	47	126.994	126.891	1.763	**0.058**	0.102	121.092	133.246	127.067	0.000
		C10 N6 N5	Not unusual (enough hits)	15	117.419	118.913	1.088	**1.373**	1.494	117.419	120.816	118.696	0.000
		C11 C10 N6	Not unusual (enough hits)	37	114.417	114.933	1.651	**0.312**	0.515	112.356	120.514	114.515	0.000
		O1 C10 N6	Not unusual (enough hits)	37	121.348	121.538	1.427	**0.133**	0.189	116.489	123.542	121.784	0.000
		O1 C10 C11	Not unusual (enough hits)	4907	124.224	122.048	1.806	**1.205**	2.177	91.903	161.131	121.976	0.000
		C13 C12 N2	Not unusual (enough hits)	34	117.582	116.154	0.932	**1.532**	1.428	114.091	117.893	116.022	0.000
		O2 C12 N2	Not unusual (enough hits)	34	117.664	119.326	0.983	**1.690**	1.662	117.131	121.407	119.472	0.000
		O2 C12 C13	Not unusual (enough hits)	4135	124.750	122.007	3.849	**0.713**	2.743	85.274	175.076	121.832	0.000
		N5 C8 N2	Not unusual (few hits)	4	123.936	123.637	0.517	**0.578**	0.299	123.145	124.209	123.597	0.000
		C12 N2 C8	Unusual (enough hits)	8	118.784	120.955	1.018	**2.132**	2.171	118.784	122.010	120.992	0.000
torsion													
	AABHTZ												

Single click on a row to view result in Mercury

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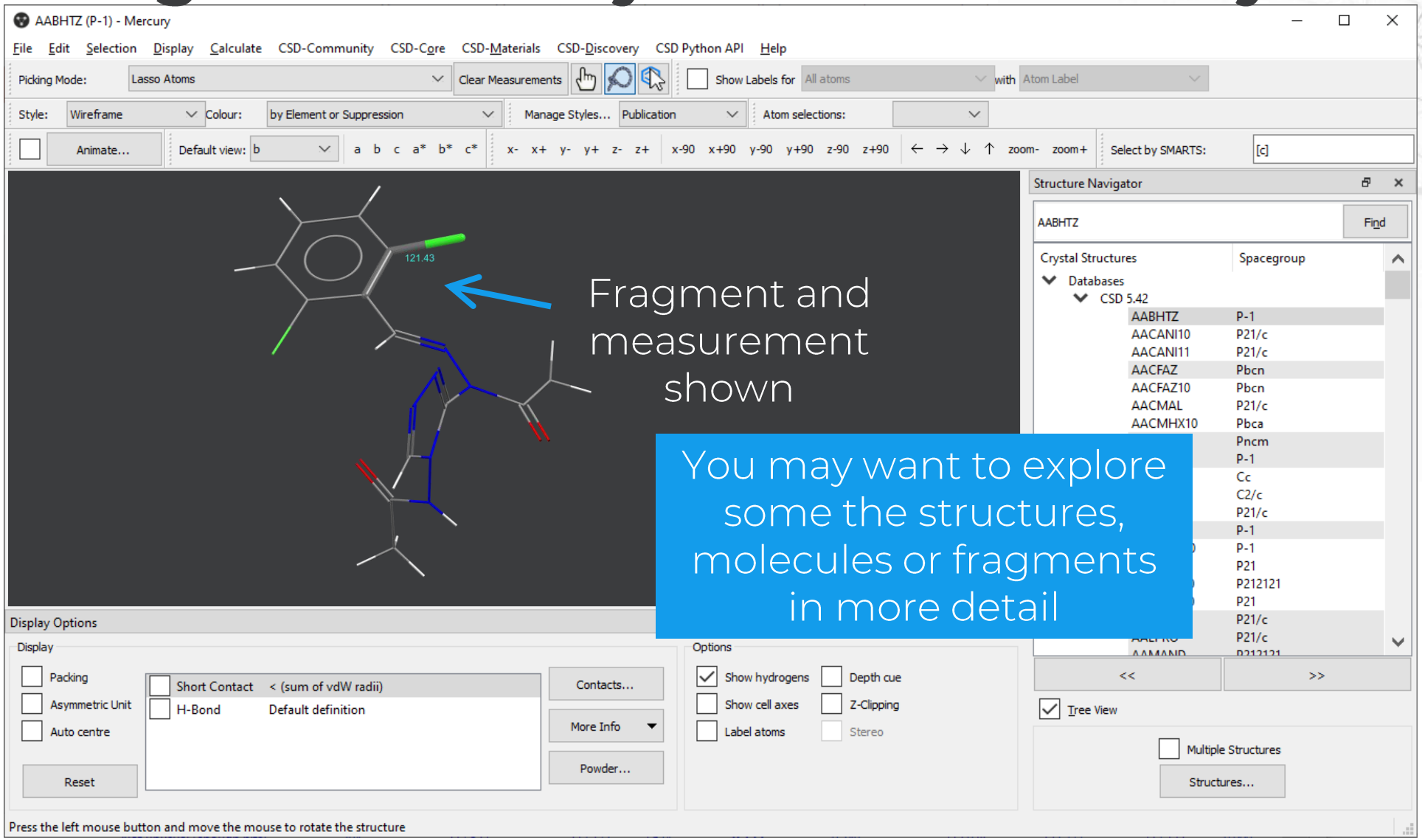
Mogul Geometry Check – Mercury view



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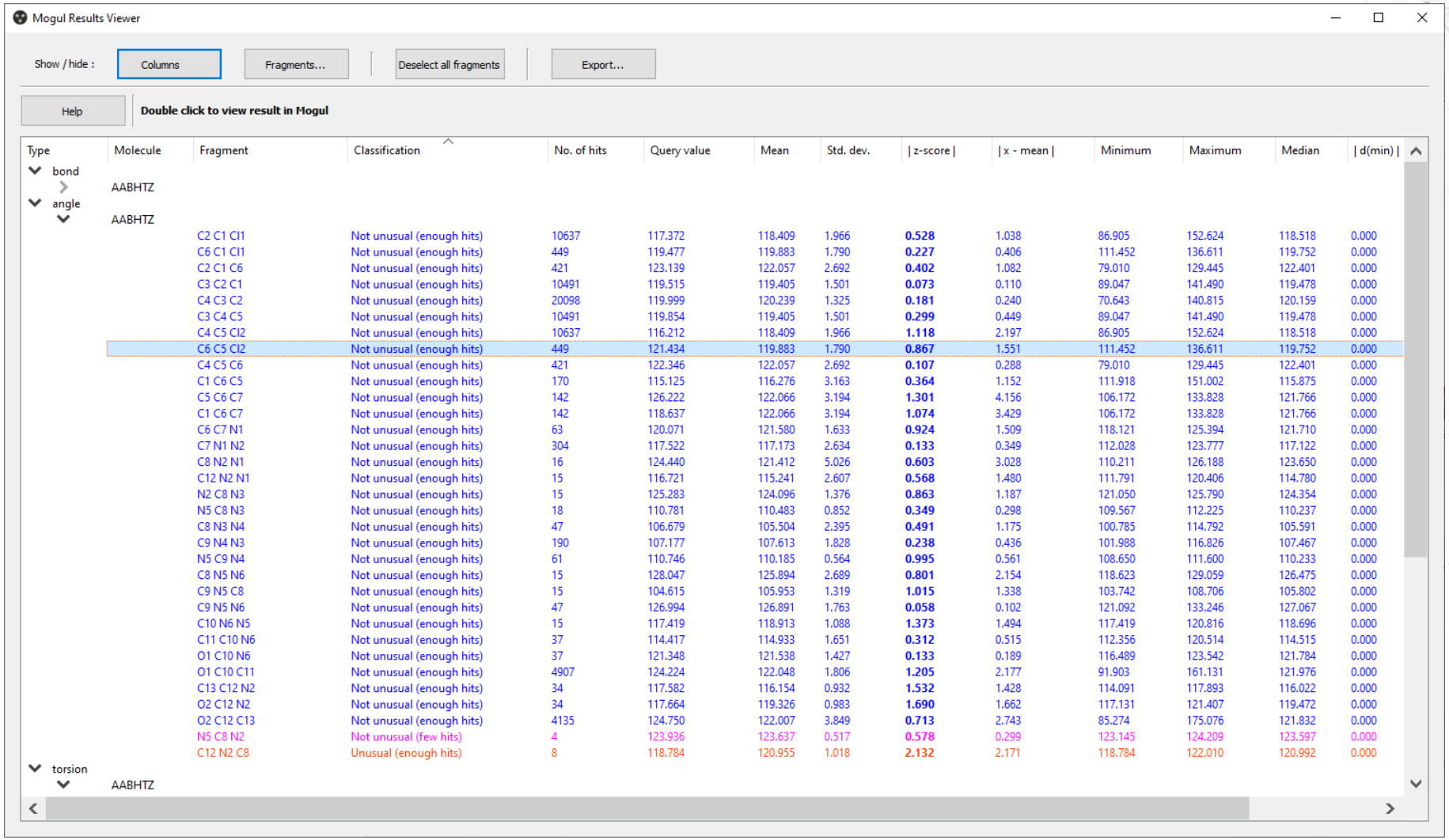

