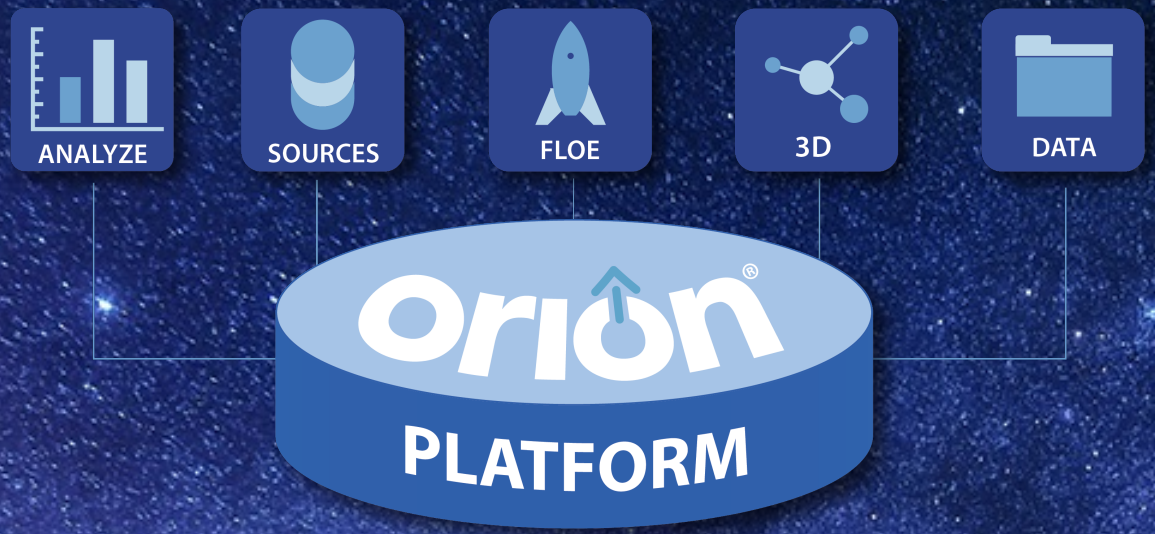

Crystal Structure prediction (CSP) is difficult, but not impossible!

Hari Muddana

OpenEye

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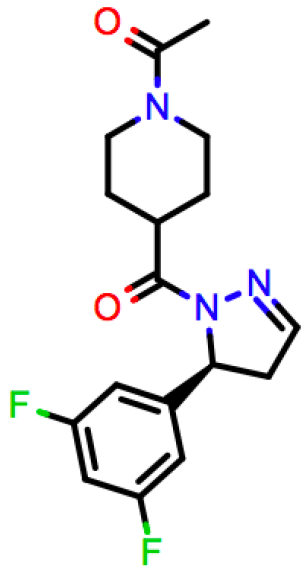
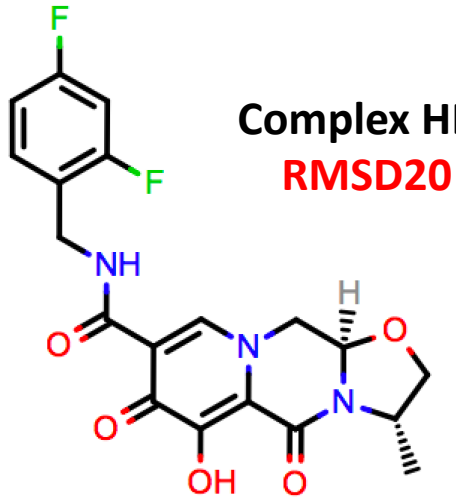
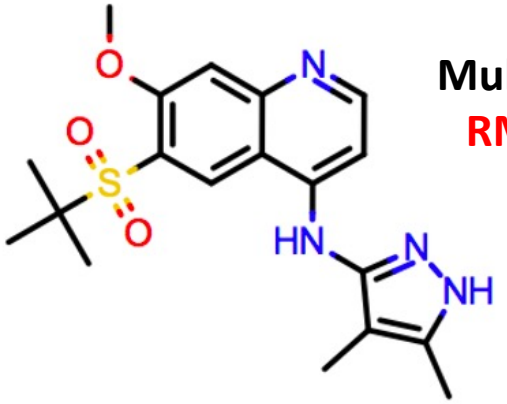
OpenEye-GSK blind challenges



