Applying structural informatics approaches to pharmaceutical supply chain processes

Andrew G.P. Maloney, Mathew J. Bryant and Neil Feeder

The Cambridge Crystallographic Data Centre

The ADDoPT Project

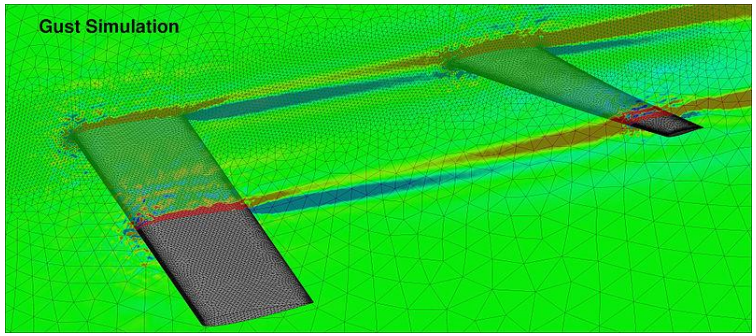
Advanced **D**igital **D**esign **o**f **P**harmaceutical **T**herapeutics

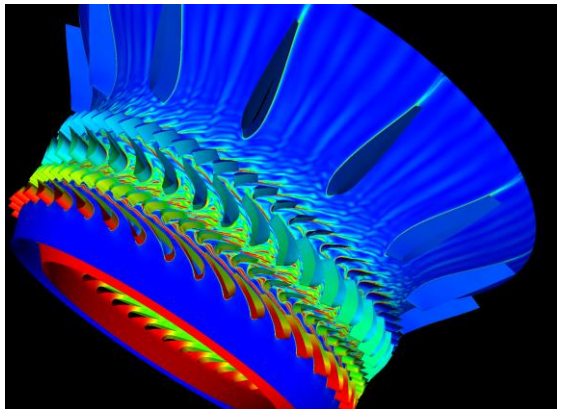
- Four year collaboration between government, industry and academia
- Instigated by the Medicines Manufacturing Industry Partnership and part funded under the **Advanced Manufacturing Supply Chain Initiative**

ADDOPT

Digital Design

If we designed airplanes like we design drugs…





"Why has pharmaceutical research and development lagged so far behind other industries in the development and application of simulation and modelling for research and development?"

W.S Woltosz, *J. Comput. Aided Mol. Des.* (2012), **26**, 159-163

ADD PT

Digital Design: Molecules to medicines

Product and Process Design

Upstream

Materials properties
Surface chemistry
Release profiles
Manufacturing classification
Particle attributes
Processing rules
Quality systems
Formulation

Product Performance

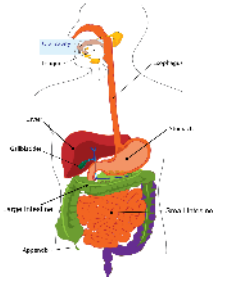
Downstream

Primary Manufacturing - Secondary Manufacturing

Active Ingredient (API)

Crystallisation
Filtration
Washing
Drying

Milling
Blending
Compaction
Coating



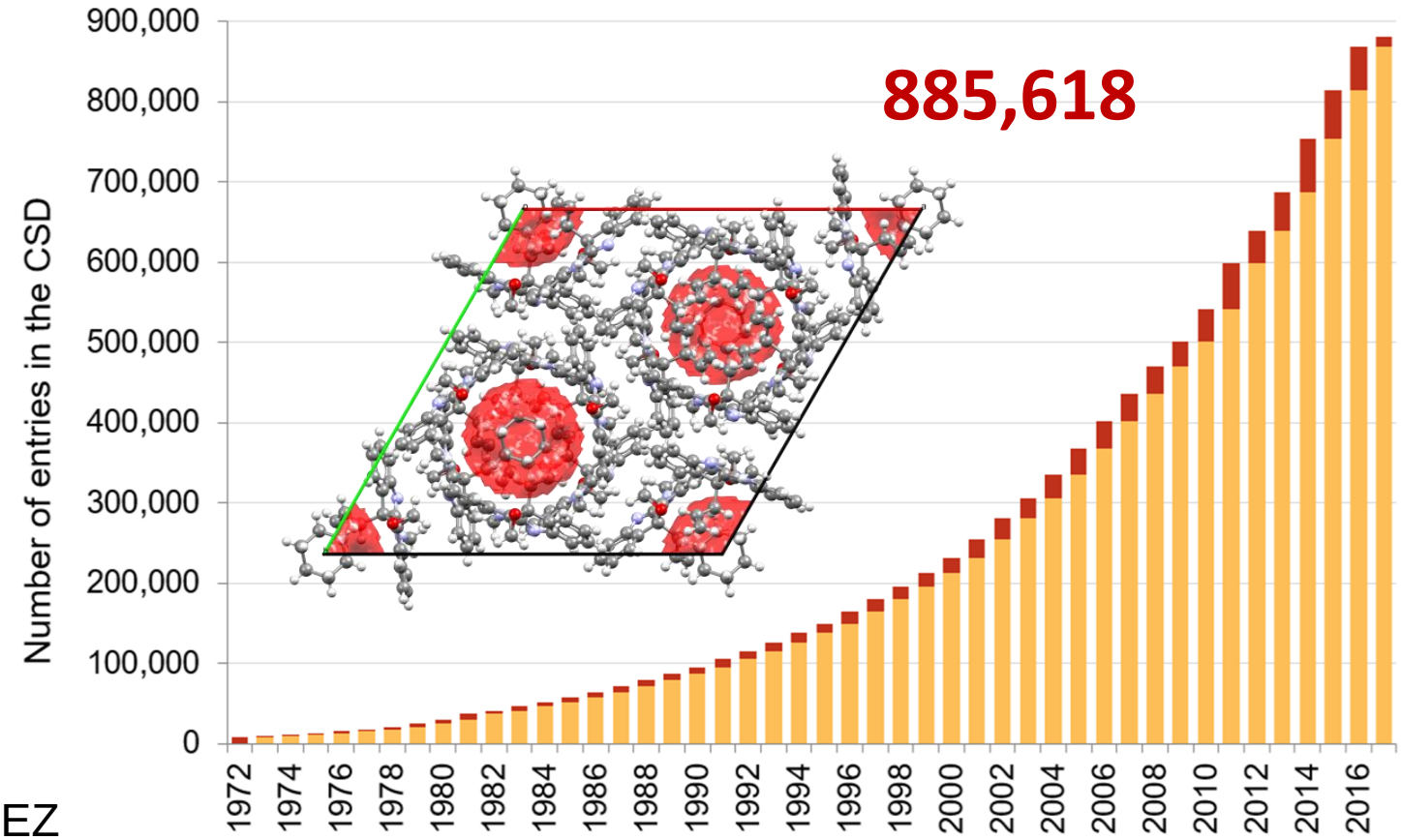
Processes **Products** **Performance**

Design and control of optimised development & manufacturing processes through data analysis and first principle models

ADDOPT

The Cambridge Structural Database

All small-molecule organic & metal-organic crystal structures ever published.



USOPEZ
Natural product intermediate, crystallised as a cyclohexane solvate

R. P. Wilkie *et al., Chem. Commun.* (2016), **52**, 10747-10750

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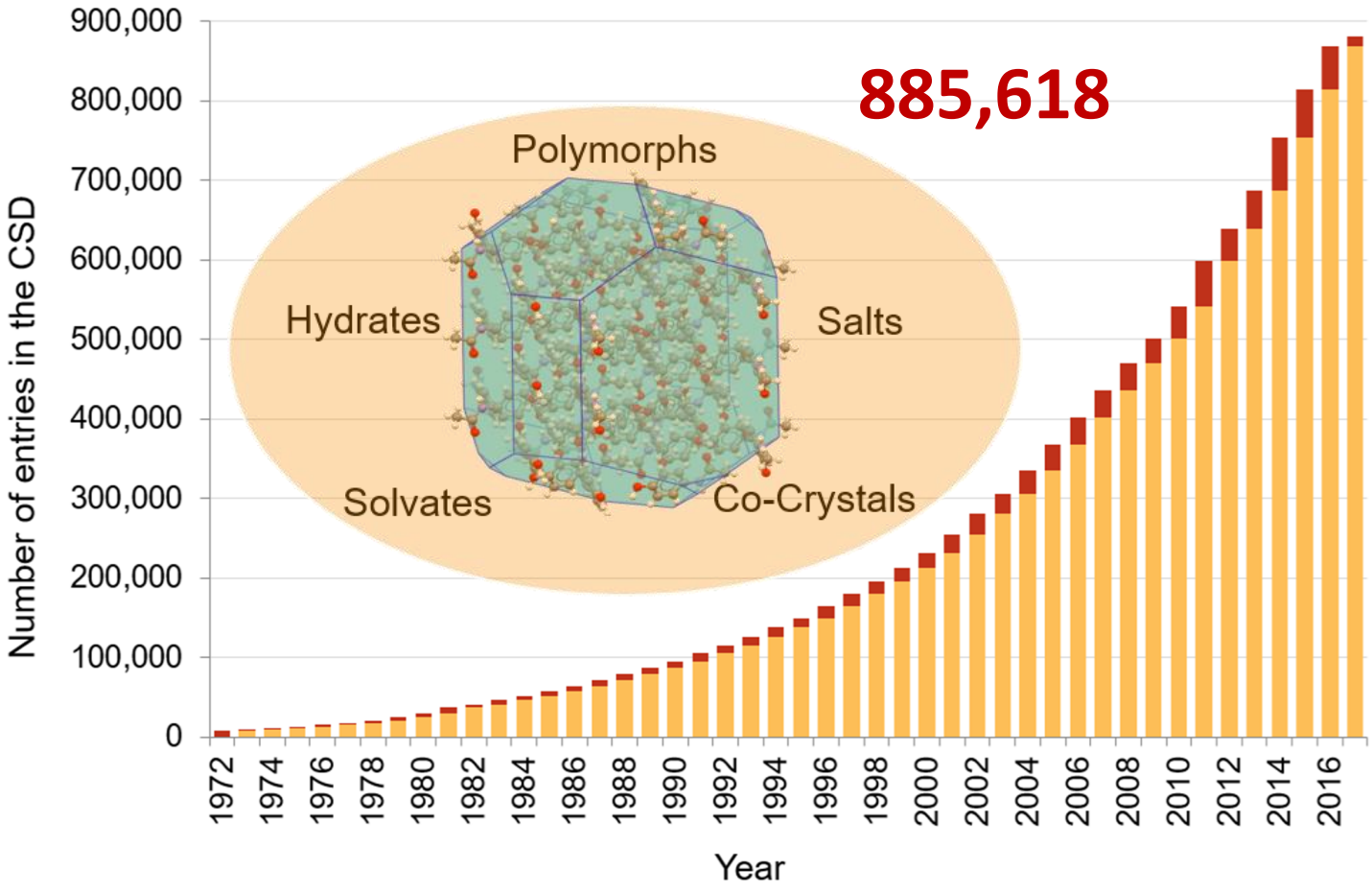
The Cambridge Structural Database