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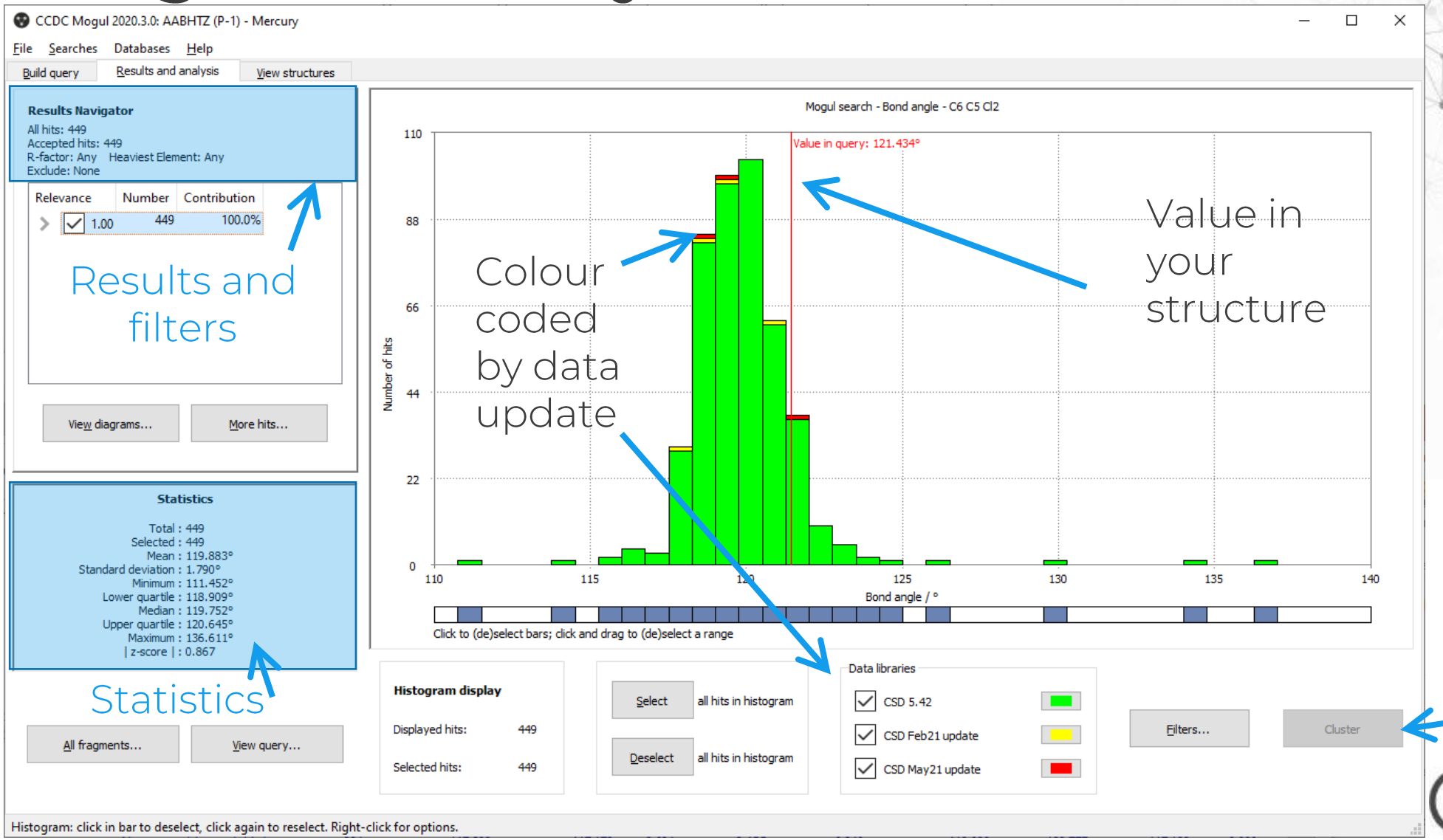
	AABHTZ												
angle													
	AABHTZ												
		C2 C1 Cl1	Not unusual (enough hits)	10637	117.372	118.409	1.966	**0.528**	1.038	86.905	152.624	118.518	0.000
		C6 C1 Cl1	Not unusual (enough hits)	449	119.477	119.883	1.790	**0.227**	0.406	111.452	136.611	119.752	0.000
		C2 C1 C6	Not unusual (enough hits)	421	123.139	122.057	2.692	**0.402**	1.082	79.010	129.445	122.401	0.000
		C3 C2 C1	Not unusual (enough hits)	10491	119.515	119.405	1.501	**0.073**	0.110	89.047	141.490	119.478	0.000
		C4 C3 C2	Not unusual (enough hits)	20098	119.999	120.239	1.325	**0.181**	0.240	70.643	140.815	120.159	0.000
		C3 C4 C5	Not unusual (enough hits)	10491	119.854	119.405	1.501	**0.299**	0.449	89.047	141.490	119.478	0.000
		C4 C5 Cl2	Not unusual (enough hits)	10637	116.212	118.409	1.966	**1.118**	2.197	86.905	152.624	118.518	0.000
		C6 C5 Cl2	Not unusual (enough hits)	449	121.434	119.883	1.790	**0.867**	1.551	111.452	136.611	119.752	0.000
		C4 C5 C6	Not unusual (enough hits)	421	122.346	122.057	2.692	**0.107**	0.288	79.010	129.445	122.401	0.000
		C1 C6 C5	Not unusual (enough hits)	170	115.125	116.276	3.163	**0.364**	1.152	111.918	151.002	115.875	0.000
		C5 C6 C7	Not unusual (enough hits)	142	126.222	122.066	3.194	**1.301**	4.156	106.172	133.828	121.766	0.000
		C1 C6 C7	Not unusual (enough hits)	142	118.637	122.066	3.194	**1.074**	3.429	106.172	133.828	121.766	0.000
		C6 C7 N1	Not unusual (enough hits)	63	120.071	121.580	1.633	**0.924**	1.509	118.121	125.394	121.710	0.000
		C7 N1 N2	Not unusual (enough hits)	304	117.522	117.173	2.634	**0.133**	0.349	112.028	123.777	117.122	0.000
		C8 N2 N1	Not unusual (enough hits)	16	124.440	121.412	5.026	**0.603**	3.028	110.211	126.188	123.650	0.000
		C12 N2 N1	Not unusual (enough hits)	15	116.721	115.241	2.607	**0.568**	1.480	111.791	120.406	114.780	0.000
		N2 C8 N3	Not unusual (enough hits)	15	125.283	124.096	1.376	**0.863**	1.187	121.050	125.790	124.354	0.000
		N5 C8 N3	Not unusual (enough hits)	18	110.781	110.483	0.852	**0.349**	0.298	109.567	112.225	110.237	0.000
		C8 N3 N4	Not unusual (enough hits)	47	106.679	105.504	2.395	**0.491**	1.175	100.785	114.792	105.591	0.000
		C9 N4 N3	Not unusual (enough hits)	190	107.177	107.613	1.828	**0.238**	0.436	101.988	116.826	107.467	0.000
		N5 C9 N4	Not unusual (enough hits)	61	110.746	110.185	0.564	**0.995**	0.561	108.650	111.600	110.233	0.000
		C8 N5 N6	Not unusual (enough hits)	15	128.047	125.894	2.689	**0.801**	2.154	118.623	129.059	126.475	0.000
		C9 N5 C8	Not unusual (enough hits)	15	104.615	105.953	1.319	**1.015**	1.338	103.742	108.706	105.802	0.000
		C9 N5 N6	Not unusual (enough hits)	47	126.994	126.891	1.763	**0.058**	0.102	121.092	133.246	127.067	0.000
		C10 N6 N5	Not unusual (enough hits)	15	117.419	118.913	1.088	**1.373**	1.494	117.419	120.816	118.696	0.000
		C11 C10 N6	Not unusual (enough hits)	37	114.417	114.933	1.651	**0.312**	0.515	112.356	120.514	114.515	0.000
		O1 C10 N6	Not unusual (enough hits)	37	121.348	121.538	1.427	**0.133**	0.189	116.489	123.542	121.784	0.000
		O1 C10 C11	Not unusual (enough hits)	4907	124.224	122.048	1.806	**1.205**	2.177	91.903	161.131	121.976	0.000
		C13 C12 N2	Not unusual (enough hits)	34	117.582	116.154	0.932	**1.532**	1.428	114.091	117.893	116.022	0.000
		O2 C12 N2	Not unusual (enough hits)	34	117.664	119.326	0.983	**1.690**	1.662	117.131	121.407	119.472	0.000
		O2 C12 C13	Not unusual (enough hits)	4135	124.750	122.007	3.849	**0.713**	2.743	85.274	175.076	121.832	0.000
		N5 C8 N2	Not unusual (few hits)	4	123.936	123.637	0.517	**0.578**	0.299	123.145	124.209	123.597	0.000
		C12 N2 C8	Unusual (enough hits)	8	118.784	120.955	1.018	**2.132**	2.171	118.784	122.010	120.992	0.000
torsion													
	AABHTZ												

