CSD-CrossMiner

Pharmacophore search: basics and applications

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Learning outcomes

- An understanding of the pharmacophore concept.
- Familiarity with the CSD-CrossMiner interface and how it can be used in your research.
- How to perform pharmacophore searches biologically relevant subsets of the CSD and PDB.
- How to set up an interactive pharmacophore query and save the results.
- How to analyse and interact with your results.

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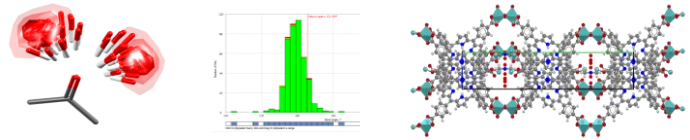
Show One: The CSD Portfolio

CSDEnterprise.

CSDCore.

Search, visualise, analyse and communicate structural data
Insights into molecular and crystal shape and interactions

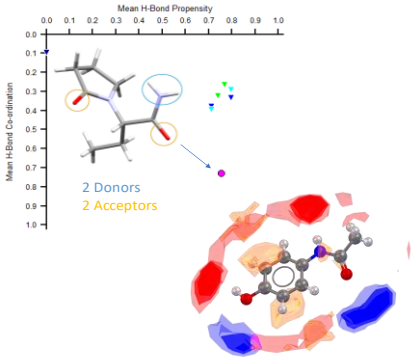


CSDDiscovery.

Design of new molecules

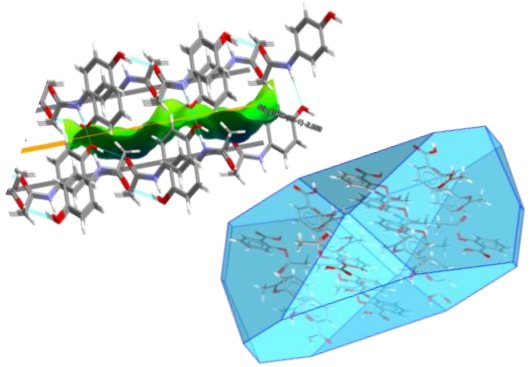
CSDMaterials.

Assessment of solid form stability and properties



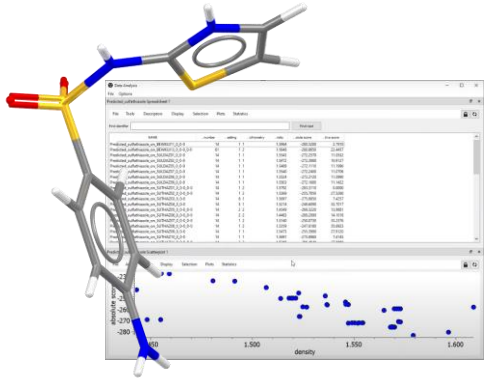
CSDParticle.

Anticipate particle properties and behaviour



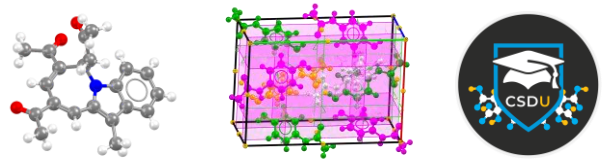
CSDTheory.

Generate solid form landscapes



CSDCommunity.

Deposit, publish, access and visualise structural data
Free functionality to share and learn from structures



Medicinal & Computational Chemists ♦ Crystallographers & Structural Biologists ♦ Solid Form & Crystallisation Scientists ♦ Functional Materials Scientists ♦ Educators ♦ Industry and Academia

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CSD-CrossMiner - origin

- Developed in collaboration with **Roche**.

*"We exemplify the utility of the approach by **showing applications relevant to real-world drug discovery** projects, including the identification of novel fragments for a specific protein environment or scaffold hopping."*

*"We believe that CSD-CrossMiner **closes an important gap in mining structural data** and will allow users to extract more value from the growing number of available crystal structures."*

Interactive and Versatile Navigation of Structural Databases

Oliver Korb [1], Bernd Kuhn [2], Jérôme Hert [2], Neil Taylor [3], Jason Cole [1], Colin Groom [1], Martin Stahl [2]

Affiliations + expand

PMID: 26745458 DOI: 10.1021/acs.jmedchem.5b01756

Abstract

We present CSD-CrossMiner, a novel tool for pharmacophore-based searches in crystal structure databases. Intuitive pharmacophore queries describing, among others, protein-ligand interaction patterns, ligand scaffolds, or protein environments can be built and modified interactively. Matching crystal structures are overlaid onto the query and visualized as soon as they are available, enabling the rese
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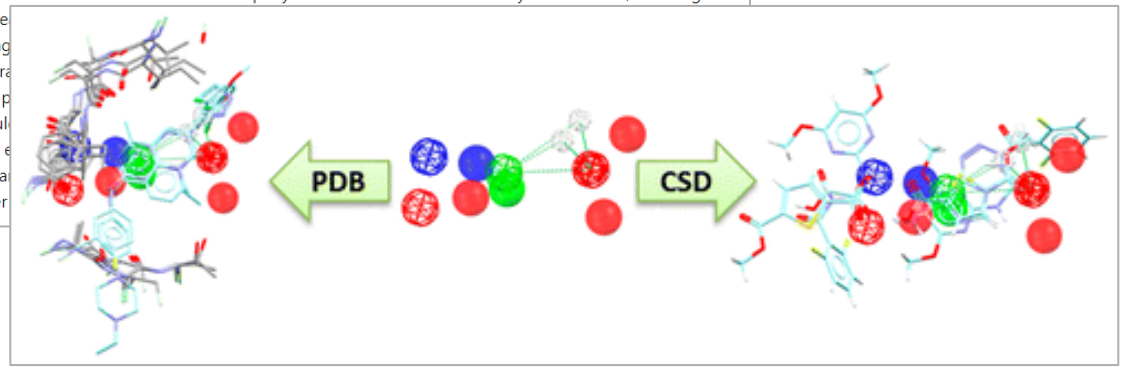

https://doi.org/10.1021/acs.jmedchem.5b01756

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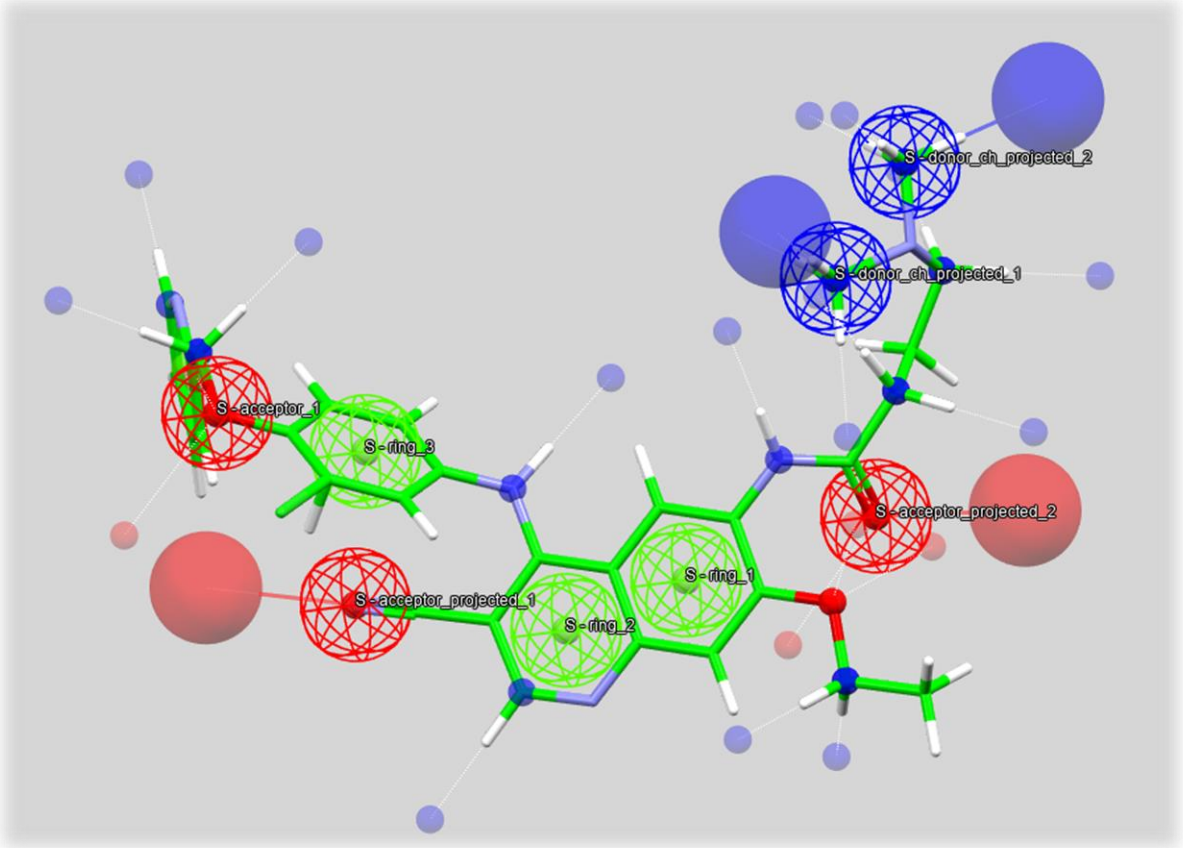
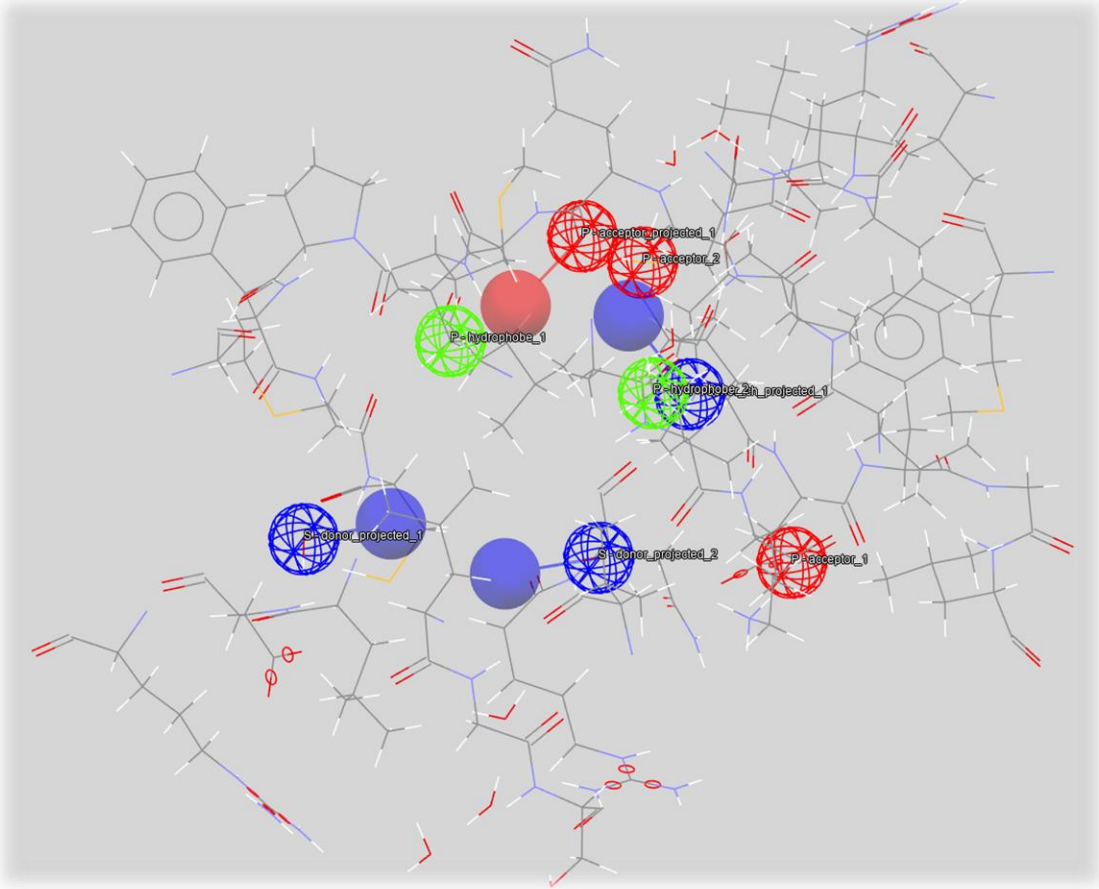
CSD-CrossMiner: why you may need it