All small-molecule organic & metal-organic crystal structures ever published.



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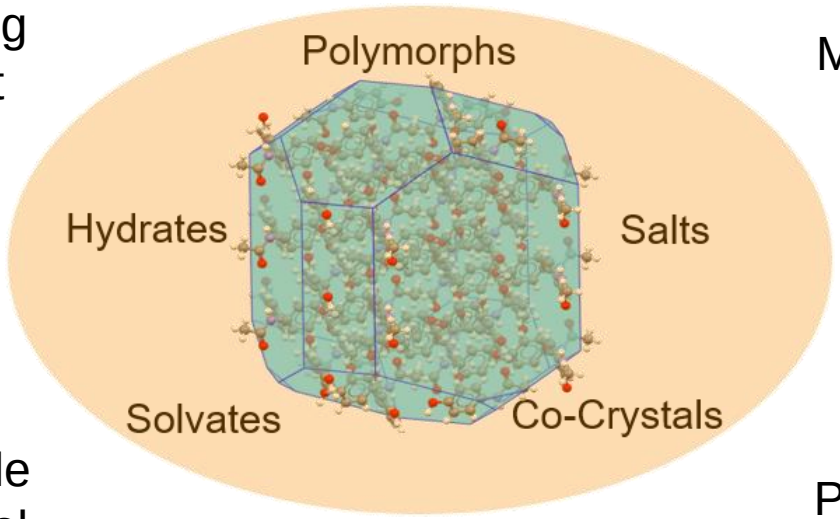
Crystal structure is important…

Chemical & Physical Stability

Melting Point

Morphology



Solubility

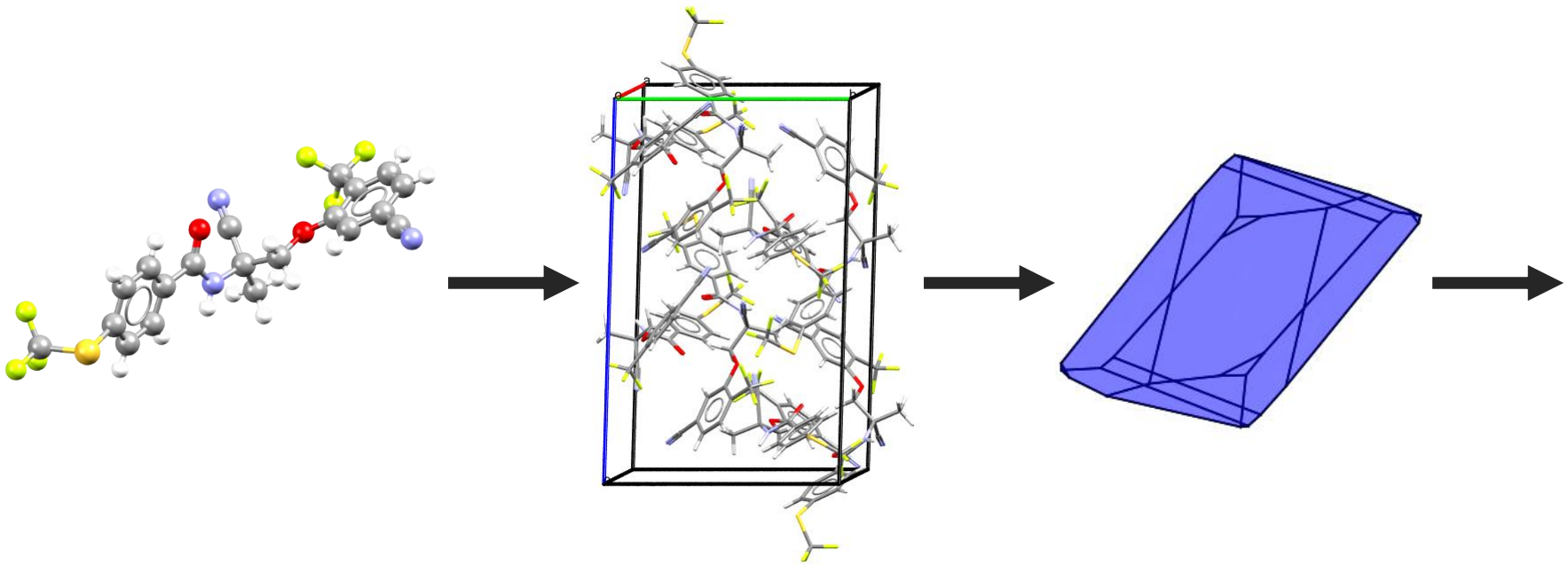
Mechanical Properties

Particle Control

Purification

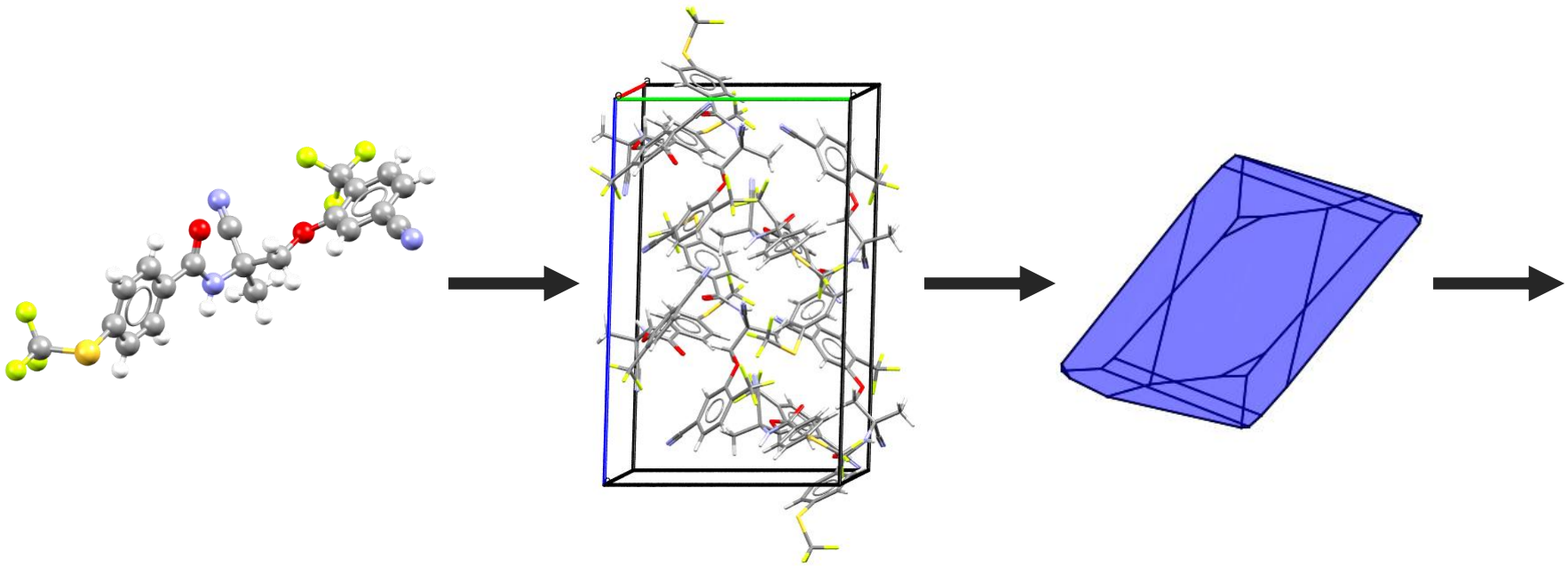
Product Process Control

Drug product design and development



Molecule **Form** **Particle**

Drug product design and development



Molecule **Form** **Particle**

Making a CSD Drug Subset

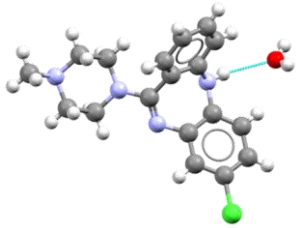
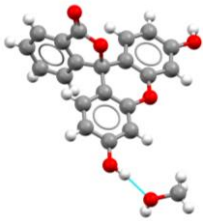
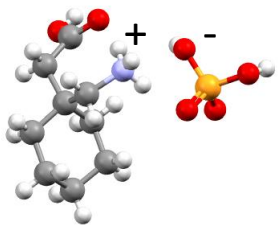
Drug definition taken from the approved drug database of Drugbank.ca

