Lessons Learned from 30 Commercial Pharmaceutical Crystal Structure Prediction Studies

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Sponsored by The International Centre for Diffraction Data

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ICDD Website - www.icdd.com

Crystal Structure Prediction (CSP)

Crystal Structure Prediction

Also called “polymorph prediction”

In silico polymorph screening

Does not suffer from kinetics

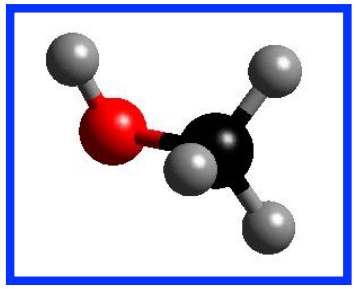
The calculations take several months…

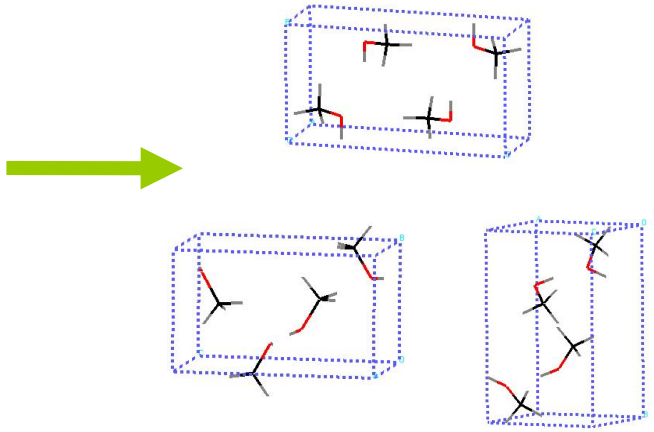
Crystal Structure Prediction

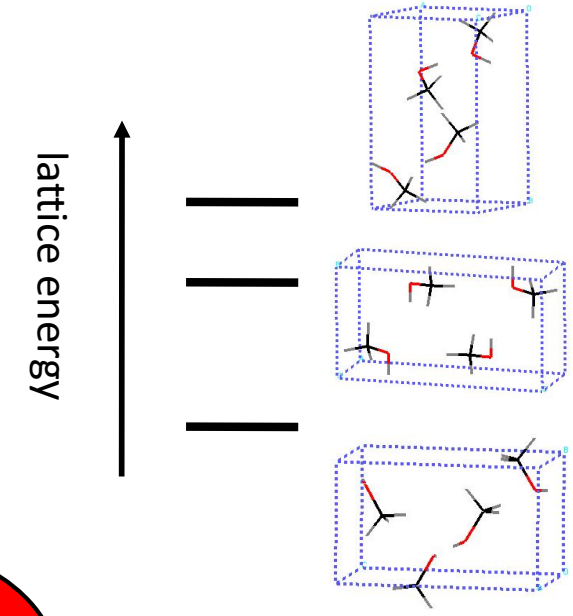