- You have a known ligand and want to find a new one with better properties but able to keep the same interactions with the target



CSD-CrossMiner: why you may need it

- You have a known target with a known binding pocket and want to find compounds which can bind to the pocket



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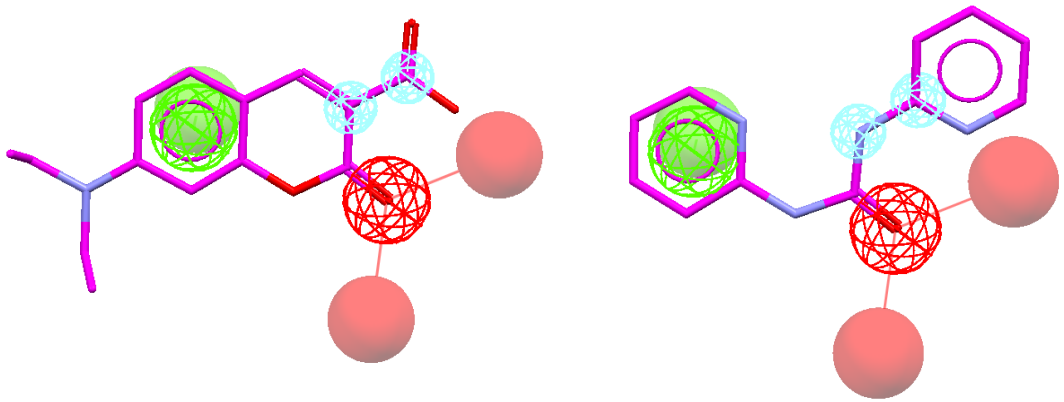
CSD-CrossMiner - applications

- Advance **hit-to-lead**
- Lead **optimisation**
- Find **scaffold hops** to improve pharmacokinetics



- Identify **off-target** effects
- Understand which **modifications** are tolerated in the binding site
- Generate **new ideas** in drug discovery projects

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Pharmacophore search applications

- **Design novel motifs** that mimic established ligands to improve physicochemical properties or solve patent issues.
- **Scaffold-hopping**: retrieve a diversity of ligand topologies that can be used as scaffolds for lead optimization.
- Look at chemistries that interact with **unexplored parts** of the binding site to improve binding properties of a ligand.

CSD-CrossMiner specific

- Determine **common protein binding sites** to predict selectivity.
- Shed light into **cross-pharmacology** between protein targets.
- Determine **structural motifs** that bind in **similar environments** to find insights for drug design and optimization.

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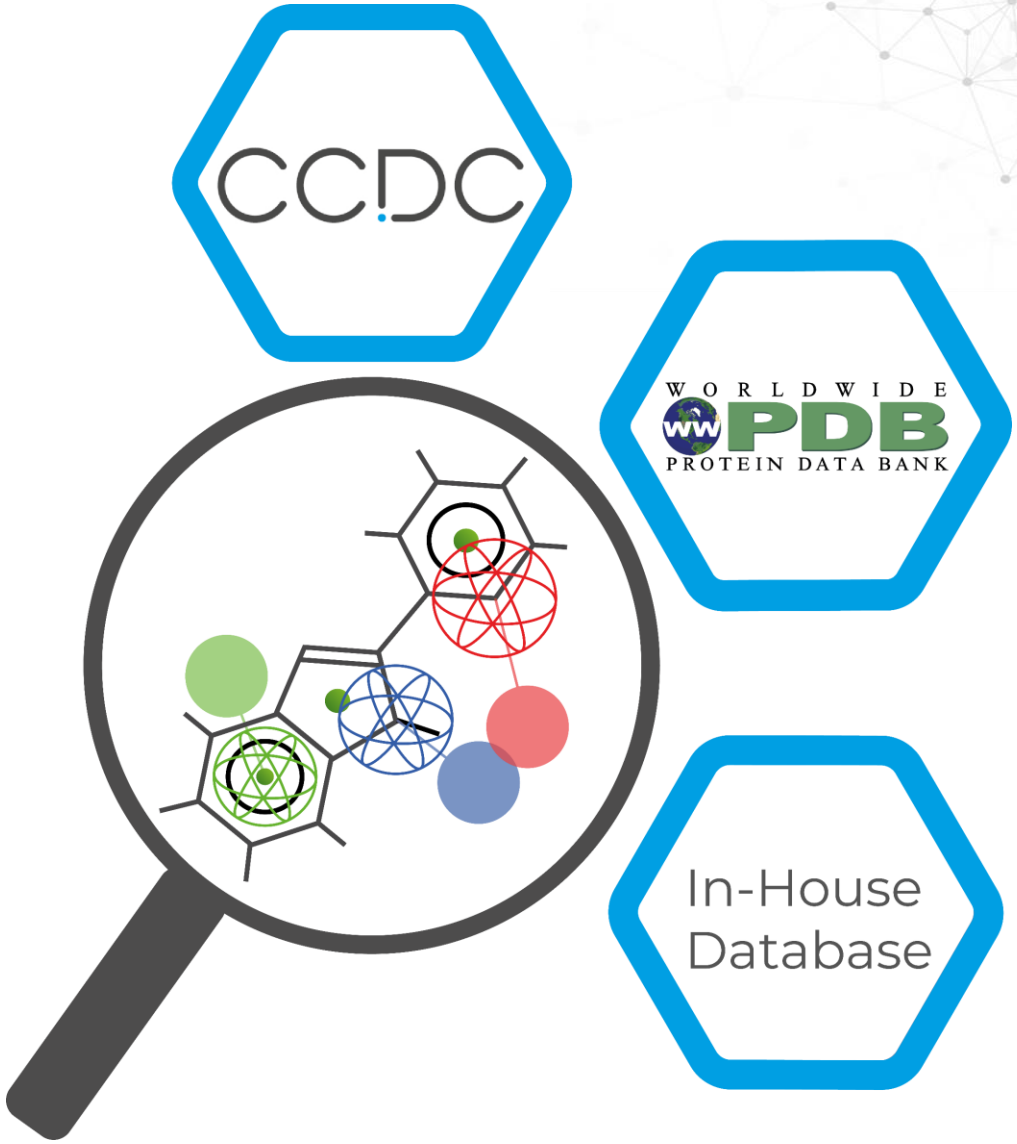
CSD-CrossMiner

- Tool for building pharmacophore queries.
- Tool for searching structural databases by pharmacophore.
- Simultaneously search the PDB, CSD and your in-house database.
- Designed for speed – modify hypotheses on the fly.
- Structures are annotated for easy filtering of hits.



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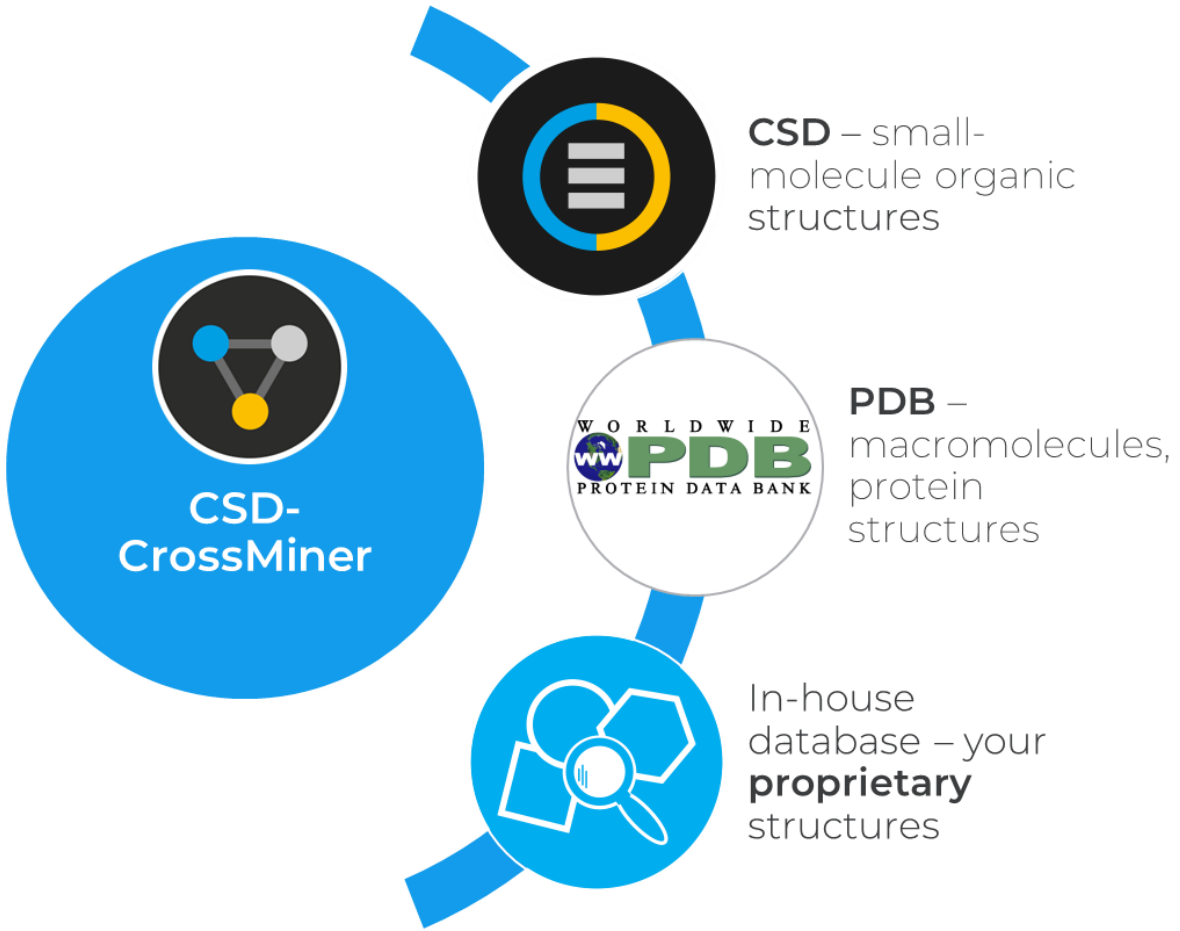
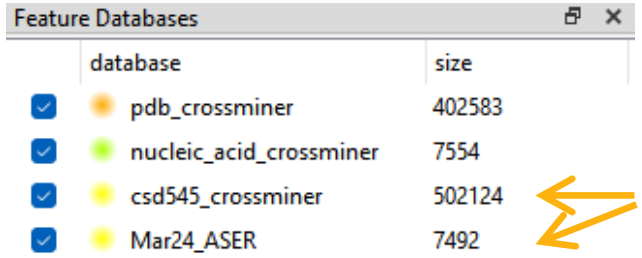
Korb *et al,. J. Med. Chem.* **2016,** 59, 4257-4266. DOI: 10.1021/acs.jmedchem.5b01756

CSD-CrossMiner: Feature Databases



https://www.ccdc.cam.ac.uk/solutions/software/csd-crossminer/

- **Simultaneously mine data sources.**
- Public and proprietary.
- Find matches by pharmacophore.
- These are **annotated versions** of the original databases, to include pharmacophore features information.



- Building of in-house databases and their integration into CSD-CrossMiner is possible.

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Basics

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Show One: The basics – A pharmacophore

"A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interaction with a specific biological target structure and to trigger (or block) its biological response."