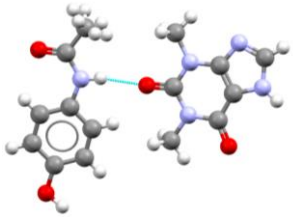
DRUGBANK
Open Data Drug & Drug Target Database

Generated using InChi strings and the CSD Python API

8632 crystal structures representing 785 drug molecules

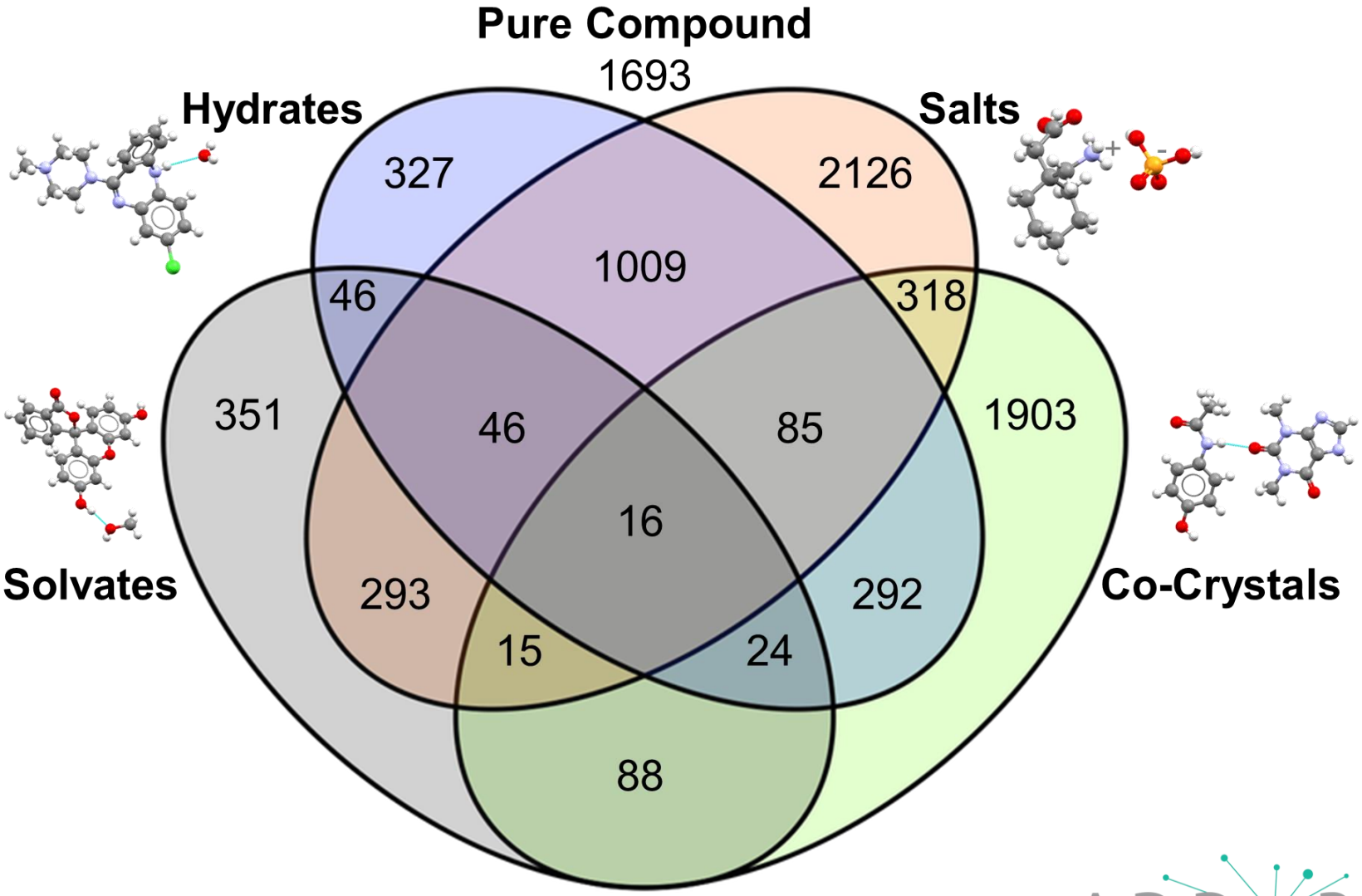
Searchable and sortable by categories like hydrates, solvates, salts, co-crystals, pure drug (or any combination of these)

