

A faint, light gray network pattern of interconnected lines and nodes is visible in the background, resembling a molecular or structural diagram.

ccDC

advancing structural science

# What's Up

## Customer Update Webinar

19 March 2020



# Today's presenters



Sophie Bryant  
Marketing Manager



Pete Wood  
Senior Product Manager

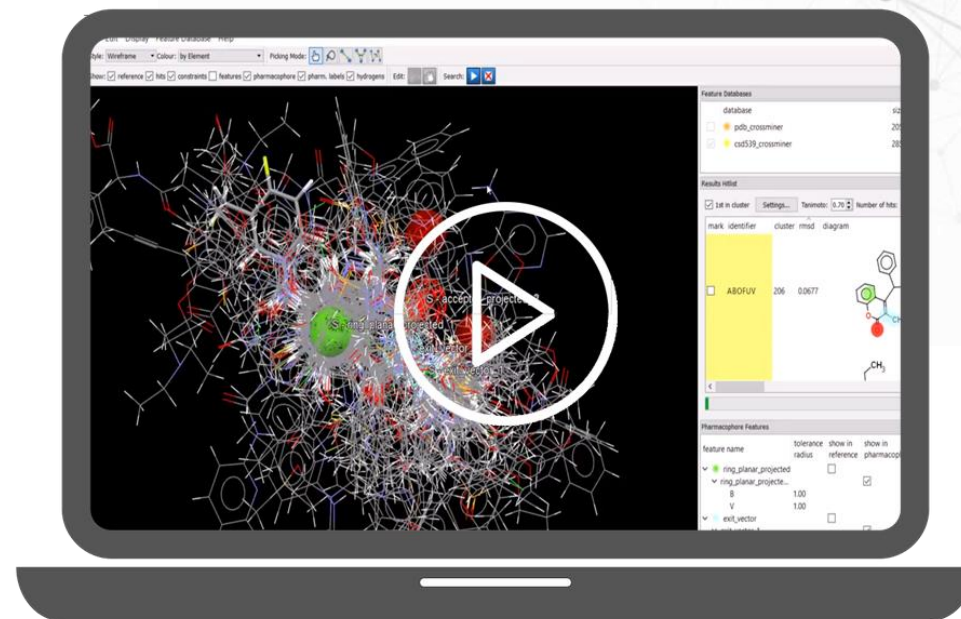


Francesca Stanzione  
Research and Applications Scientist

# 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](mailto:hello@ccdc.cam.ac.uk) any questions or concerns
- [support@ccdc.cam.ac.uk](mailto:support@ccdc.cam.ac.uk) for technical support
- [admin@ccdc.cam.ac.uk](mailto:admin@ccdc.cam.ac.uk) for licence or account queries

# Conferences and events

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

The screenshot displays the CCDC website interface. At the top, there is a navigation bar with links for DEPOSIT STRUCTURES, ACCESS STRUCTURES, and CONTACT US. Below this, the CCDC logo is prominently displayed. A search bar and a user profile dropdown for Sophie Bryant are also visible. The main navigation menu includes Community, Research & Consultancy, Solutions, News & Events, Support & Resources, and About Us. The News & Events dropdown menu is open, showing options for News, Events (highlighted with a red circle), Newsletters, CSD 1 Million, and Webinars. The main content area features a large banner for 'EVENTS' with the text 'Event cancellations: check here for updates.' and a 'Find out more' button. A footer section provides information about the Cambridge Structural Database reaching 1,000,000 structures, with a 'Find out more here.' link. Below this, a 'Daily CSD Total' is shown as 1047311, with each digit in a separate blue box.

DEPOSIT STRUCTURES | ACCESS STRUCTURES | CONTACT US

CCDC

Search Q Sophie Bryant Trustees Area SAB Area

Community Research & Consultancy Solutions News & Events Support & Resources About Us

News & Events  
News  
Events  
Newsletters  
CSD 1 Million  
Webinars

EVENTS

Event cancellations: check here for updates.

Find out more

World-leading experts in structural chemistry data, software and knowledge for materials and life science research and application

Big data leads the way for structural chemistry  
The Cambridge Structural Database reaches 1,000,000 structures. [Find out more here.](#)

Daily CSD Total

1 0 4 7 3 1 1



# USA User Group Meeting – now virtual

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

Friday 24<sup>th</sup> April – 09:00 – 13:00 EST

Register online

[HOME](#) / [NEWS & EVENTS](#) / [UPCOMING EVENTS](#)

## Upcoming Events

[Calendar](#) [Upcoming](#) [Past](#)



### Cancelled - ACS Spring Meeting

22 March 2020 – 26 March 2020

Philadelphia, USA



### Cancelled - BCA Spring Meeting

06 April 2020 – 09 April 2020

University of Leeds, UK



### Postponed - Drug Discovery Chemistry

13 April 2020 – 17 April 2020

San Diego, USA



### Postponed - Bio-IT World Conference & Expo

21 April 2020 – 23 April 2020

Boston, USA



### Virtual Meeting - US Spring UGM

24 April 2020 – 24 April 2020

Cambridge, MA, USA



Workshop on Computational Tools for Drug Discovery 2020

# 2020.0.1 CSD Release

What has changed?



Pete Wood  
Senior Product Manager



# 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

# 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

# CSD-CrossMiner key applications

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



Francesca Stanzione

Research and Applications Scientist

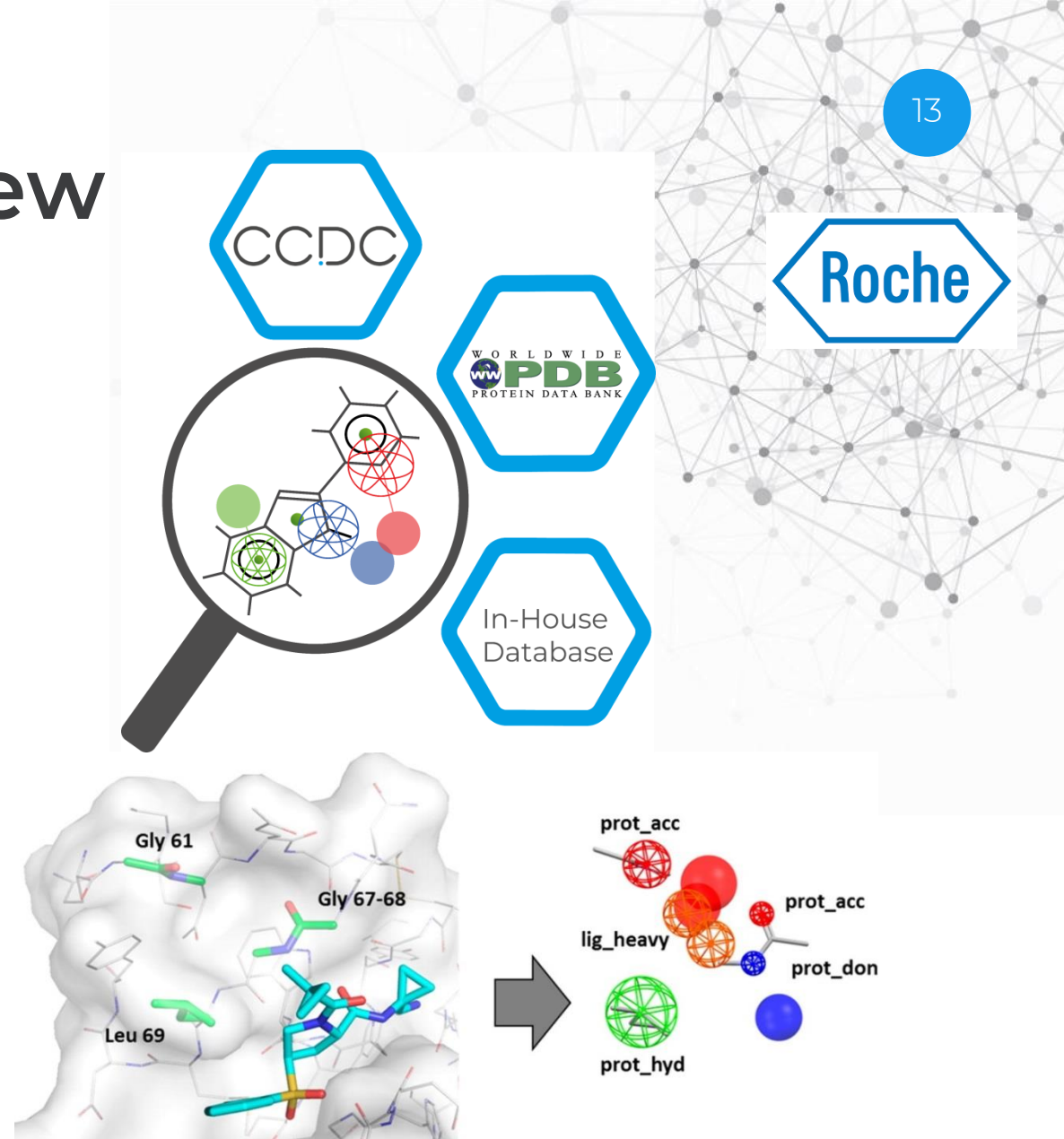
# How to access to CSD-CrossMiner



- 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*)