C.G.Wermuth, C.R.Ganellin, P.Lindberg, L.A. Mitscher (1998). "Glossary of terms used in medicinal chemistry (IUPAC Recommendations 1998)" DOI: 10.1351/pac199870051129

A concept is originated by Paul Ehrlich (1909) and developed by Schueler in his book "*Chemobiodynamics and Drug Design*" (1960)

Osman F. Güner and J. Phillip Bowen (2014). "Setting the Record Straight: The Origin of the Pharmacophore Concept" DOI: 10.1021/ci5000533

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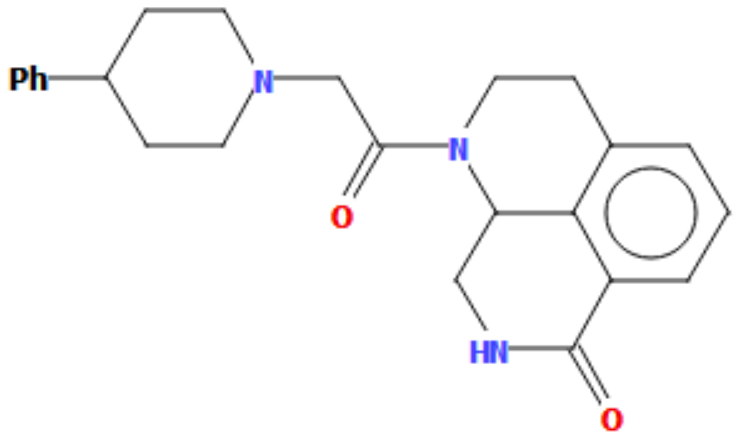
Pharmacophore feature



Pharmacophore feature – an atom or a group of atoms with sterical or electrostatic properties essential for the activity to a target protein.

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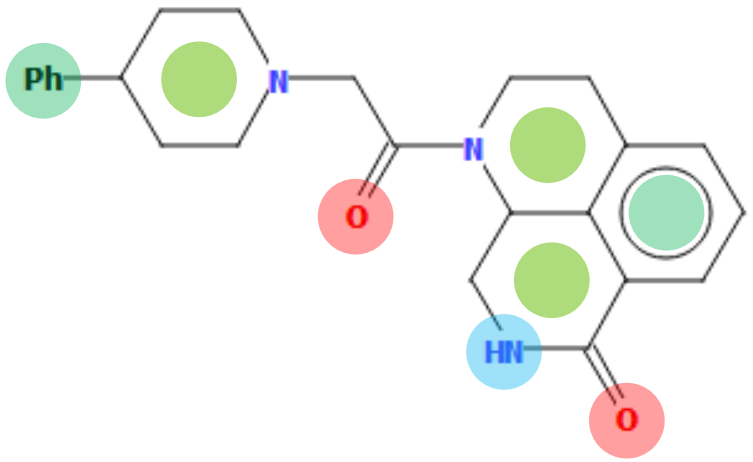
Pharmacophore feature



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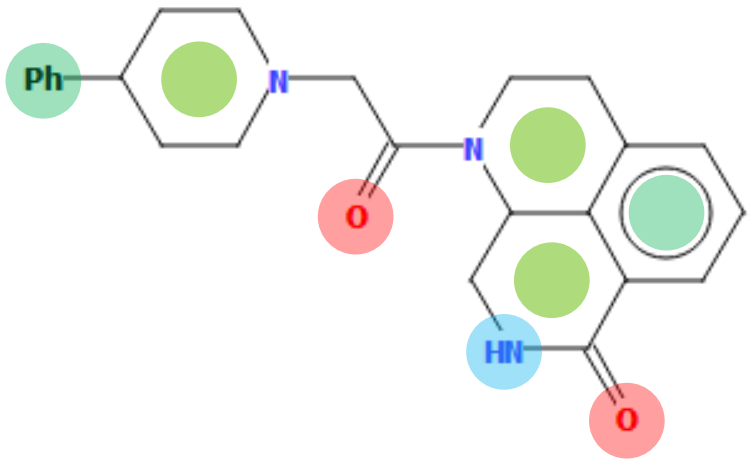
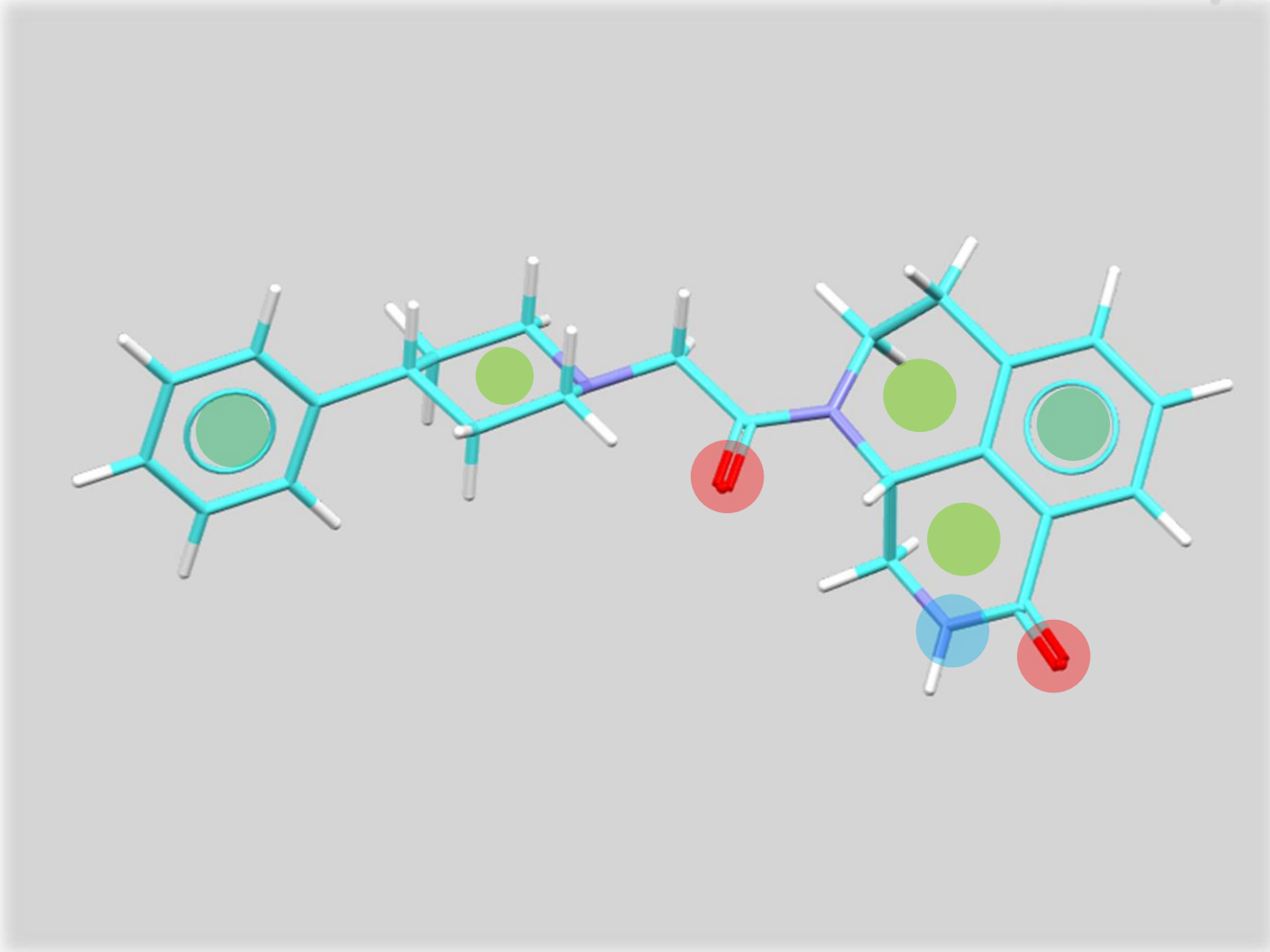
Pharmacophore feature



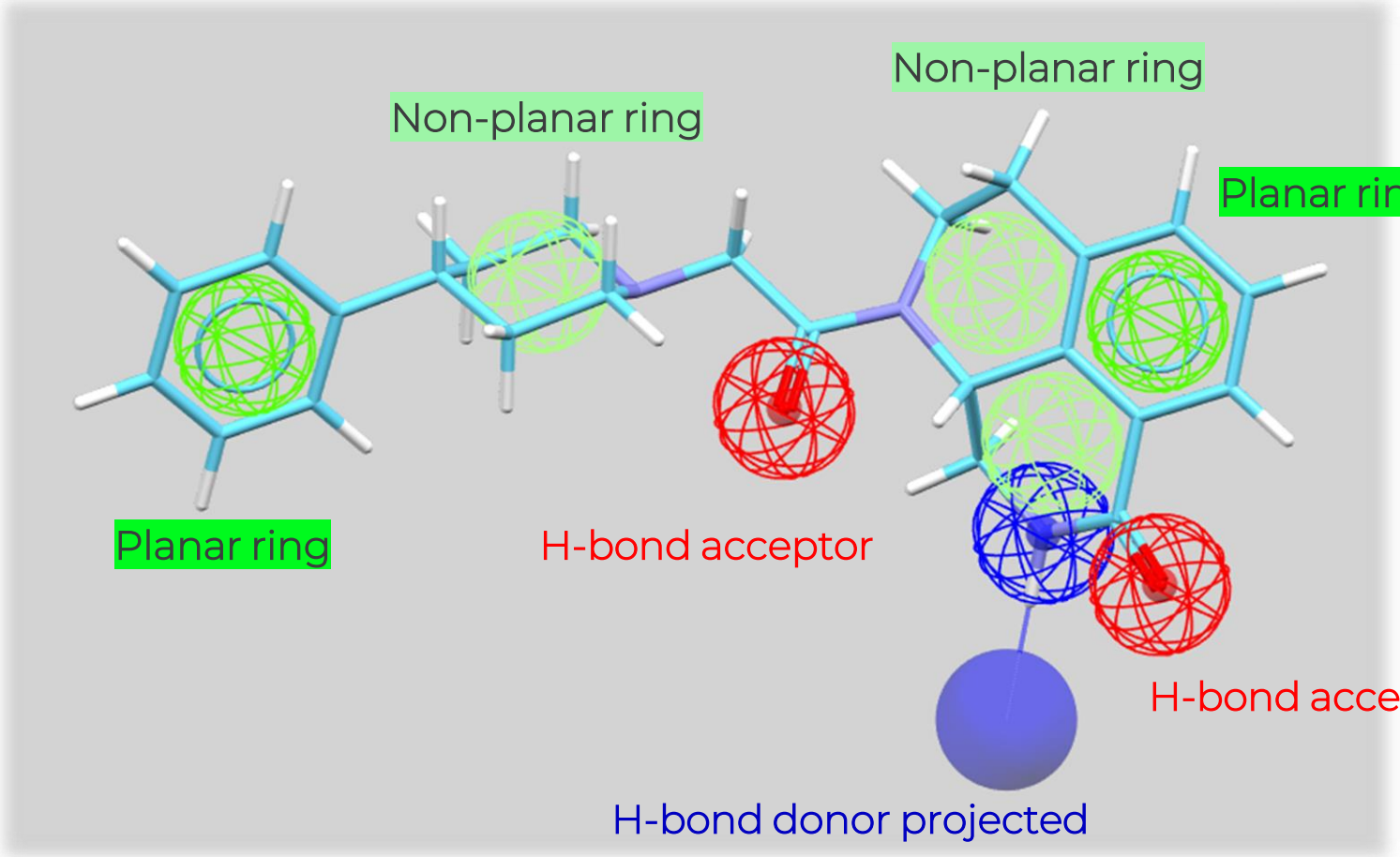


Pharmacophore features in CrossMiner

- acceptor
- acceptor_projected
- donor_ch_projected
- donor_projected
- heavy_atom
- hydrophobe
- ring
- ring_non_planar
- ring_planar_projected
- purine
- pyrimidine
- adenine
- cytosine
- guanine
- thymine
- uracil
- deoxyribose
- ribose
- exit_vector
- halogen
- bromine
- chlorine
- fluorine
- metal
- water

