CCDC

advancing structural science

What's Up

Customer Update Webinar

19 March 2020

CCDC

advancing structural science

Today’s presenters

Sophie Bryant

Marketing Manager

Francesca Stanzione

Research and Applications Scientist

Pete Wood

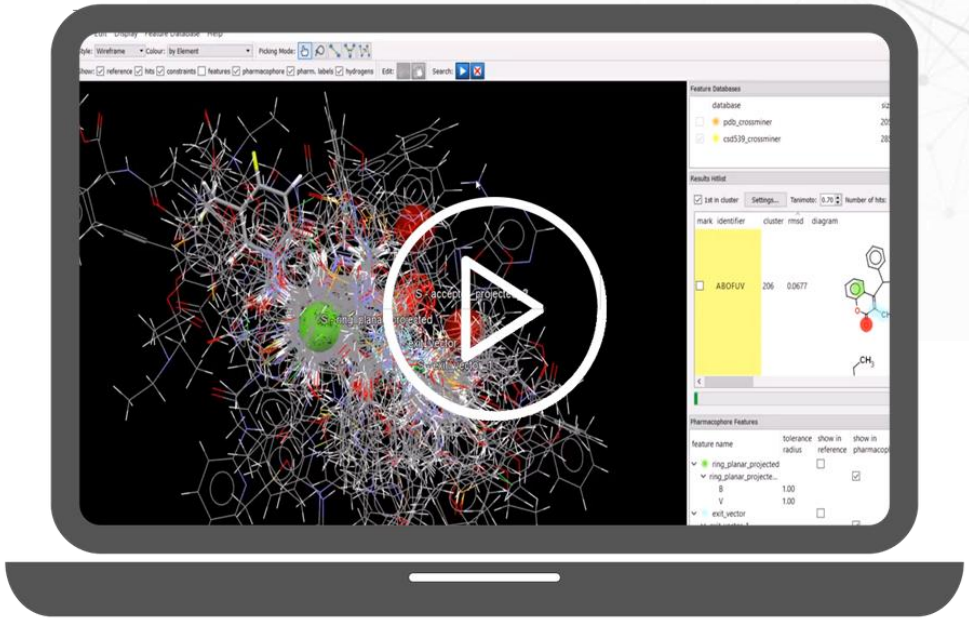
Senior Product Manager

CCDC

Overview

A regular update on what's happening with CCDC and an opportunity for your news/feedback and suggestions:

- Conferences and events
- CCDC update: 2020.0.1 CSD Release
- CSD-CrossMiner applications
- Coming up in 2020
- The floor is yours



COVID-19 – CCDC Response

- Our team is working from home
- SLA's still in place

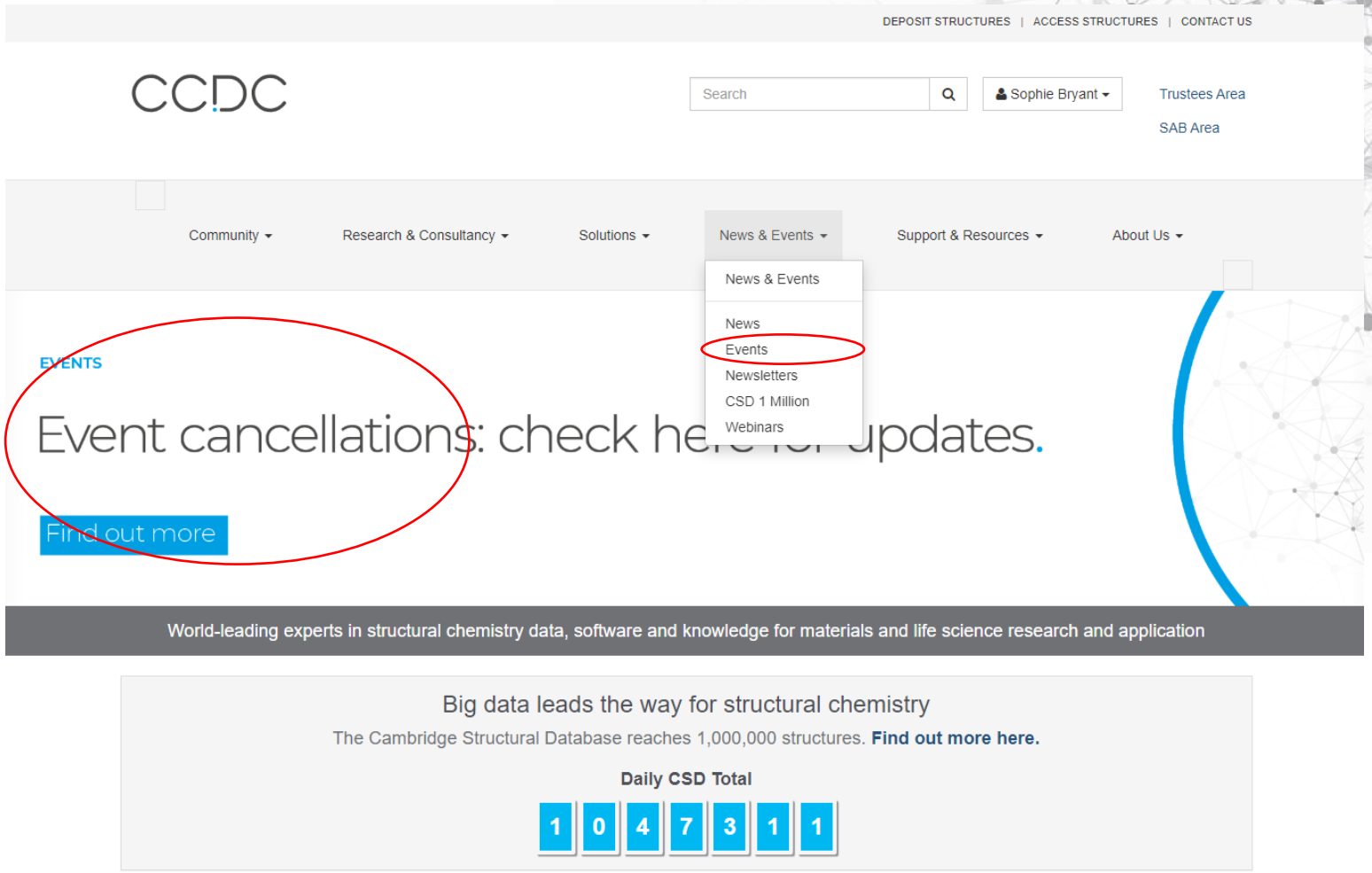
- We will support remote access where possible
- Normal service will continue to our customers

- hello@ccdc.cam.ac.uk any questions or concerns
- support@ccdc.cam.ac.uk for technical support
- admin@ccdc.cam.ac.uk for licence or account queries

CCDC

Conferences and events

- Check our website events page
- We will go virtual where possible



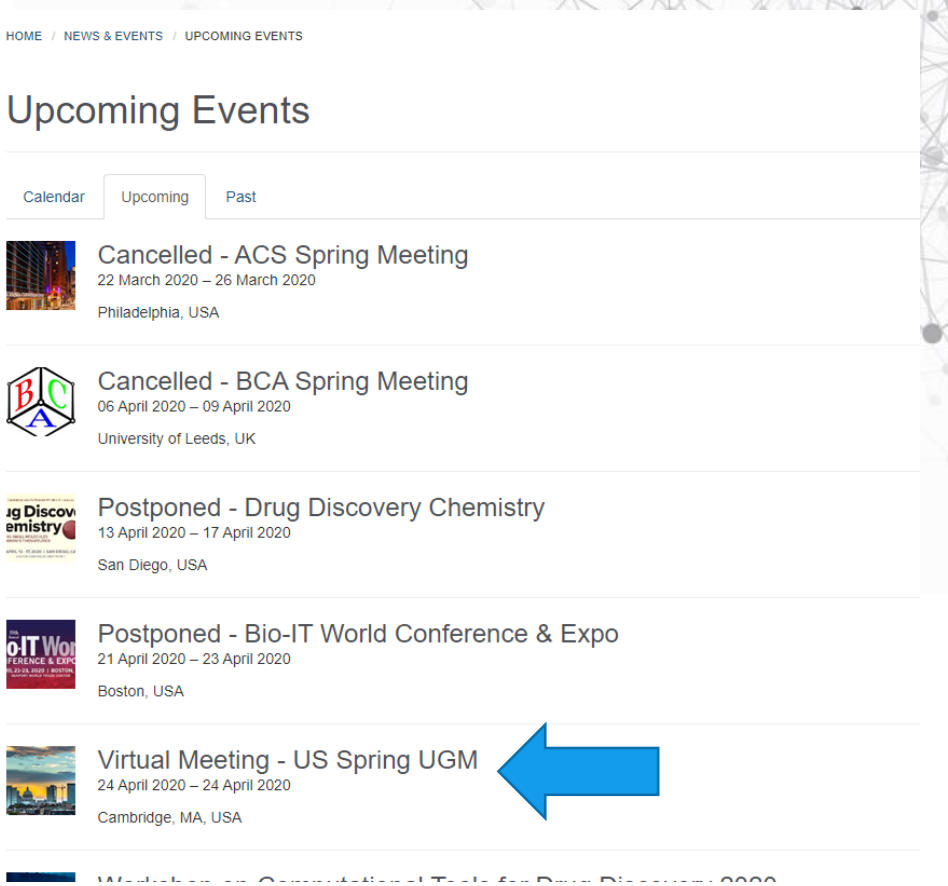
CCDC

USA User Group Meeting – now virtual

- Presentations from speakers and CCDC
- Interactive discussions
- “Handouts” and slides made available

Friday 24th April – 09:00 – 13:00 EST

Register online



2020.0.1 CSD Release

What has changed?