# CSD-CrossMiner Overview

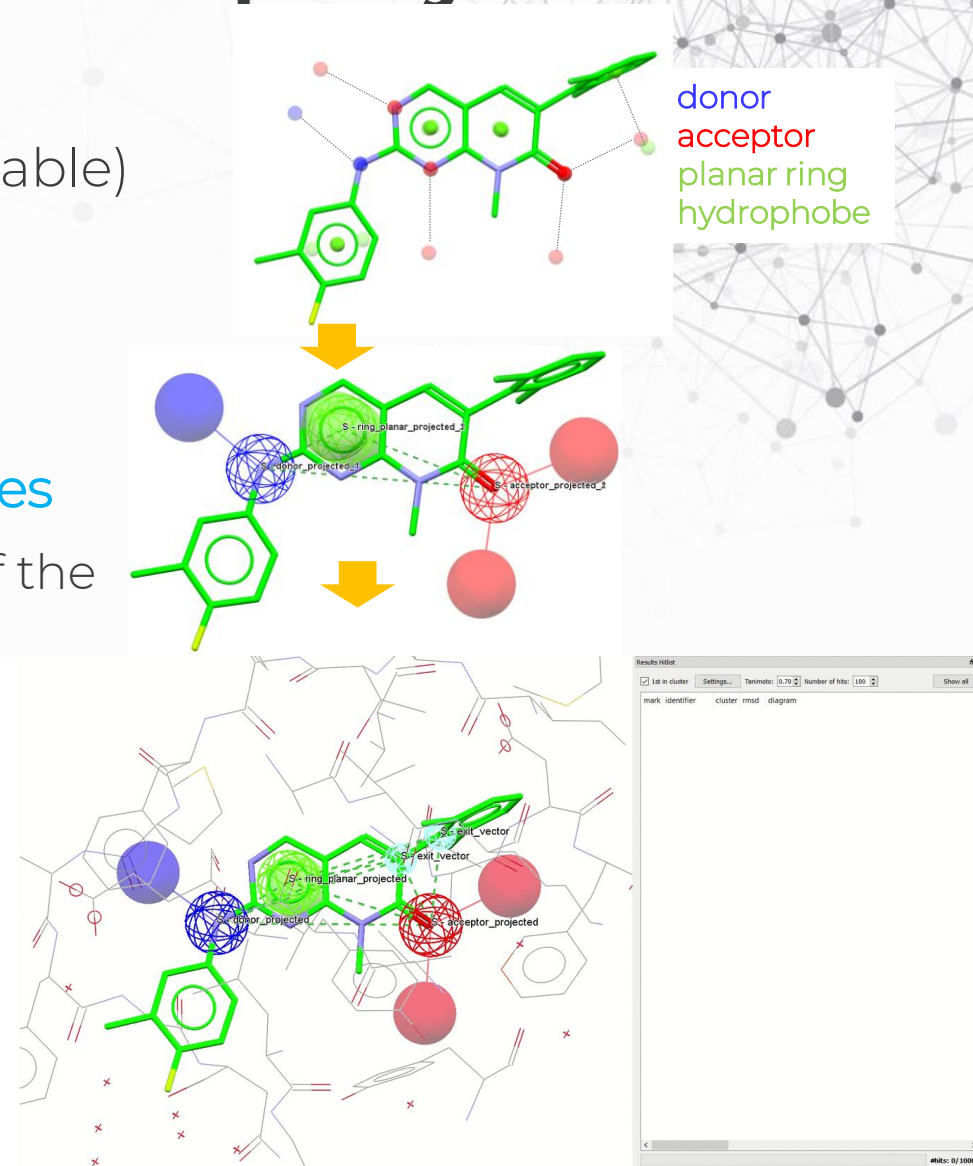
- Pharmacophore-based searches of structural databases (CSD & PDB & any in-house databases, **simultaneously**)
  - From IUPAC: “an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions
  - Wikipedia: “abstract description of molecular features”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





# How to build a pharmacophore query

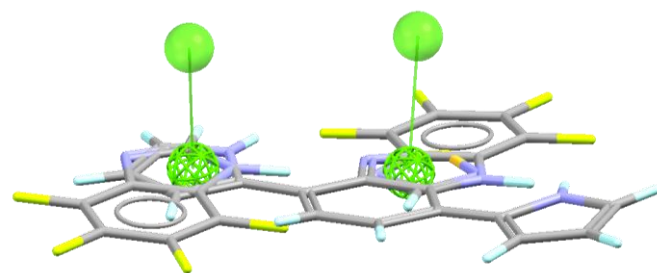
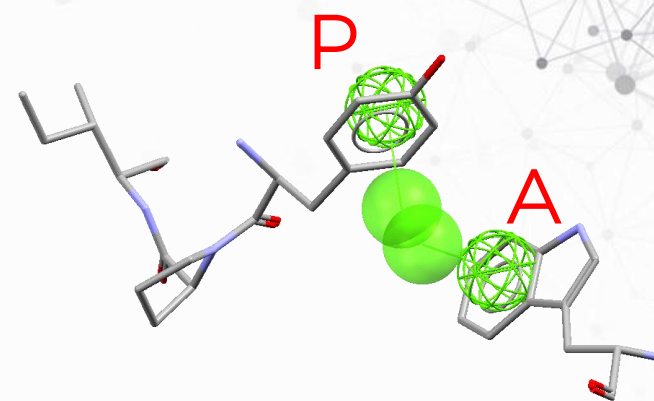
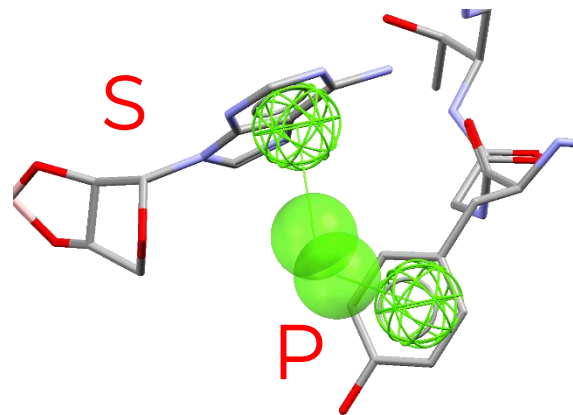
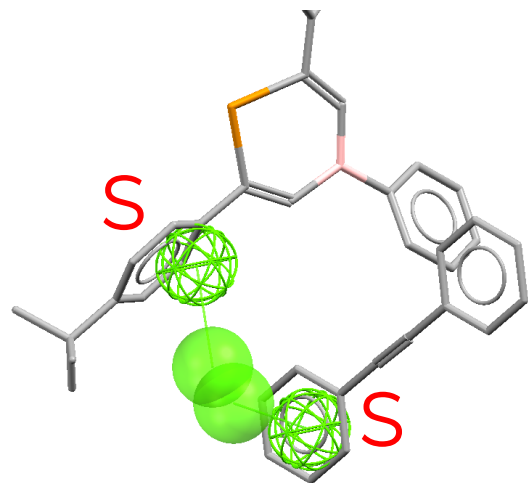
- Molecular structures are annotated with (customisable) **features**
  - Based on SMARTS patterns
  - Stored in feature database
- Pharmacophore query is based on **tolerance spheres**
  - Sphere radii reflect uncertainty in the position of the features
  - Large sphere → less strict
- Pharmacophore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



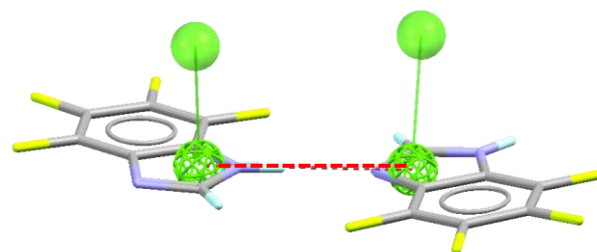
# Customising a pharmacophore query

Molecule class & constraints

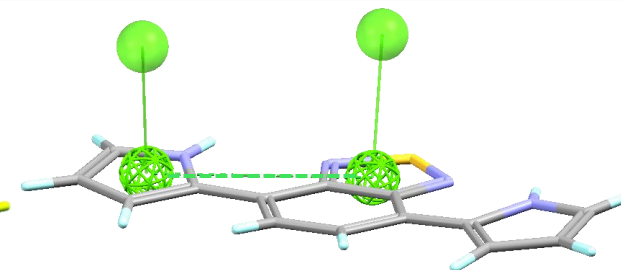
Protein (P)  
Small molecule (S)  
Any molecule (A)