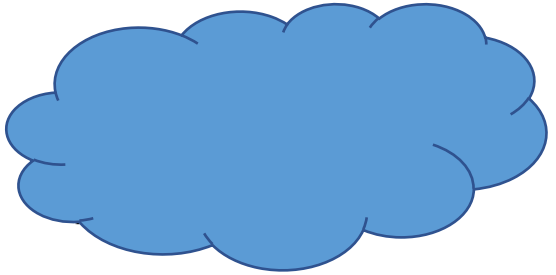
No hydrogen bonding
RMSD20 = 0.18A



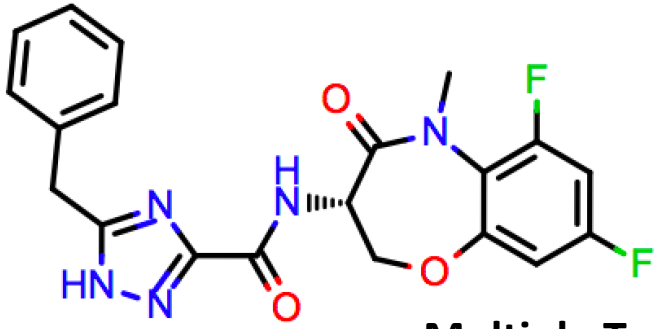
Complex HB network
RMSD20 = 0.18A



Multiple Tautomers
RMSD20 = 0.16A



Monohydrate
RMSD40 = 0.47A



Multiple Tautomers &
7-membered ring
RMSD20 = 0.23A

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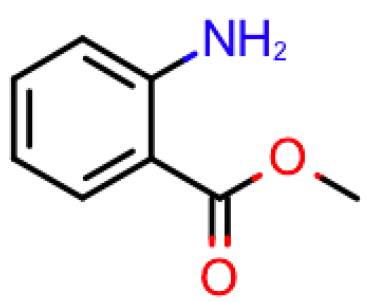
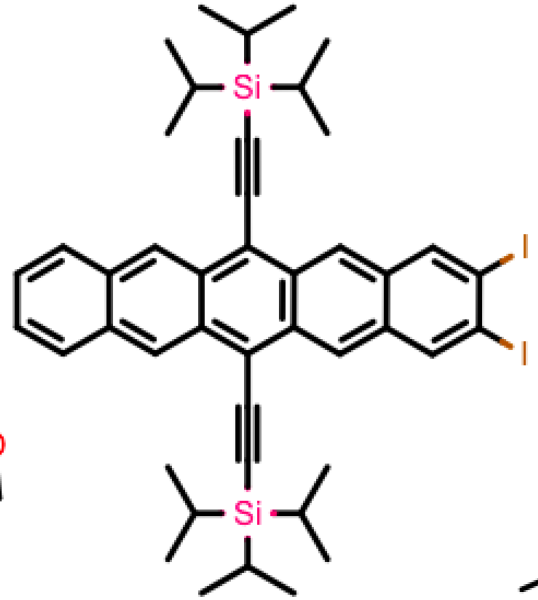
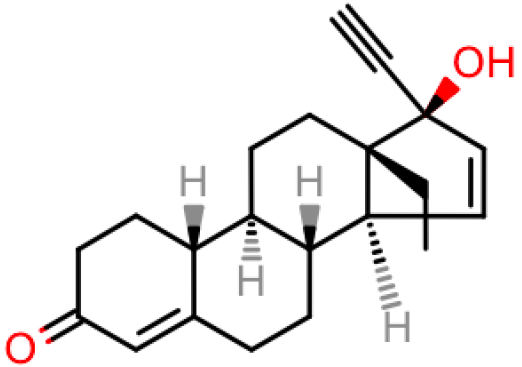
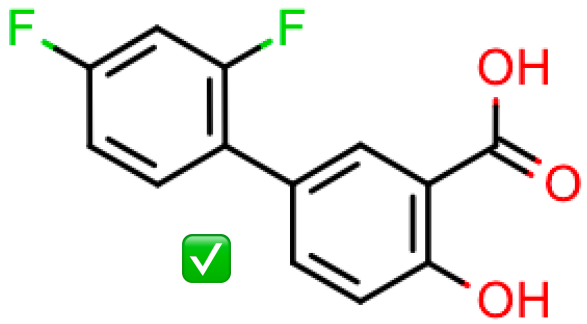
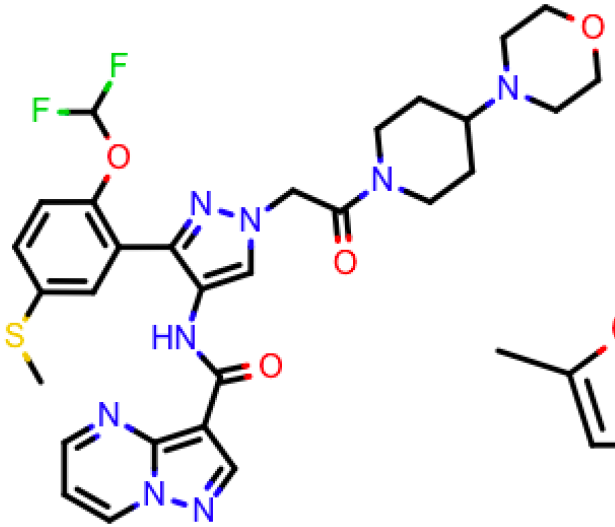
CCDC7 challenge & others