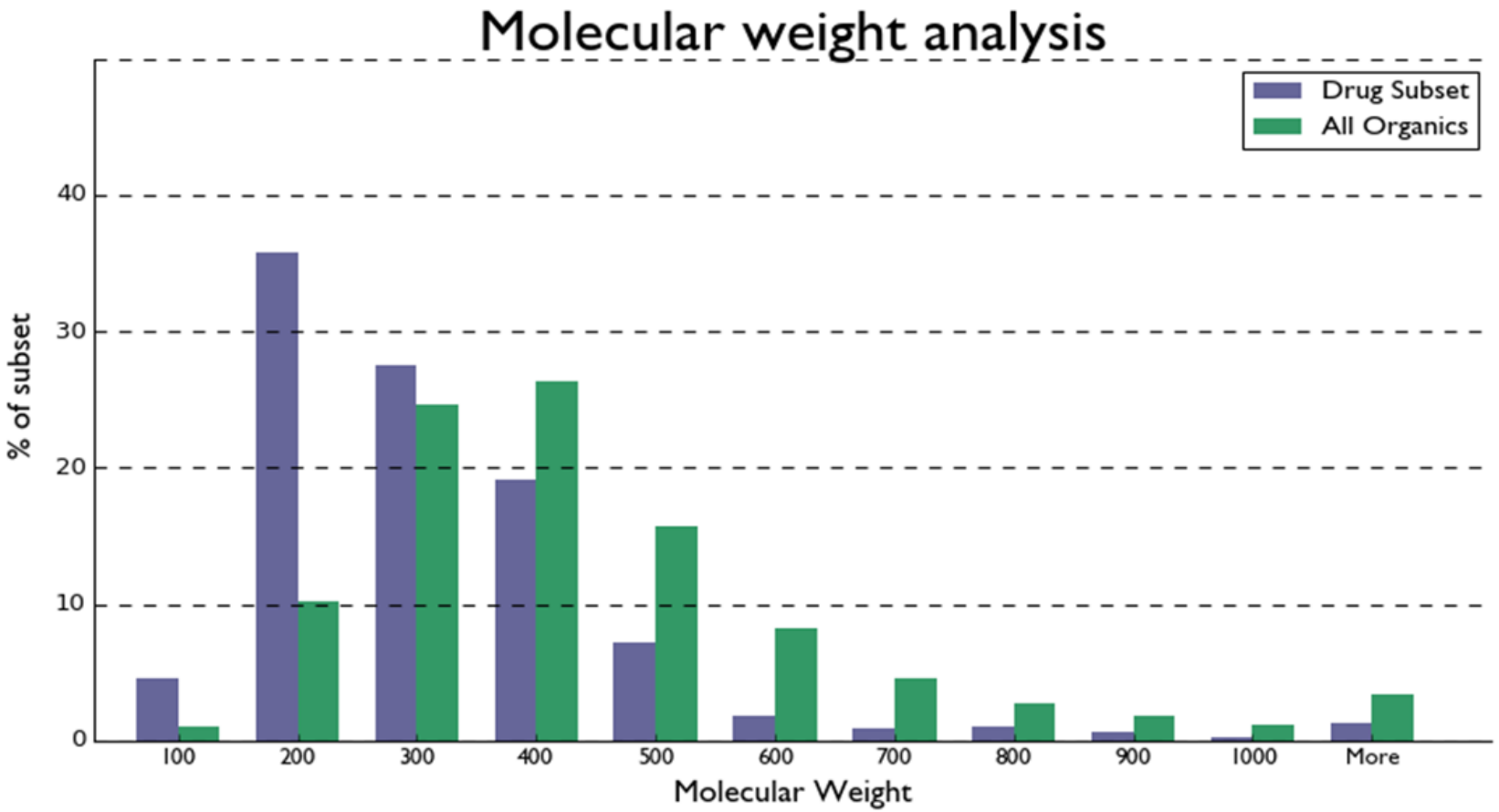


ADD PT

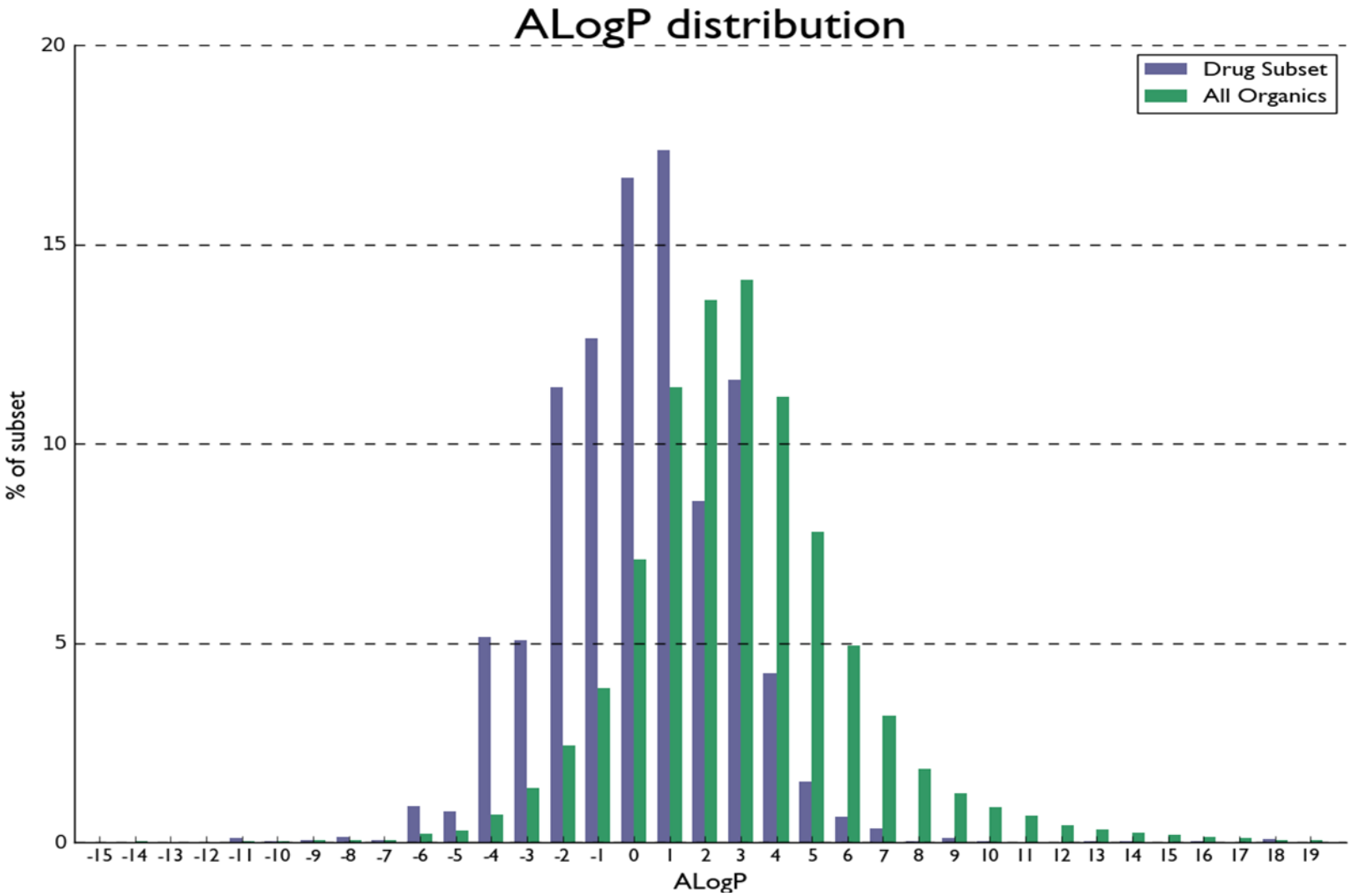
Making a CSD Drug Subset



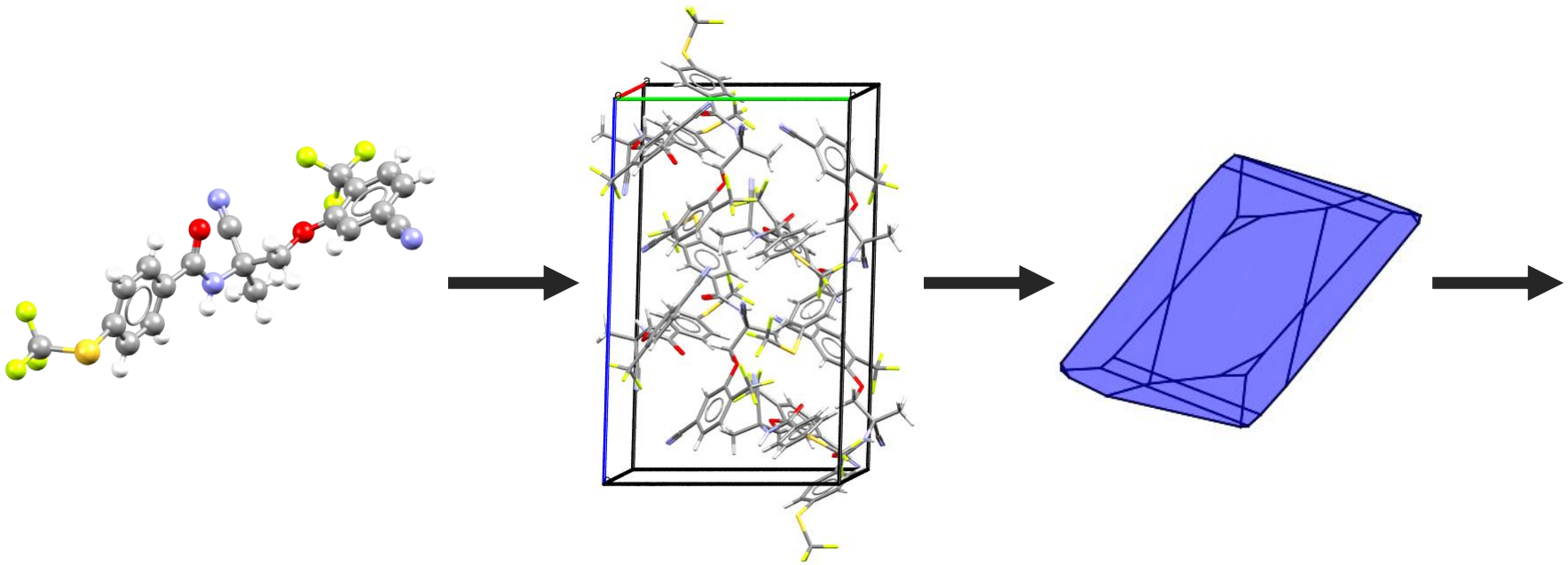
Comparison to organic molecules in the CSD



Comparison to organic molecules in the CSD

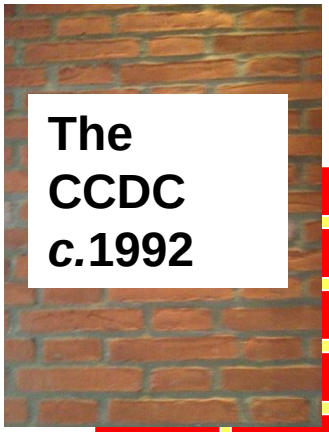


Drug product design and development



Molecule **Form** **Particle**

Which is the stable wall?