No constraint



Inter-molecular constraint

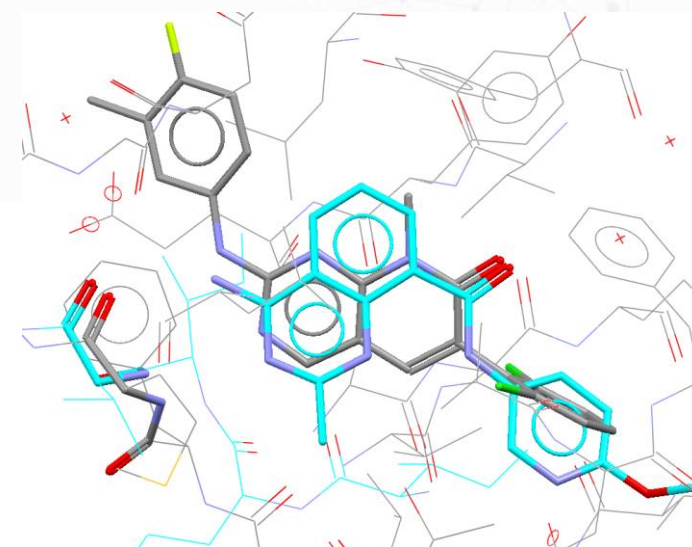
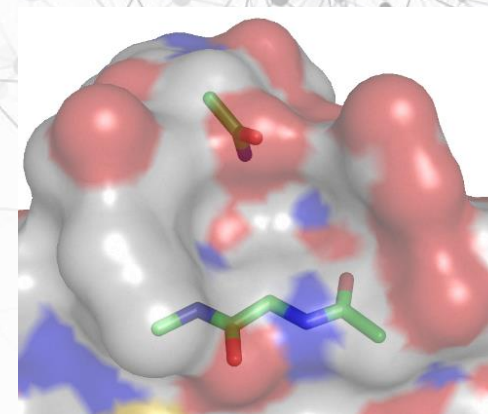


Intra-molecular constraint



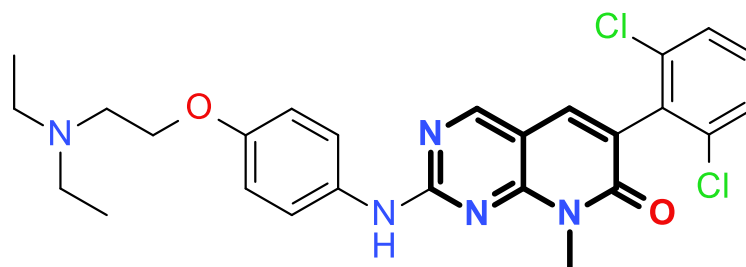
# CSD-CrossMiner Applications

- 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 established 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

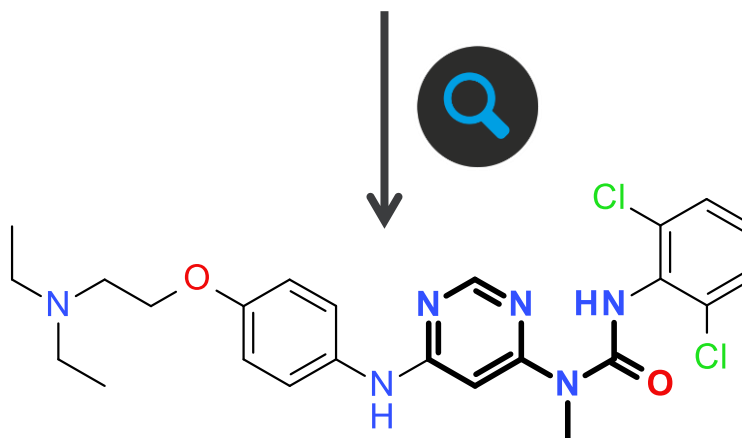


# Scaffold-hopping

Kinase inhibitor scaffold-hopping based on ligand features



PD166285 tyr-kinase inhibitor



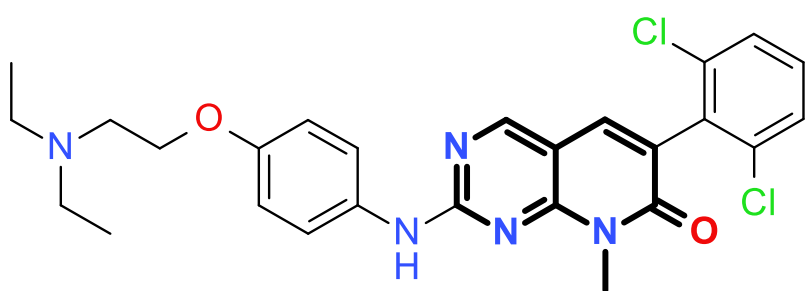
Prototype compound 1

$IC_{50} < 1 \mu M$  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

# Scaffold-hopping

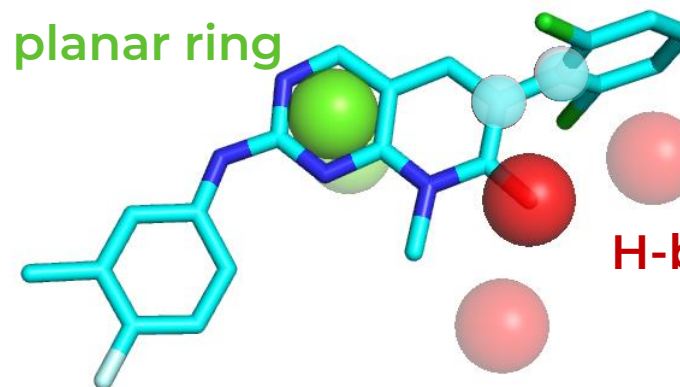
Kinase inhibitor scaffold-hopping based on ligand features



PD166285 tyr-kinase inhibitor



planar ring



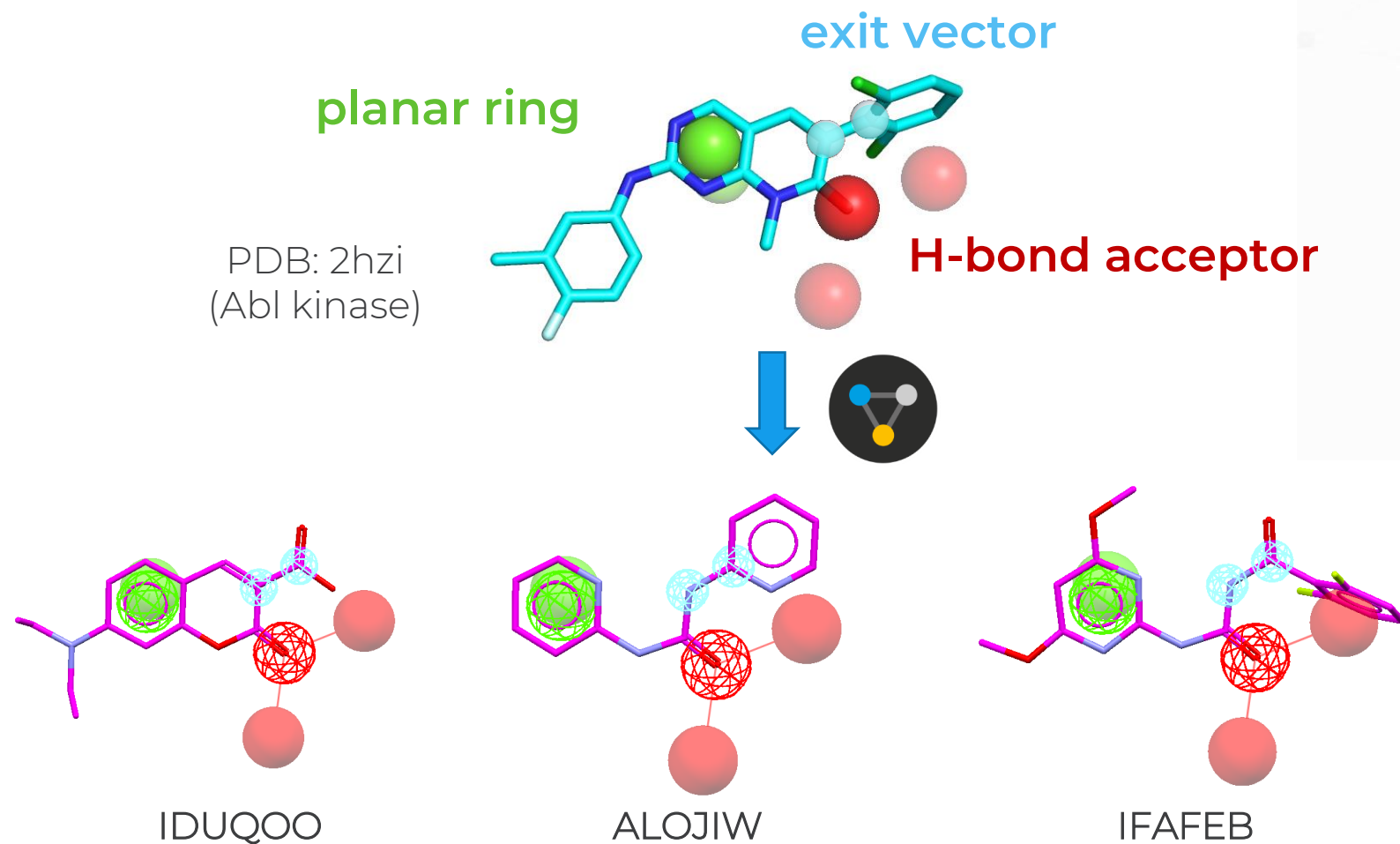
PDB: 2hzi  
(Abl kinase)