Double click on a row to view result in Mogul

CCDC

Mogul Geometry Check – Results

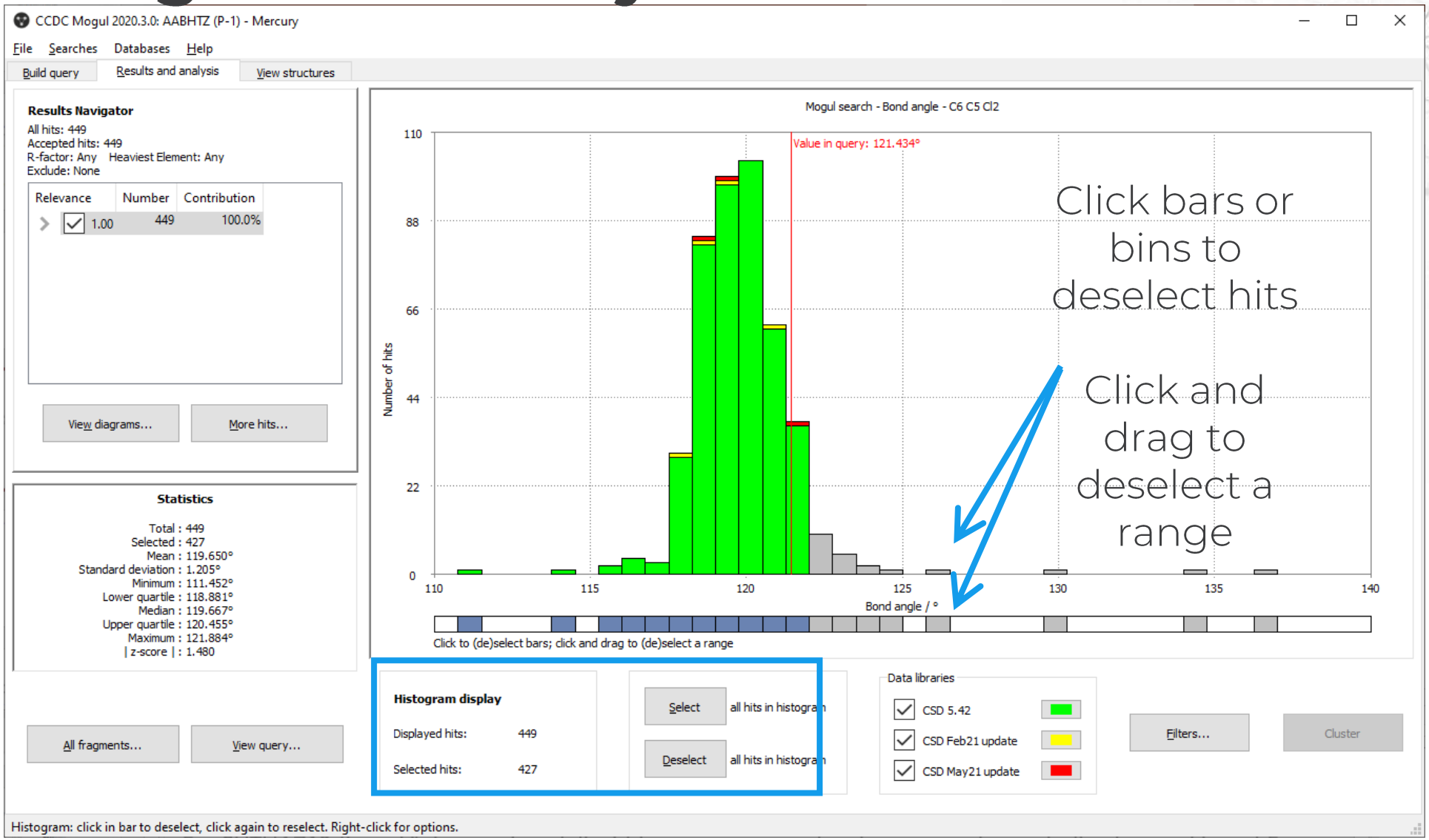


Histogram built with data from structures in the CSD

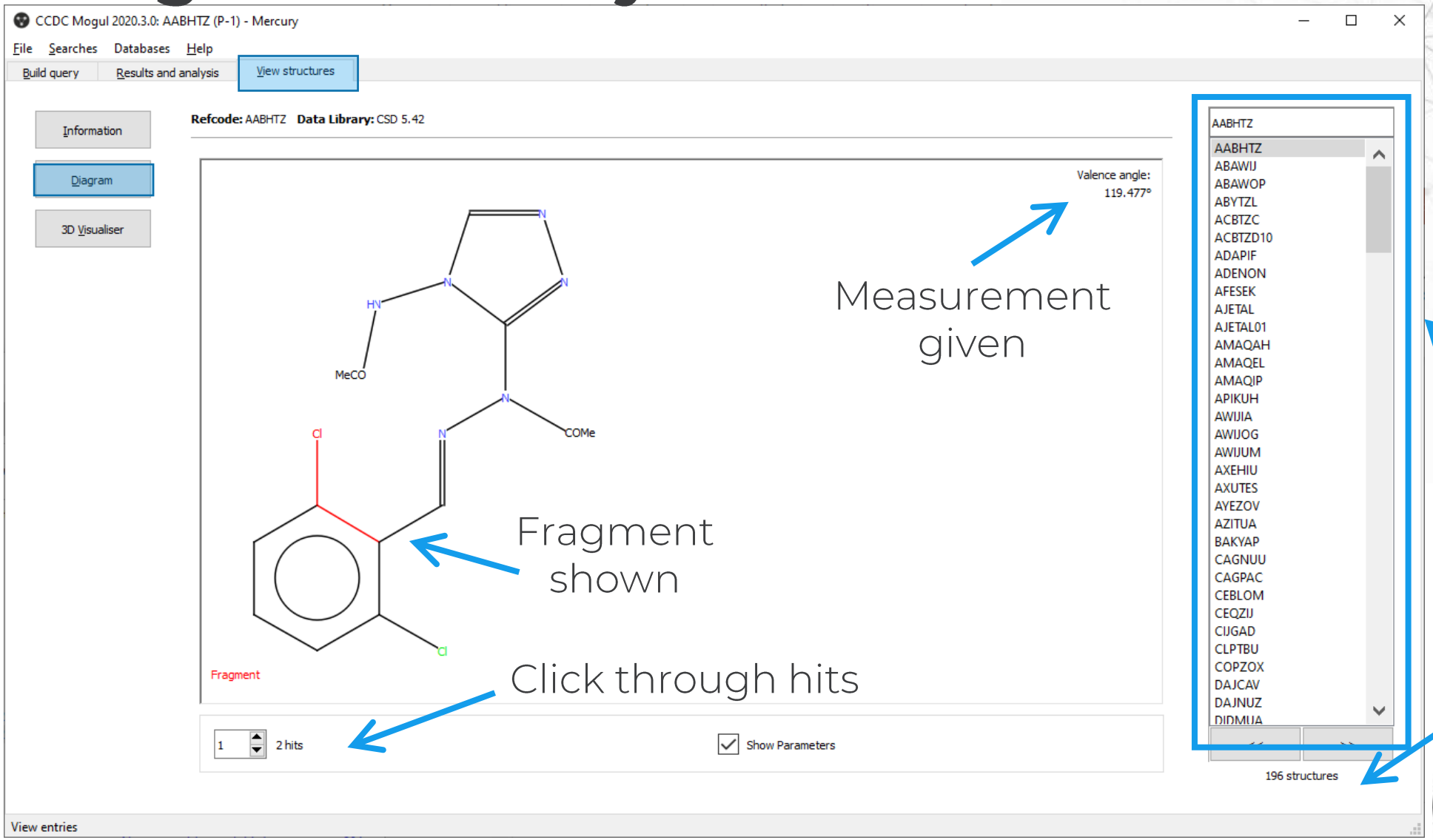
Cluster only available for rings

CCDC

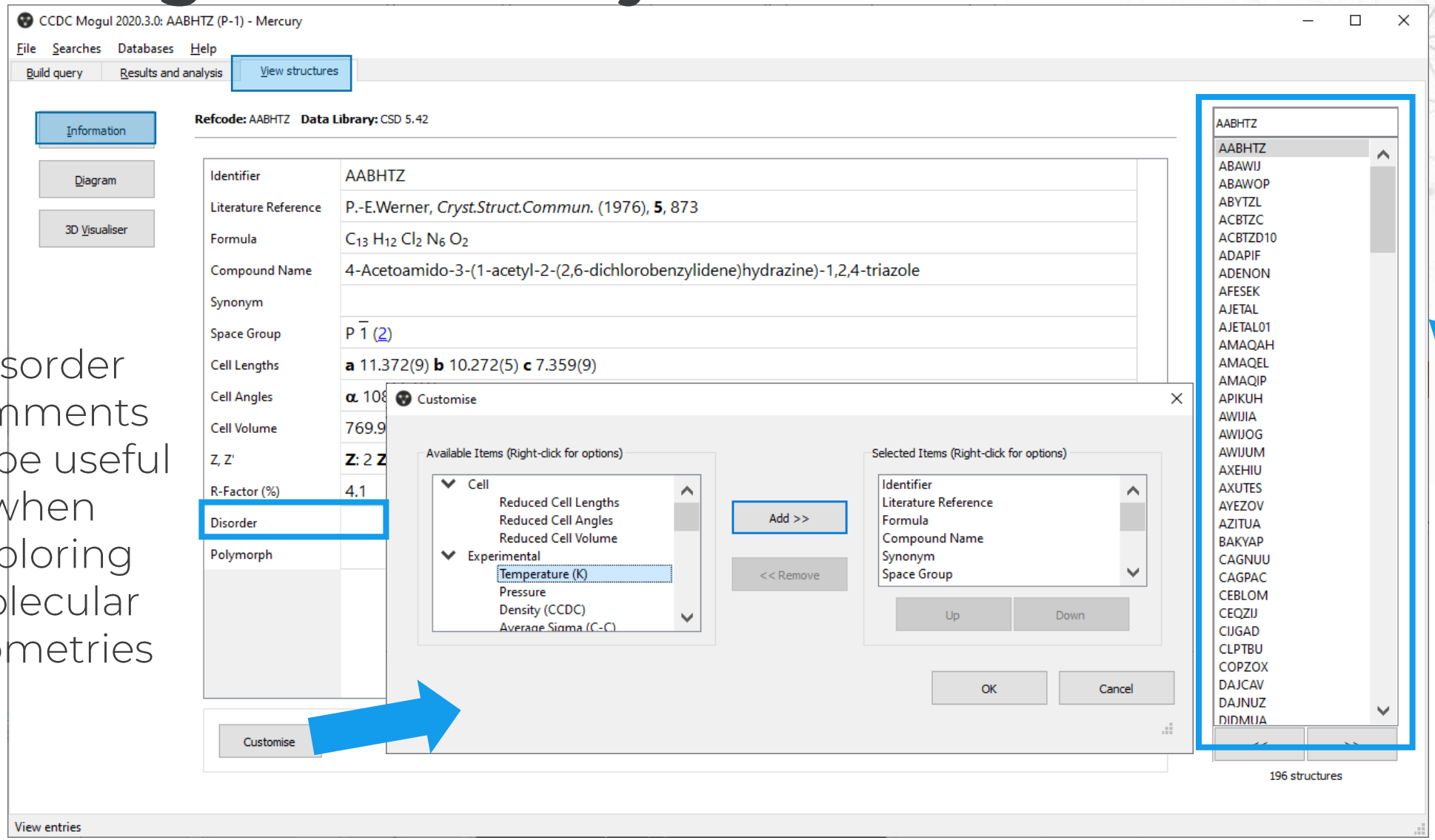
Mogul Geometry Check – Results