The CCDC *c.*1992

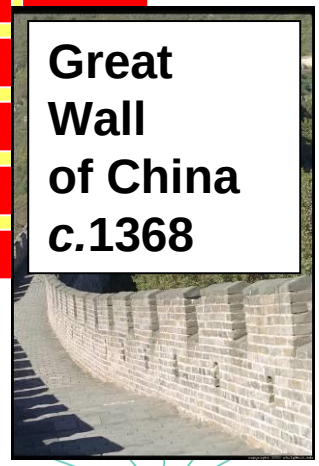
Great Pyramid of Giza *c.*2560 BC

Hadrian's Wall *c.*122

A

B

My House *c.*1968



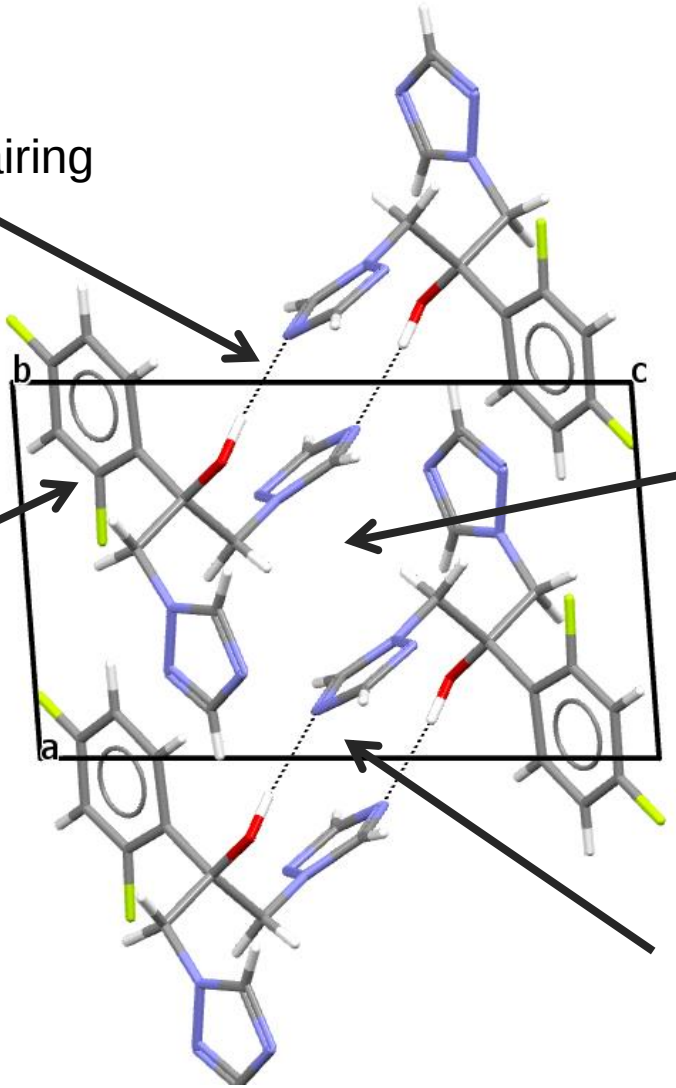
Great Wall of China *c.*1368

The database of walls indicates that A is the frequently observed arrangement and therefore the one that achieves stability.

ADD PT

Characteristics that influence stability

Hydrogen Bond
Donor/Acceptor Pairing



'Non-Hydrogen Bond'
Intermolecular
Interactions

Molecular
Conformation

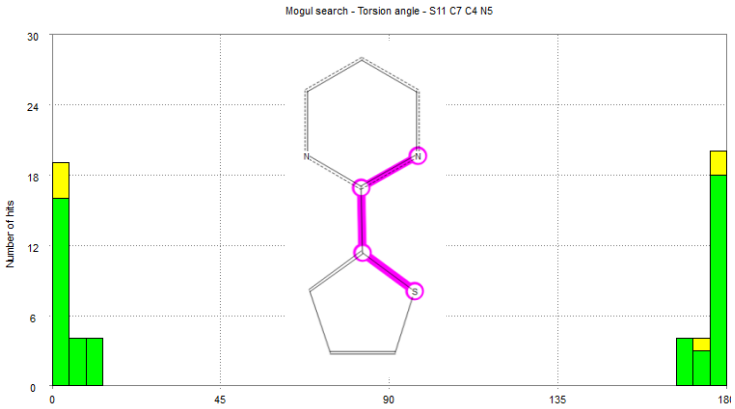
We mine the CSD to identify these intra- and intermolecular geometric preferences.

Hydrogen Bond
Geometry, Symmetry
and Motif

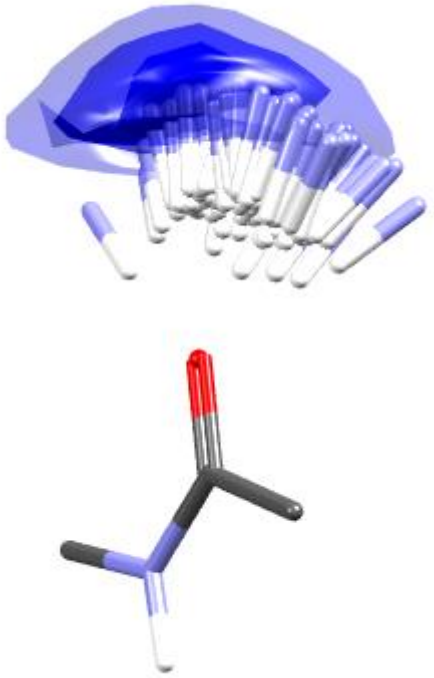
ADDOPT

CSD derived knowledge bases

Number of hits



Tosion angle (º)



Mogul

Molecular geometry distributions

- Bond lengths
- Valence angles
- Torsion angles
- Rings

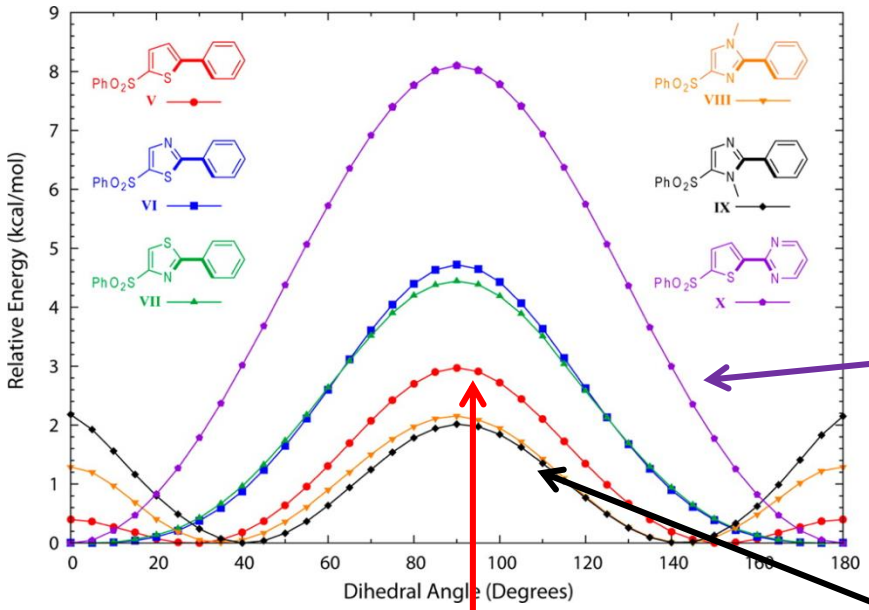
IsoStar

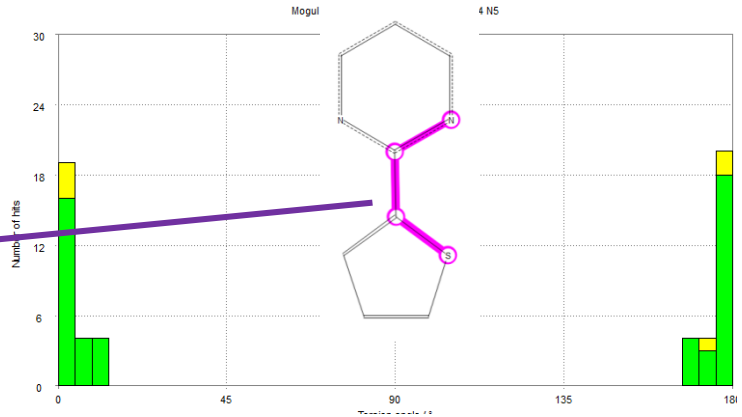
Intermolecular geometry analysis

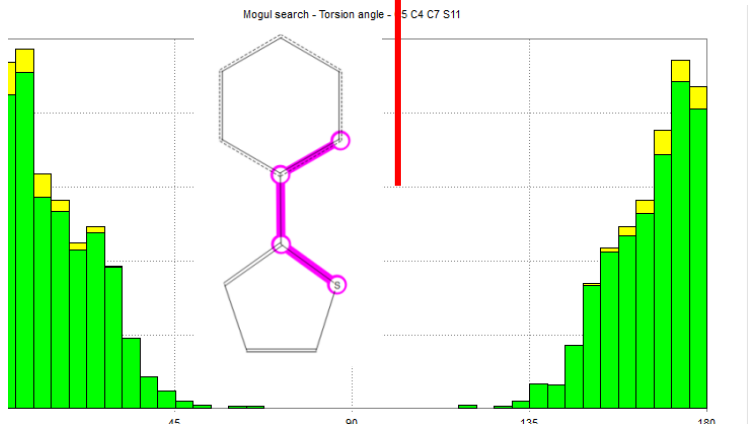
- Interaction distributions displayed as scatterplots or contour surfaces
- 18,000 pre defined interaction scatter plots