H-bond acceptor

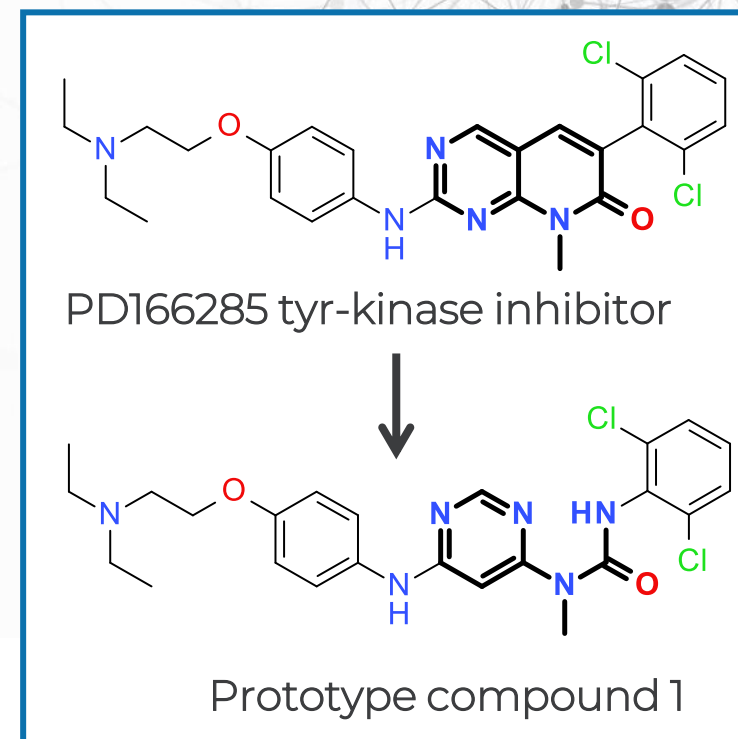
exit vector

# Scaffold-hopping

Kinase inhibitor scaffold-hopping based on ligand features



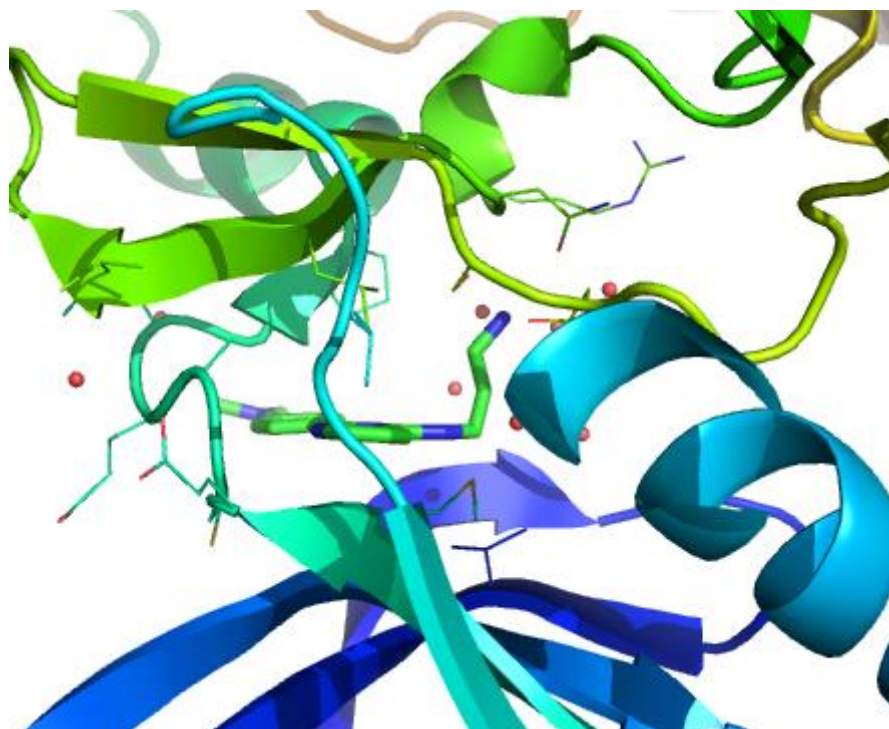
Furet et al., *Bioorg. Med. Chem. Lett.* 2008, 18, 897-900. DOI: [10.1016/j.bmcl.2007.12.041](https://doi.org/10.1016/j.bmcl.2007.12.041)