Mogul Geometry Check – View structures



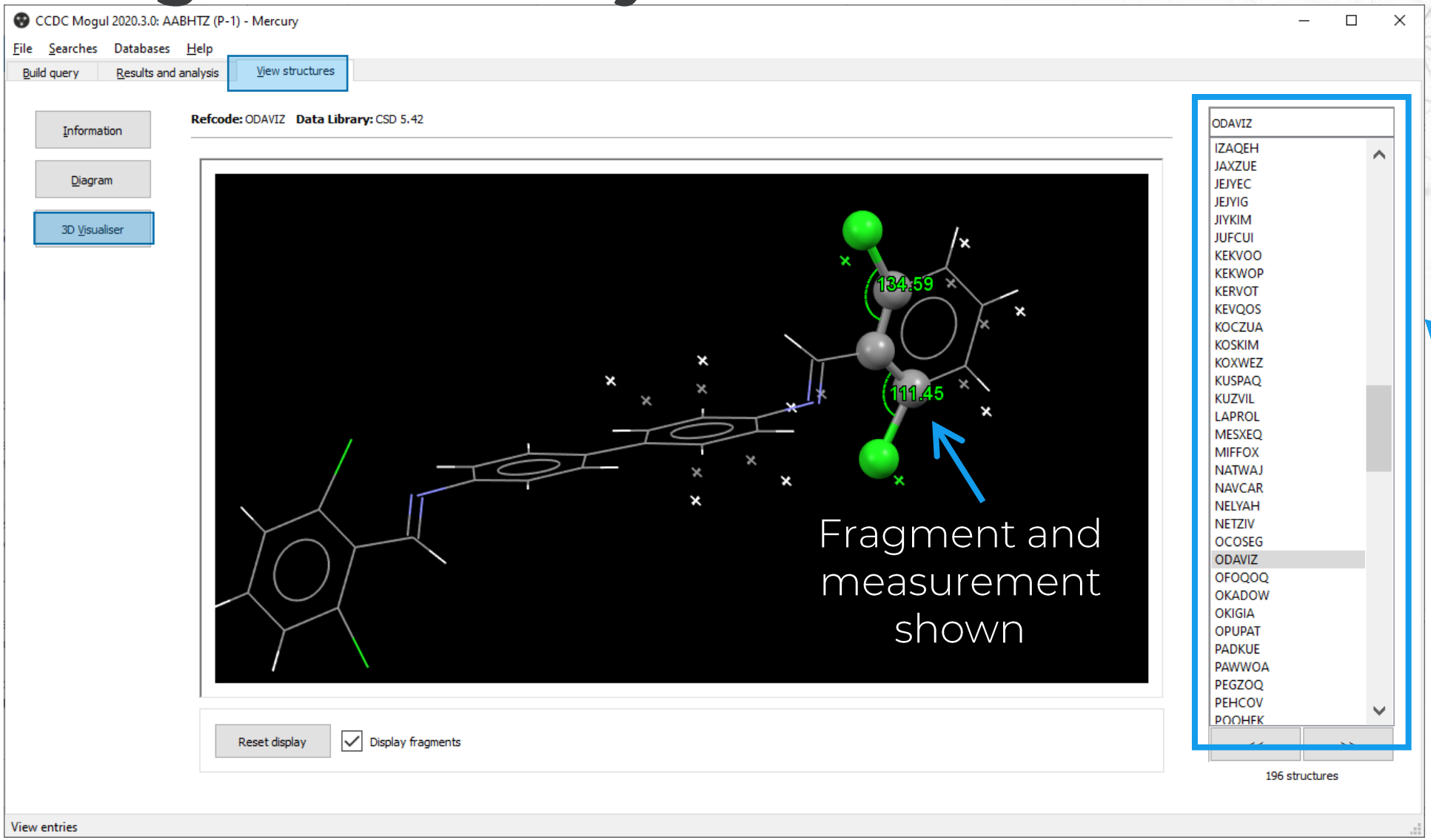
Mogul Geometry Check – View structures



Disorder comments can be useful when exploring molecular geometries

Click through the refcode list

Mogul Geometry Check – View structures



Click through the refcode list

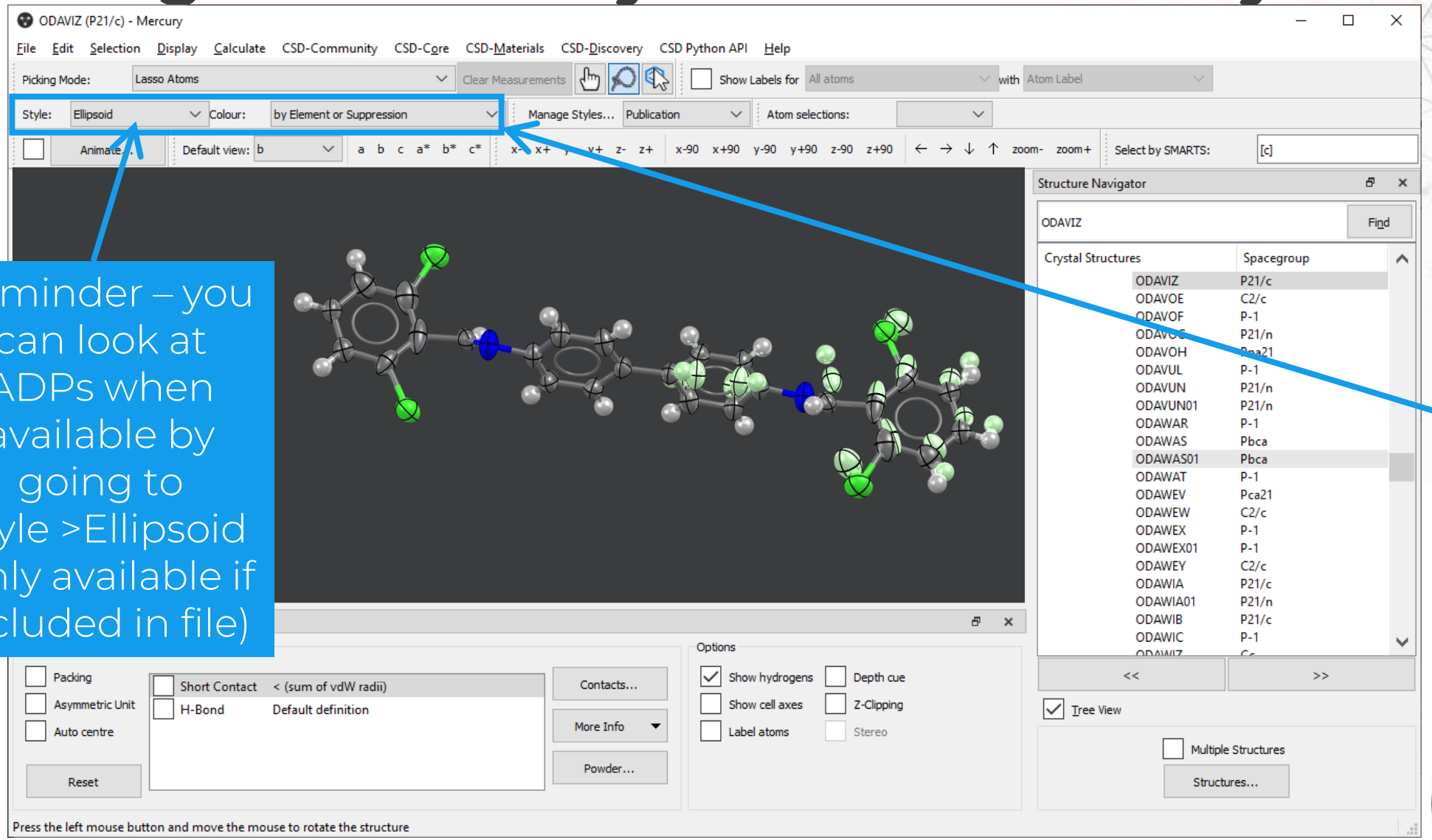
CCDC