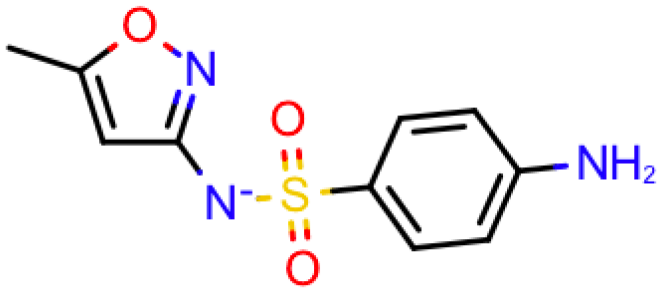


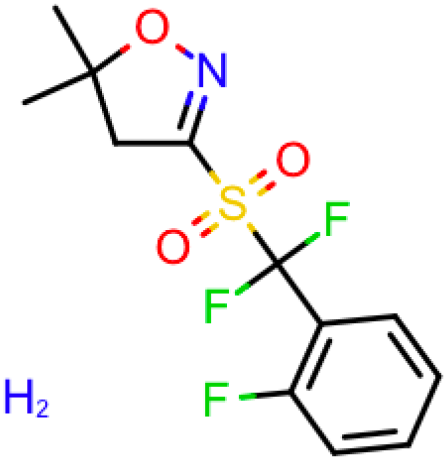


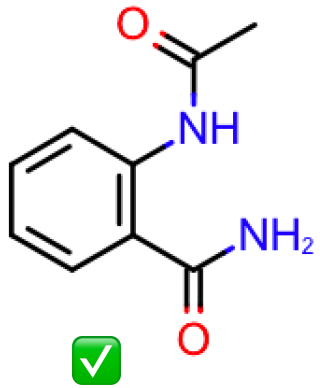


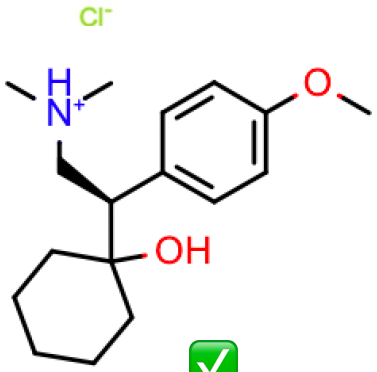






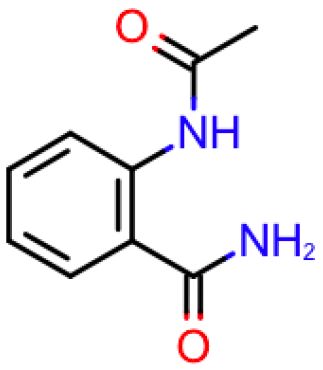




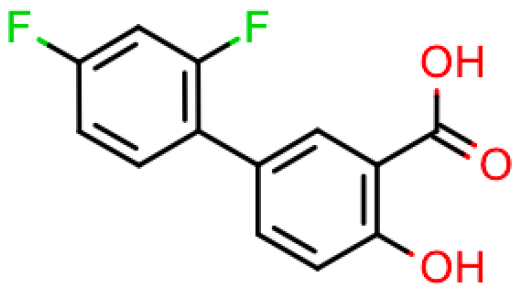


Outline

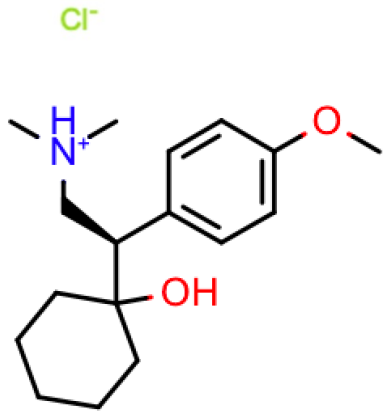
- CSP workflow
- IEFF and QM/MM energy model
- Case study 1: O-acetamidobenzamide
- Case study 2: Diflunisal
- Case study 3: Venlafaxine
- Summary