Pete Wood

Senior Product Manager

CCDC

2020.0.1 CSD Release

- In December 2019 we launched the 2020.0 CSD Release which incorporated some major new features including:
  - **Ultra-Large Docking** in GOLD, **H-Bond Coordination Quick View** in Mercury, **Py3 CSD Python API**, upgraded **Product Telemetry** and a new **Licensing** system
- We always monitor feedback from users, both in person and via e-mail, regarding our software & particularly around major releases
- If there are reports of significant issues we will always consider when and how best to handle them, sometimes that might required fixes ahead of a major release
- In this case we identified some issues which we have prioritised and fixed straight away via the 2020.0.1 CSD Release

https://www.ccdc.cam.ac.uk/solutions/whats-new/

CCDC

2020.0.1 CSD Release

- Smaller scale improvements for robustness, stability and smoother third-party integrations, including:
  - Fixed an issue with command-line Mogul access which was affecting third-party integrations with programs such as GRADE, MOE and Maestro among others, as well as internal workflows
  - Fixed a graphics issue affecting some users on start-up of Mercury
  - Fixed an issue in ConQuest with finding CSD databases correctly
  - Fixed an issue in Mercury regarding the ability to control preferred orientation in powder pattern simulation
  - Fixed an issue in DASH observed when generating Z-matrices

https://www.ccdc.cam.ac.uk/solutions/whats-new/

CCDC

CSD-CrossMiner key applications

Scaffold hopping - detecting Cross-reactivity – pocket detection and pocket filling

Francesca Stanzione

Research and Applications Scientist

CCDC

How to access to CSD-CrossMiner

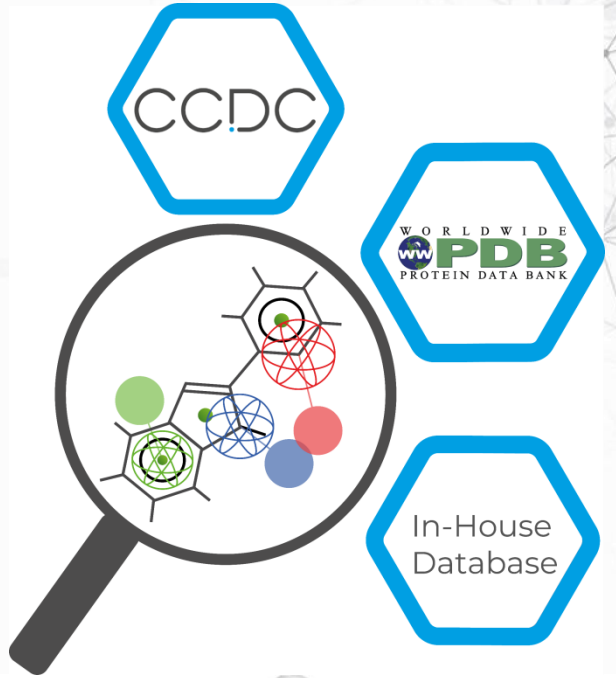
- CSD-CrossMiner is part of the CSD-Discovery Suite
- It comes with a stand-alone installer!

- Access the installer;
  - Most accounts: https://www.ccdc.cam.ac.uk/support-and-resources/csdsdownloads/
  - Research Partners: https://www.ccdc.cam.ac.uk/support-and-resources/downloads/ *(must be logged in to website)*

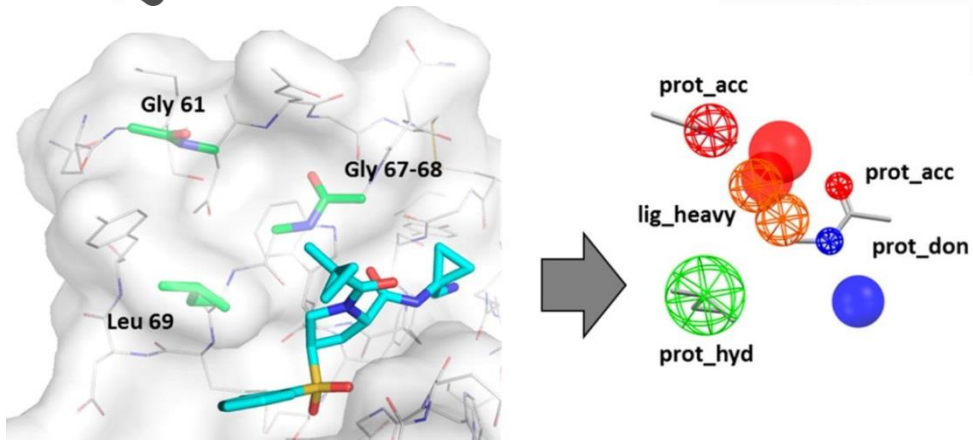
CCDC

CSD-CrossMiner Overview

- Pharmacophore-based searches of structural databases (CSD & PDB & any in-house databases, simultaneously)
  - From IUPAC: “an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions
  - Wikipedia: “abstract description of molecular features”
- Modify a hypothesis/results on the fly: interactive tool
- Annotated for easy filtering of hits



Roche

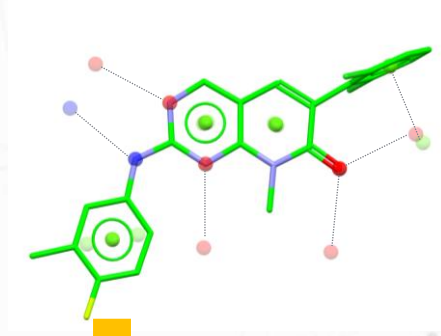


Korb *et al,. J. Med. Chem.* **2016,** 59, 4257-4266. DOI: 10.1021/acs.jmedchem.5b01756

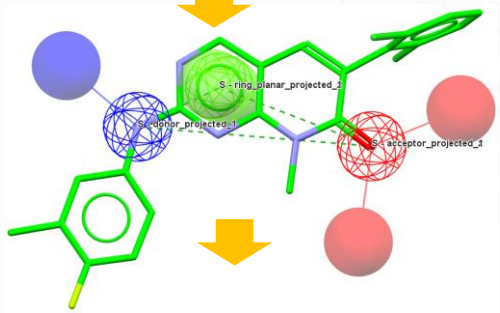
CCDC

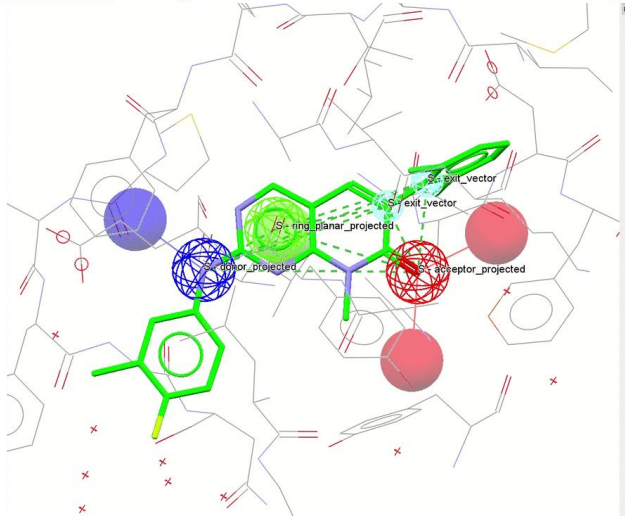
How to build a pharmacophore query

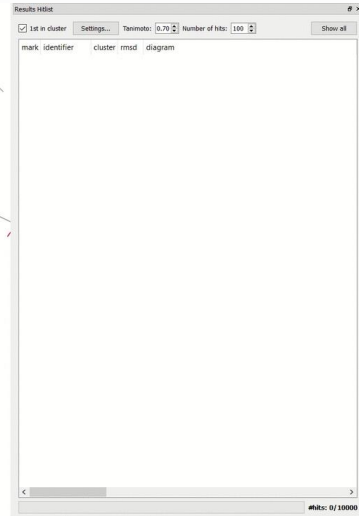
- Molecular structures are annotated with (customisable) features
  - Based on SMARTS patterns
  - Stored in feature database
- Pharmacophore query is based on tolerance spheres
  - Sphere radii reflect uncertainty in the position of the features
  - Large sphere → less strict
- Pharmacophore points can be:
  - Single point
  - Directional (two points)



donor
acceptor
planar ring
hydrophobe



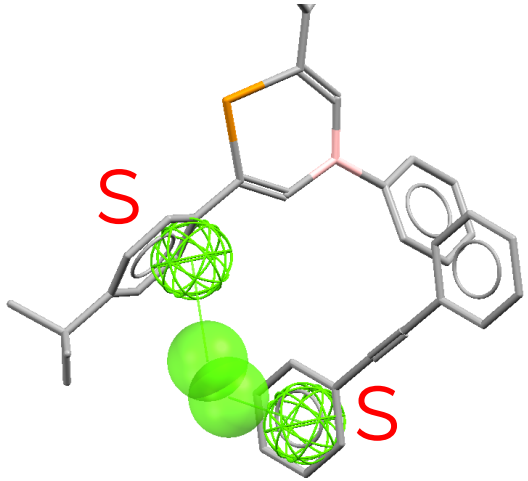


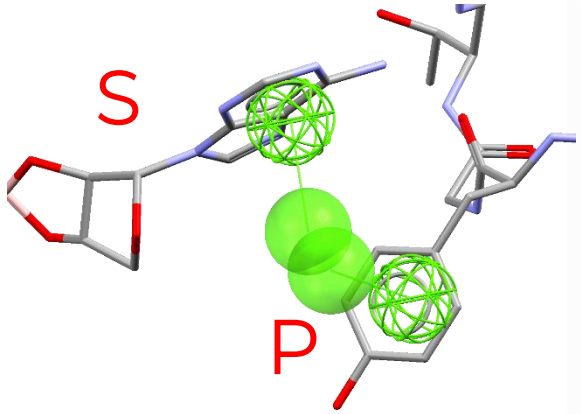


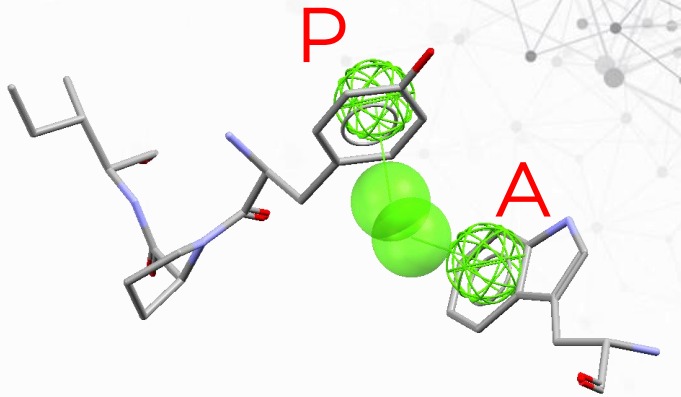
Customising a pharmacophore query

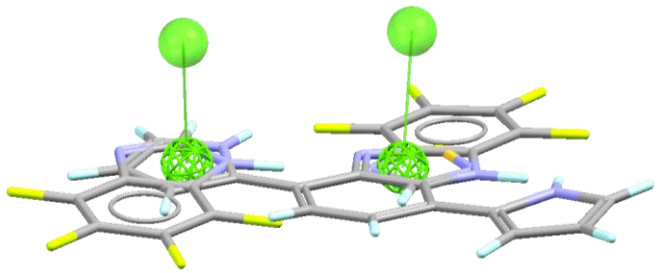
Molecule class & constraints

Protein (P)
Small molecule (S)
Any molecule (A)