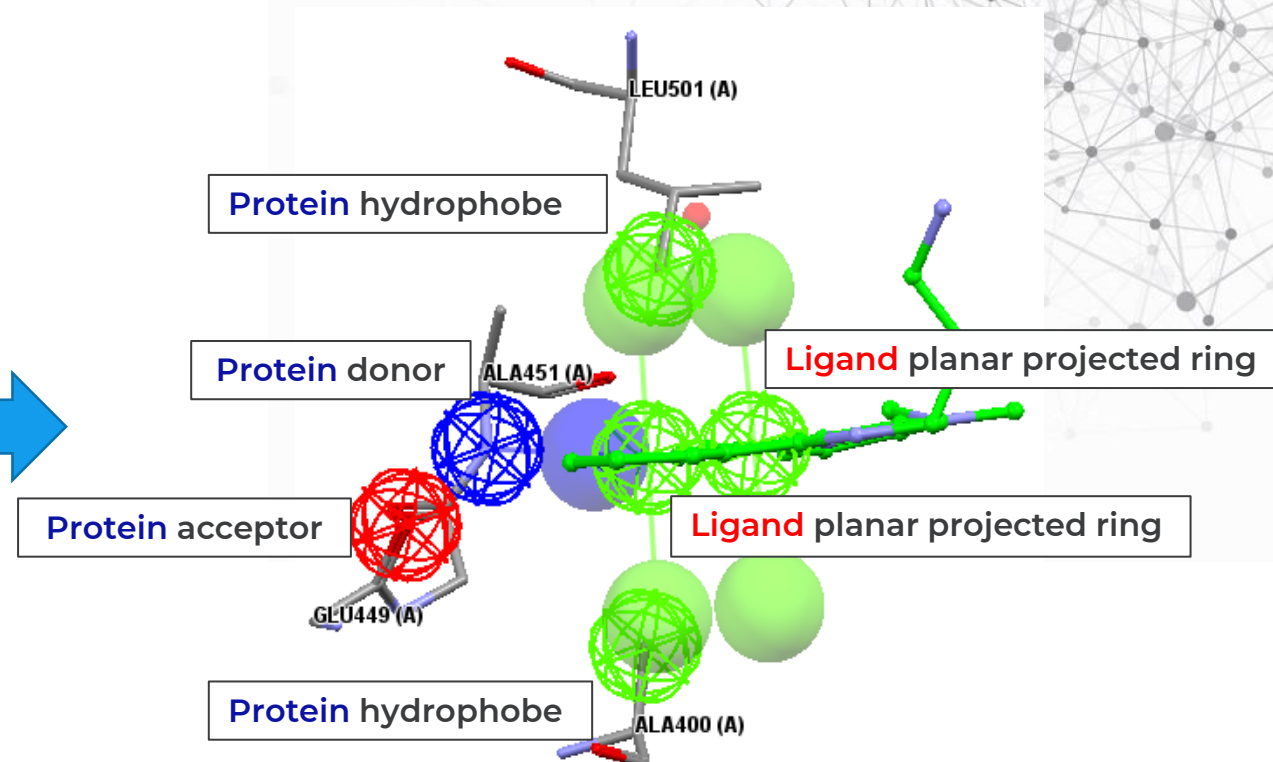


# Cross Reactivity

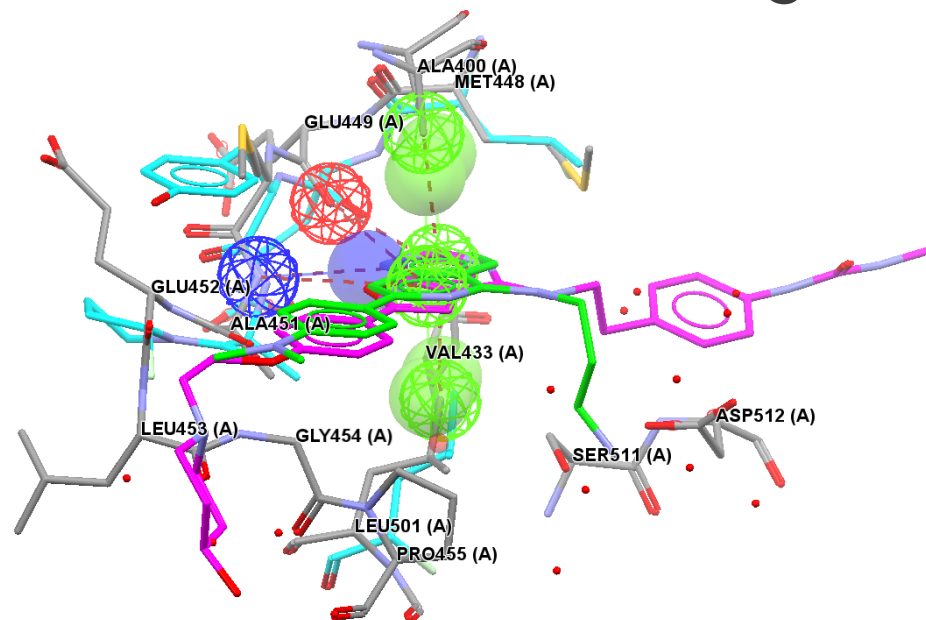
Syk inhibitor (Naphthyridine) bound to Syk kinase domain



PDB: 5cxz



# Cross Reactivity



Results Hitlist

1st in cluster Settings... Tanimoto: 0.70 Number of hits: 650 Show all

mark	identifier	cluster	rmsd	chain	deposition_date	ec_num
	3E7V_m1_A.bs_D2O_A_1_1	385	0.695	A	2008-08-19	2.7.11.1
	3KFA_m1_B.bs_B91_B_1_1	381	0.695	B	2009-10-27	2.7.10.2
	4G17_m1_A.bs_OVN_A_401	384	0.695	A	2012-07-10	2.7.11.1
	4PNN_m1_A.bs_JPZ_A_1202	383	0.695	A	2014-05-24	2.4.2.30
	4UXQ_m1_A.bs_OLI_A_1752_1	382	0.695	A	2014-08-27	2.7.10.1
	5KHX_m1_A.bs_6TE_A_4000_1	380	0.695	A	2016-06-16	2.7.10.2
	2XEY_m1_A.bs_YVQ_A_1270_1	387	0.696	A	2010-05-19	2.7.11.1
	4KQ6_m1_J.bs_DLZ_J_204_1	386	0.696	J	2013-05-14	2.5.1.78
	1ACJ_m1_A.bs_THA_A_999_1	392	0.697	A	1993-08-18	3.1.1.7
	2XIR_m1_A.bs_OOI_A_2169_1	389	0.697	A	2010-06-30	2.7.10.1
	3CGF_m1_A.bs_JNF_A_523	390	0.697	A	2008-03-05	2.7.11.24
	3PMN_m1_A.bs_IGC_A_1_1	393	0.697	A	2010-11-17	
	4CCR_m1_B.bs_FAD_D_1316	394	0.697	D	2013-10-25	
	4JBP_m1_A.bs_YPH_A_501	391	0.697	A	2013-02-20	
	5KBW_m1_A.bs_RBF_A_201	388	0.697	A	2016-06-03	
	4ASE_m1_A.bs_AV9_A_3169_1	395	0.698	A	2012-04-30	
	4EUE_m1_A.bs_NAI_A_1001	398	0.699	A	2012-04-25	
	4YTH_m1_A.bs_467_A_4000_1	396	0.699	A	2015-03-17	2.7.10.2
	5VYH_m1_A.bs_FOL_A_409_1	397	0.699	A	2017-05-25	
	15OM_m1_A.bs_DTP_A_803_1	401	0.7	A	2003-12-31	2.7.7.7
	2R3K_m1_A.bs_SCQ_A_501	399	0.7	A	2007-08-29	2.7.11.22
	3CQU_m1_A.bs_CQU_A_999	403	0.7	C	2008-04-03	2.7.11.26
	3E87_m1_A.bs_G95_A_1	400	0.7	C	2008-08-19	
	4AGW_m1_A.bs_NG7_A_1534	404	0.7	A	2012-02-01	2.7.10.2
	5JAX_m1_A.bs_617_A_401_1	405	0.7	A	2016-04-12	2.7.11.2
	5L6P_m1_A.bs_6P8_A_1001	402	0.7	A	2016-05-30	2.7.10.1
	2R0C_m1_A.bs_FAD_A_1430_1	407	0.701	A	2007-08-18	
	4KXJ_m1_A.bs_P34_A_201	406	0.701	A	2013-05-27	
	2C6L_m1_A.bs_DT4_A_1299_1	411	0.702	A	2005-11-10	2.7.1.37
	3ZCL_m1_A.bs_5TF_A_1_1	408	0.702	A	2012-11-20	2.7.10.1
	4K77_m1_B.bs_1Q4_B_1201_1	409	0.702	B	2013-04-16	2.7.10.2
	4WUJ_m1_C.bs_FMN_C_5201	410	0.702	C	2014-10-31	
	1DL5_m1_A.bs_SAH_A_699	412	0.703	A	1999-12-08	2.1.1.77

0.097	D	2013-10-25	1.0.1.9	amoxicillin
0.697	A	2013-02-20	2.7.11.1	aurora kinase a
0.697	A	2016-06-03		riboflavin trans

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



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

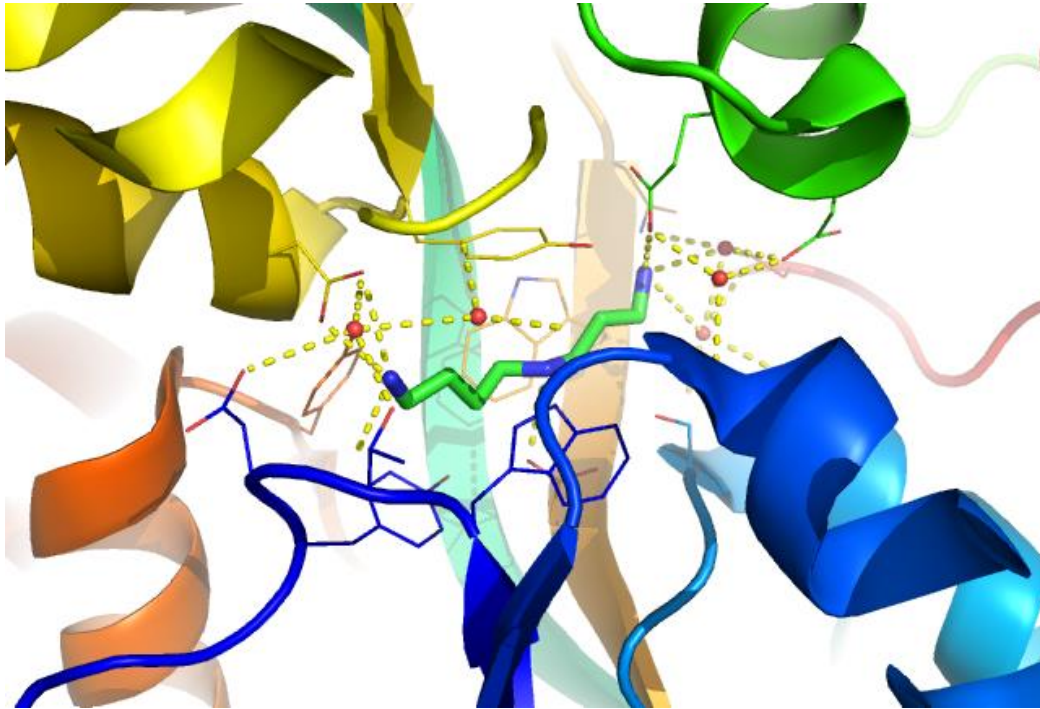
Gebhard Thoma <sup>a</sup>, Siem Veenstra <sup>a</sup>, Ross Strang <sup>a</sup>, Joachim Blanz <sup>b</sup>, Eric Vangrevelinghe <sup>c</sup>, Jörg Berghausen <sup>c</sup>, Christian C. Lee <sup>a</sup>, Hans-Günter Zerwas <sup>d</sup>