Mogul Geometry Check – Mercury view

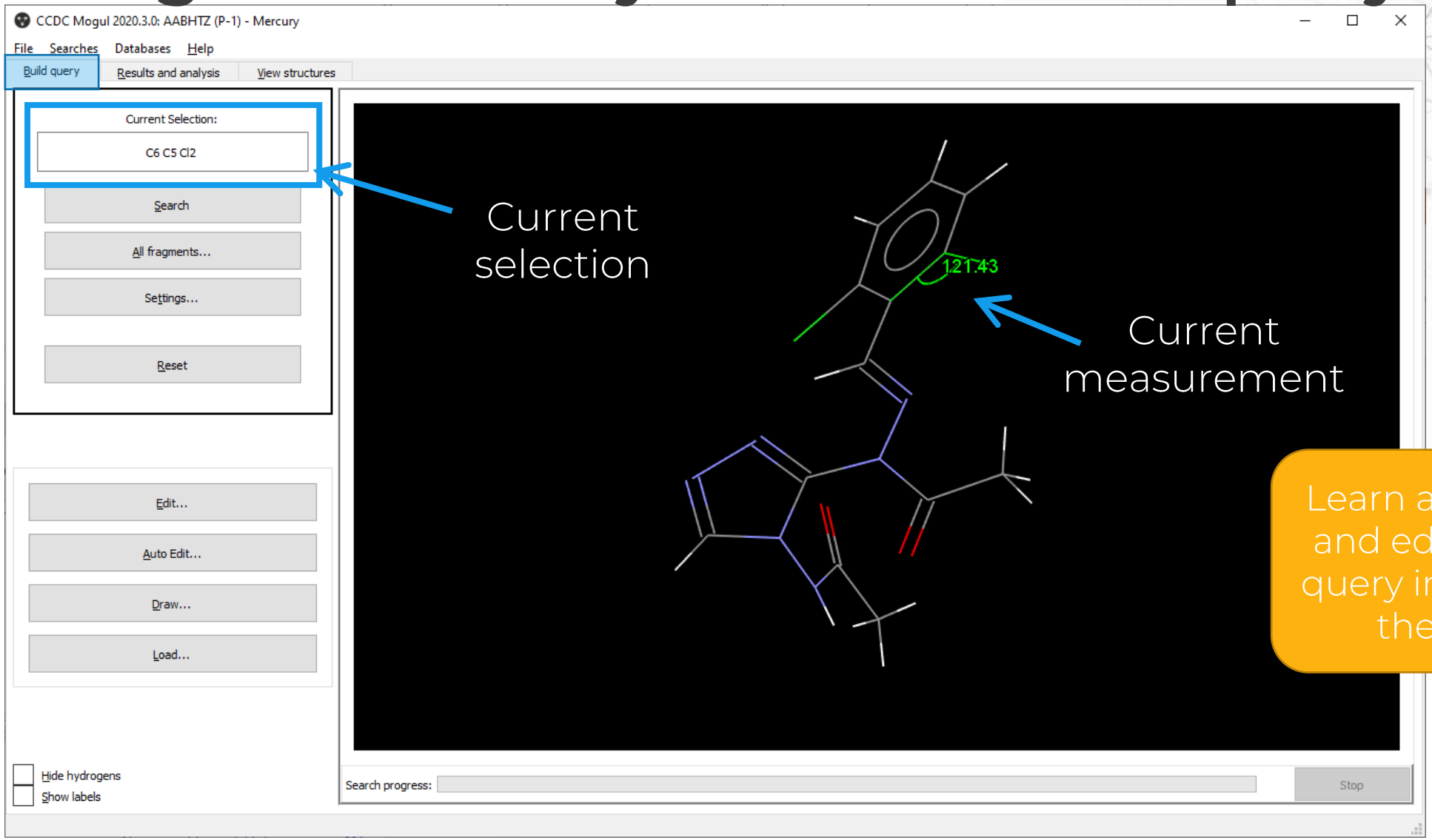
CSD Refcode
ODAVIZ

Reminder – you can look at ADPs when available by going to Style >Ellipsoid (only available if included in file)

Reminder – disordered atoms in the CSD are often *suppressed* and can be coloured differently using Colour > by Element or Suppression