Compound

Trial structures

Predicted structures





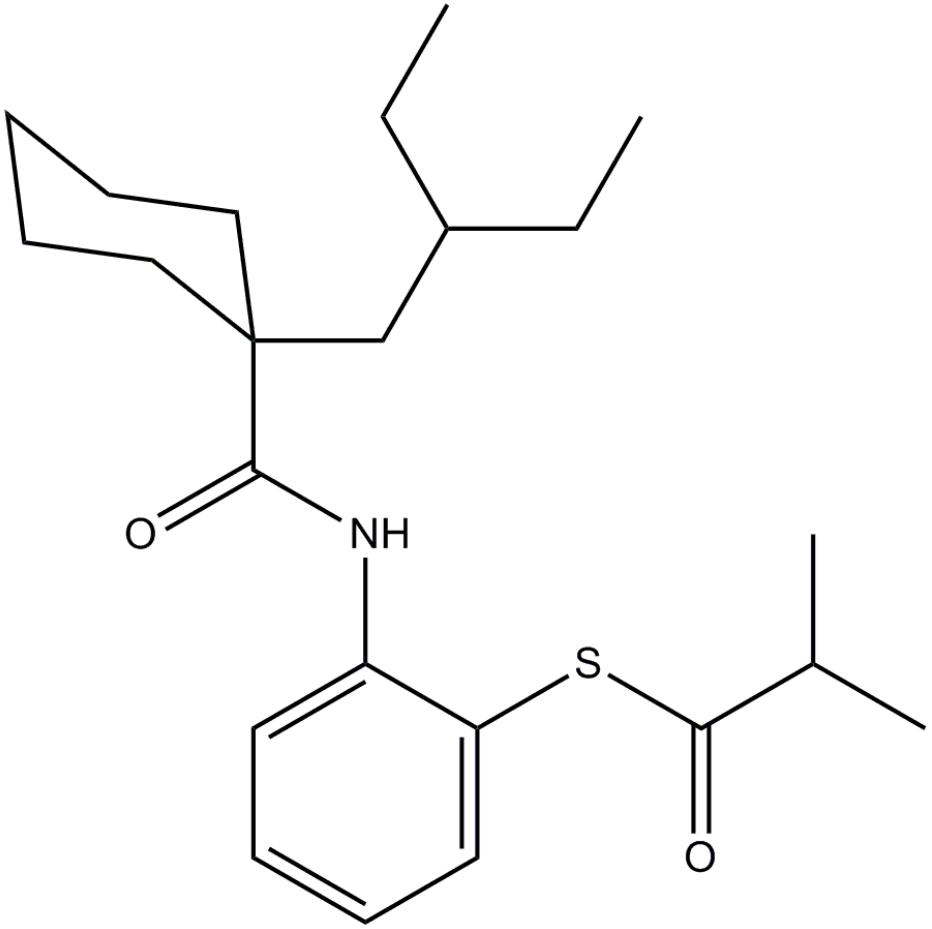


structure generation

energy ranking

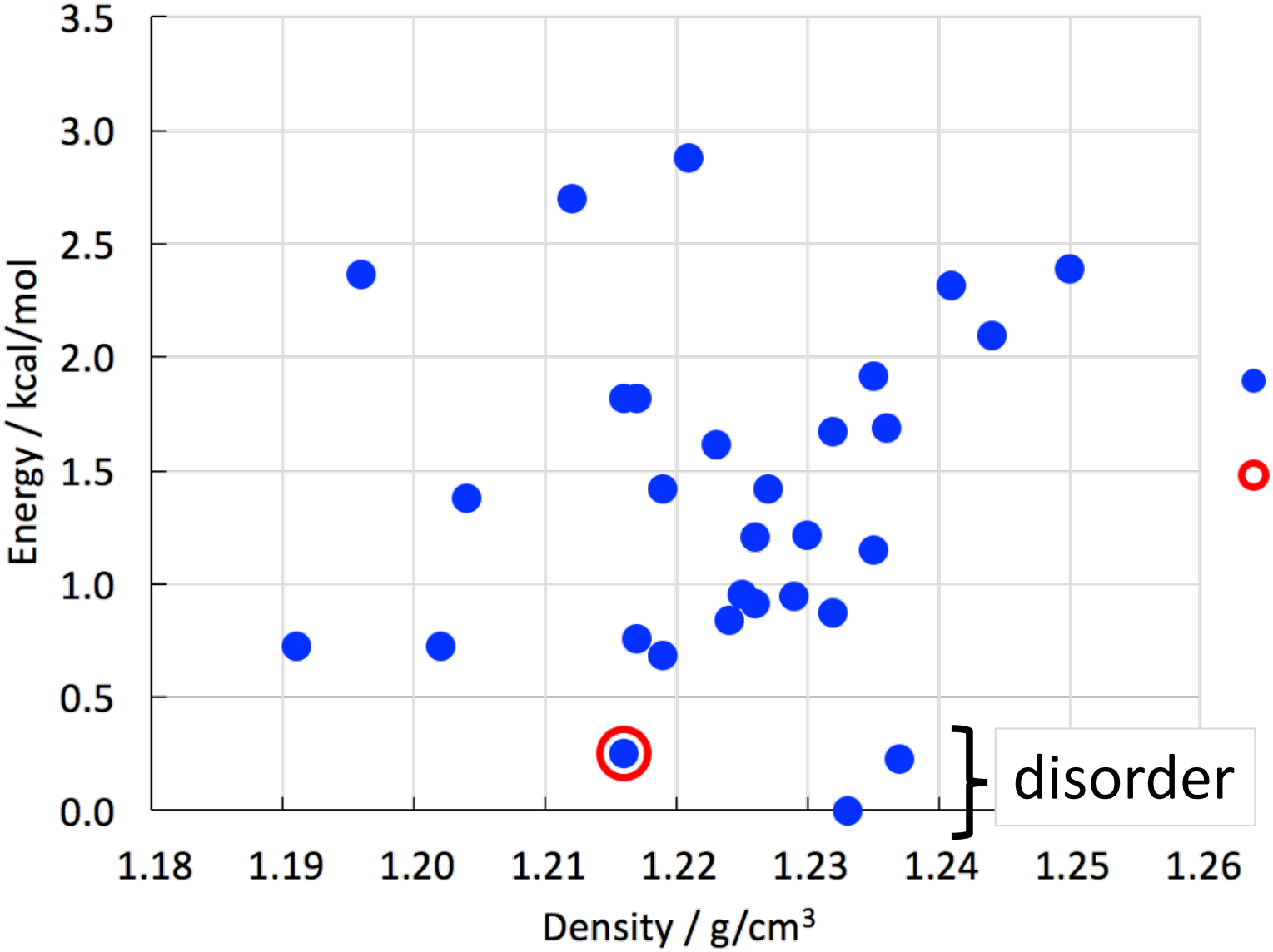
Avant-garde Materials Simulation

Example: CSP of Dalcetrapib



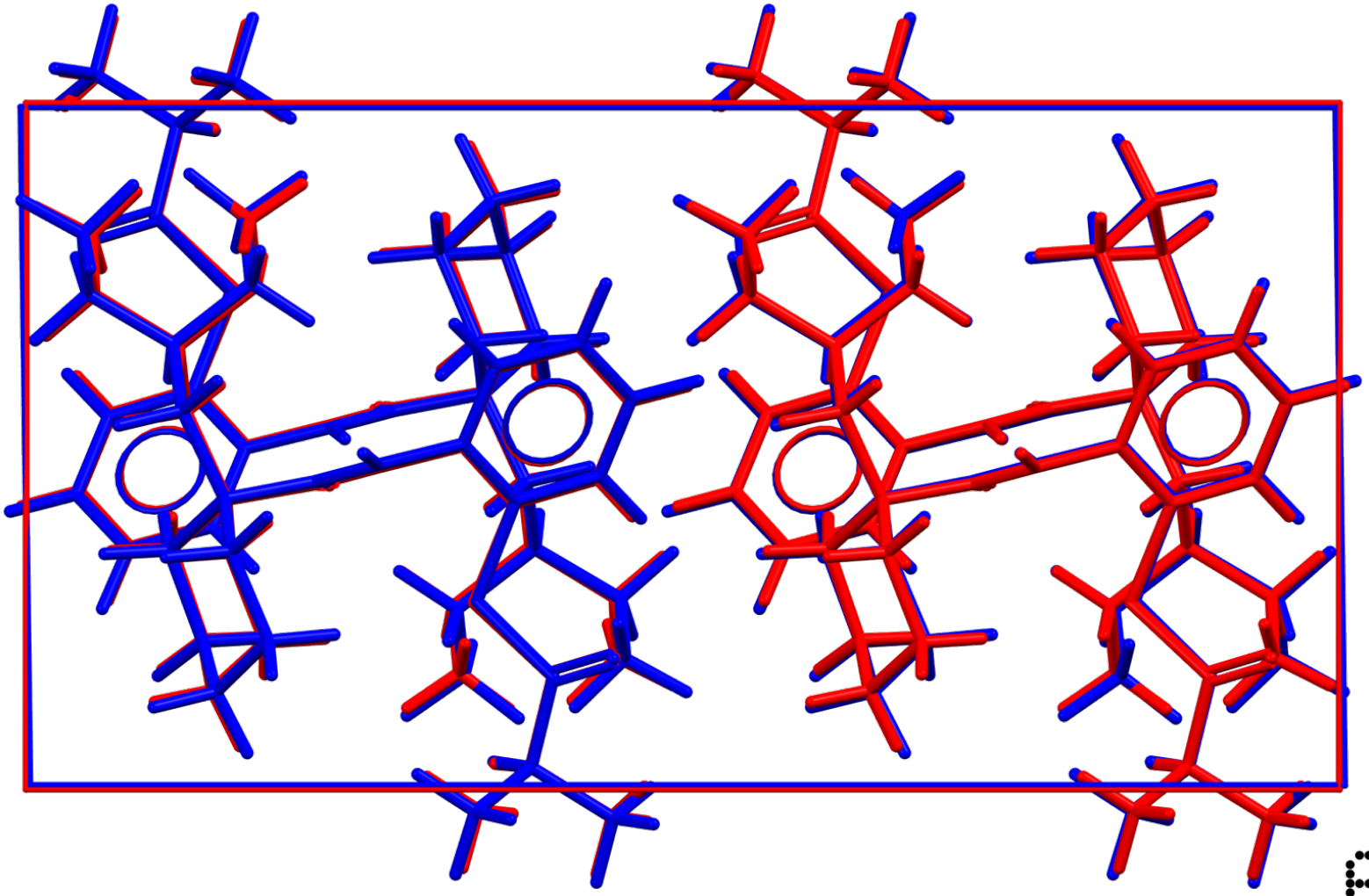
Avant-garde Materials Simulation

Energy Landscape of Dalcetrapib



Avant-garde Materials Simulation

CSP of Dalcetrapib

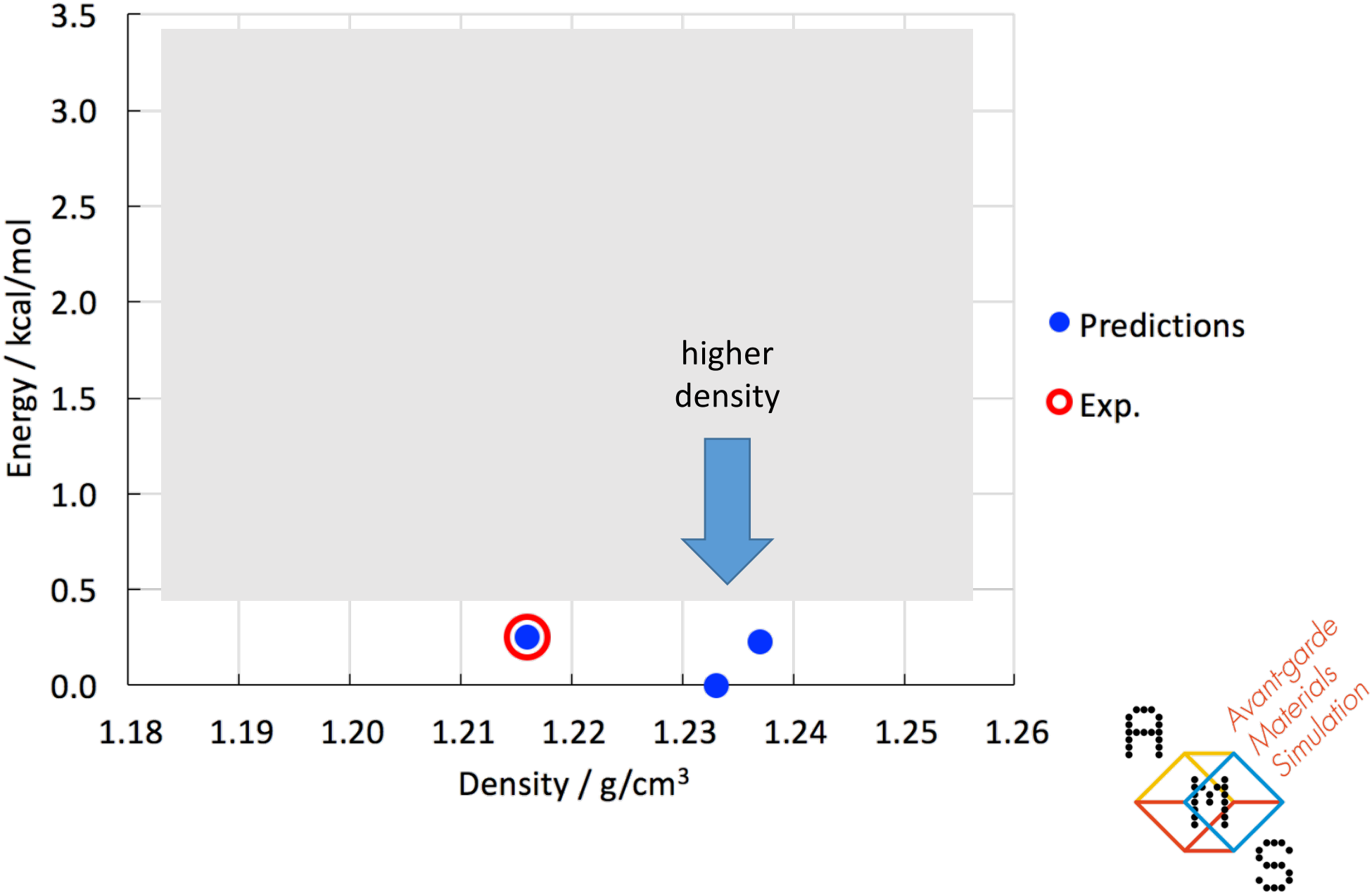


Predicted #2

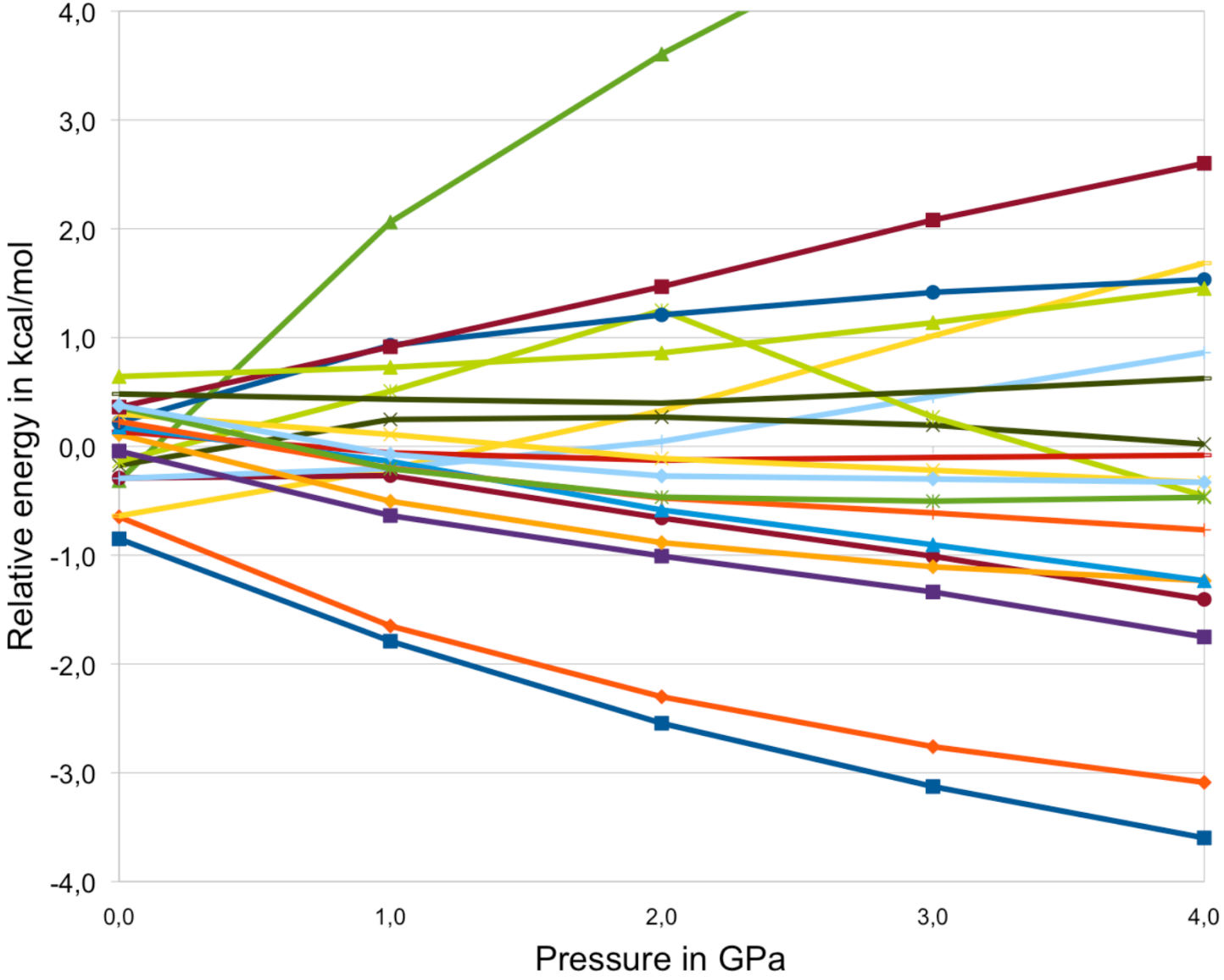
Experiment

Avant-garde Materials Simulation

Energy Landscape of Dalcetrapib



Pressure Scan of Dalcetrapib