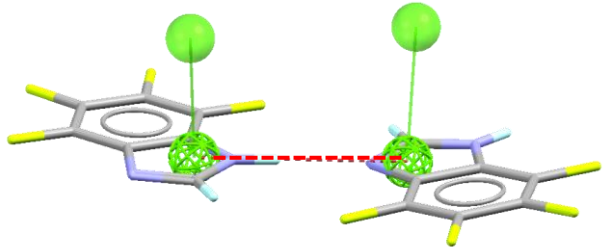




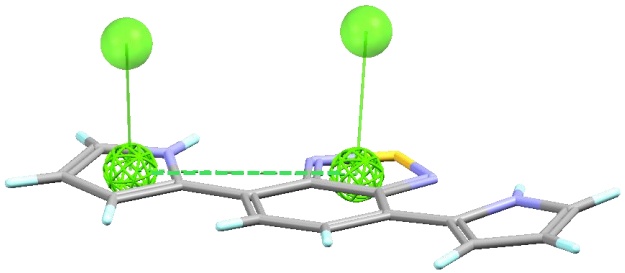




No constraint



Inter-molecular constraint



Intra-molecular constraint

CCDC

CSD-CrossMiner Applications

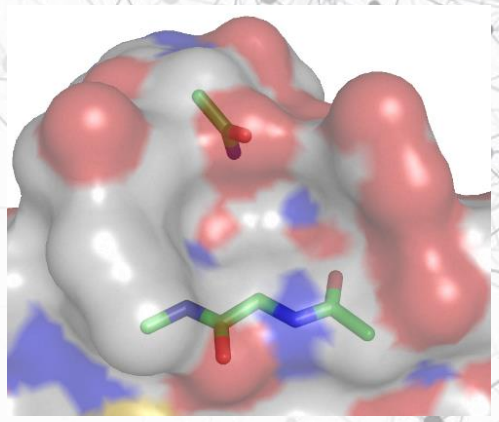
- Determine common protein binding sites in PDB structures
- Determine structural motifs that bind in similar environments
- Inform cross-pharmacology between protein targets
- Generate new ideas:
  - Design novel motifs that mimic extablished ligands

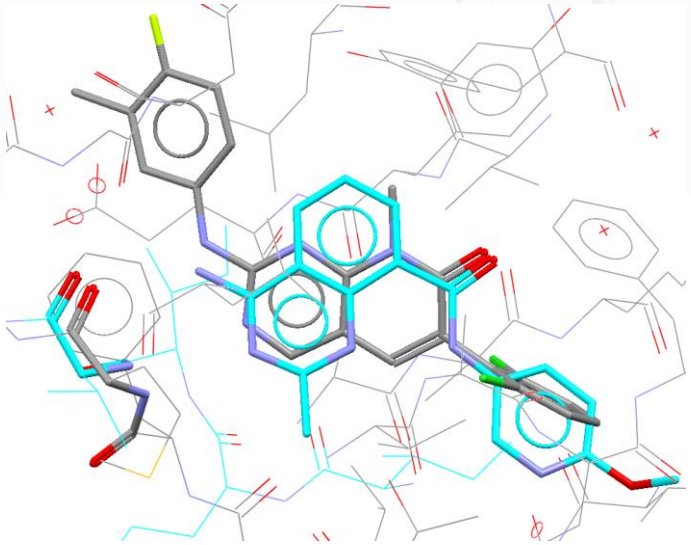
    ➔ improve molecular properties; solve patent issue
  - Scaffold-hopping: retrieve a diversity of ligand topologies that can be used as scaffolds

    ➔ quickly advance a project with known ligands; optimise leads

  - Growing into other regions of a binding site

    ➔ improve selectivity; improve bioactivity; reduce cross-reactivity

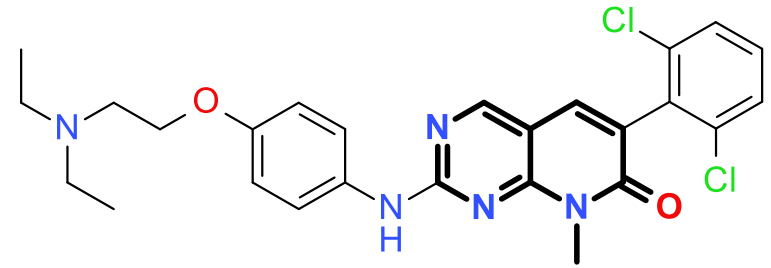




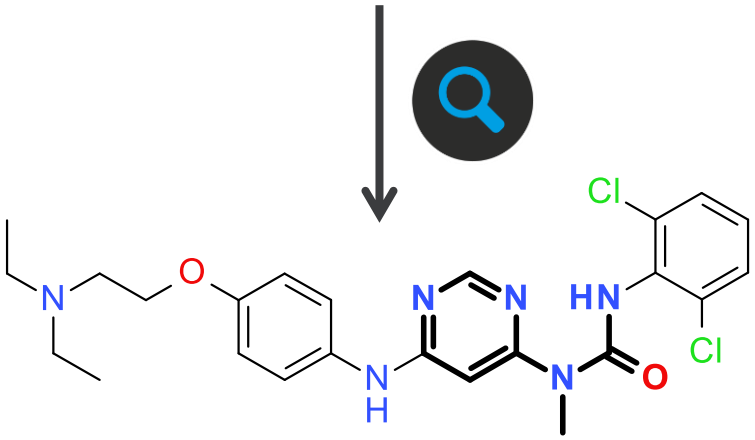
CCDC

Scaffold-hopping

Kinase inhibitor scaffold-hopping based on ligand features



PD166285 tyr-kinase inhibitor



Prototype compound 1

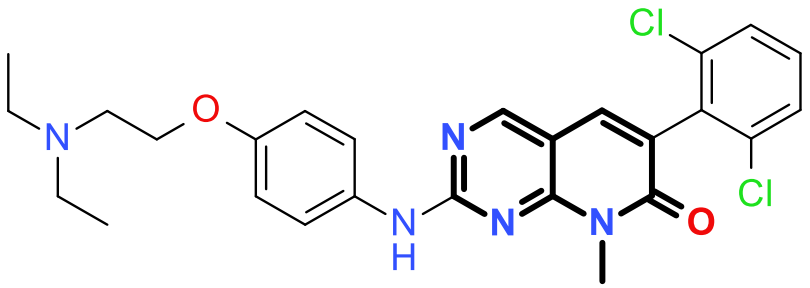
IC_{50} < 1 uM against different kinases

c-Src	0.066
EGF-R	0.38
c-Abl	0.25
FGFR-1	0.57
c-Kit	0.93
KDR	0.96
Tie-2	0.30
p38	0.35
EphB4	0.43

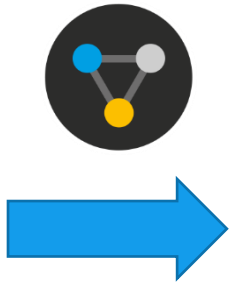
Furet *et al., Bioorg. Med. Chem. Lett.* **2008,** 18, 897-900. DOI: 10.1016/j.bmcl.2007.12.041

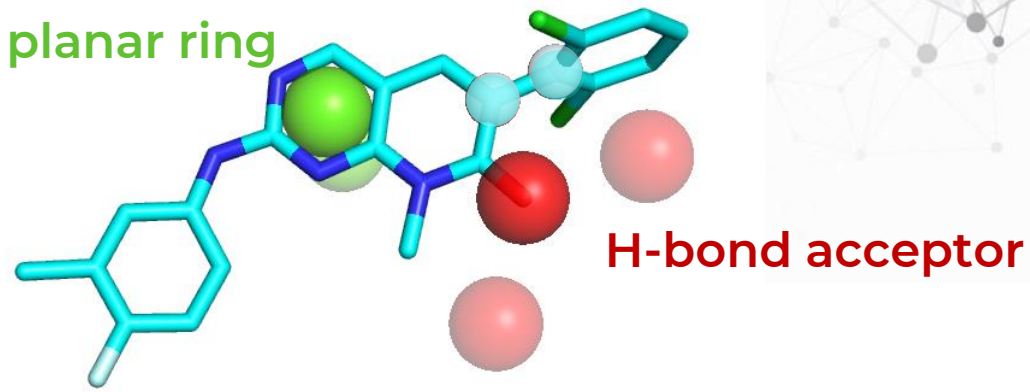
Scaffold-hopping

Kinase inhibitor scaffold-hopping based on ligand features



PD166285 tyr-kinase inhibitor





PDB: 2hzi
(Abl kinase)

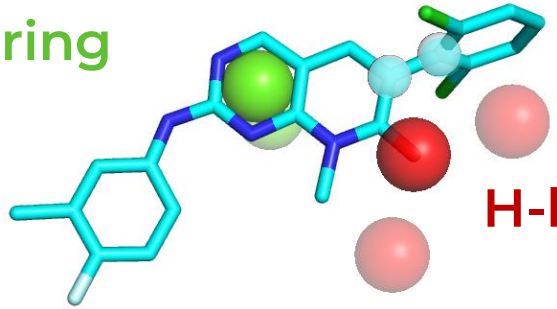
Furet *et al., Bioorg. Med. Chem. Lett.* **2008,** 18, 897-900. DOI: 10.1016/j.bmcl.2007.12.041