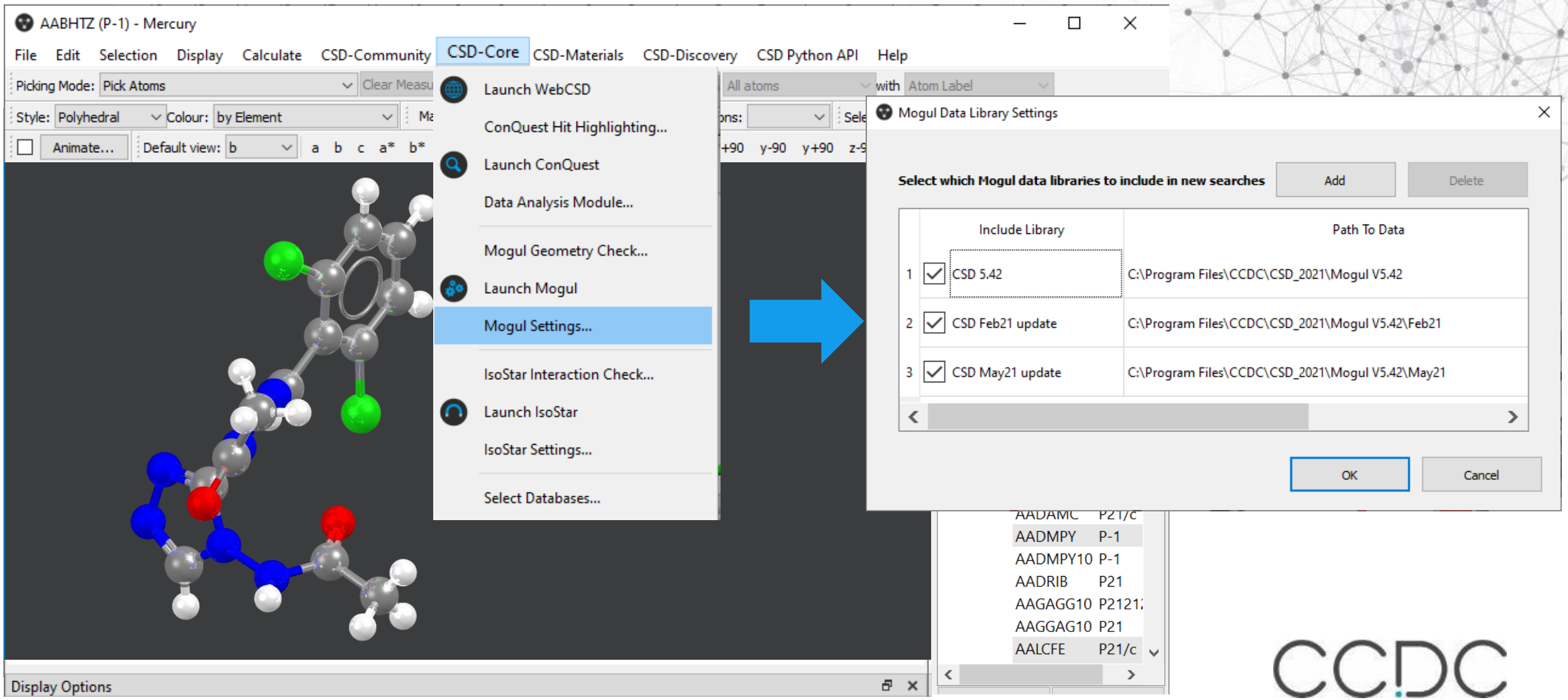


Mogul Geometry Check – Build query

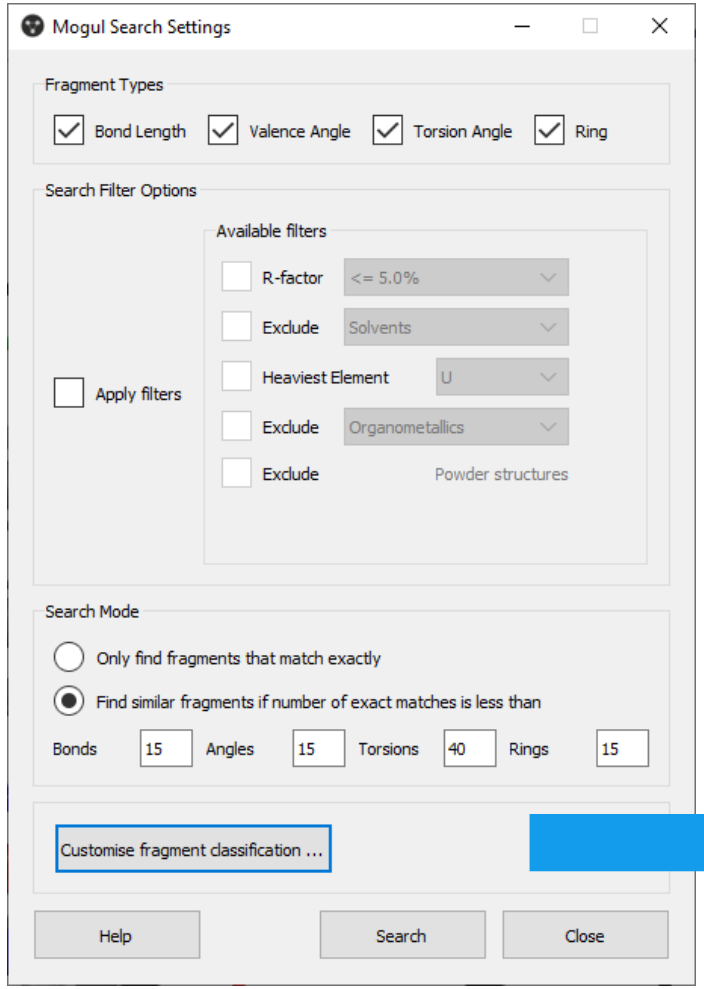


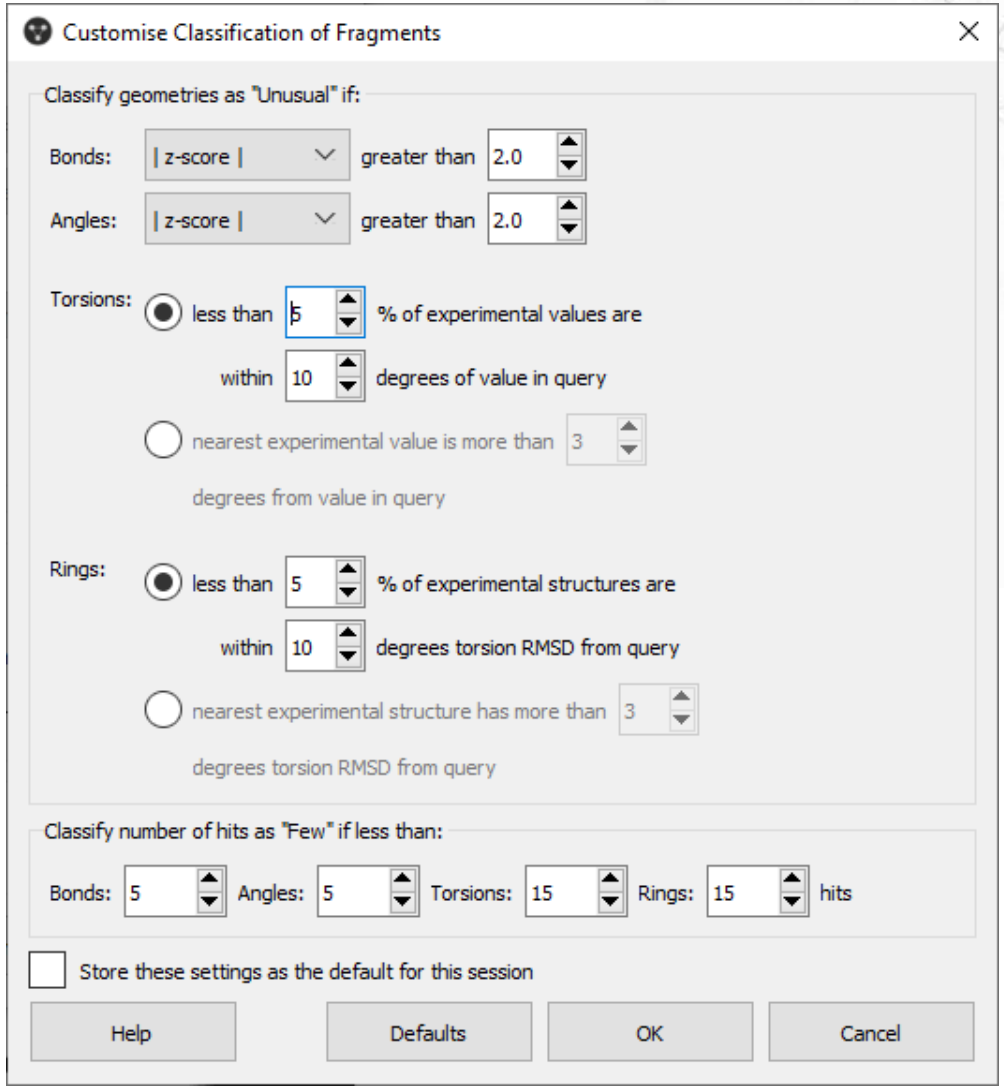
Learn about building and editing a Mogul query in Exercise 2 of the handout.

Mogul Settings



Customise fragment classification

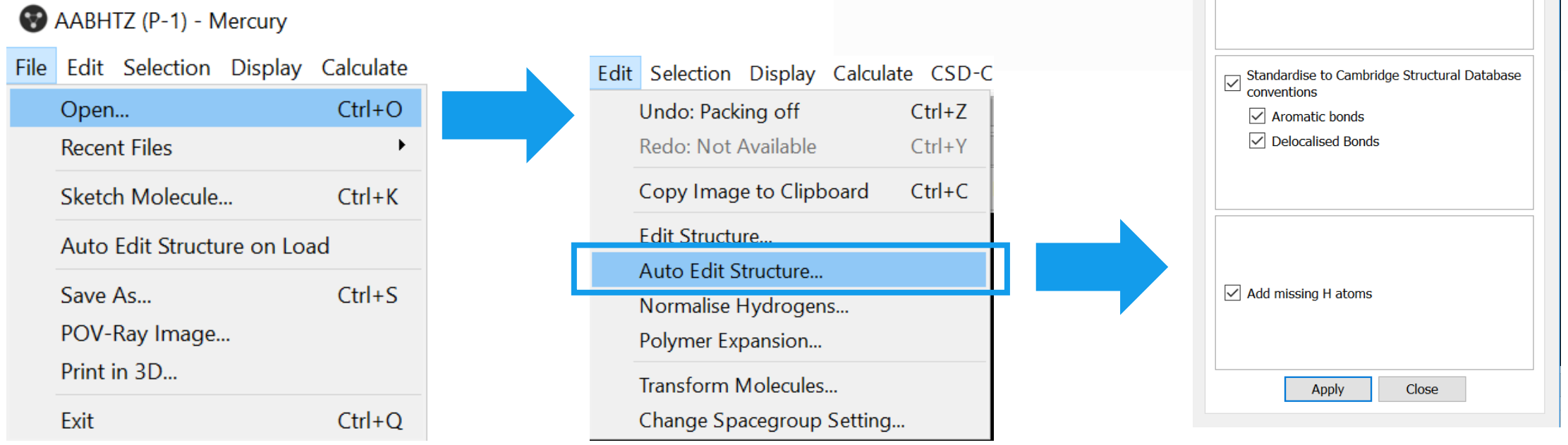




Using Mogul to check a new structure

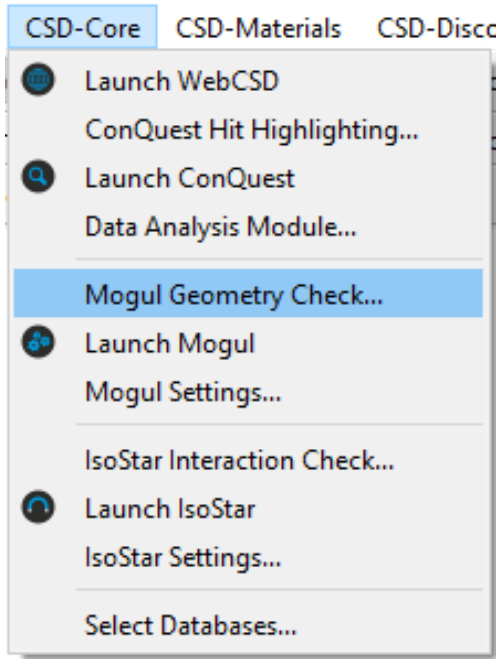
1. Load your structure in Mercury
   - Do you remember how to do it from the Visualisation session?