Avant-garde Materials Simulation

High-Pressure Crystallisation

Francesca Fabbiani crystallised Dalcetrapib at “high pressure” and found the new form (which turned out to be less stable at ambient pressure).

Neumann *et al*. (2015) *Nature Comm.* **6**, doi:10.1038/ncomms8793

CCDC Blind Test Statistics

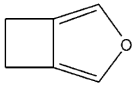
CSP Blind Tests

Crystal-structure Prediction Blind Tests:
Organised by CCDC and Dr Graeme Day

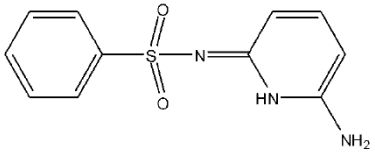
Blind Tests in 1999, 2001, 2004, 2007, 2010 and 2015

Reilly *et al*. (2016) *Acta Cryst.* B**72**, 439-459

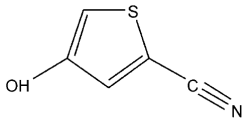
CSP Blind Tests



1 & 2



1, 2 & 3



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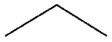

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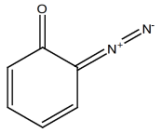

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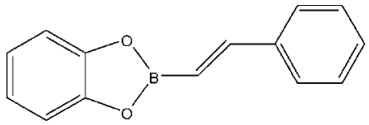

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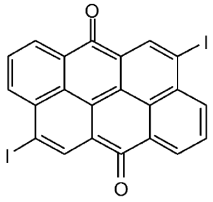

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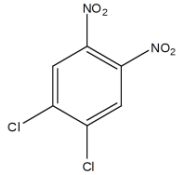

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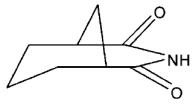
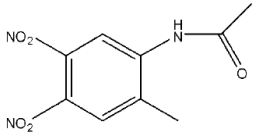


1 & 2



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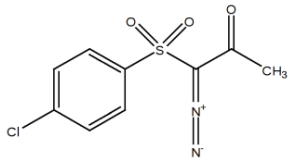

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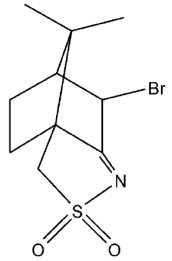

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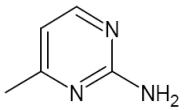

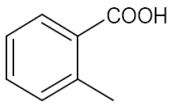

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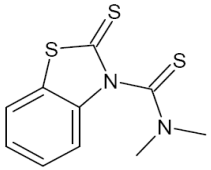

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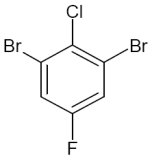

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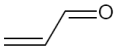