## 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.

CCDC

# Pocket Detection & Pocket Filling

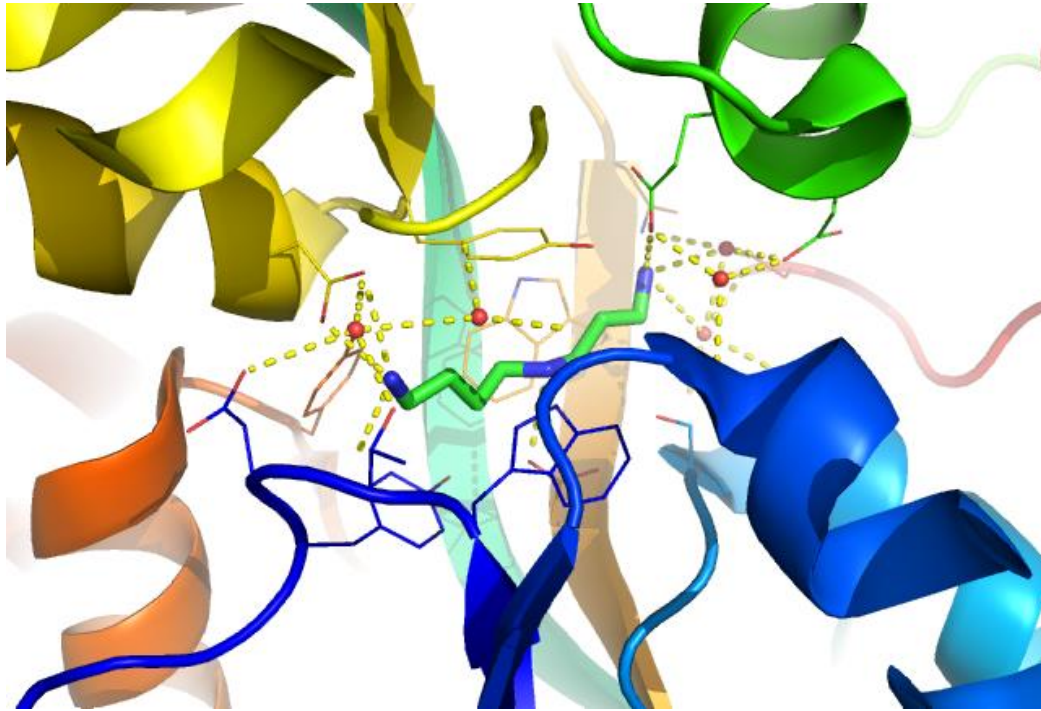


PDB: 3ttn

- 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?