O-acetamidobenzamide

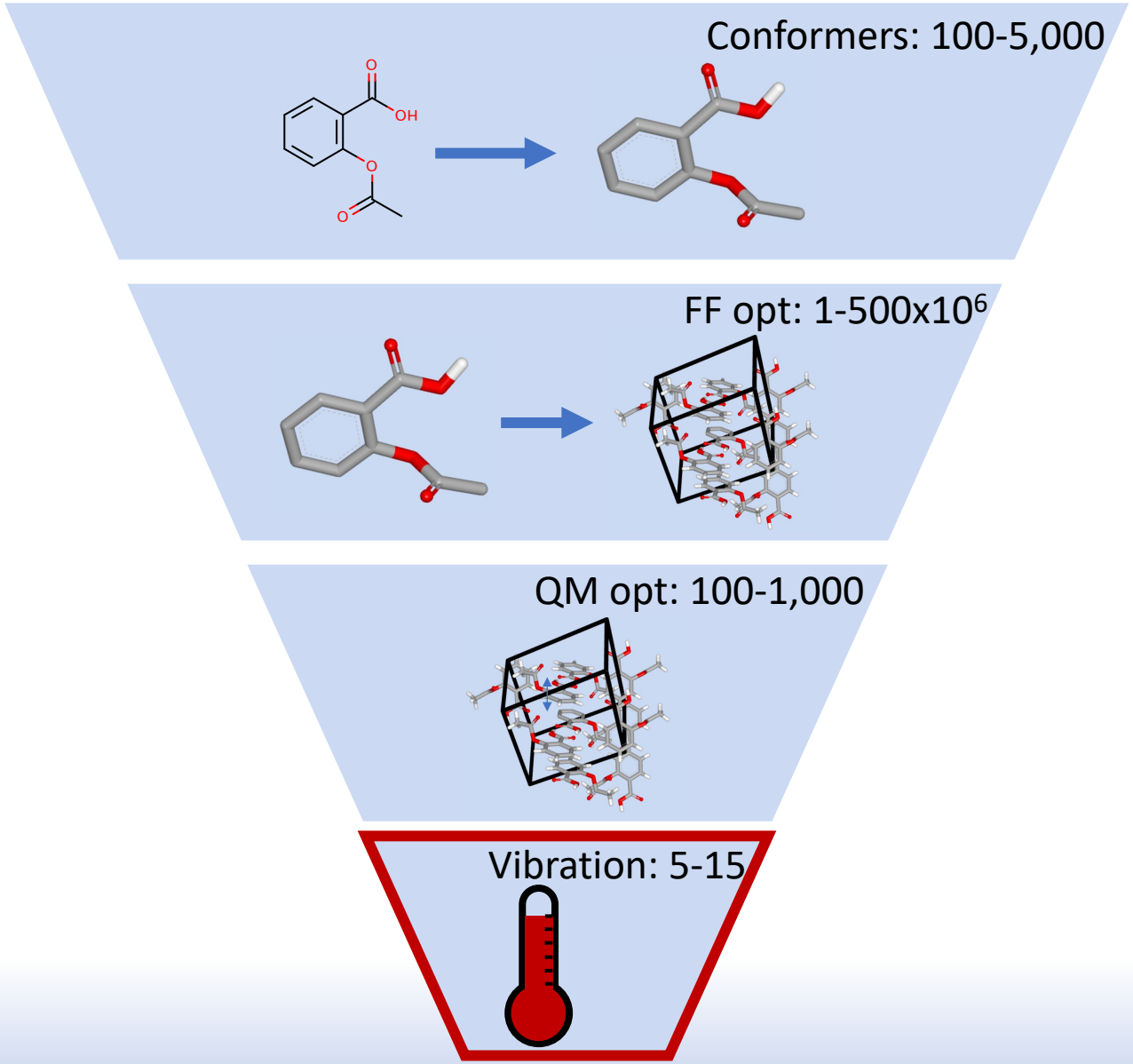


Diflunisal



Venlafaxine

CSP Workflow



- Tautomer selection
- Torsion scanning
- Conformer generation (Omega)
- QM conformer optimization
- Multi-level conformer sampling

- Random packing generation
- IEFF optimization
- IEFF energy filtering

- HF3c optimization (loose and tight)
- DFT single-point scoring

- HF3c entropy (Harmonic approximation)