1

Asmadi *et al*. (2009) *J. Phys. Chem. B* **113**, 16303-16313

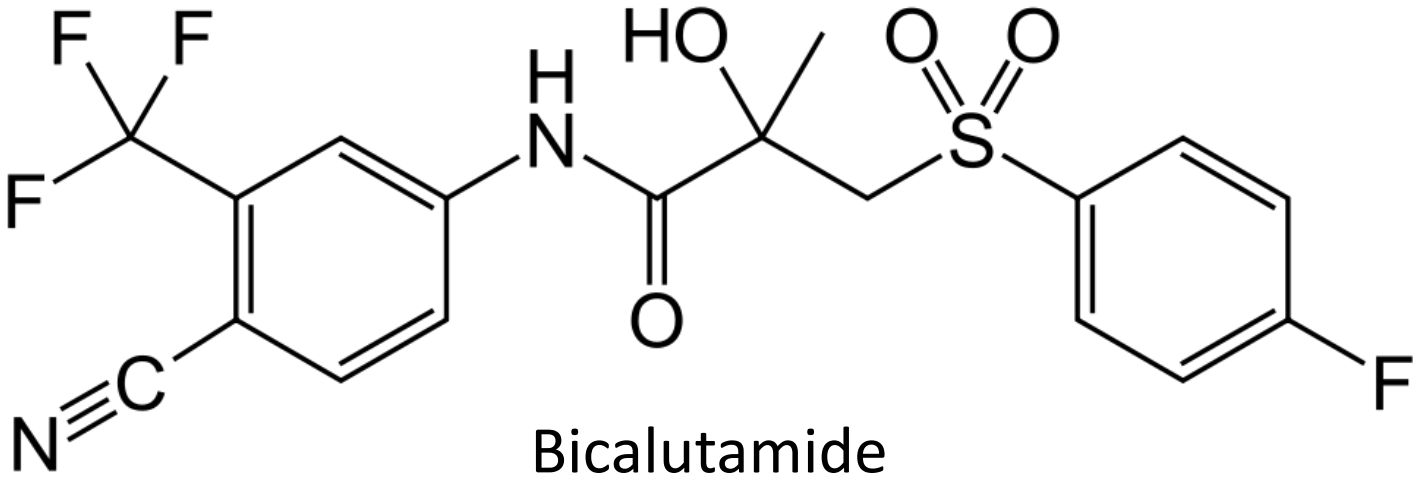
Commercial CSP Statistics

The 30 Compounds

On average:

30 non-H atoms
23 H atoms
3 trivial flexible torsion angles (*e.g.* CH_3)
6 non-trivial flexible torsion angles
1 flexible ring