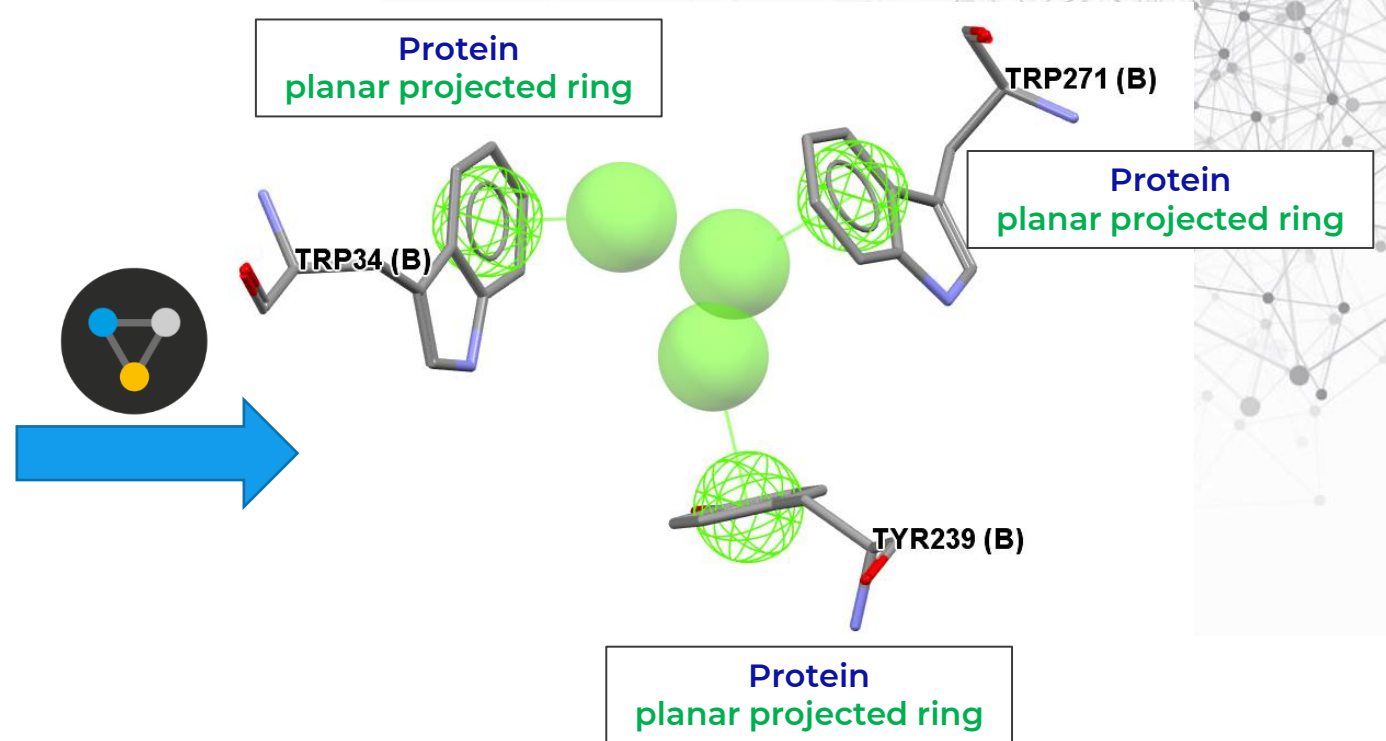


# Pocket Detection & Pocket Filling



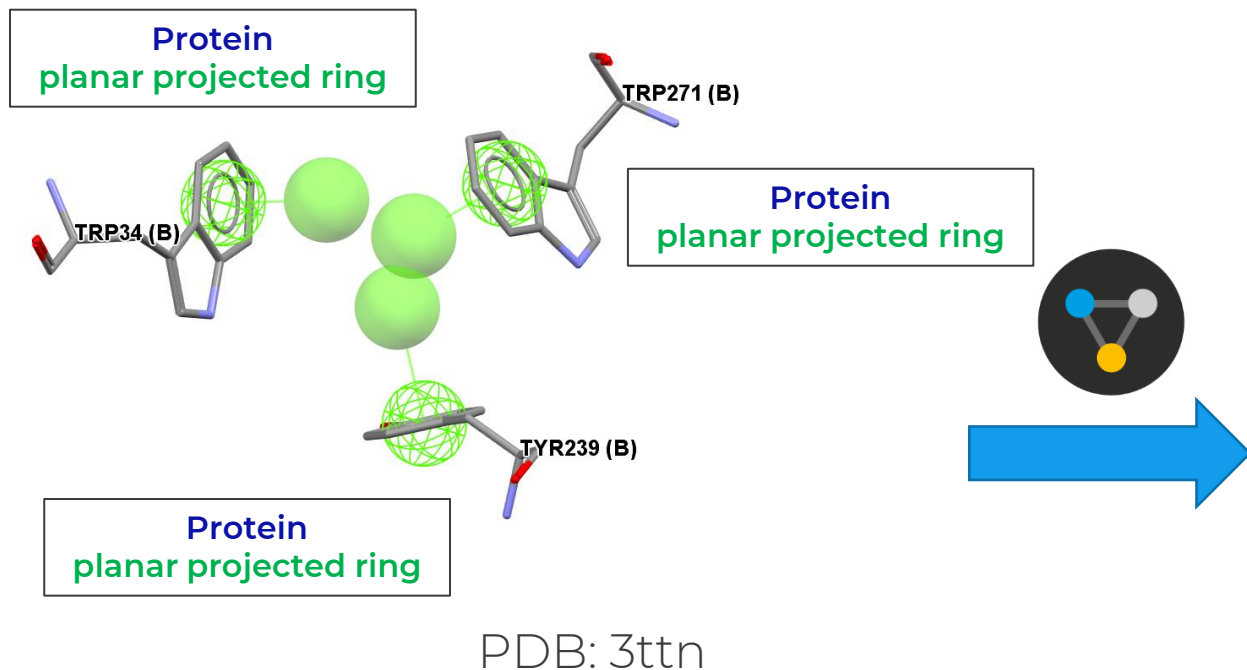
PDB: 3ttn

*Pseudomonas aeruginosa* in complex with spermidine



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

# Aromatic Cages in Proteins



- Aromatic cages occur in a large number of functional proteins

Results Hitlist

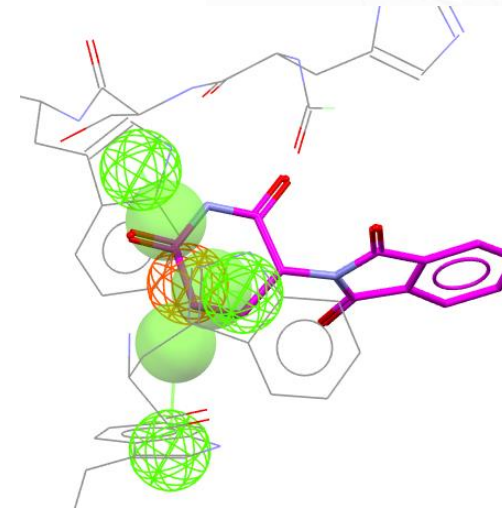
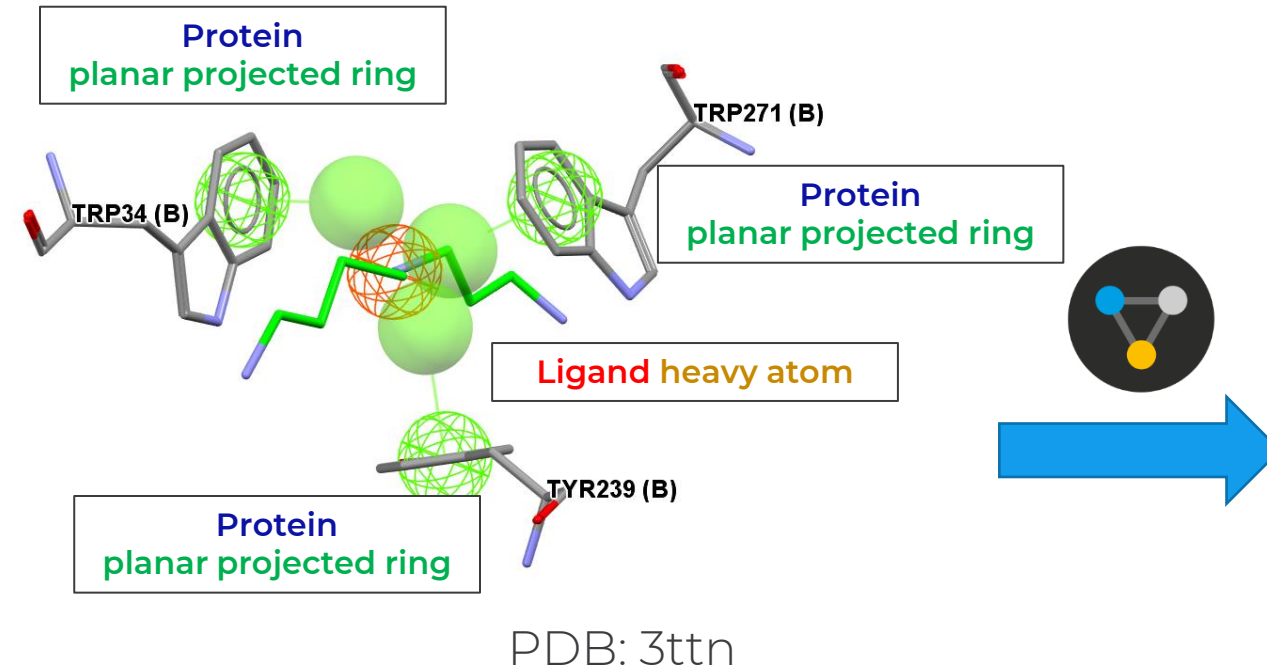
☒ 1st in cluster Settings... Tanimoto: 0.70 Number of hits: 100 Show all

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

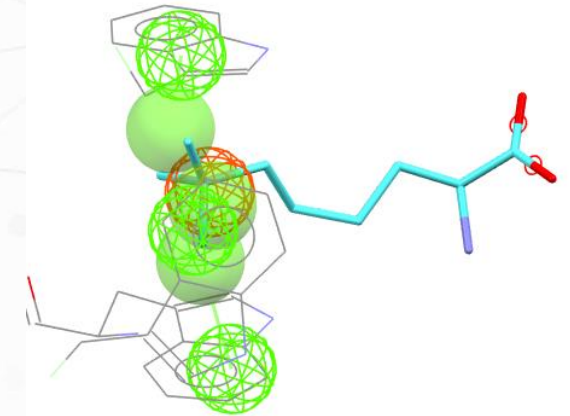
#hits: 1633/10000

*Which ligand motifs interact with this environment?*

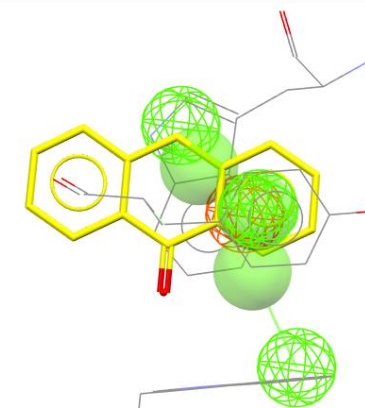
# Pocket Filling



PDB: 5yj1  
(thalidomide)



PDB: 4yhy  
(trimethylated Lys)



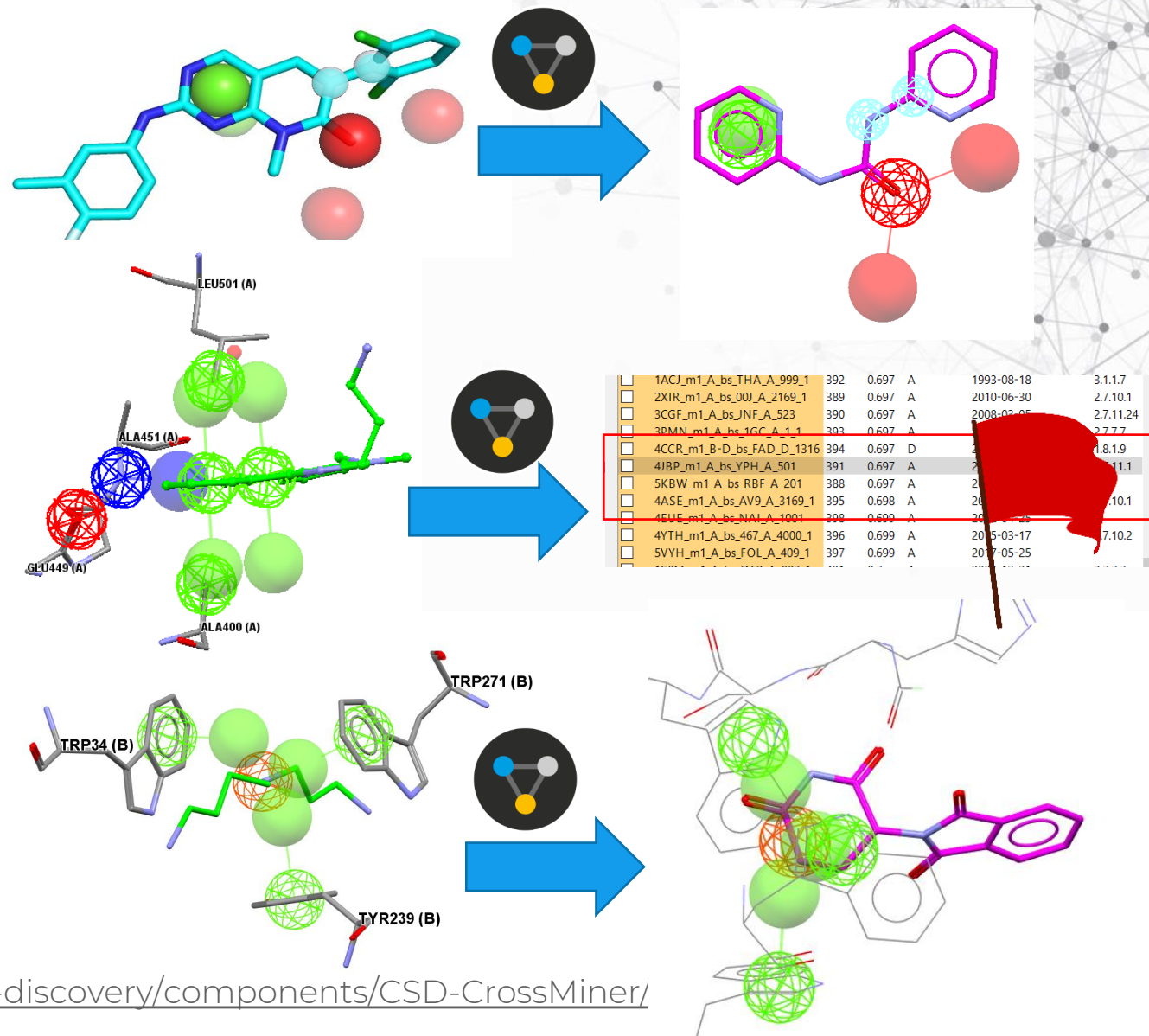
PDB: 2bjm  
(tricyclic structure)

- 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.