Scaffold-hopping

Kinase inhibitor scaffold-hopping based on ligand features

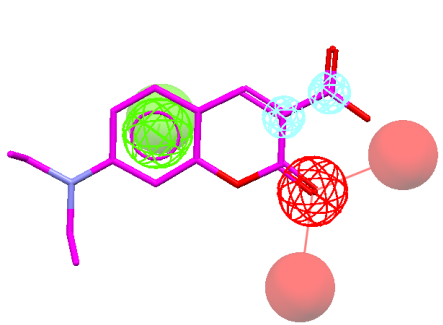
exit vector

planar ring

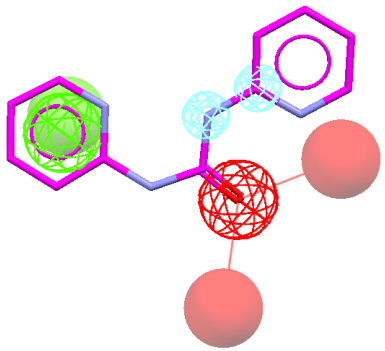


H-bond acceptor

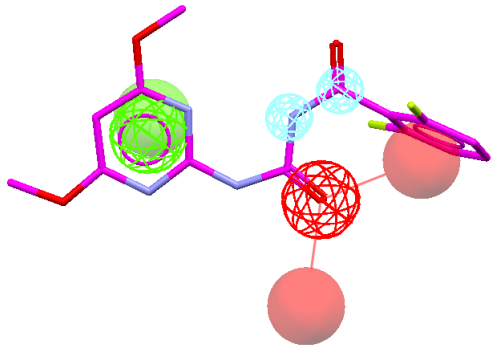
PDB: 2hzi
(Abl kinase)



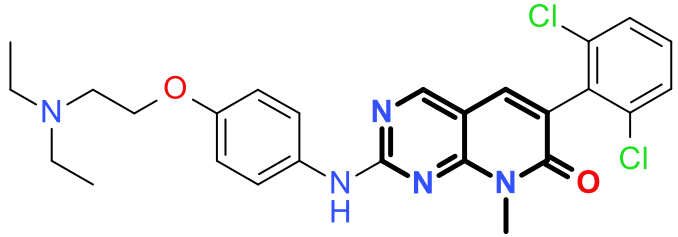
IDUQOO



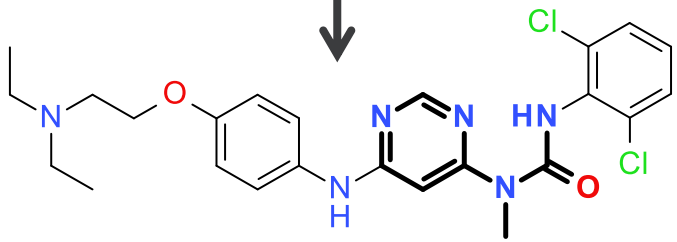
ALOJIW



IFAFEB



PD166285 tyr-kinase inhibitor

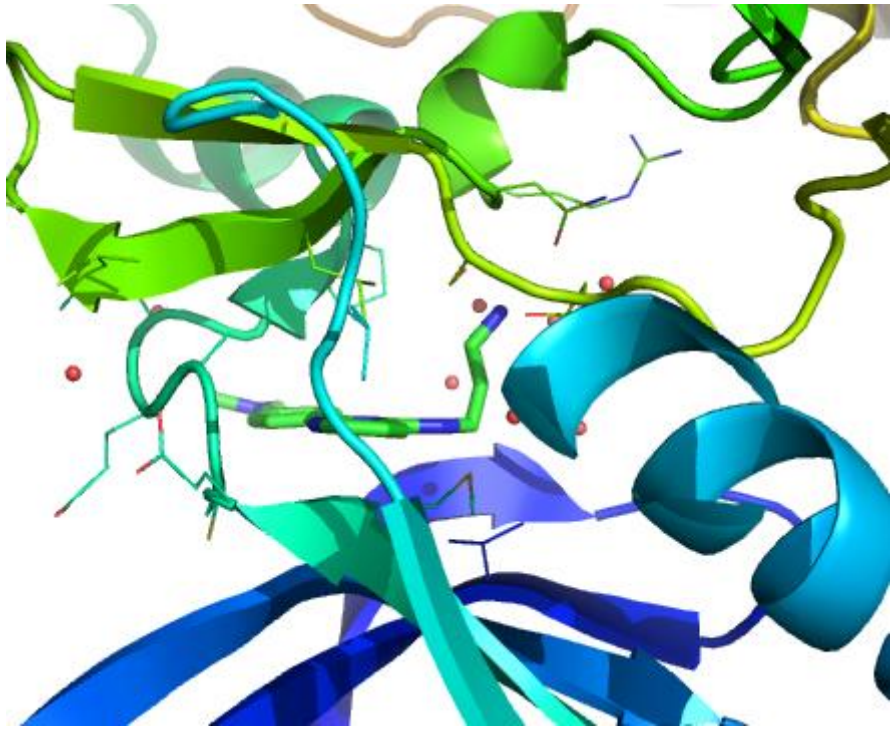


Prototype compound 1

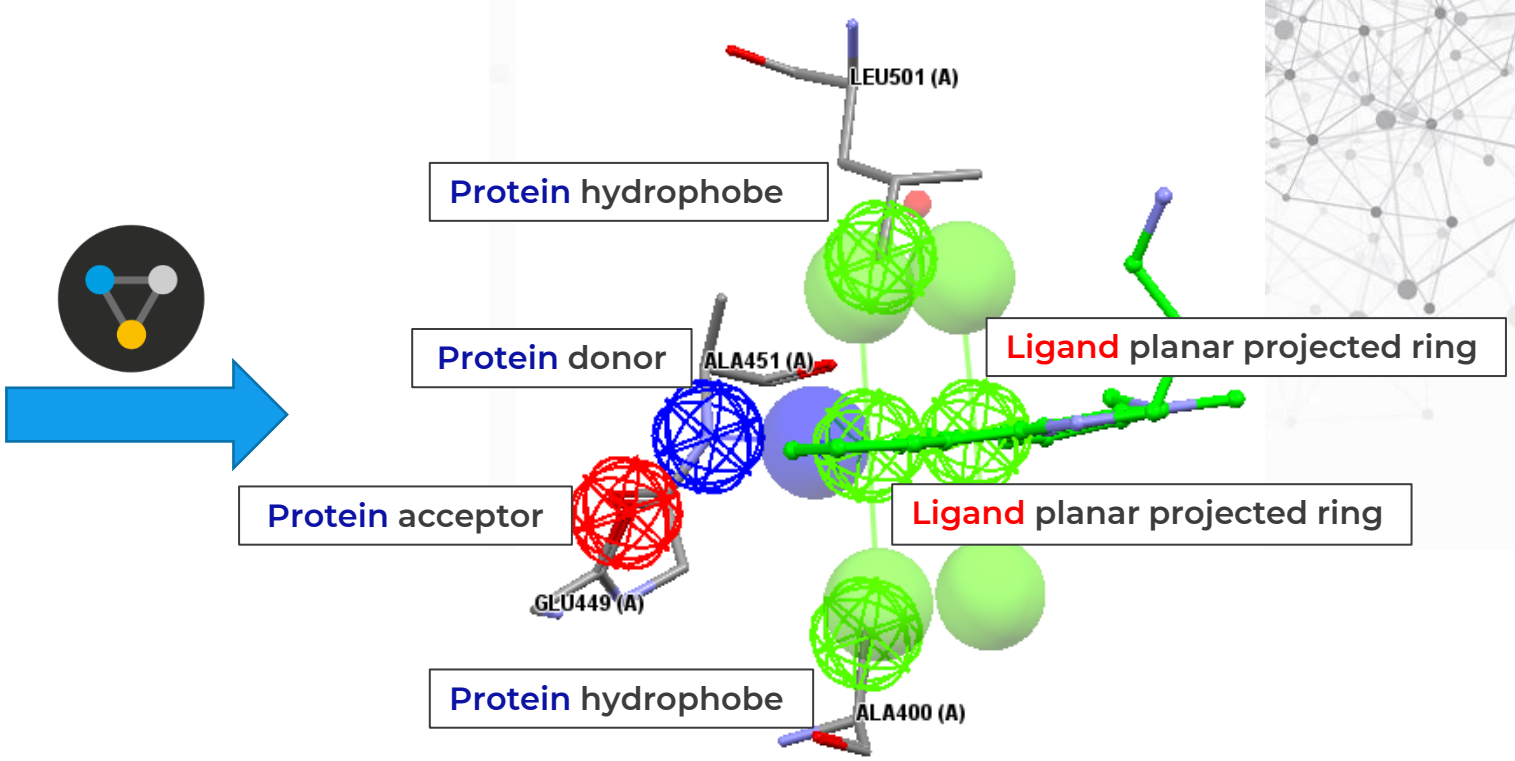
Furet *et al., Bioorg. Med. Chem. Lett.* **2008,** 18, 897-900. DOI: 10.1016/j.bmcl.2007.12.041