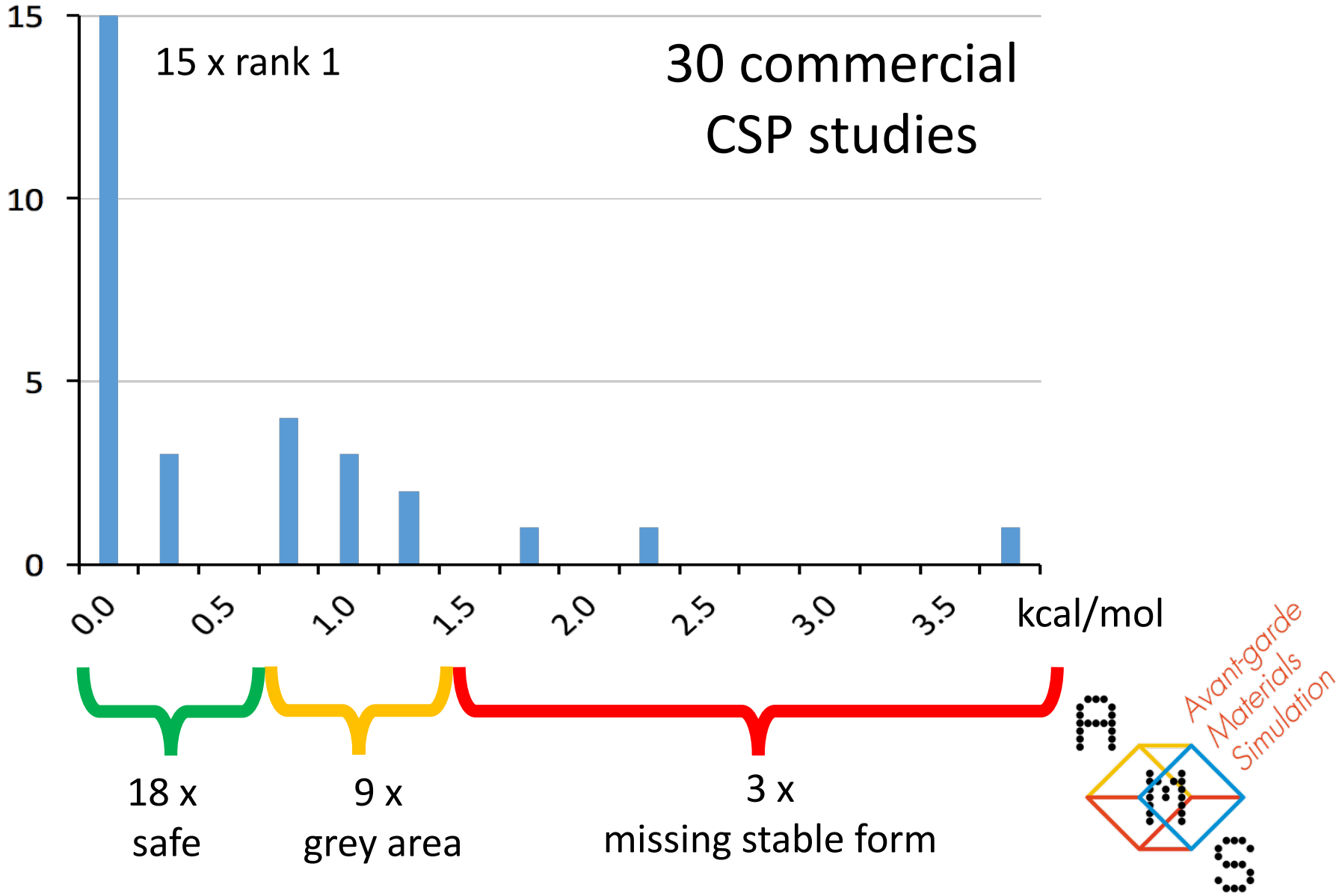
4 hydrates
2 zwitterions
20 chiral



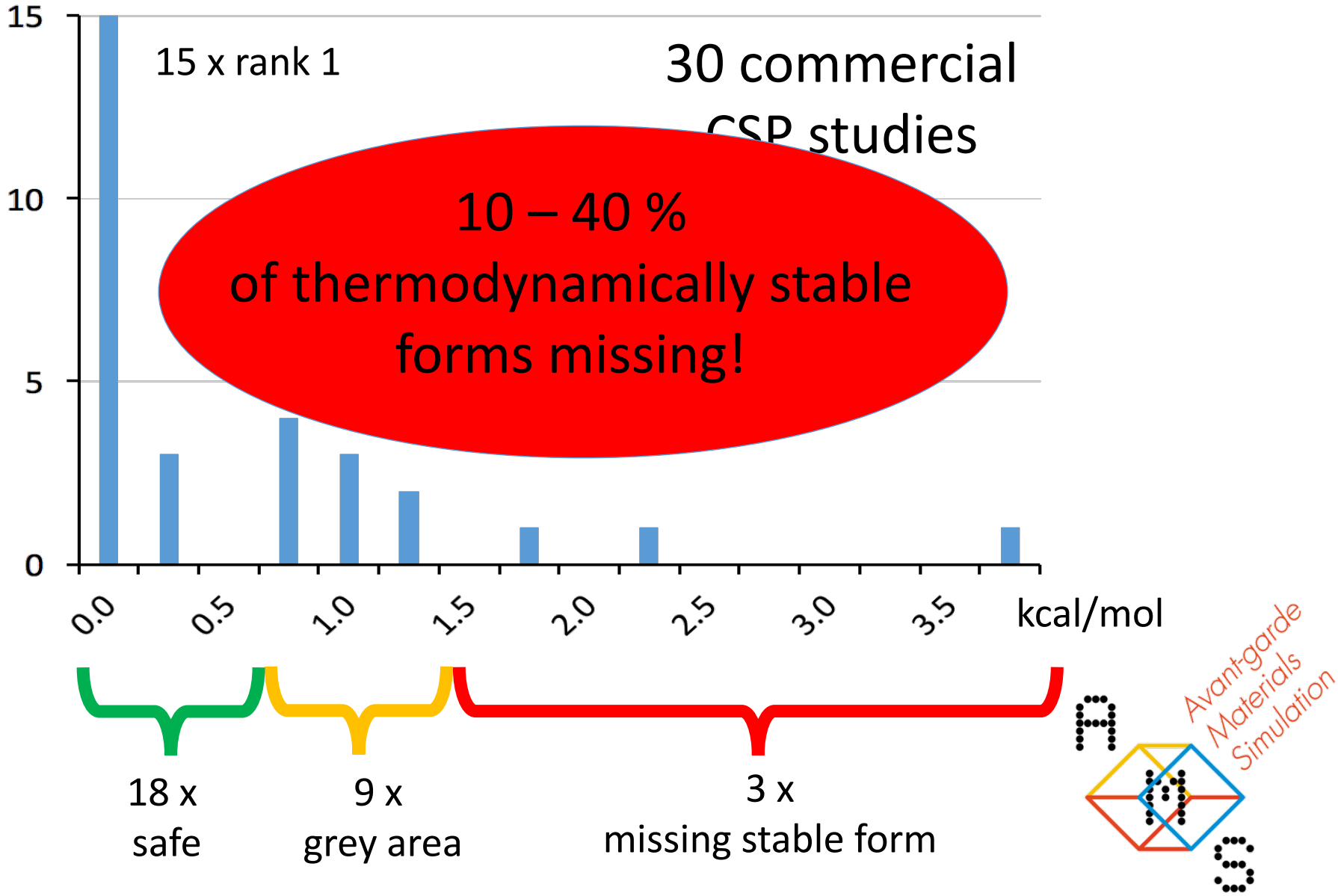
Bicalutamide

Avant-garde Materials Simulation

Energy Gap (Exp. - #1)

