CSD-Discovery
Discover new molecules

Overview

For discovery chemists, the components in CSD-Discovery provide the means to:

- Interrogate protein ligand complexes
- Dock small molecules, generate probable molecular conformations
- Search for likely overlays of active ligands
- Propose scaffold hops or isosteric replacements
- Produce easy integrations into internal systems

Bringing together the Protein Data Bank (PDB) and Cambridge Structural Database (CSD) and much more.

CSD-Discovery components

Protein-Ligand Docking
Dock small molecules into proteins flexibly; optionally sampling protein flexibility and solvent location during docking using the world-renowned docking package, GOLD to provide fast and accurate binding mode prediction in lead discovery and lead optimisation.
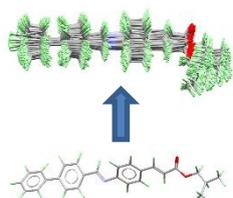
Generation of Molecular Conformations
Generate plausible molecular conformations by using the wealth of information available in the Cambridge Structural Database rapidly and effectively to benefit ligand-based molecular screening and pharmacophore prediction.
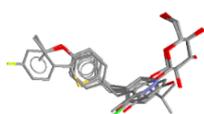
Flexible Alignment of Ligands
Align ligands using generated conformations to build realistic pharmacophore hypotheses for use in field-based virtual ligand screening or scaffold hopping.

Searching for Scaffold Hops and Pharmacophoric Patterns
Mine both the CSD and the PDB using pharmacophores or substructure searching *interactively* to find repeated patterns of interactions or possible suggestions for potential scaffold hops using CSD-CrossMiner. Such information can lead to credible and non-obvious ideas and directions for lead development.
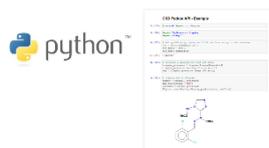
Script-based Interfaces
Create tailored Python scripts using the whole spectrum of CSD functionality to answer your targeted research questions. Integrate access to CSD-Discovery workflows seamlessly with 3rd party software.

Case studies

(a) Probing enantiomeric specificity using side-chain and water flexibility in docking

Understanding the selective inhibition of Adenosine Receptors (ARs) is of interest in drug discovery, as ARs mediate many physiological processes and so are potential therapeutic targets. Carbajales and co-workers[1] explored the binding behaviour of new antagonists to the AR hA$_{2B}$AR to determine which enantiomer was active in the binding site. Each docking needed to consider both side chain flexibility of certain binding residues and the role of water mediation in docking. Using GOLD, the team was able to identify that the S-form of their compound was binding to the target, and rationalise the role that side-chain motion and water plays in influencing binding.

[1]C. Carbajales, J. Azuaje, A. Oliveira, H. Gutiérrez-de-Terán, E. Sotelo, et al., J. Med. Chem. (2017) 60, 3372-3382.
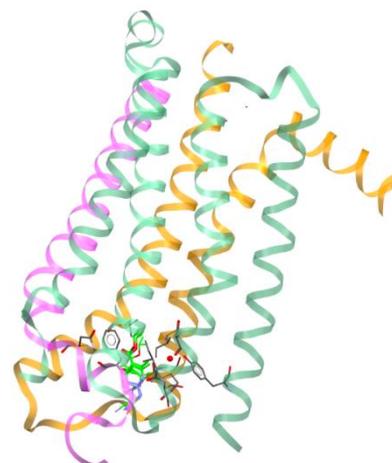
(b) Using structural data to understand conformational preferences

Conformational analysis is key to Drug Discovery, and the data in the Cambridge Structural Database can help. Kung and co-workers[2] analysed the conformational preferences of substituted benzamides in the CSD to understand how substitution at the ortho position influenced the conformational preferences when targeting EZH2. By correlating the relative activities of compounds with the CCC=O torsion angle, they were able to understand and interpret the conformational needs of their lead molecules to have high potency. A cyclisation strategy then led to a new class of active compounds.

[2]P.-P. Kung, E. Rui, S. Bergqvist, P. Bingham, W.-G. Zhang, R. A. Rollins, M. Edwards, et al., J. Med. Chem. (2016) 59, 8306–8325.
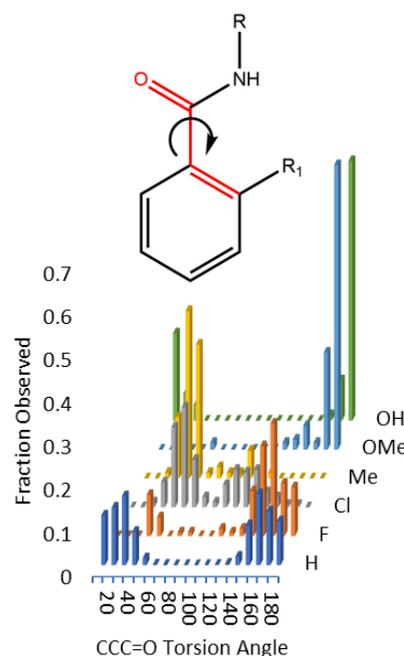
How to find out more?

Visit the CSD-Discovery page on the CCDC website to learn more about the various components within CSD-Discovery and to discover what's new in the functionality in the latest CSD release.

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

The Cambridge Crystallographic Data Centre