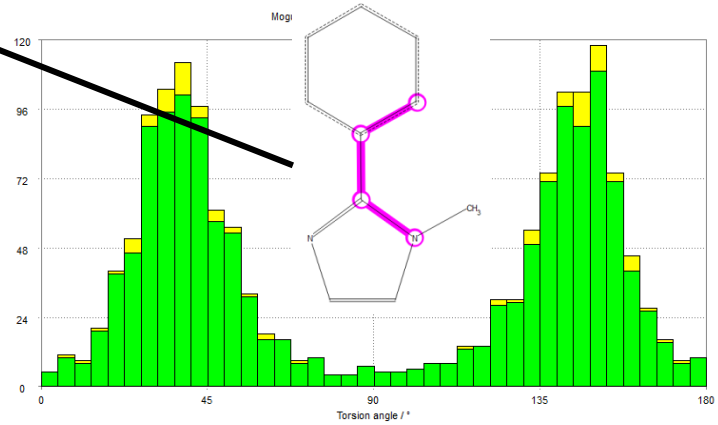
ADDOPT

Understanding conformational complexity







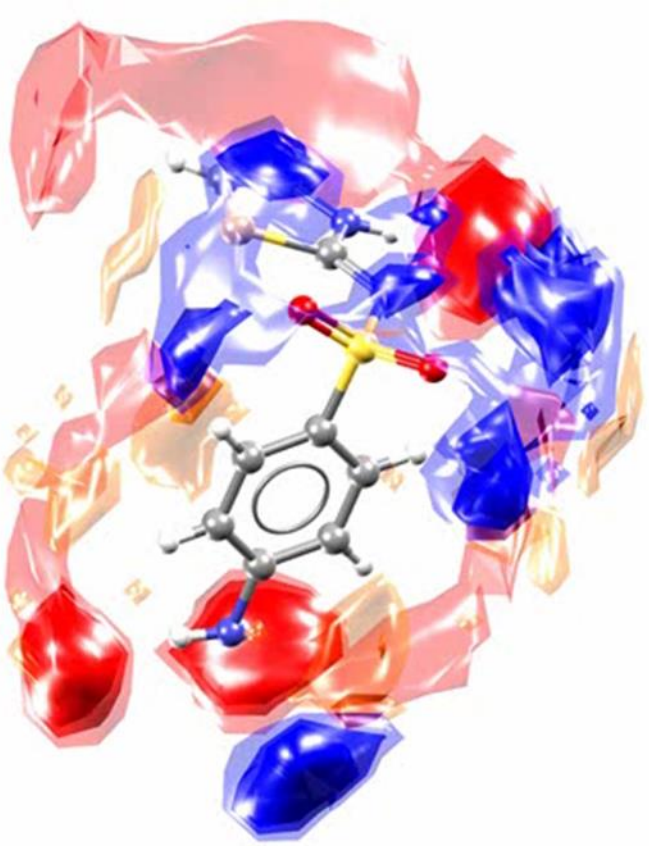


Tamayo *et al., J. Med. Chem.* (2015), **58**, 4462–4482
Pennington *et al., J. Med. Chem.* (2015), **58**, 9663−9679

Full Interaction Maps

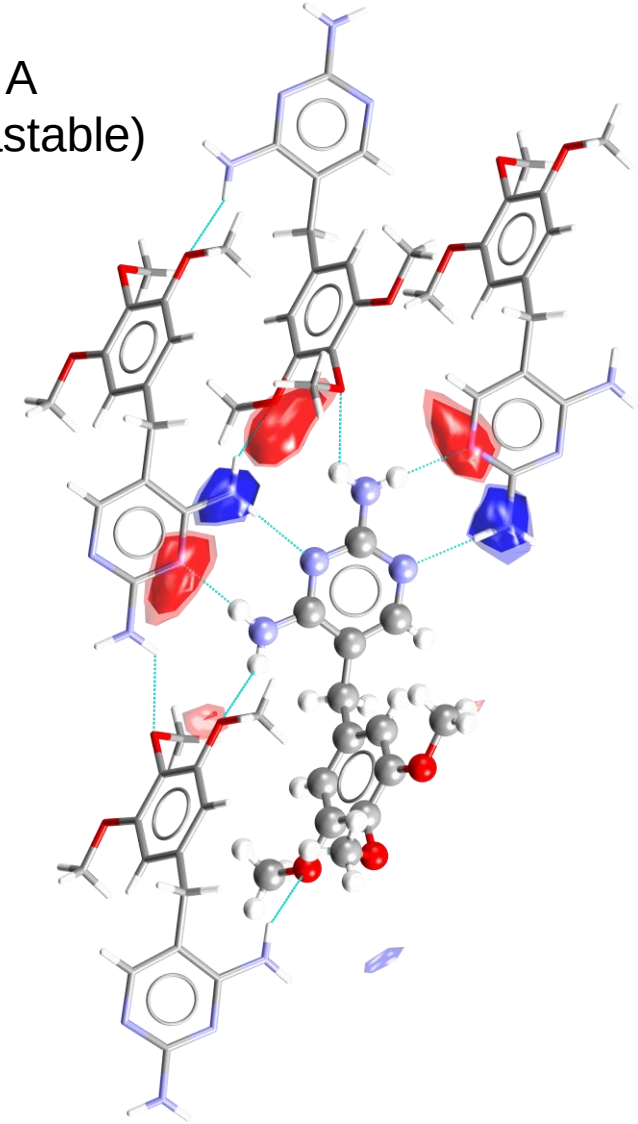
IsoStar libraries used to map interaction preferences around complete molecules in a crystal structure

The satisfaction of the Full Interactions Maps by the packing shell of the crystal structure can then be used to assess stability

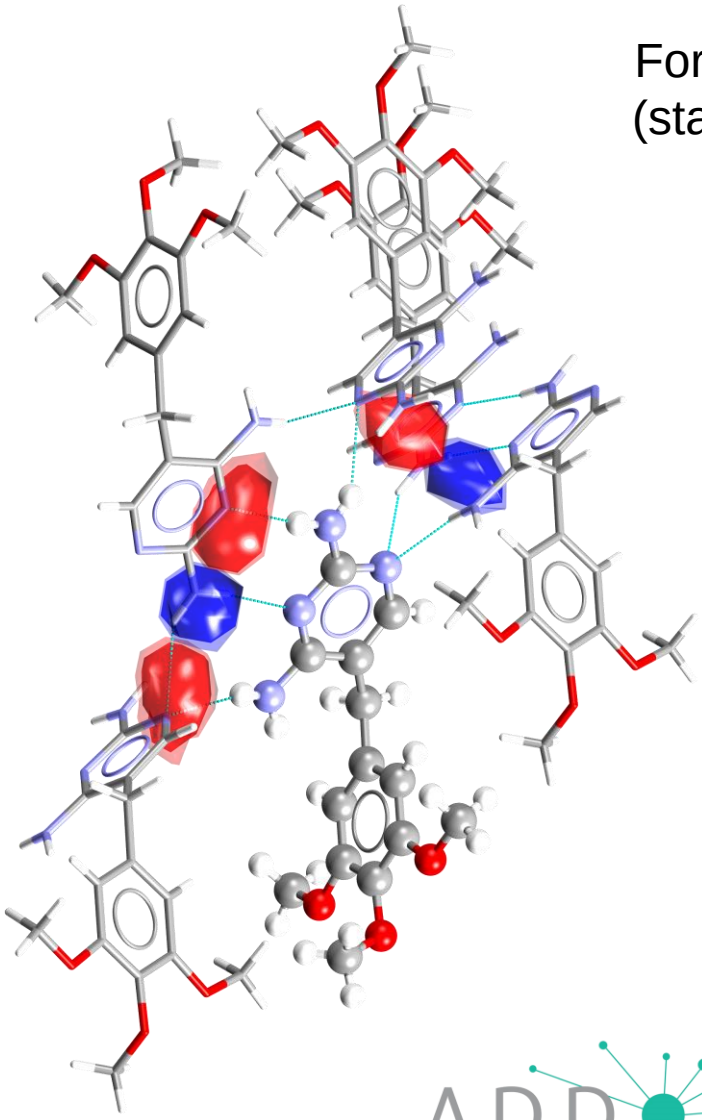


Using Full Interaction Maps to assess stability

Form A
(metastable)

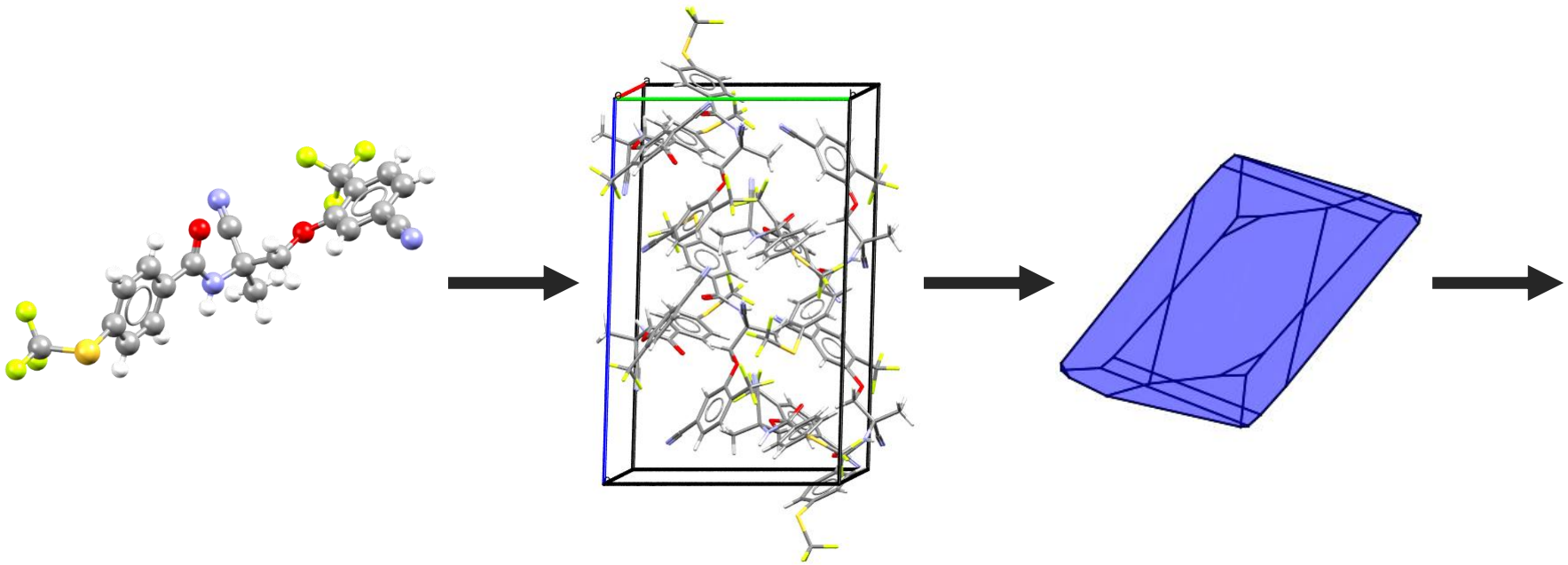


Form B
(stable)