Cross Reactivity

Syk inhibitor (Naphthyridine) bound to Syk kinase domain

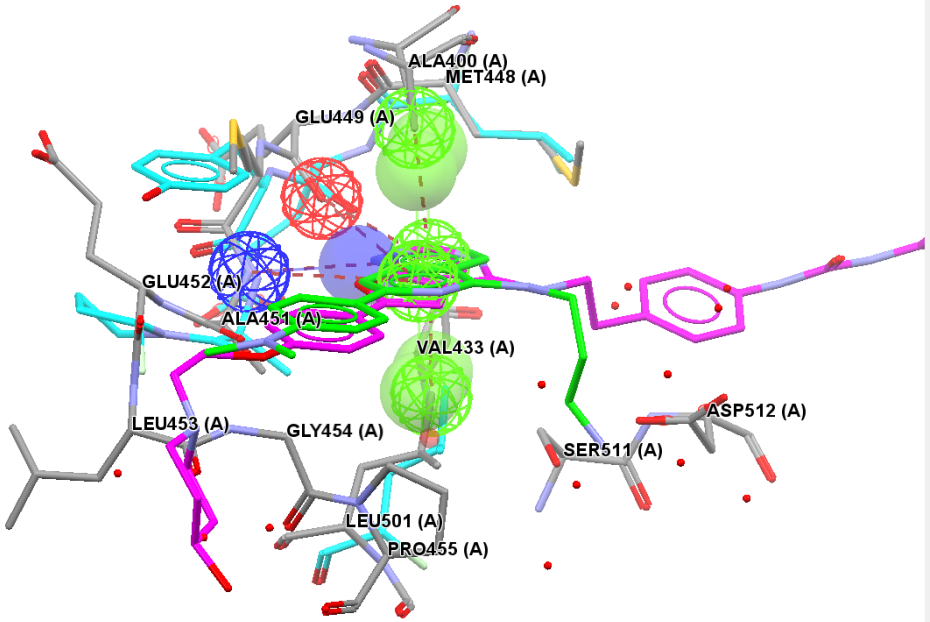


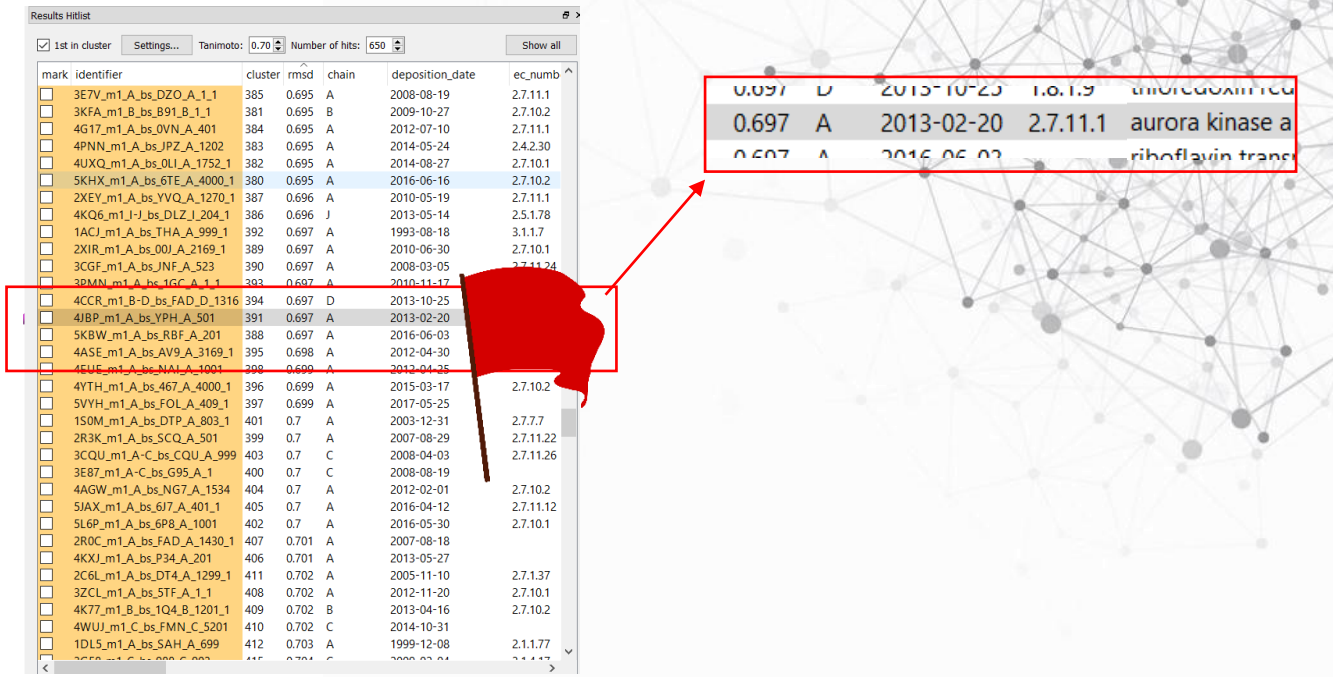
PDB: 5cxz



Thoma et al., *Bioorg. Med. Chem. Lett.* **2015**, *25 (20)*, 4642-4647. DOI: 10.1016/j.bmcl.2015.08.037

Cross Reactivity





Pharmacophore that describes binding to 5CXZ also describes binding to 4JBP (EC code 2.7.11.1 – An Aurora Kinase)

ELSEVIER

Bioorganic & Medicinal Chemistry Letters

Volume 25, Issue 20, 15 October 2015, Pages 4642-4647

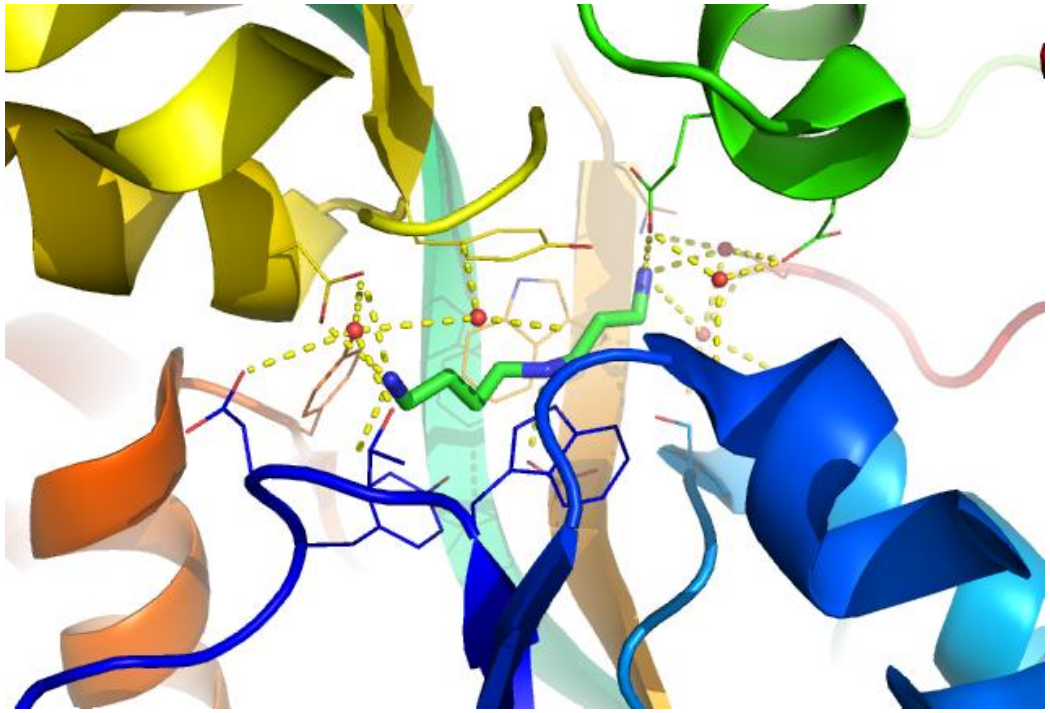
Orally bioavailable Syk inhibitors with activity in a rat PK/PD model

Gebhard Thoma [a], Siem Veenstra [a], Ross Strang [a], Joachim Blanz [b], Eric Vangrevelinghe [a], Jörg Berghausen [c], Christian C. Lee [e], Hans-Günter Zerwes [d]

Abstract

Design and optimization of benzo- and pyrido-thiazoles/isothiazoles are reported leading to the discovery of the potent, orally bioavailable Syk inhibitor **5**, which was found to be active in a rat PK/PD model. Compound **5** showed acceptable overall kinase selectivity. However, in addition to Syk it also inhibited Aurora kinase in enzymatic and cellular settings leading to findings in the micronucleus assay. As a consequence, compound **5** was not further pursued.

Pocket Detection & Pocket Filling



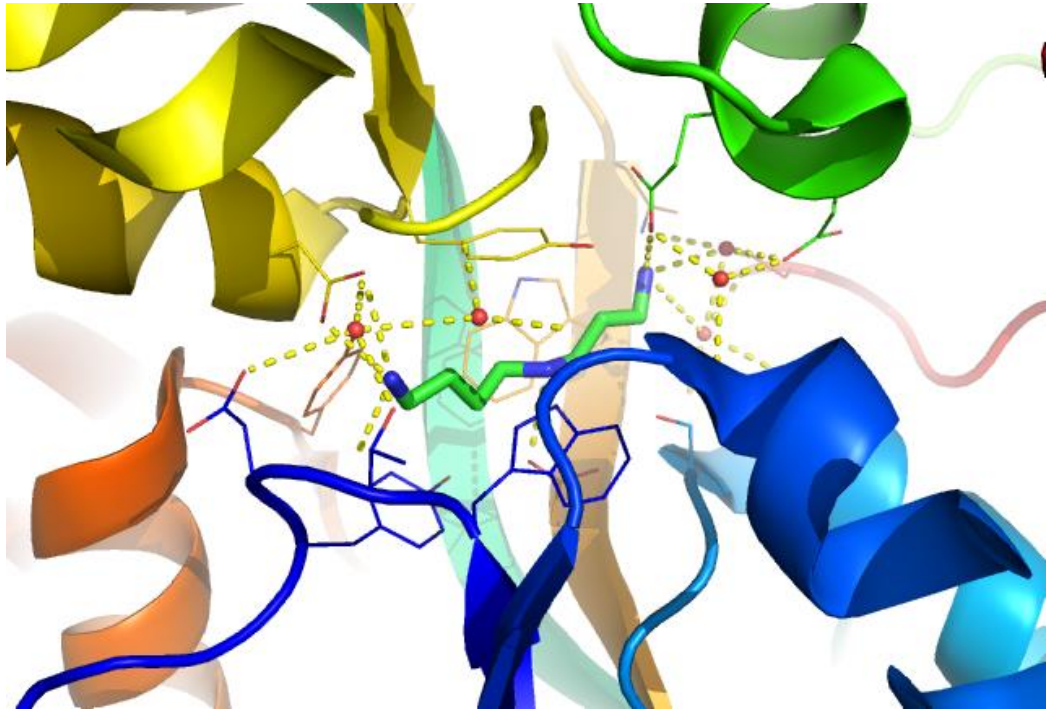
PDB: 3ttn

- Starting from the crystallographic structure of polyamine receptor of *Pseudomonas aeruginosa* in complex with spermidine:
  - Which protein structures feature aromatic cages?
  - Which ligand interact with such aromatic cages?
  - Which proteins interact with the same chemical fragment?

Wu *et al.*, *J. Mol. Biol.* **2012**, 416, 697-712. DOI: 10.1016/j.jmb.2012.01.010.