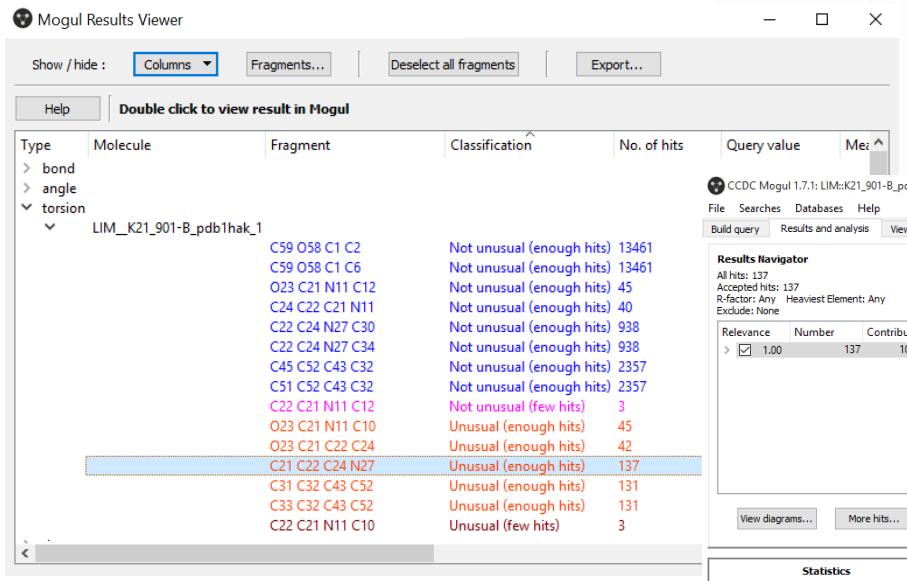
- File > Open – to open one of your own files for example a CIF
- Edit > Auto Edit Structure to assign bond types
- File > Auto Edit Structure on Load to automate

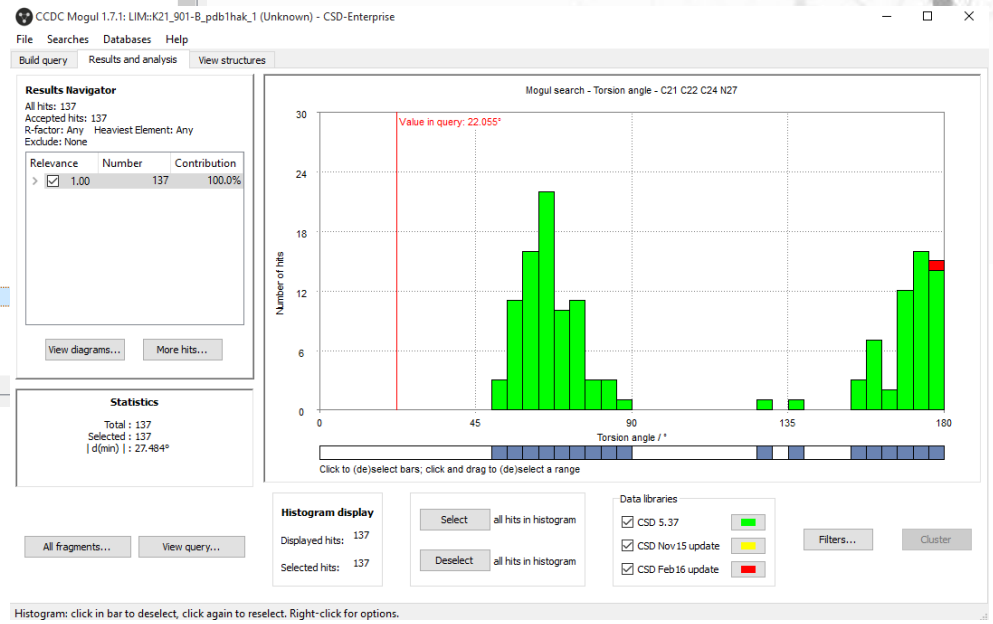


Using Mogul to check a new structure

2. Repeat the procedure you did before







Why use Mogul?

- To enable you to validate the complete geometry of a given query structure and identify any unusual features
  - Could be useful when looking at your own structure or a CSD structure or in fact ligands in the PDB
- To rapidly retrieve geometric data and gain new insights from structures in the CSD

A few more tips & tricks

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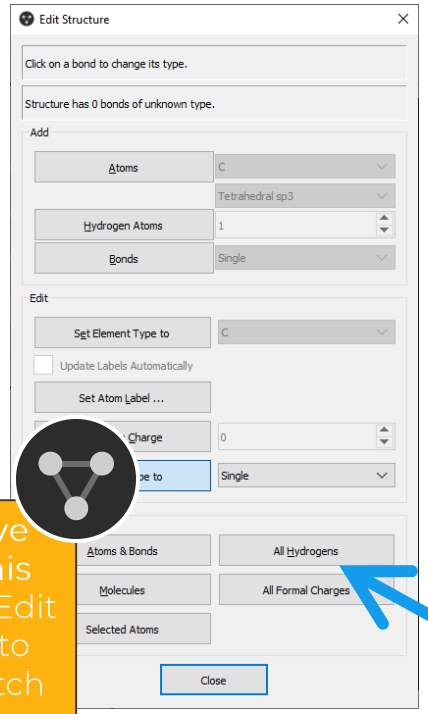
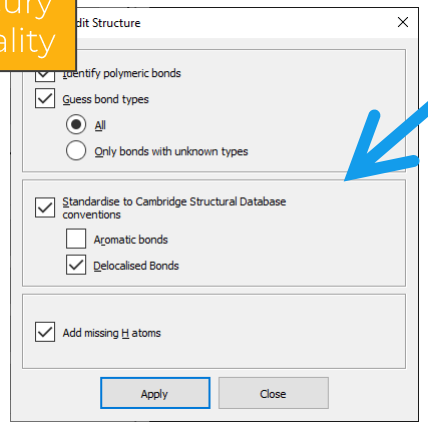
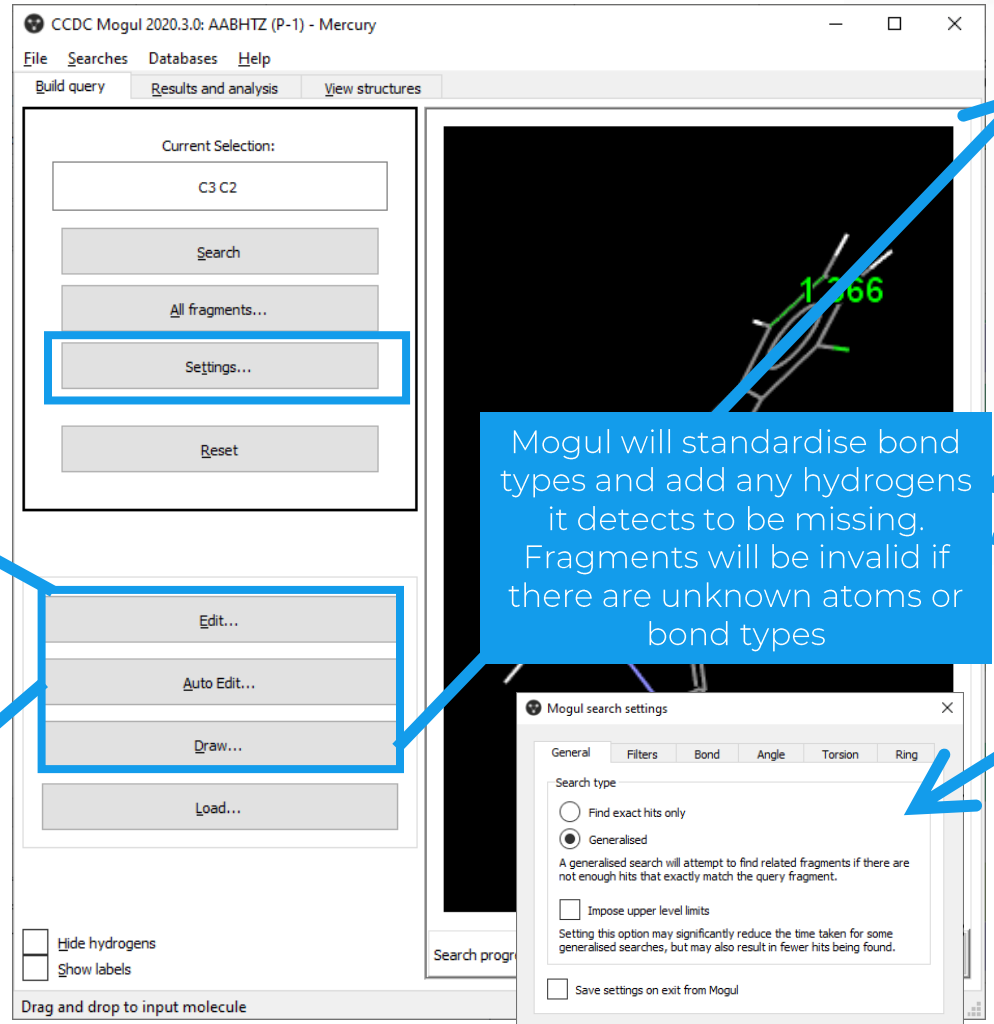
advancing structural science