- ALA
- ARG
- ASN
- ASP
- CYS
- GLN
- GLU
- GLY
- HIS
- ILE
- LEU
- LYS
- MET
- PHE
- PRO
- SER
- THR
- TRP
- TYR
- VAL

- excluded_volume
- annotation_filter
- substructure_filter



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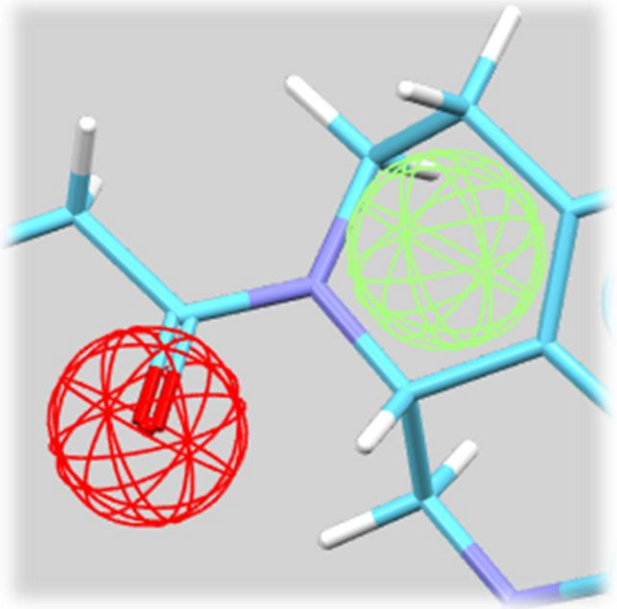
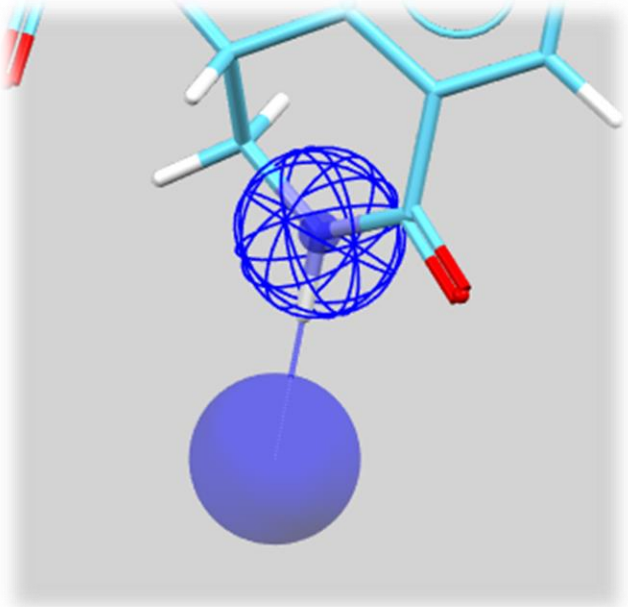
Pharmacophore features in CrossMiner

A pharmacophore point is a feature that has been selected to be in a pharmacophore because its presence is necessary

- Single point, acceptor

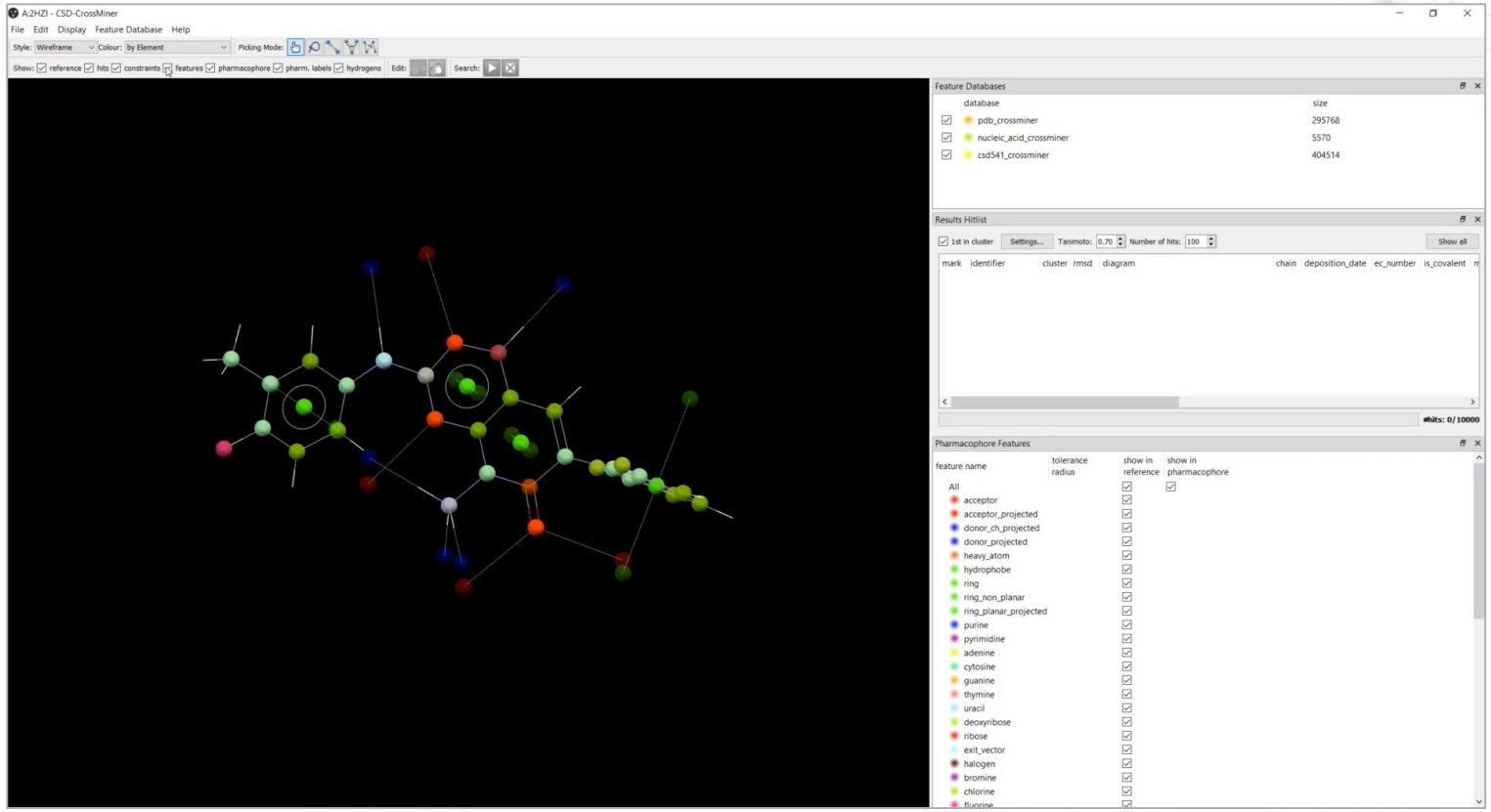


- Between two points, donor_projected



CSD-CrossMiner - features

- **Customise** feature definitions
  - Explore new chemistry
  - Improve search granularity
- **Excluded** volume
  - Cut noise by removing occupational volume



Pharmacophore query

Pharmacophore query (or just pharmacophore) is ensemble of steric and electronic features that characterise a protein and/or a small molecule.

- What interactions are present and most common in protein-ligand complexes you have?
- Which pharmacophore features are the most common among known ligands binding to a same target?
- Are there any unsatisfied interactions in the target's pocket?
- Are there any interactions you'd like to eliminate?

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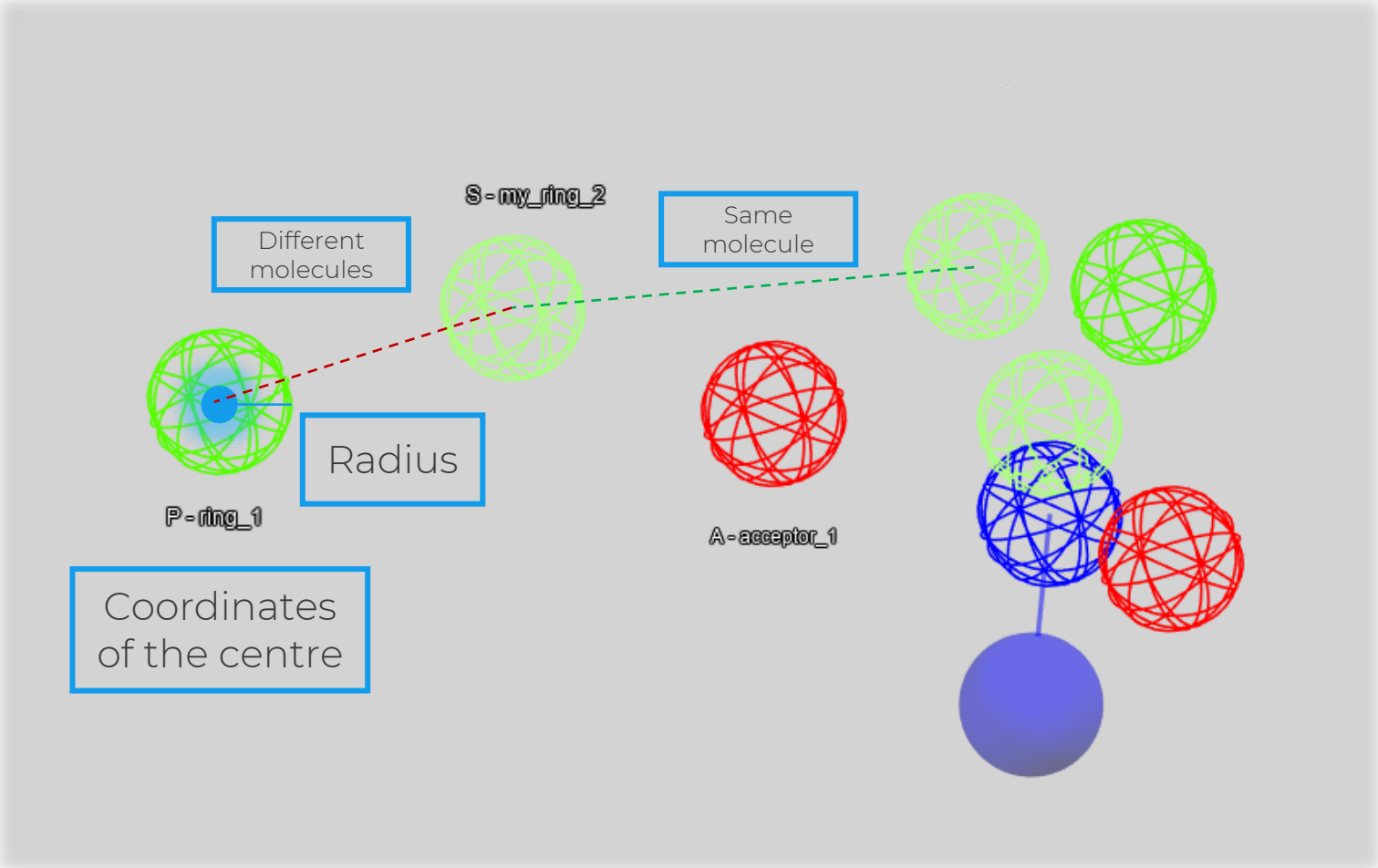
Pharmacophore query



Pharmacophore features and queries

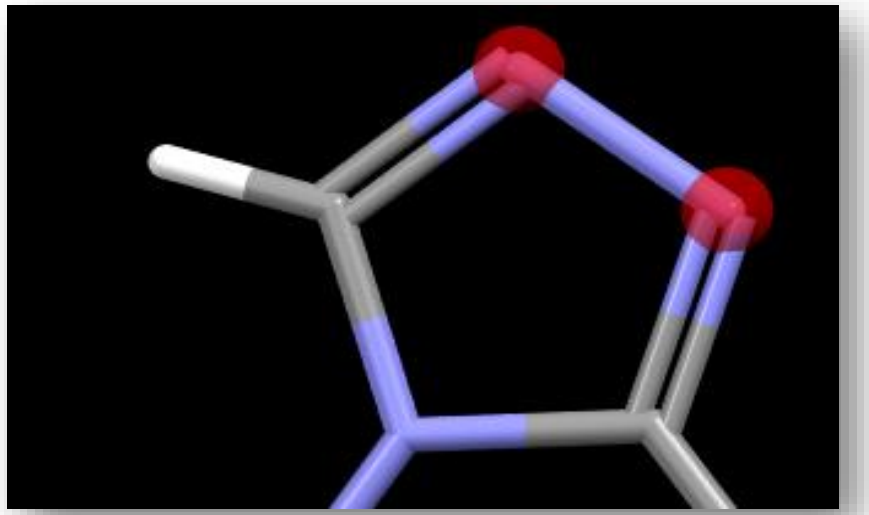
Features: *.cpf files

SMARTS

```
SMARTS_DEF [*]=[#7X2]-[*]
FEATURE ACCEPTOR_SP2 1
```

Type

Atom index in SMARTS



Queries: *.cm files

Name

```
PHARMACOPHORE_FEATURE ring
PHARMACOPHORE_SPHERE -4.53263 1.5178 -5.09123 1
PHARMACOPHORE_FEATURE_SMALL_MOLECULE
PHARMACOPHORE_FEATURE_DESCRIPTION ring_1

PHARMACOPHORE_FEATURE ring
PHARMACOPHORE_SPHERE 0.3942 -0.933317 6.5668 1
PHARMACOPHORE_FEATURE_SMALL_MOLECULE
PHARMACOPHORE_FEATURE_DESCRIPTION ring_2

PHARMACOPHORE_FEATURE acceptor
PHARMACOPHORE_SPHERE -1.0059 -0.8408 1.3053 1
PHARMACOPHORE_FEATURE_SMALL_MOLECULE
PHARMACOPHORE_FEATURE_DESCRIPTION acceptor_1
```