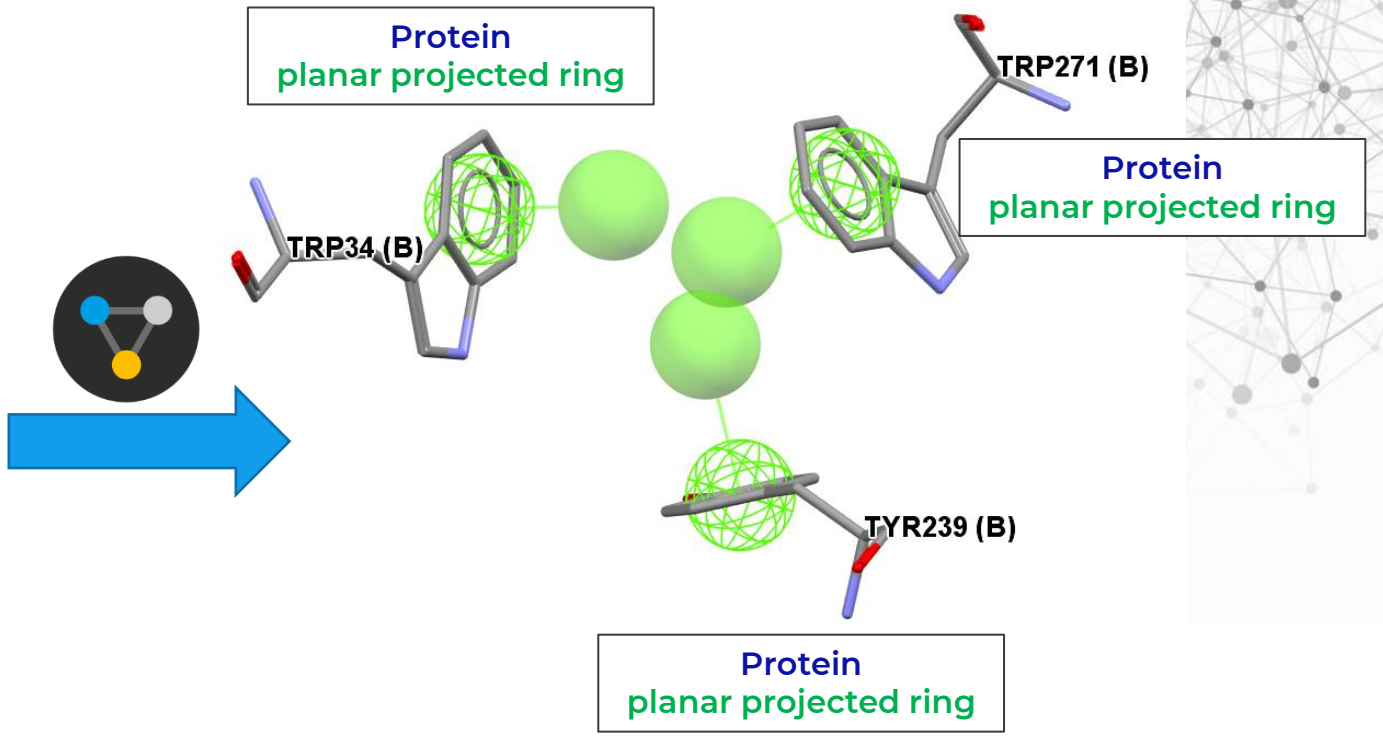
CCDC

Pocket Detection & Pocket Filling



PDB: 3ttn

Pseudomonas aeruginosa in complex with spermidine

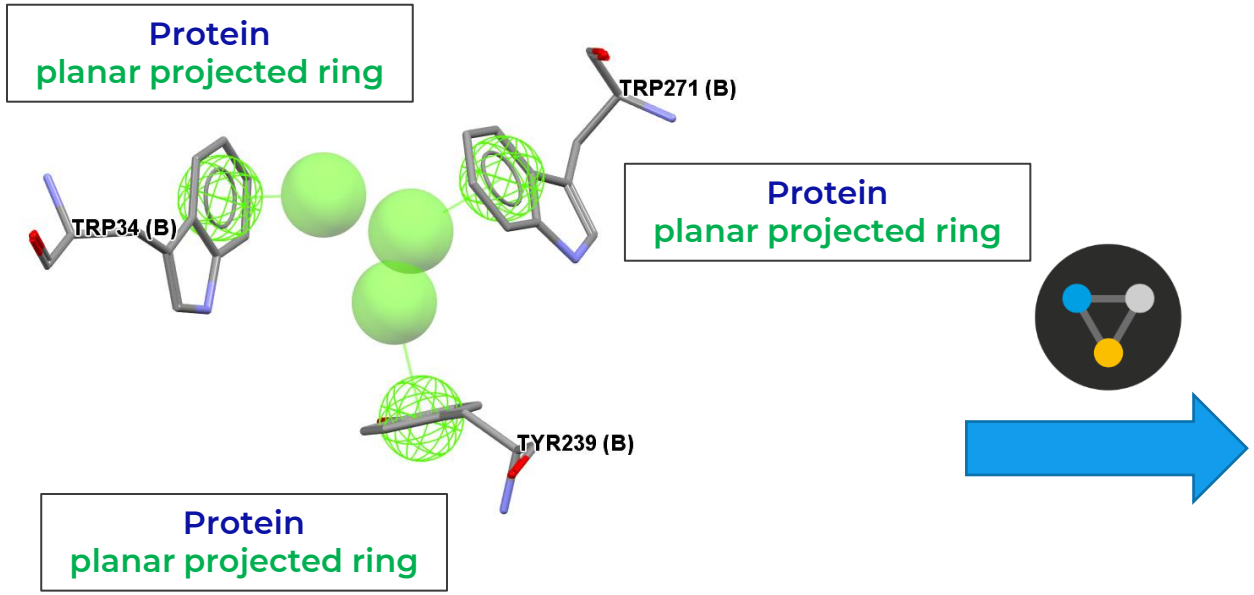


Which protein structures feature such a hydrophobic space in their binding pocket?

Wu *et al.*, *J. Mol. Biol.* **2012**, 416, 697-712. DOI: 10.1016/j.jmb.2012.01.010.

CCDC

Aromatic Cages in Proteins



PDB: 3ttn

- Aromatic cages occur in a large number of functional proteins

Results Hitlist

1st in cluster | Settings... | Tanimoto: 0.70 | Number of hits: 100 | Show all

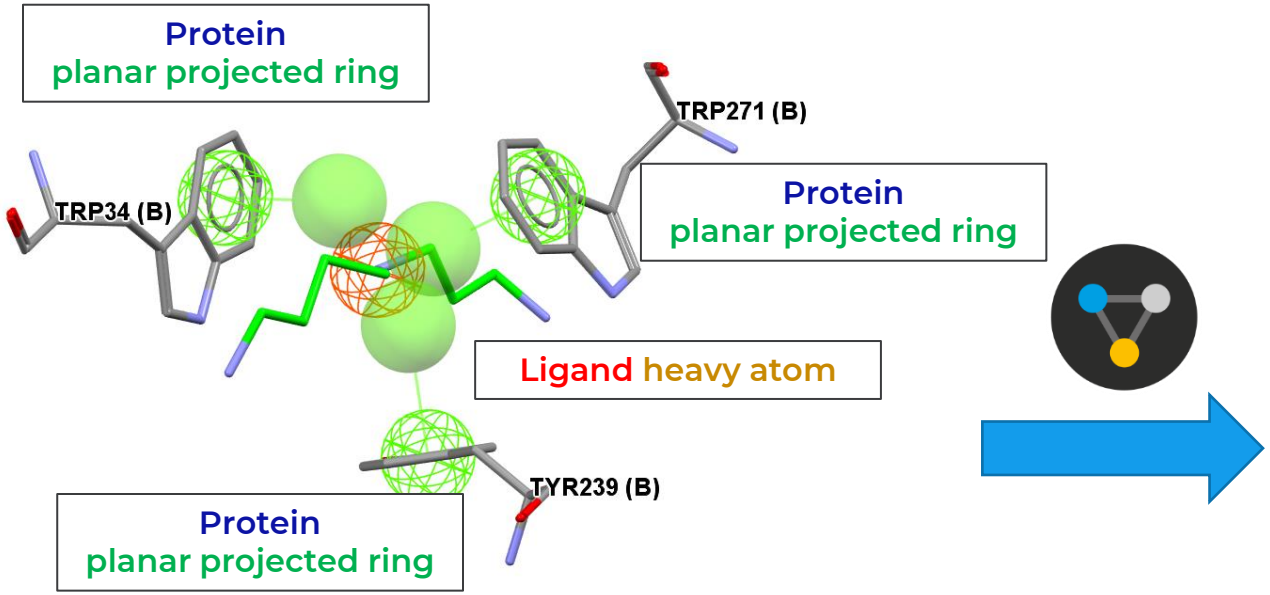
mark	identifier	cluster	rmsd	chain	molecule	deposition_d
	3TTN_m1_B_bs_SPD_B_363_1	1	5.75...	B	polyamine transport p...	2011-09-15
	5YJ1_m1_G-Y_bs_6EL_G_501_1	2	0.289	G	protein cereblon	2017-10-06
	6CQW_m1_A_bs_HI6_A_607_2	3	0.594	A	acetylcholinesterase	2018-03-16
	5H25_m1_B_bs_LQH_B_501	4	0.6	B	polycomb protein eed	2016-10-14
	6G2B_m1_A_bs_EH8_A_401_1	5	0.632	A	histone-lysine n-meth...	2018-03-22
	5U62_m1_B_bs_7WD_B_501	6	0.637	B	polycomb protein eed	2016-12-07
	3Q9E_m1_B-F_bs_SP5_F_406	7	0.641	F	acetylpolyamine amid...	2011-01-07
	5YJ8_m1_A_bs_8W9_A_701_1	8	0.651	A	tudor domain-contain...	2017-10-09
	4YHY_m1_H-L_bs_M3L_H_301...	9	0.653	H	fab heavy chain	2015-02-27
	6J7L_m1_A_bs_TYD_A_401_2	10	0.655	A	pseudomonas aerugin...	2019-01-18
	4QQU_m1_A_bs_39S_A_805_1	11	0.658	A	5-methyltetrahydropt...	2014-06-29
	5OH8_m1_B_bs_ROL_B_202_2...	12	0.691	B	cereblon isoform 4	2017-07-14
	5DC7_m1_A-B_bs_ACE_D_1_2...	13	0.695	D	fluor-de-lys tetrapepti...	2015-08-23
	5H14_m1_B_bs_LQB_B_502_2	14	0.704	B	polycomb protein eed	2016-10-08
	2BB6_m1_D_bs_B12_D_0_1	15	0.705	D	transcobalamin ii	2005-10-17
	1RTW_m1_A_bs_MP5_A_1213	16	0.707	A	transcriptional activat...	2003-12-10
	4RCM_m1_B_bs_6MZ_E_3_2_1	17	0.713	E	rna (5'-r(*up*g)-d(*(6...	2014-09-16
	5XMY_m1_A-C_bs_ALA_P_1_1	18	0.715	P	histone peptide h3(1-...	2017-05-16
	3OMG_m1_B_bs_ARG_D_3_1	19	0.723	D	dimethylated arginine...	2010-08-26
	3ZLV_m1_B_bs_HI6_B_1543_2_1	20	0.73	B	acetylcholinesterase	2013-02-04
	6MR5_m1_A-B_bs_W45_A_804	21	0.734	A	hdac6 protein	2018-10-11

#hits: 1633/10000

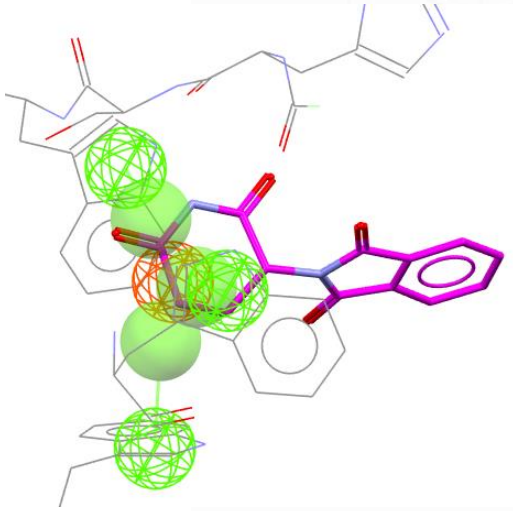
Which ligand motifs interact with this environment?.