D.Maddileti *et al.*, *Cryst.Growth Des.* (2015), **15**(4), 1745-1756

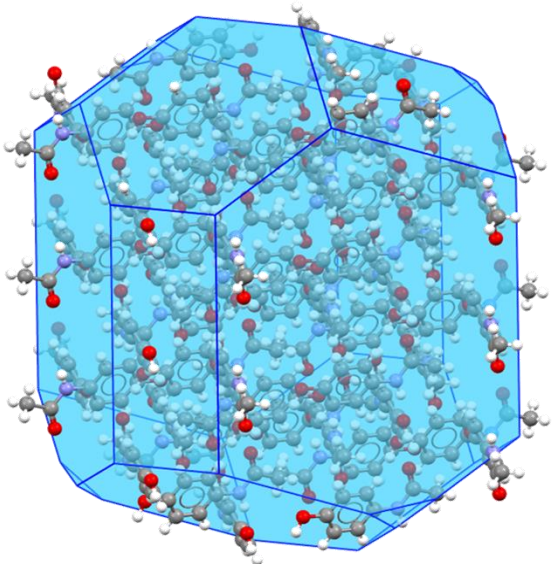
Drug product design and development



Molecule **Form** **Particle**

ADDOPT

Crystal structure directs…



- Morphology/crystal growth
- Surface chemistry
- Mechanical properties
- Solubility
- Stability
- Melting point

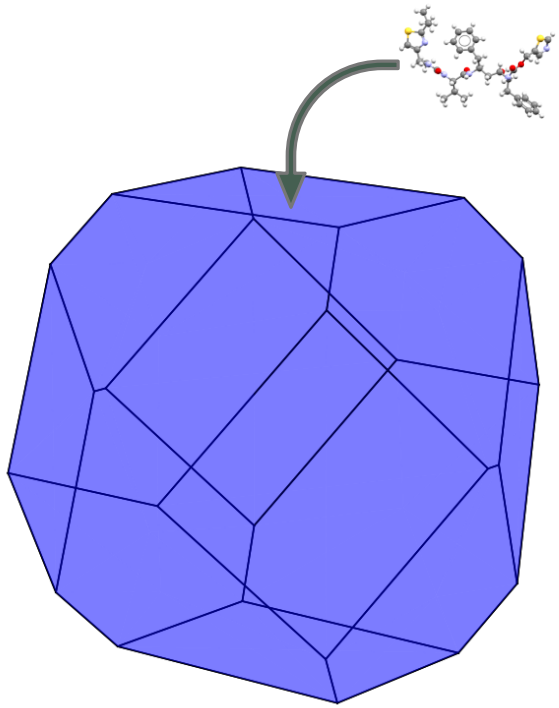
Predicting morphologies

Start from a base morphology prediction

Assume nucleation onto existing faces to be the rate limiting step in further crystal growth

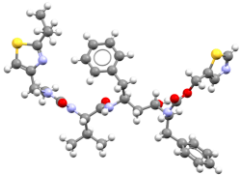
Use a forcefield to quantify the most favourable site of interaction

As growth rate is proportional to the nucleation rate, this allows us to use nucleation kinetics, including a term for supersaturation

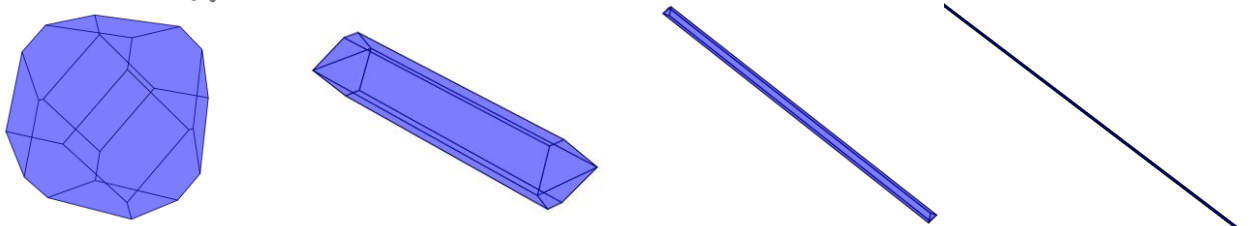


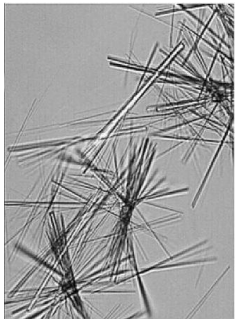
D. Vatvani, *"Predicting the morphology of crystals of organic molecules"*, PhD Thesis

Predicting morphologies

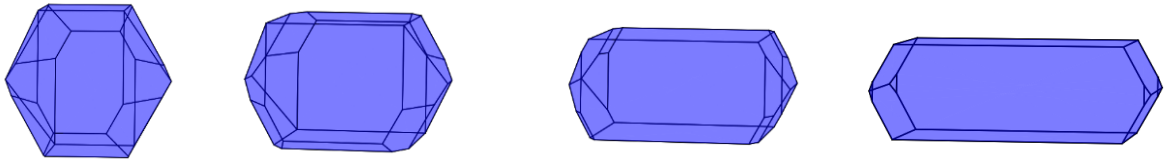


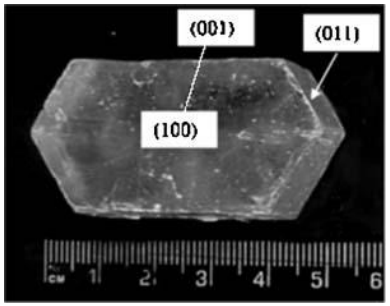
Ritonavir Form-II

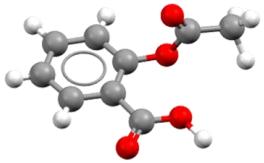




Supersaturation





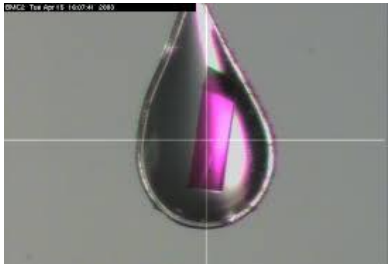


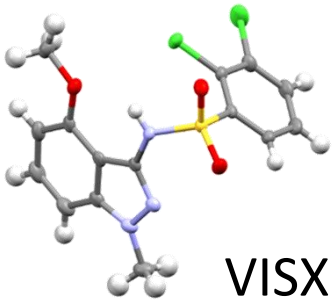
Aspirin

J.F. Bauer, *J. Valid. Technol.* (2009), **15**, 37 - 44
J.Y.Y. Heng, *J. Pharm. Sci.* (2007), **96**(8), 2134 - 2144

ADDOPT

Linking experimental and predicted crystal morphologies

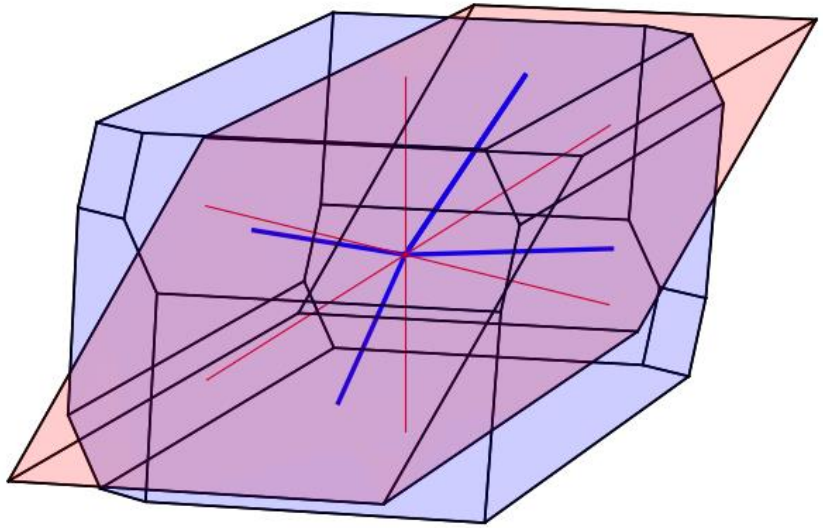




VISXUS

Crystal Face 1	Crystal Face 2	Dihedral angle
(-1, 1, 0)	(1, -1, -1)	155.8158
(-1, 1, 0)	(-1, 1, 1)	155.8158
(-1, 1, 0)	(1, 0, 0)	146.1096
(-1, 1, 0)	(1, -1, 0)	180
(-1, 1, 0)	(0, 0, 1)	95.45741
(-1, 1, 0)	(1, 0, -1)	140.2617
(-1, 1, 0)	(1, -1, -1)	155.8158

```
loop_
_exptl_crystal_face_index_h
_exptl_crystal_face_index_k
_exptl_crystal_face_index_
l_exptl_crystal_face_perp_dist
0.00 1.00 1.00 0.239
0.00 -1.00 2.00 0.451
0.00 -2.00 -1.00 0.216
0.00 0.00 -1.00 0.201
1.00 0.00 -1.00 0.574
-1.00 0.00 1.00 0.383
```