# Conclusion

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



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

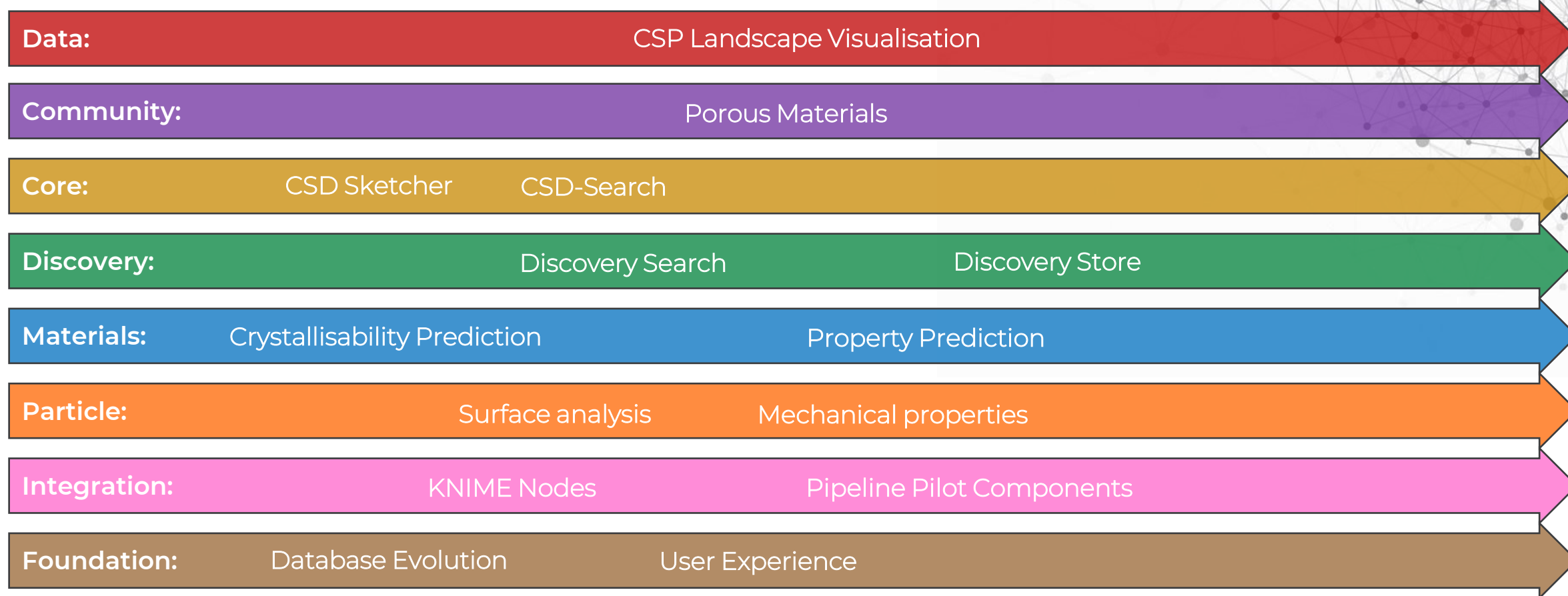
# CCDC key projects coming up in 2020

Our evolving roadmap



Pete Wood  
Senior Product Manager

# CCDC Portfolio Roadmap 2020



# Database Evolution

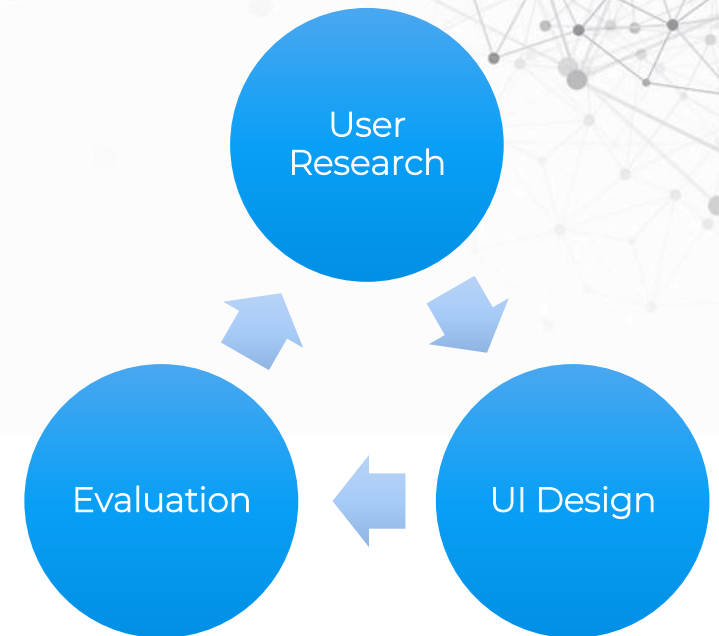
- Optimised performance for distributed deployment of database
- Consolidated into a unified platform and structure to facilitate deployment and searching
- Extended capacity to cater for increased data volumes (e.g. CSP predicted landscapes)
- Extended capabilities for additional data types and features, 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





# 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



# User Experience (UX)

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

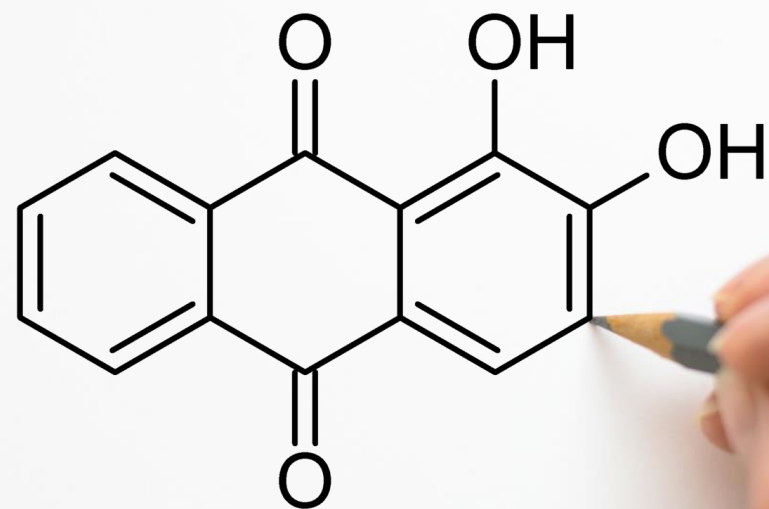
Working first on sketching and searching –  
any volunteers gratefully received!



# 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



# 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

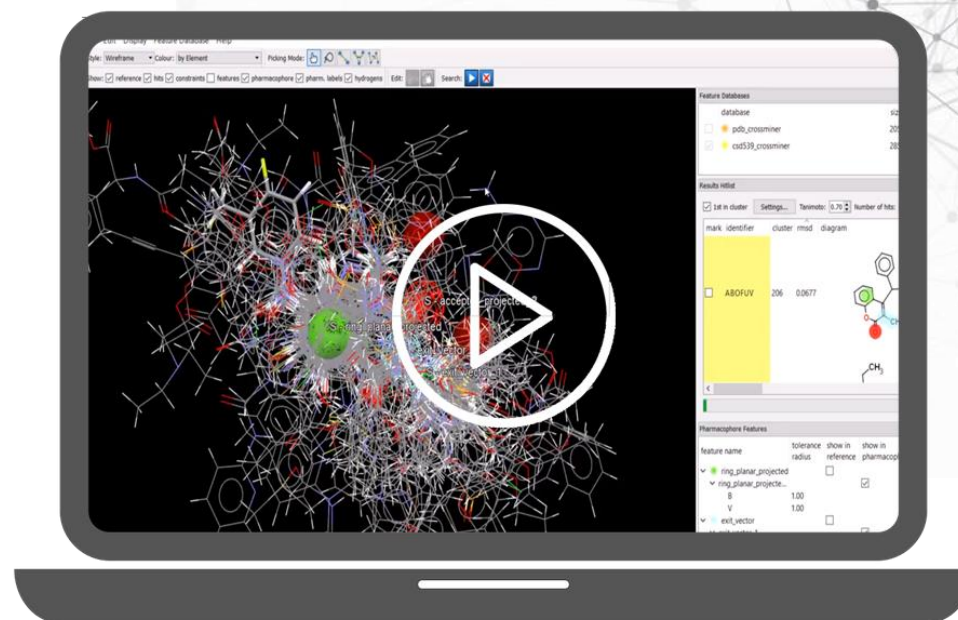




# Next What's Up Webinar

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

[hello@ccdc.cam.ac.uk](mailto:hello@ccdc.cam.ac.uk)



# Thank you

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