CCDC

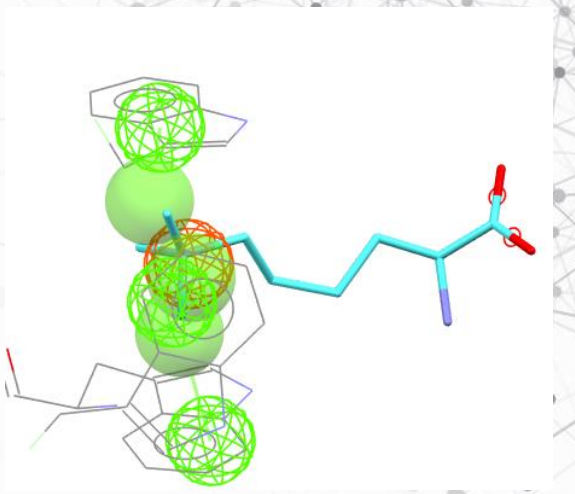
Pocket Filling



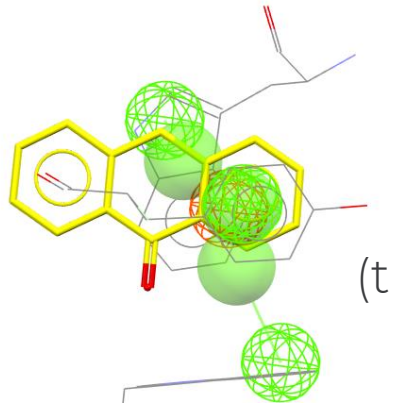
PDB: 3ttn



PDB: 5yj1
(thalidomide)



PDB: 4yhy
(trimethylated Lys)



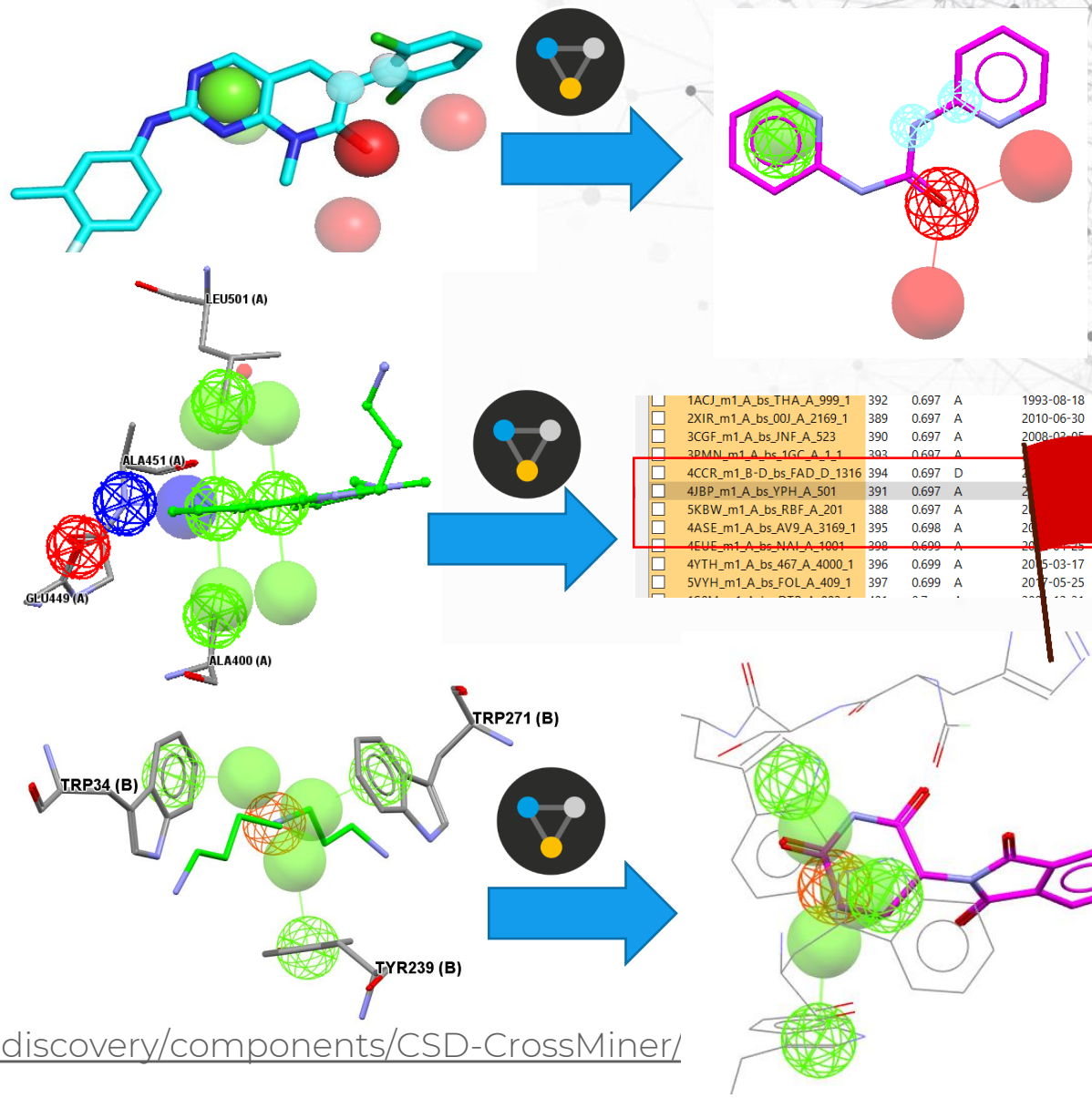
PDB: 2bjm
(tricyclic structure)

- Many of the ligands interacting with such aromatic cages are composed of polyamine
- Very different ligand chemistries that interact with aromatic cages such as a thalidomide ring, a tricyclic structure.

CCDC

Conclusion

- Scaffold-hopping
- Cross-reactivity detection
- Pocket similarities and filling



More here: https://www.ccdc.cam.ac.uk/solutions/csd-discovery/components/CSD-CrossMiner/