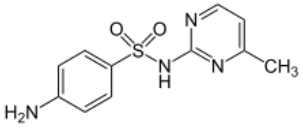


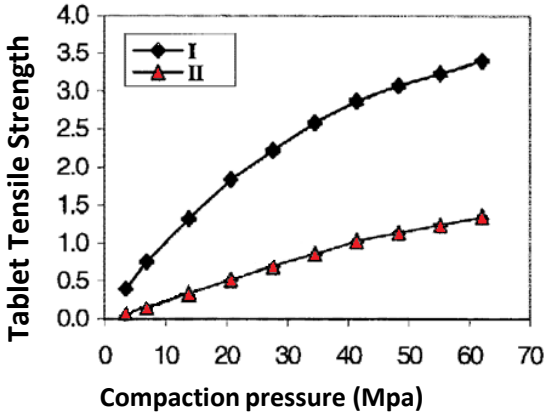
RMSD: 10.14

ADDOPT

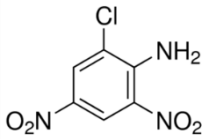
Mechanical properties from structure

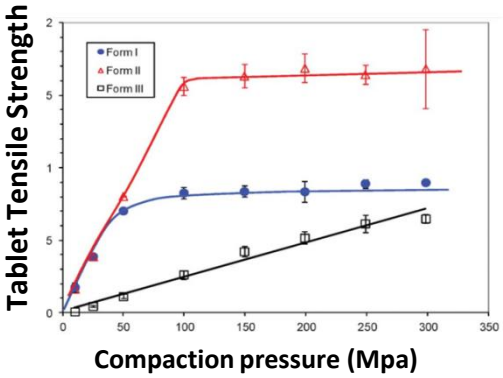
Sulfamerazine



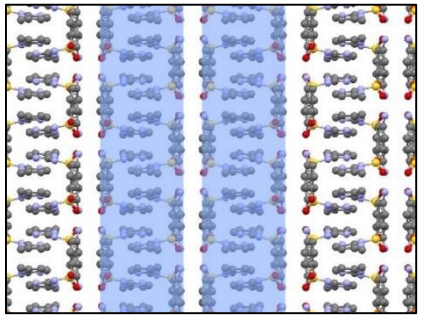


6-chloro-2,4-dinitroanilene

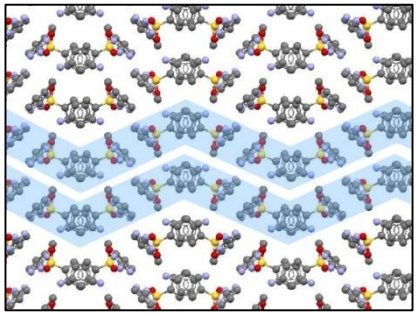




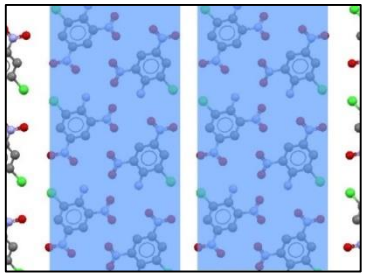
Form-I



Form-II



Form-I



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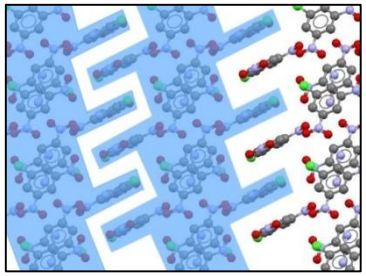
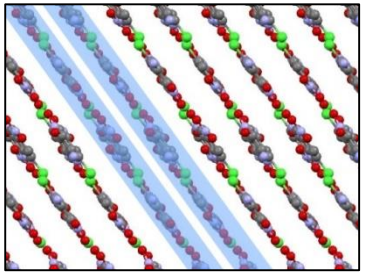


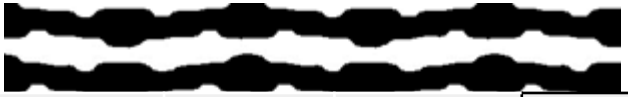
Form-II



C.C. Sun, *J. Adhes. Sci. Technol.* (2011), **25**, 483 - 499

ADD PT

Predicting slip planes



Crystal	Observed	Dreiding	cvff	compass	CCDC Rugosity tool
SLFNMA01	**020**	002	002	002	**010**
SLFNMA02	**020**	020	020	020	**010**
260457 (UCECAG03)	**001**	001	001	001	**001**
CITRAC10	**002**	002	002	002	**001**
260456 (UCECAG02)	**001**	001	001	001	**001**
PUPBAD01	**10-2**	10-2	020	011	**10-2**
PUPBAD02	**101**	10-1	011	020	**101**
HXACAN	**002**	002	200	200	**001**
HXACAN01	**010**	110	110	110	**010**
DIJVOH	**002**	200	200	200	**001**
260455 (UCECAG01)	**10-1**	100	100	100	**10-1**
ethyl paraben (FEGLEI)	**101**	100	100	100	**101**
propyl paraben (DUPKAB)	**101**	100	100	100	**101**

calculate the miller plane the line follows using the CSD Python API

Plane [0 1 0]
Rugosity = 1.30

C.C. Sun and Y.-H. Kiang, *J. Pharm. Sci.* (2008), **97**, 3456-3461

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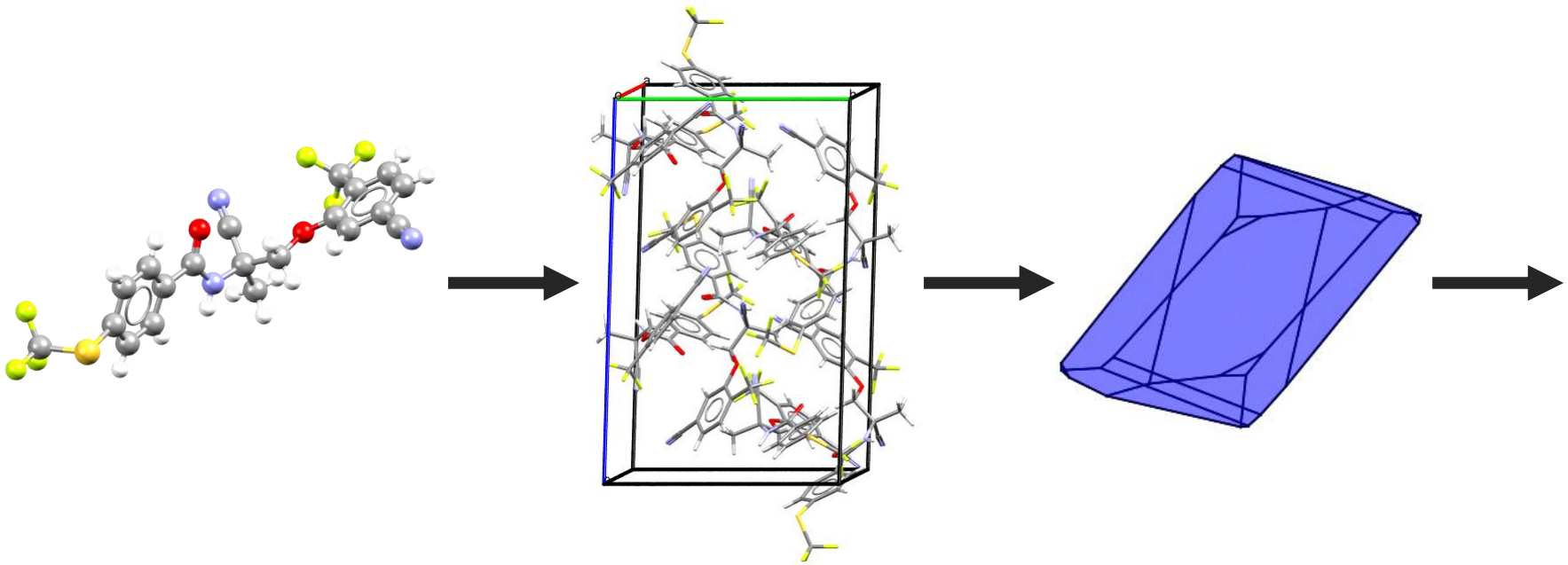
Making the most of every crystal structure ever published



Molecule **Form** **Particle**

Acknowledgements

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