Molecule type

Description

Coordinates and radius

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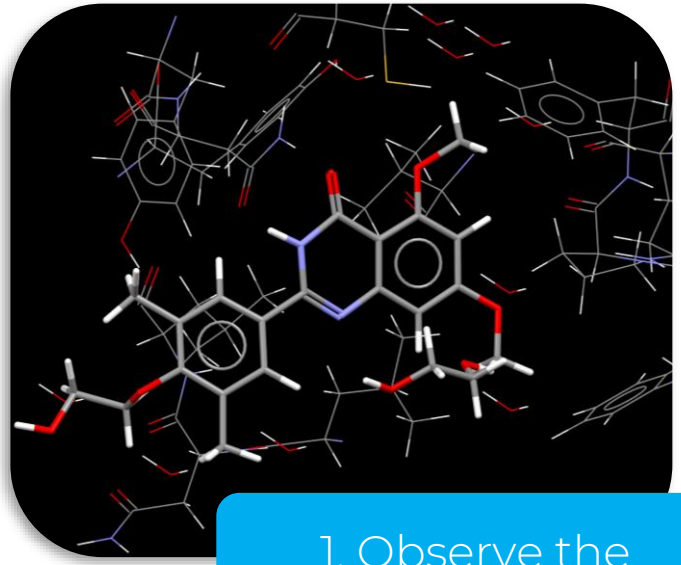
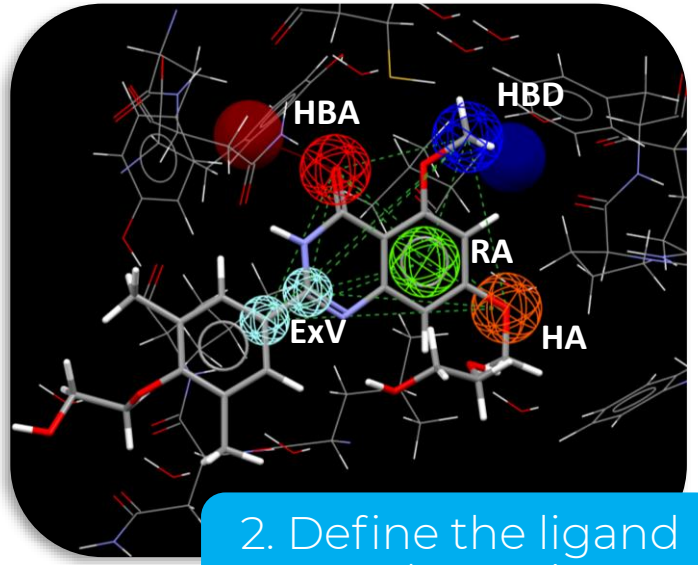
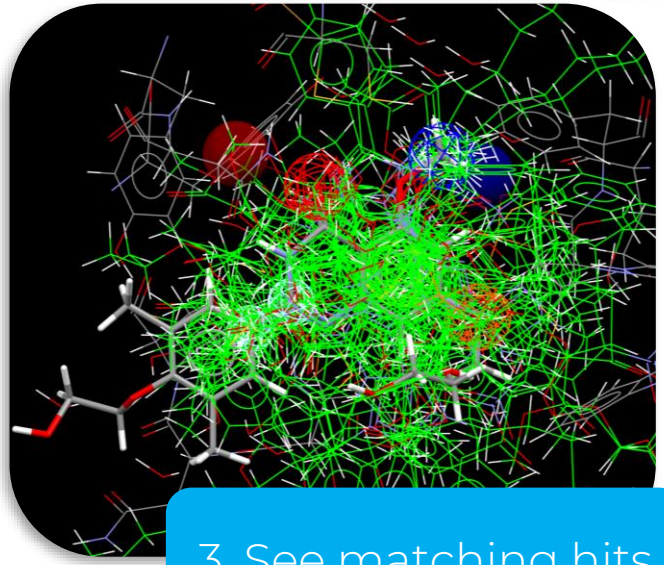
CSD-CrossMiner - workflow



1. Observe the protein-ligand complex.



2. Define the ligand and protein pharmacophore, and any constraints



3. See matching hits overlaid – explore each in the browser.

HBD – Hydrogen Bond Donor; HBA – Hydrogen Bond Acceptor; HA – Heavy Atom; RA – Ring Aromatic; ExV – Exit Vector

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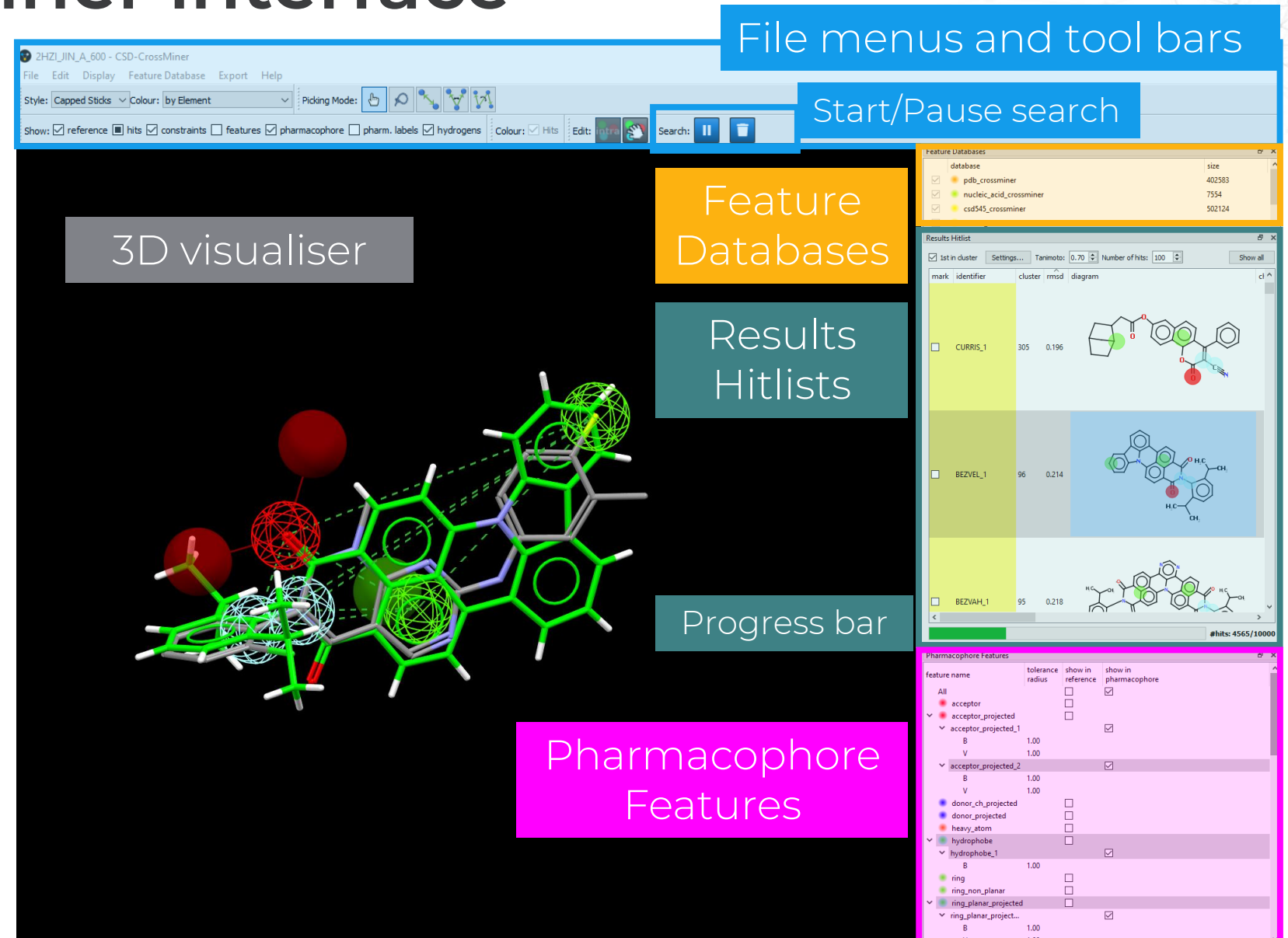
CSD-CrossMiner interface