CCDC key projects coming up in 2020

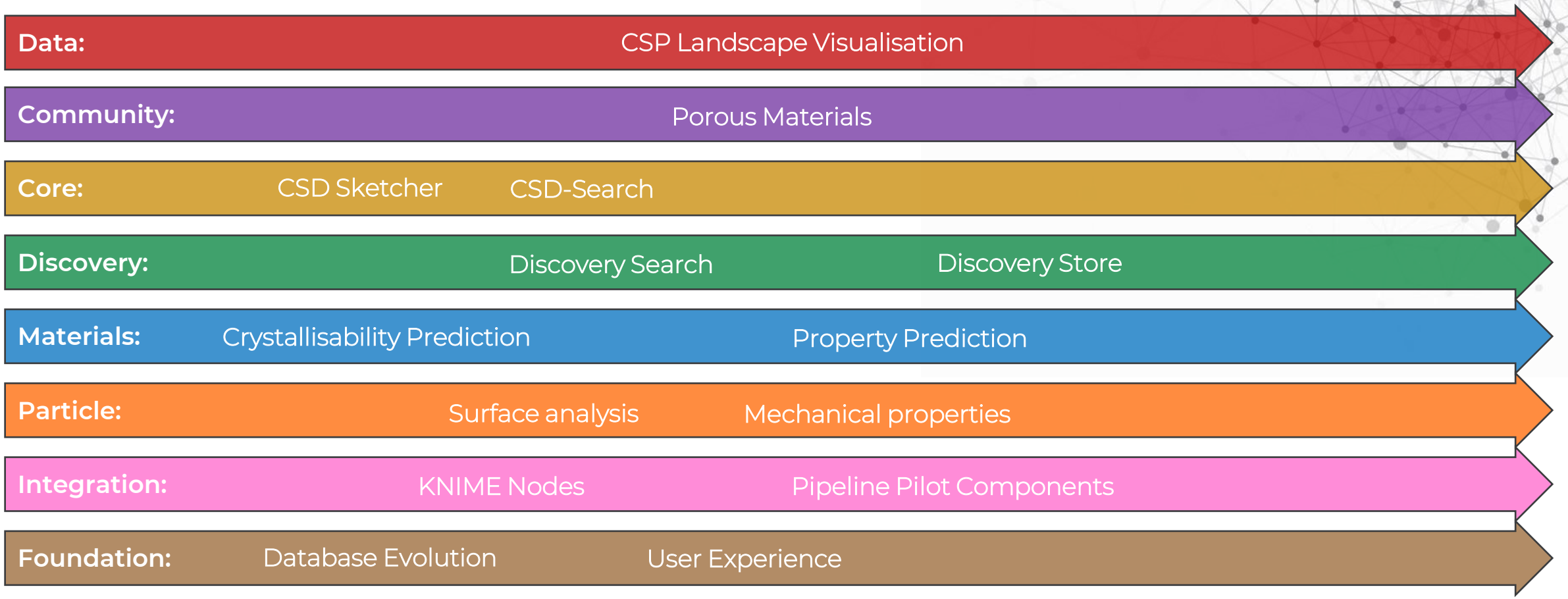
Our evolving roadmap

Pete Wood

Senior Product Manager

CCDC

CCDC Portfolio Roadmap 2020



CCDC

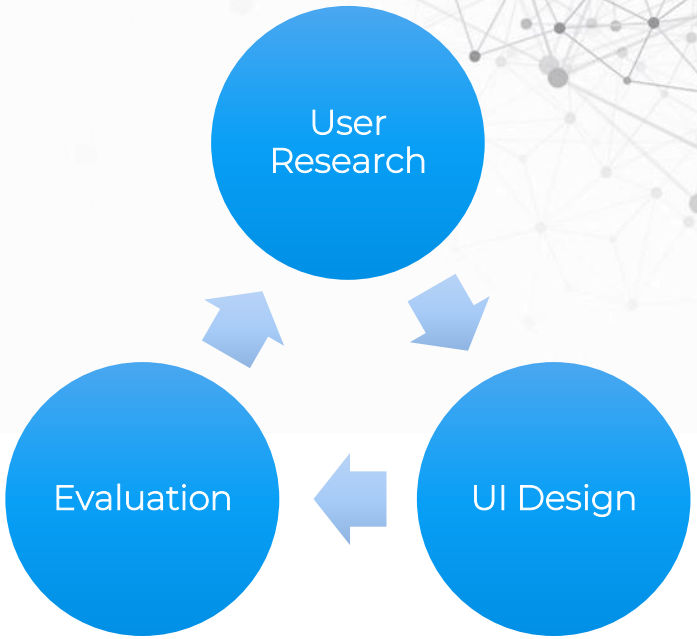
Database Evolution

- Optimised performance for distributed deployment of database
- Consolidated into a unified platform and structure to facilitate deployment and searching
- Extended capacity to cater for increased data volumes (e.g. CSP predicted landscapes)
- Extended capabilities for additional data types and features, as well as cater for increasingly complex structures
- Enabling new structure types (e.g. predicted structures, protein structures) to be managed through a common platform

CCDC

User Experience (UX)

- Improving the user experience across the CSD Portfolio, but particularly focussing on some key aspects
- Rationalising our existing user interfaces into fewer, better connected and more accessible products
- Putting industry-standard UX principles at the heart of our development process



CCDC

User Experience (UX)

- Developing user personas
- Conducting user surveys
- Carrying out user interviews
- Prototyping
- User interface design
- Usability testing

Working first on sketching and searching – any volunteers gratefully received!

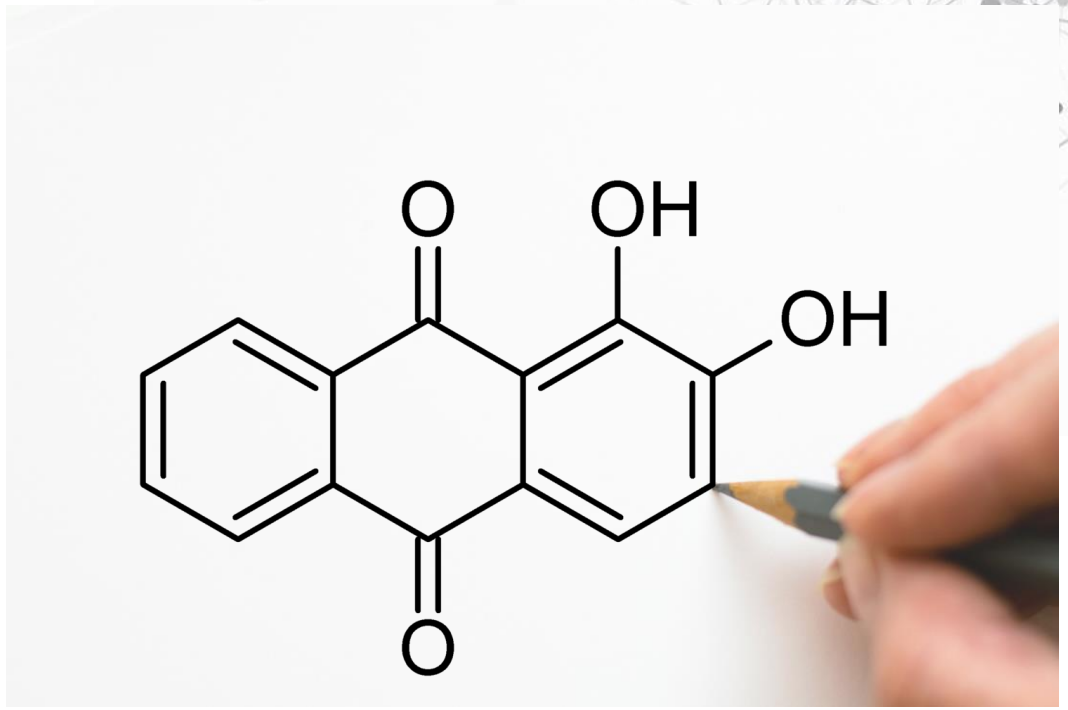
CCDC

CSD Sketcher

- Initial focus of our UX efforts in the next few weeks
- New, intuitive web-based chemical sketcher, first for use in structure searching within WebCSD
- Please engage with our user survey on chemical structure drawing to help our UX efforts!

Survey coming soon

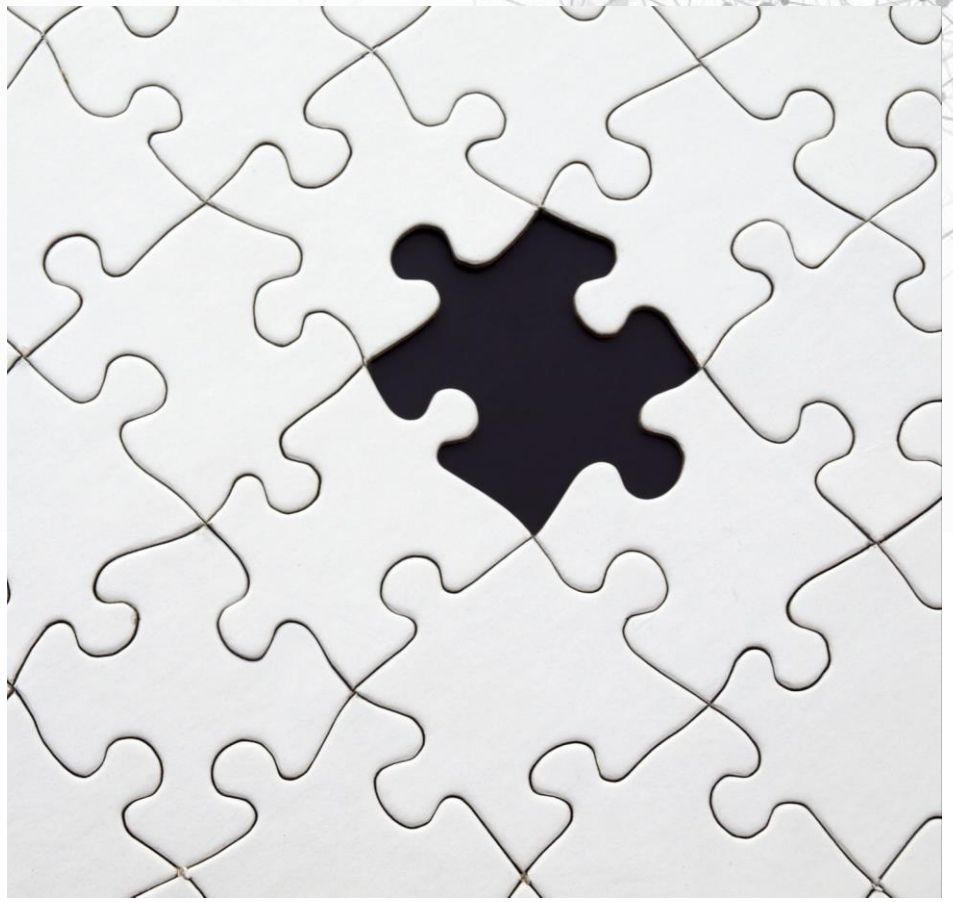
SurveyMonkey



CCDC

Search

- Broader project to work on web-based **searching** across the CCDC portfolio
- Will be looking at web-based **CSD-Search** interface encompassing 3D search as well as multiple query combinations
- Targeting web-based interface for searching **protein and protein-ligand structural data** as well

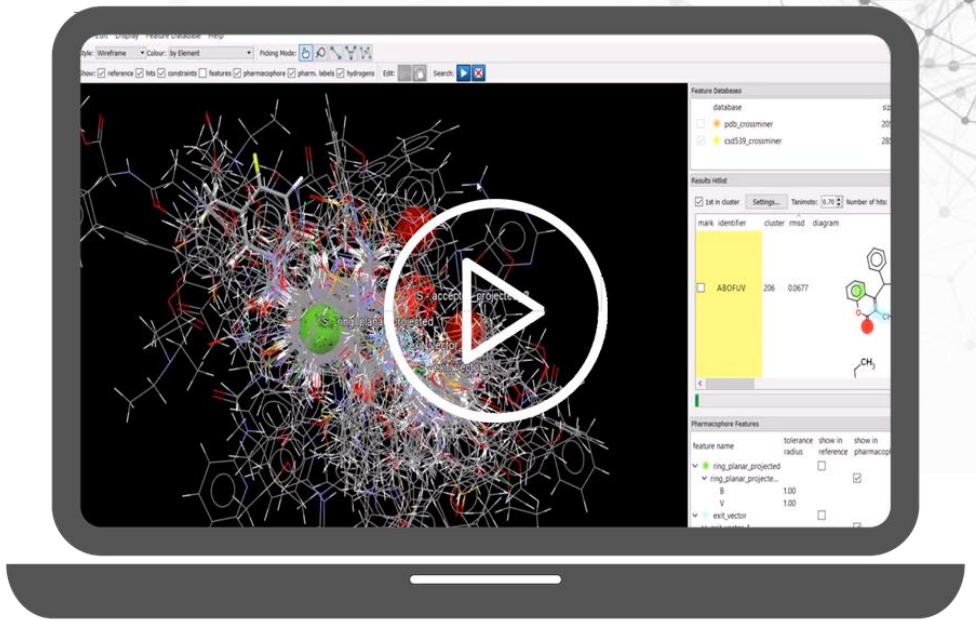


CCDC

Next What's Up Webinar

- Next webinar: May 28th
- Send us your ideas and news

  hello@ccdc.cam.ac.uk



Thank you

hello@ccdc.cam.ac.uk

The Cambridge Crystallographic Data Centre
12 Union Road, Cambridge CB2 1EZ, United Kingdom
Registered Charity No. 800579

CCDC