Using the Draw feature in a Mogul Query

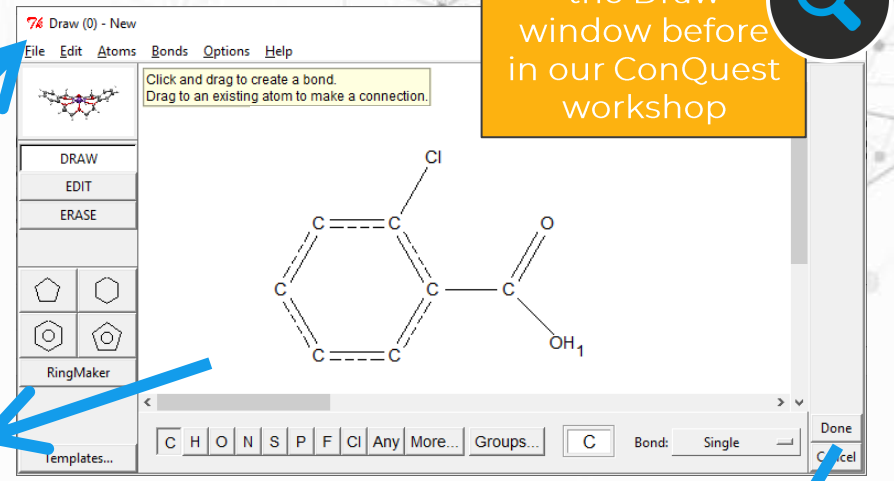




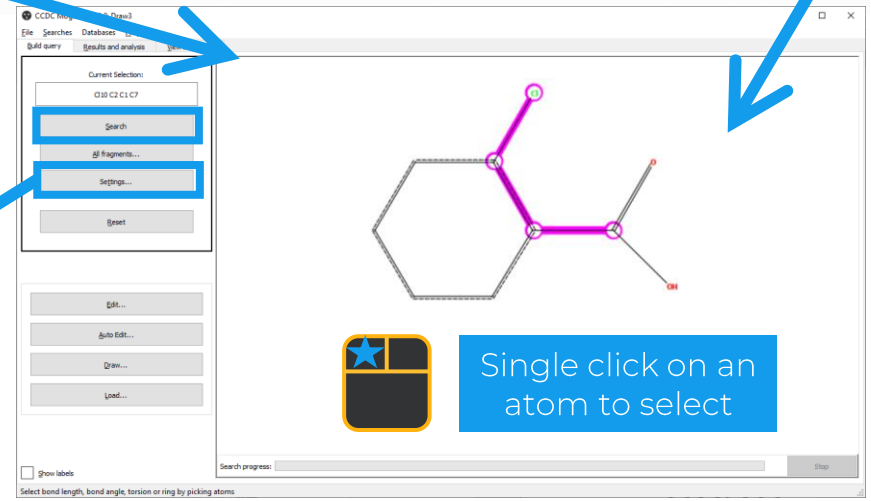
We have seen this before - Edit and Auto Edit match the Mercury functionality



Mogul will standardise bond types and add any hydrogens it detects to be missing. Fragments will be invalid if there are unknown atoms or bond types

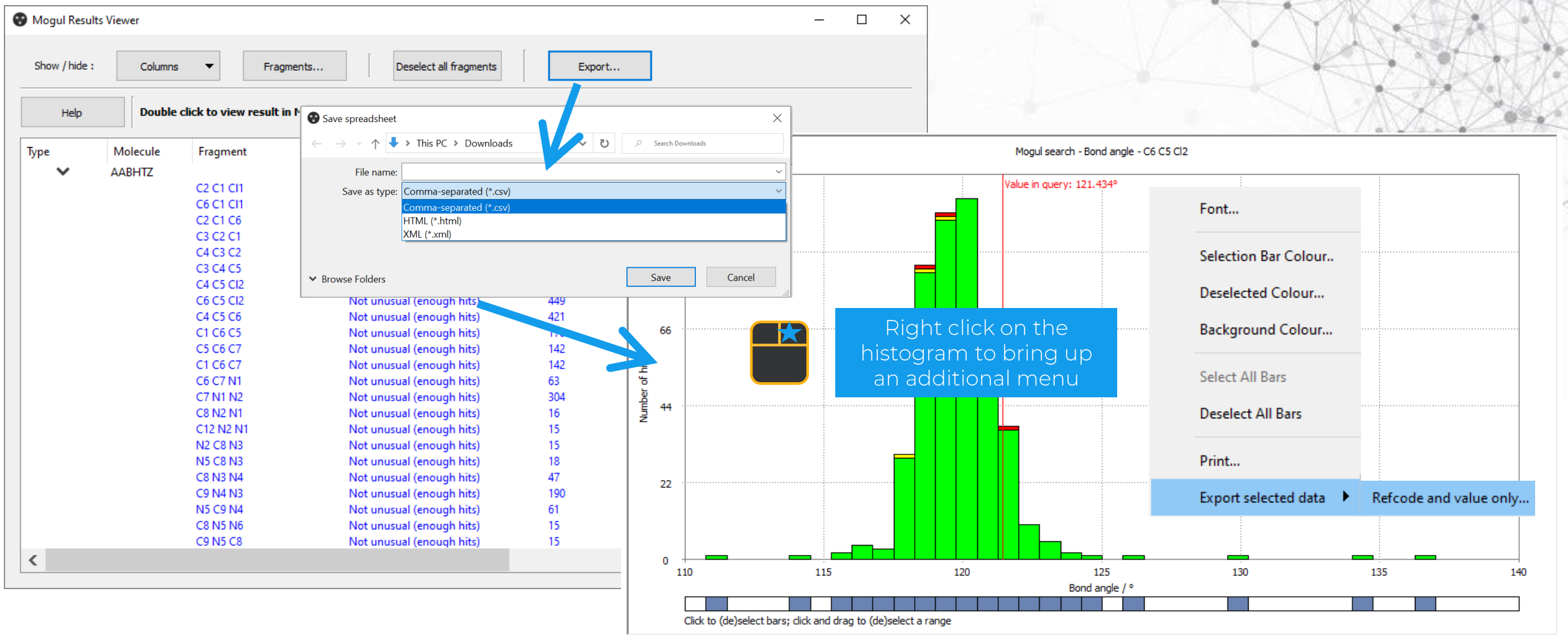


We have seen the Draw window before in our ConQuest workshop



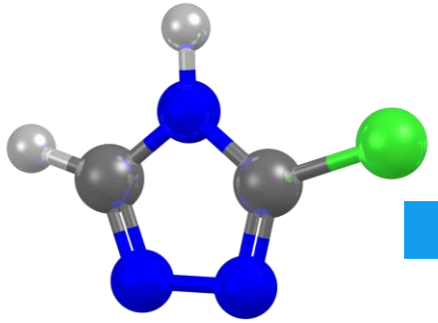
Single click on an atom to select

Exporting data from Mogul



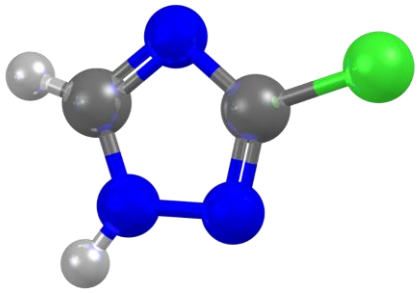
Using Mogul to assign tautomeric forms

CSD CLTRZL

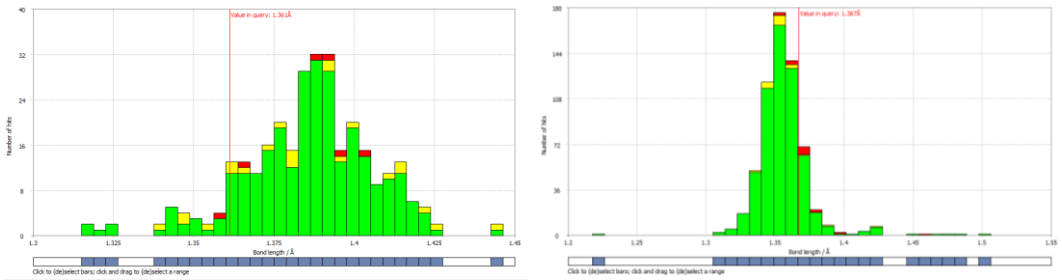


1.361 Å

CSD CLTRZL01

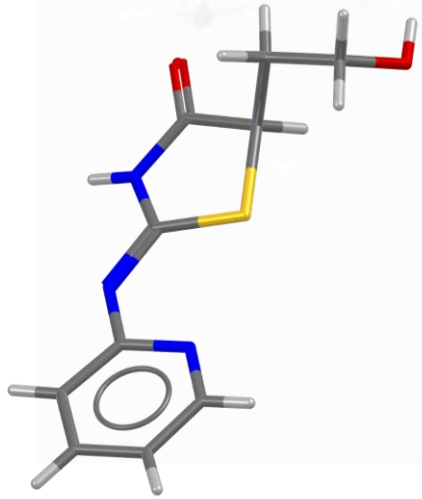


1.367 Å

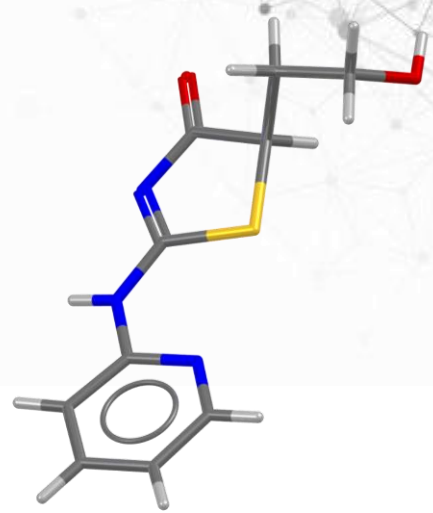


Following Mogul analysis structure re-determined in a different tautomeric form

CSD GACXOZ



CSD LOQBIE



A comparison of the 1,3-thiazol-4-one structures in which *Mogul* queries the C—N bond length of the imine of GACXOZ, but finds all geometrical parameters of the amine version to be within expected limits

B.Bax, C.Chung, C.Edge, *Acta Cryst. D,* 2017, 73, 131-140, DOI: 10.1107/S2059798316020283
R.Taylor and P.A.Wood, *Chem. Rev.,* 2019, 119, 16, 9427–9477, DOI: 10.1021/acs.chemrev.9b00155

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