How it works

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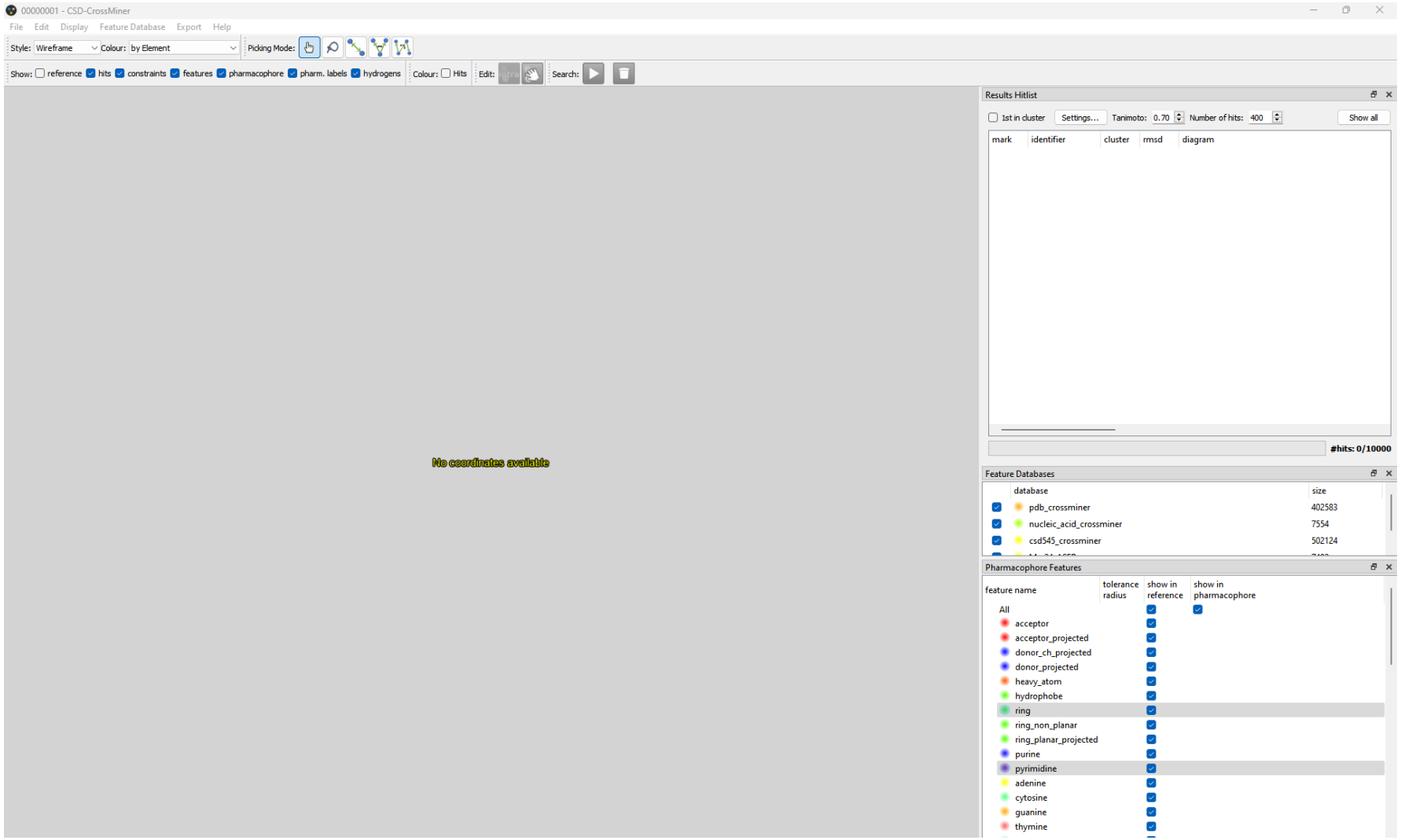
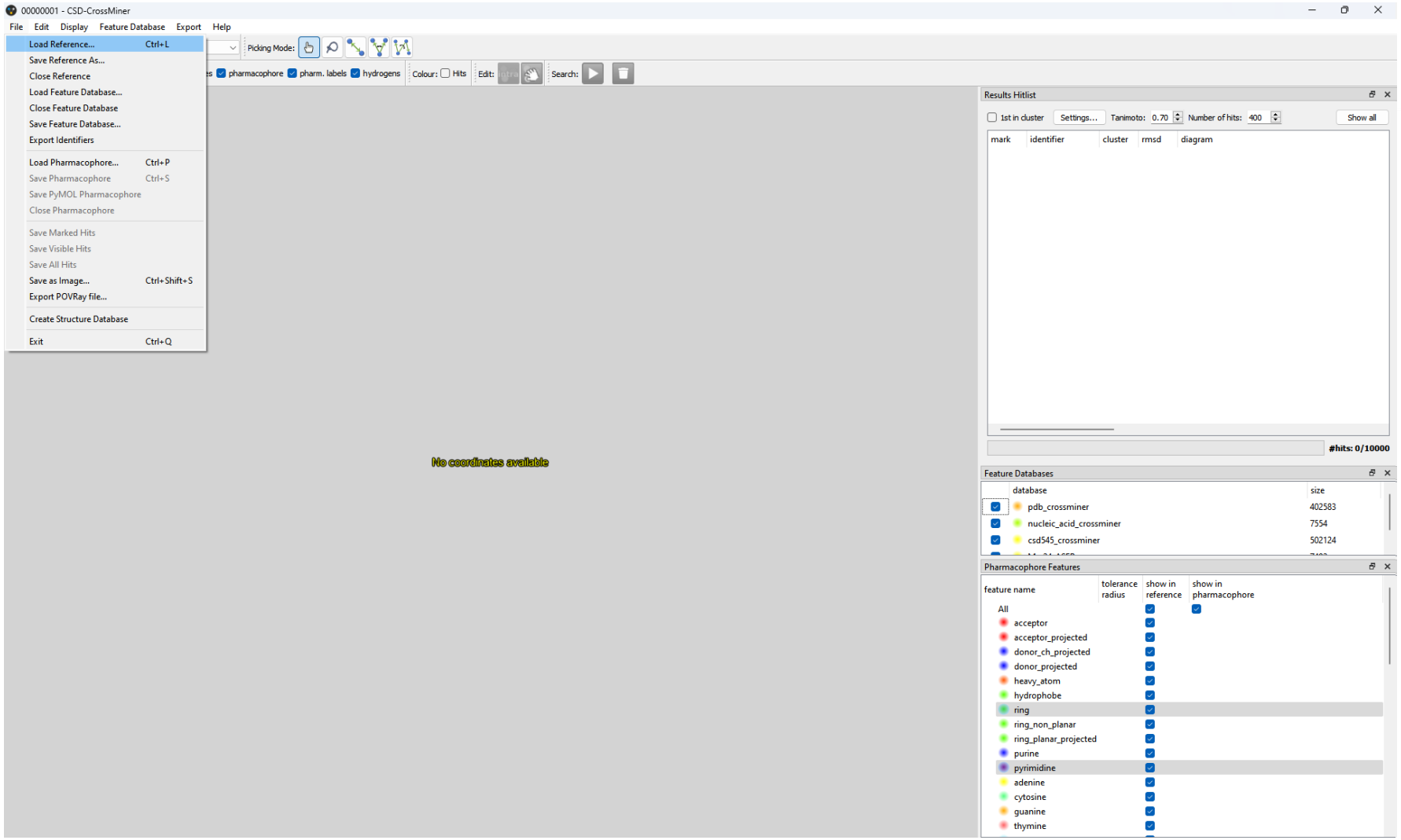
Building pharmacophore query



Building pharmacophore query



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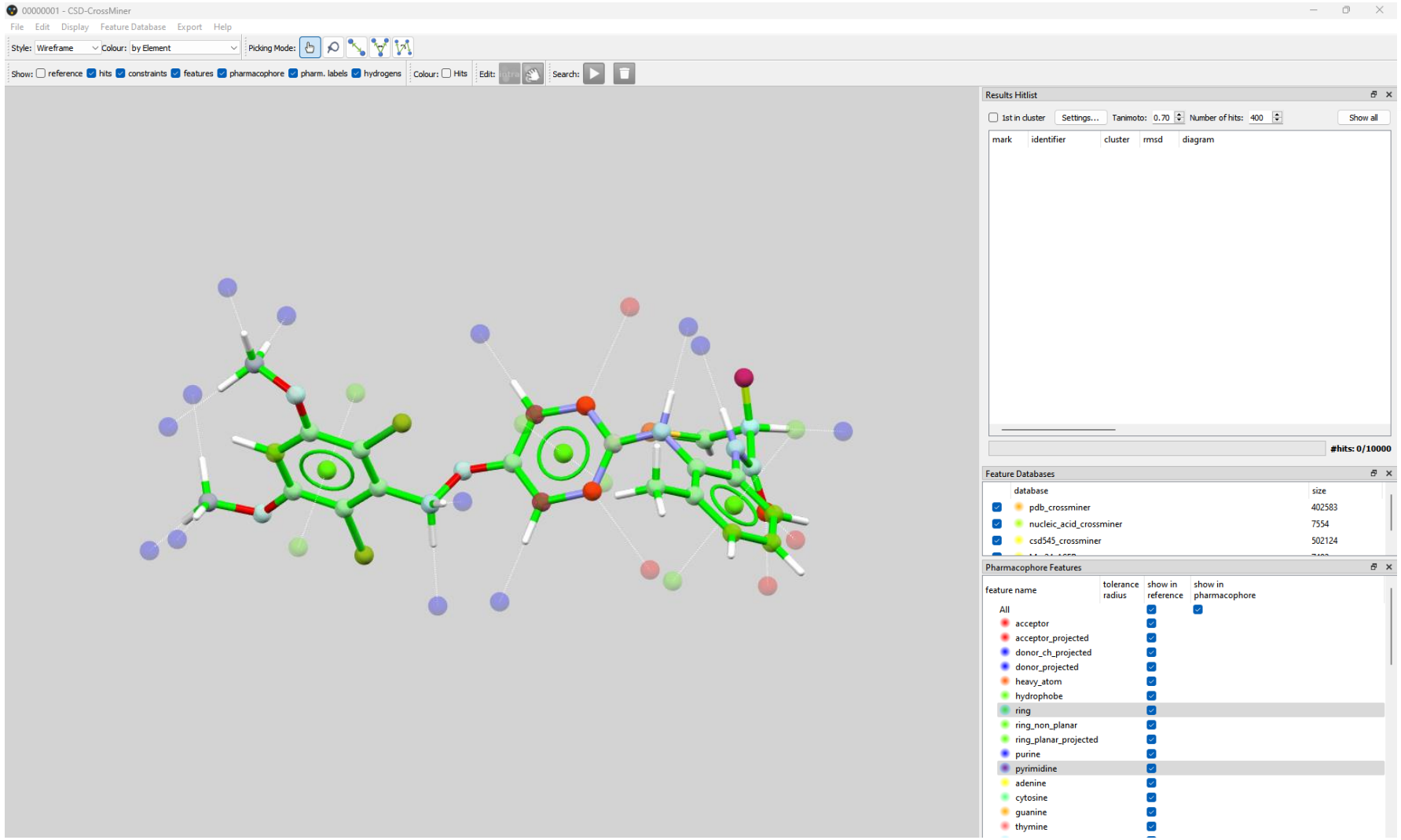
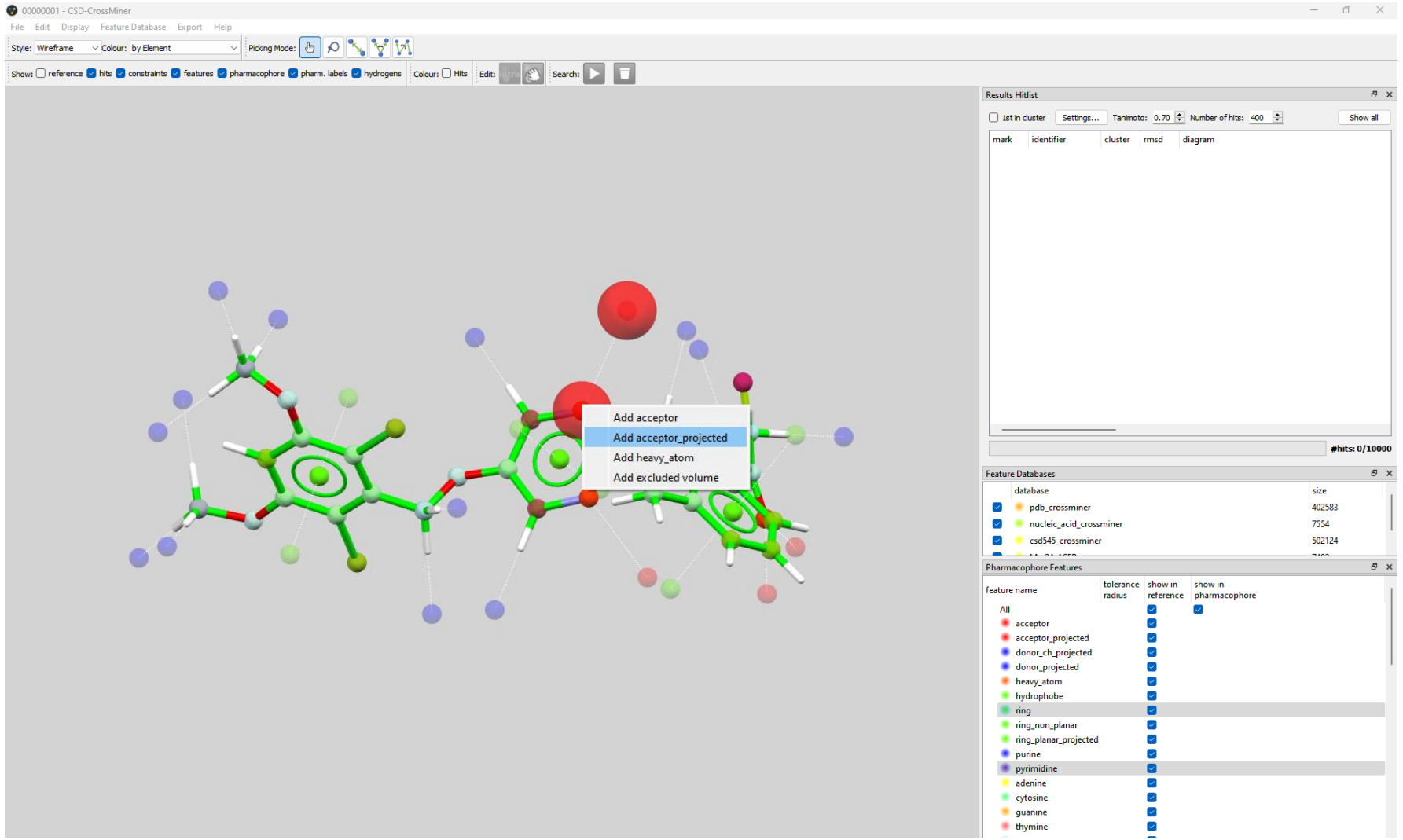