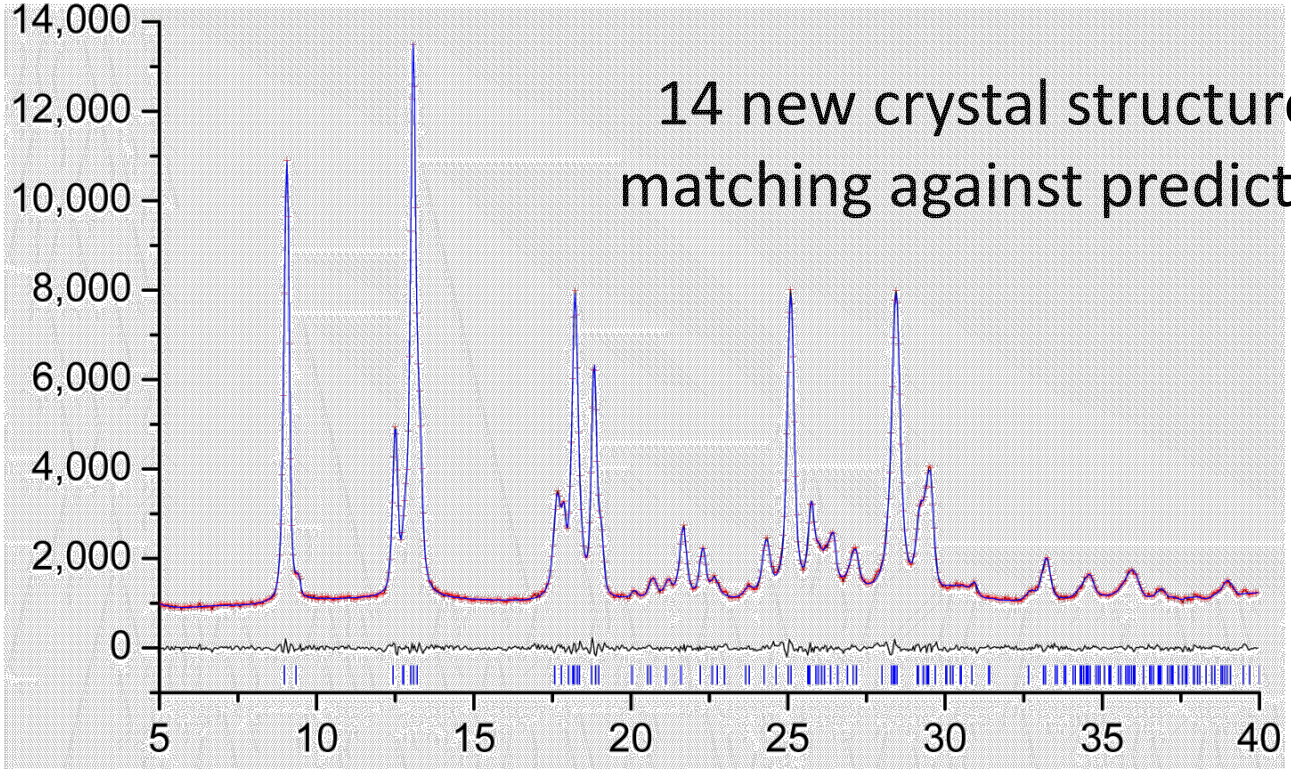


Energy Gap (Exp. - #1)



Matching XRPD Patterns

31 powder patterns made available
(including duplicates,
possible solvates,
sometimes very poor quality)



14 new crystal structures solved by
matching against predicted structures

Avant-garde Materials Simulation

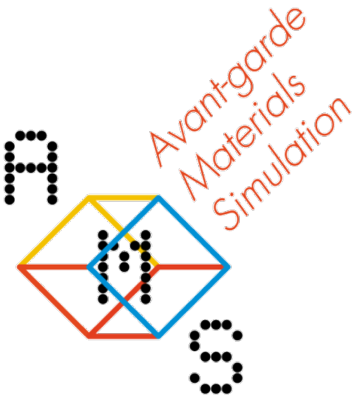
Habermehl *et al*. (2014) *Acta Cryst*. B**70**, 347-359.

Resources

On 384 cores (an average laptop has about 2 cores)
So roughly the equivalent of 200 laptops

Parameterising the tailor-made force field
Average: 2 weeks
Min: < 1 week
Max: > 1 month

CSP, Z'=1
Average: 2 weeks
Min: < 1 day
Max: > 2 months



Conclusions

At least 10% of all small-molecule drugs on the market have an as yet unknown significantly more stable polymorph

Crystal structure prediction can be used as a last resort method for crystal structure solution from powder diffraction data