Building pharmacophore query



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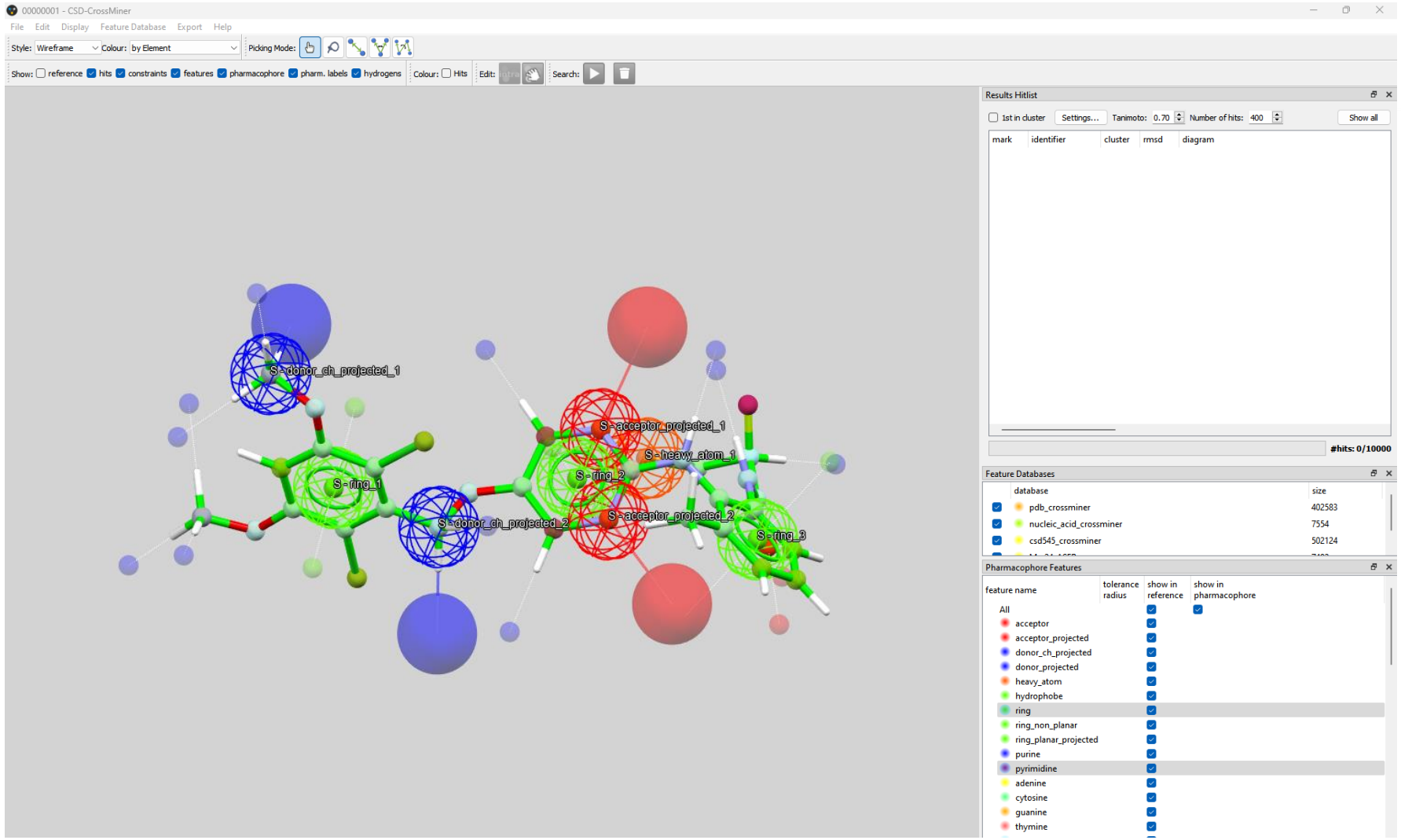
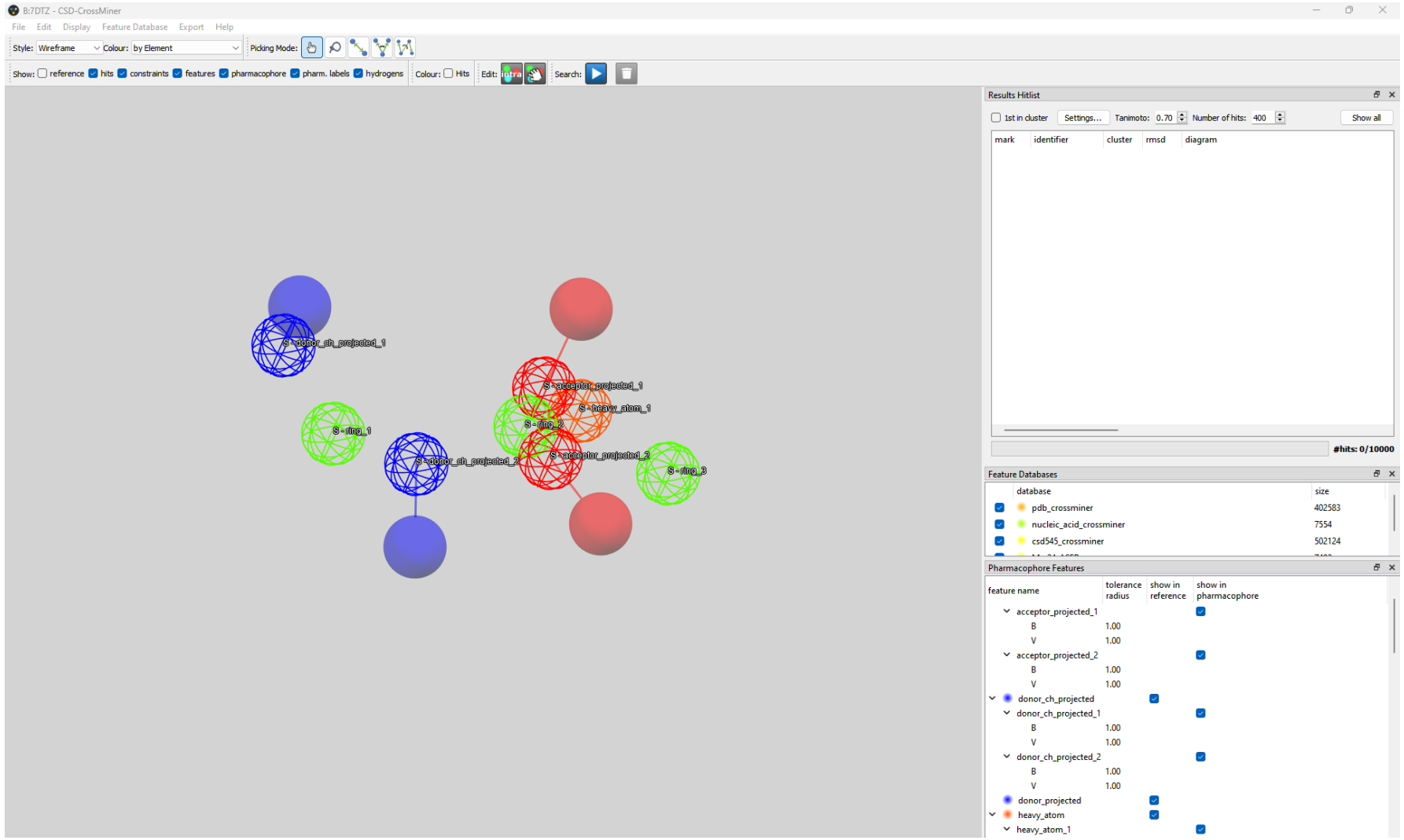
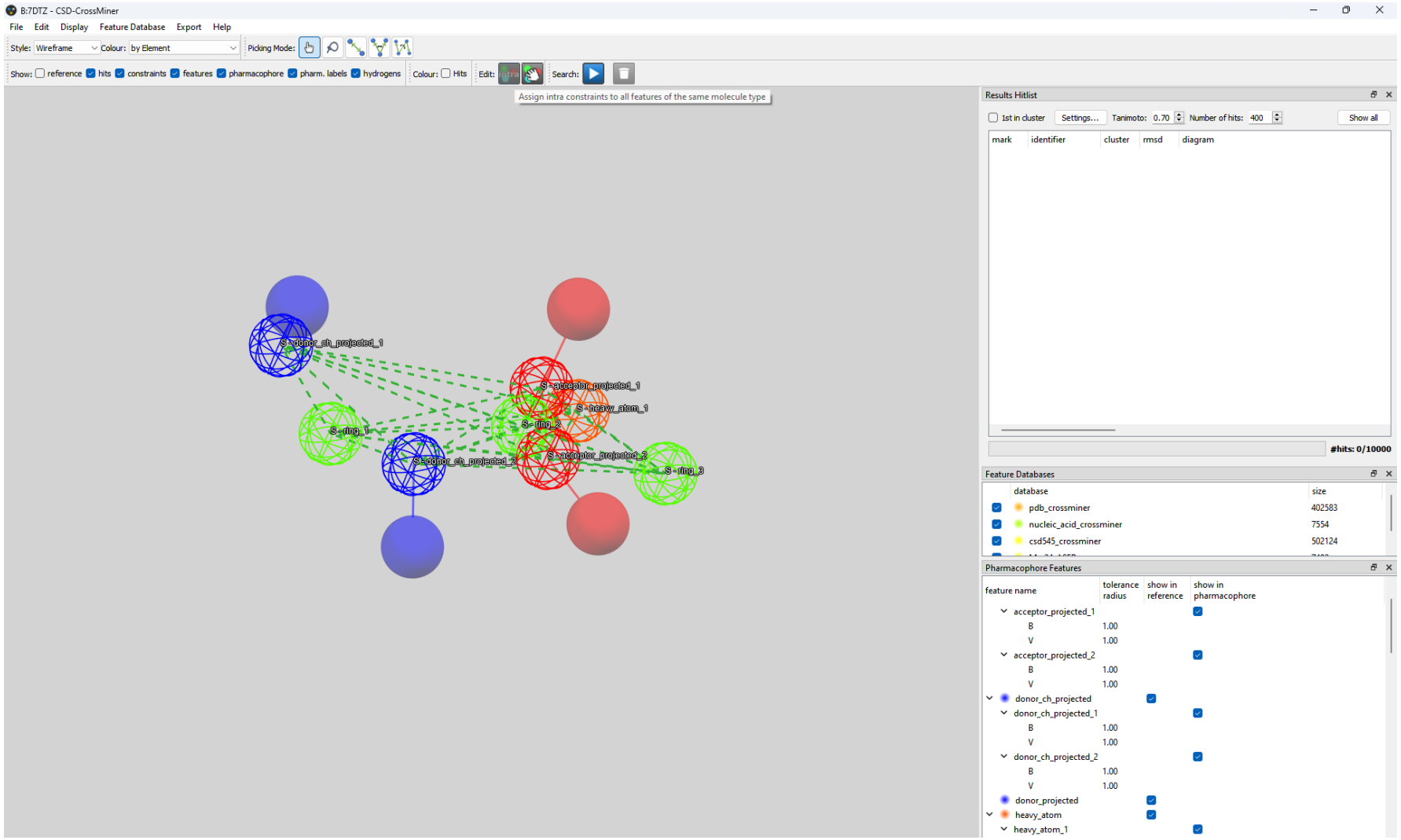
Building pharmacophore query



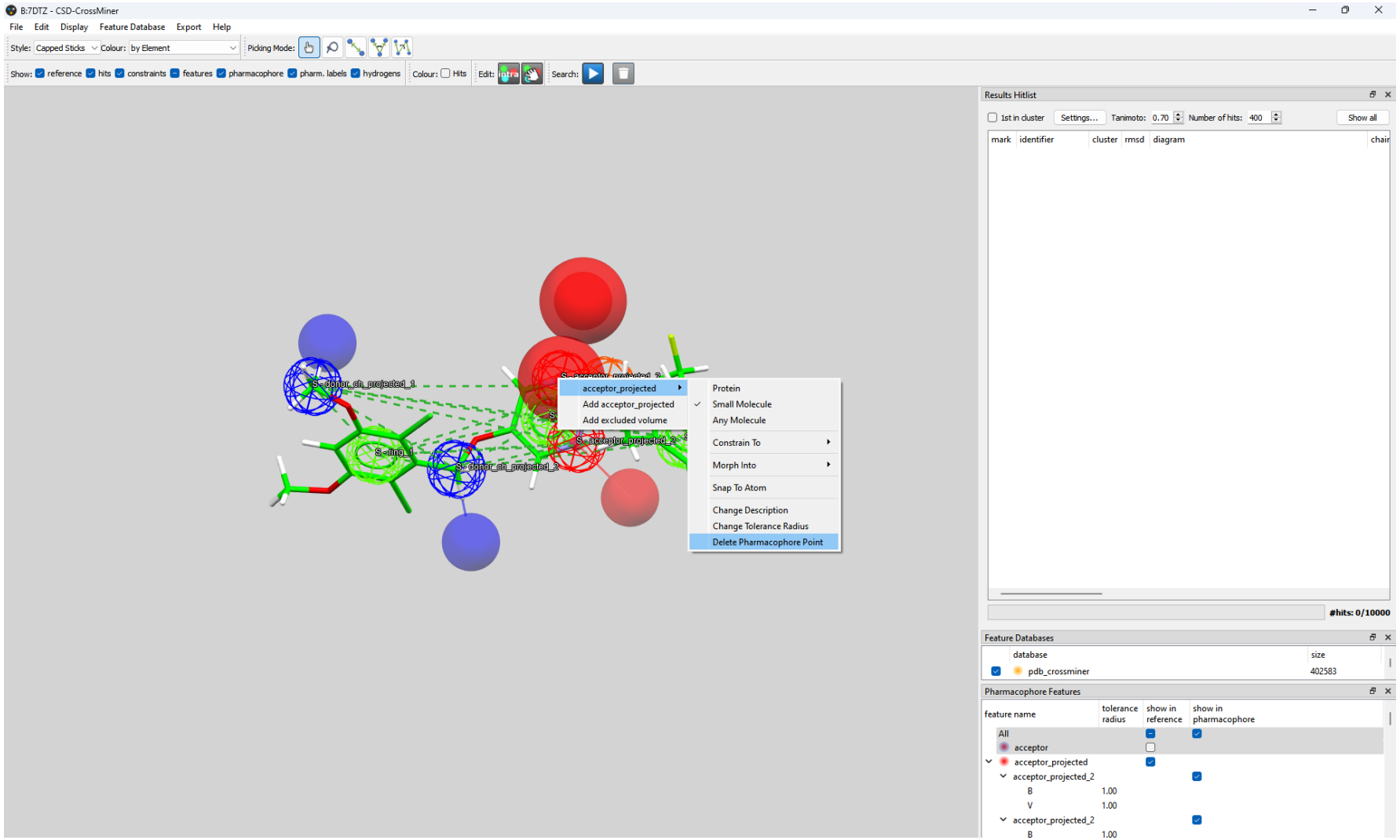
Building pharmacophore query



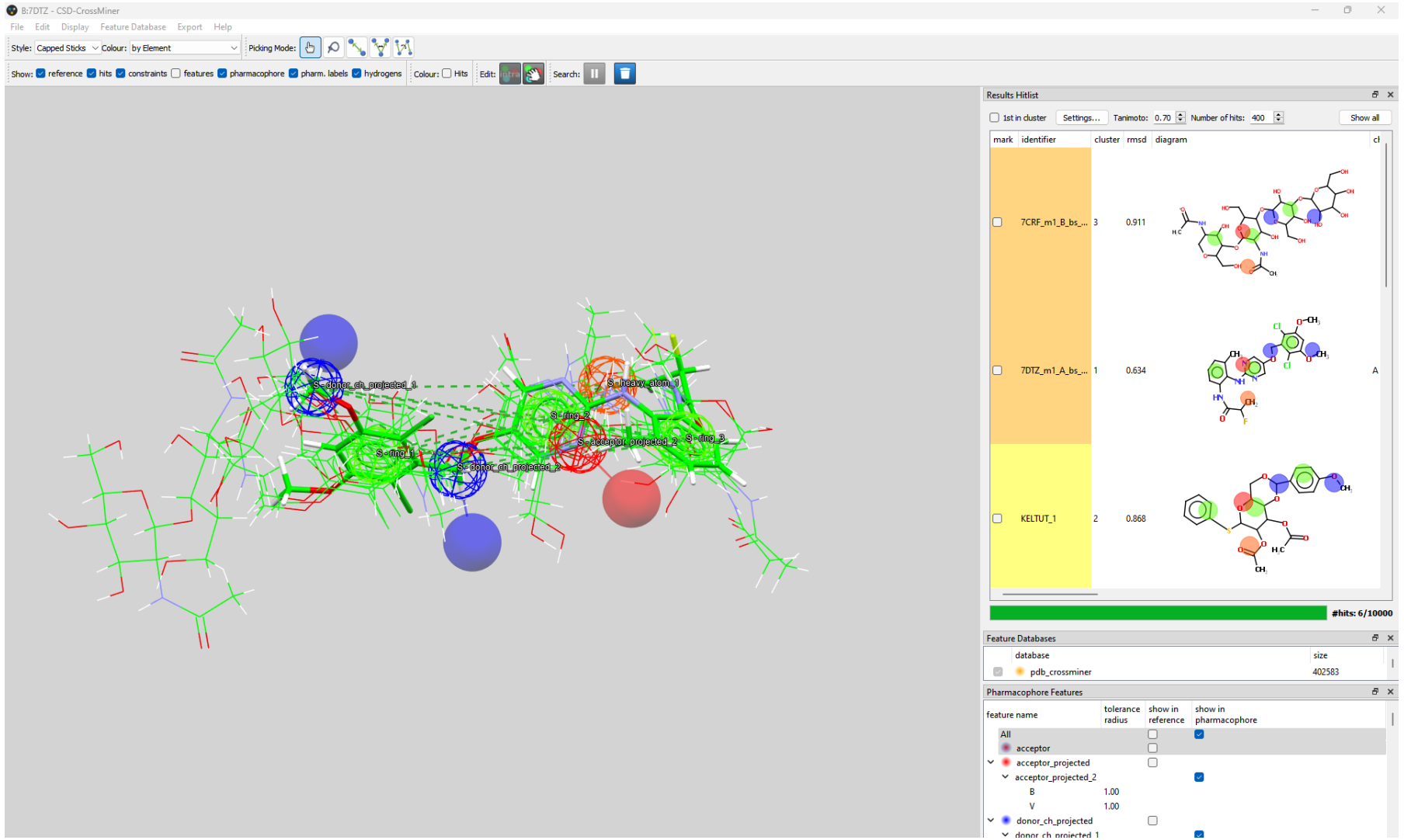
Building a pharmacophore query



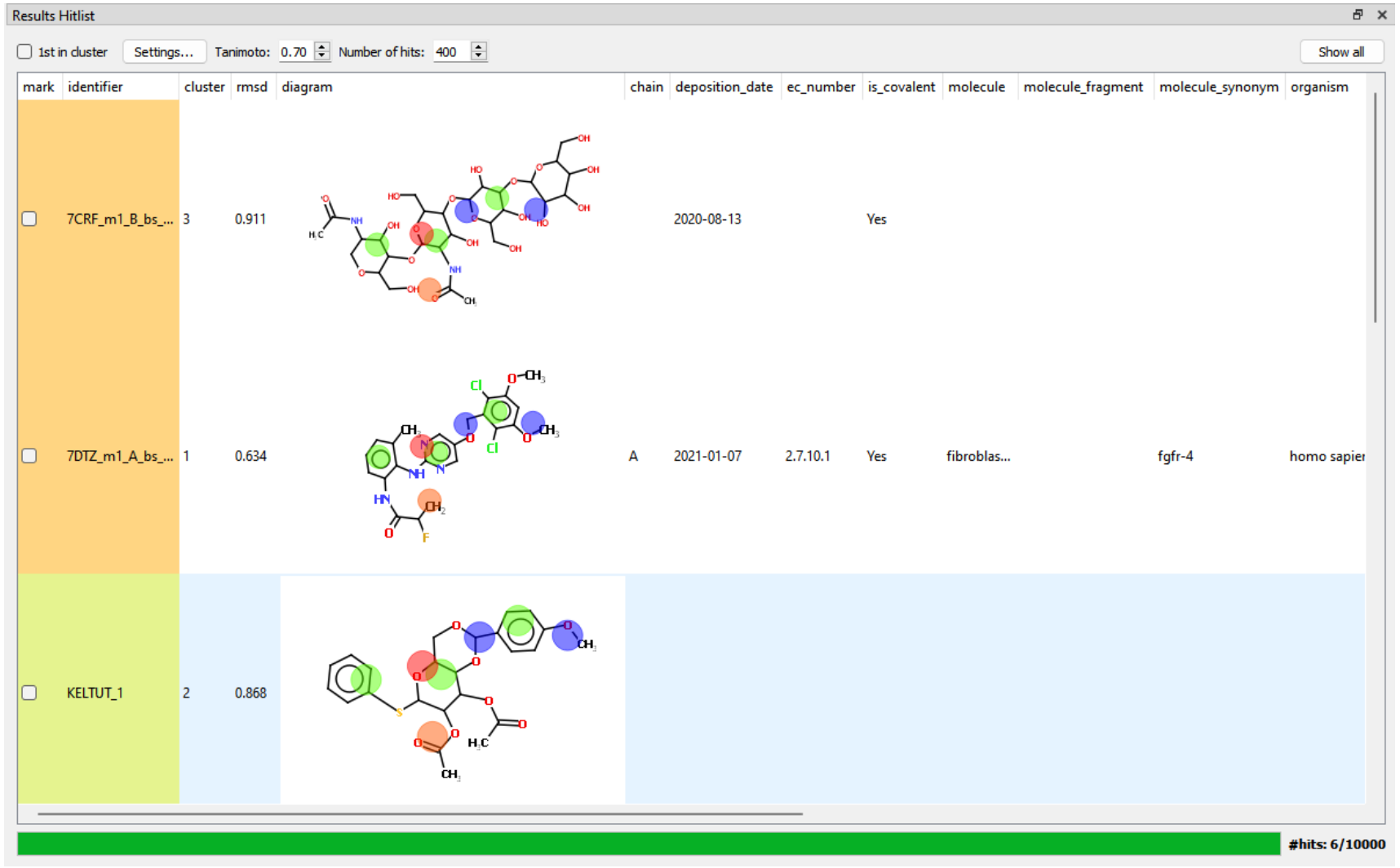
Building a pharmacophore query



Search


B:7DTZ - CSD-CrossMiner
File Edit Display Feature Database Export Help
Style: Capped Sticks Colour: by Element
Picking Mode:
Show: reference hits constraints features pharmacophore pharm. labels hydrogens
Colour: Hits
Edit:
Search:
S - donor_ch_projected_1
S - heavy_atom_1
S - ring_2
S - acceptor_projected_2
S - ring_3
S - ring_1
S - donor_ch_projected_2
Results Hitlist
1st in cluster
Settings...
Tanimoto: 0.70
Number of hits: 400
Show all
mark identifier cluster rmsd diagram cl
7CRF_m1_B_bs_... 3 0.911
7DTZ_m1_A_bs_... 1 0.634 A
KELTUT_1 2 0.868
#hits: 6/10000
Feature Databases
database size
pdb_crossminer 402583
Pharmacophore Features
feature name tolerance radius show in reference show in pharmacophore
All
acceptor
acceptor_projected
acceptor_projected_2
B 1.00
V 1.00
donor_ch_projected

Results


Results Hitlist
1st in cluster
Settings...
Tanimoto: 0.70
Number of hits: 400
Show all
mark
identifier
cluster
rmsd
diagram
chain
deposition_date
ec_number
is_covalent
molecule
molecule_fragment
molecule_synonym
organism
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2
0.868
#hits: 6/10000

Saving results