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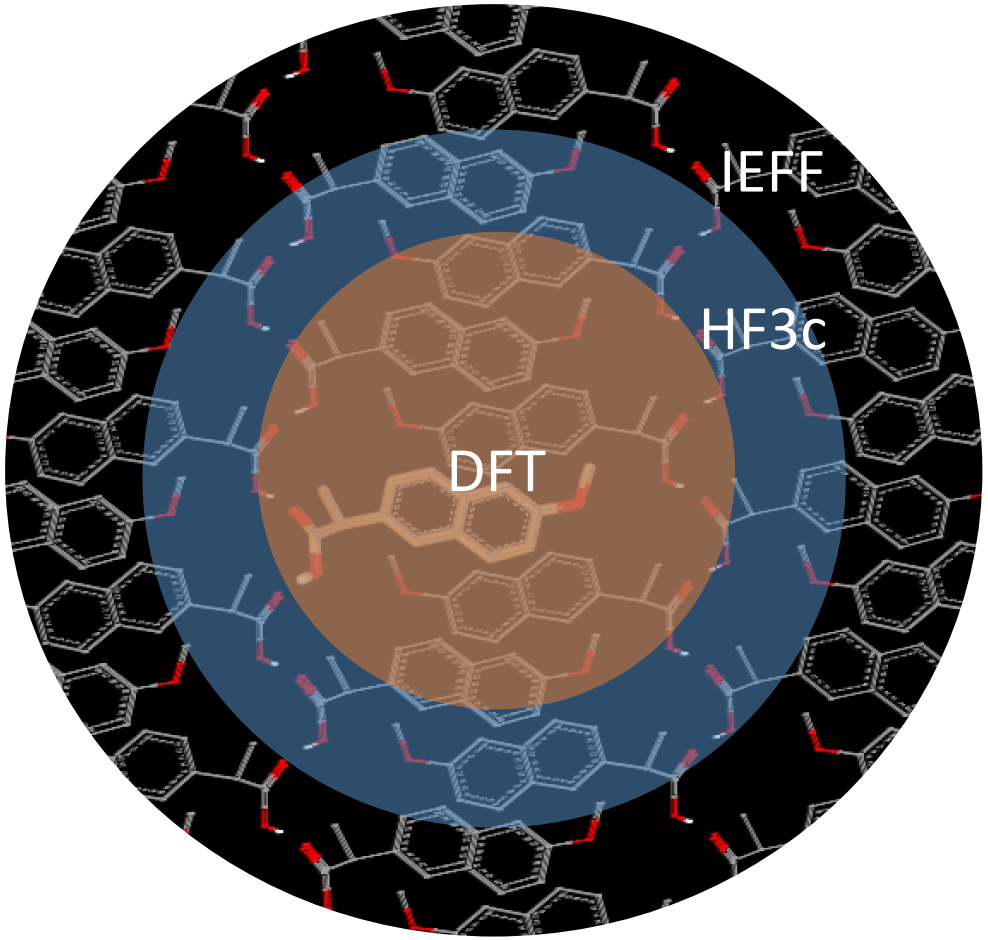
IEFF and dimer expansion QM

	Energy Model	MAD (kcal)
Plane-wave DFT	TPSS-D3	0.9
	PBE-D3	1.1
	PBEh-3C	1.3
Dimer expansion →	**IEFF+PBE-D3@SR**	**1.1**
Force Fields	FIT (S. Price)	2.2
	IEFF (OE)	**2.5**
	W99rev (G.Day)	3.4

Otero-De-La-Roza, A., & Johnson, E. R. (2012). *The Journal of Chemical Physics*, *137*(5), 054103.

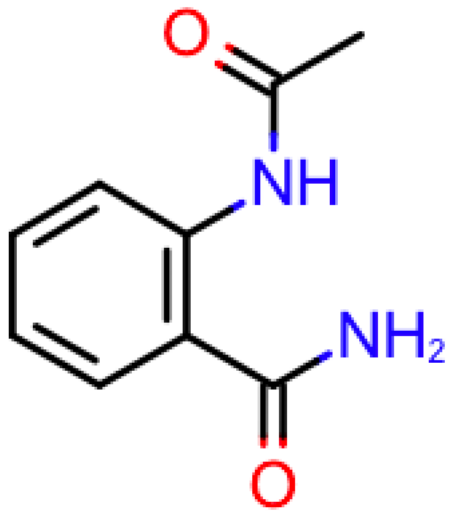


3-layer hybrid QM/MM

Highlights

- QM conformer ensemble
  - Tautomer selection
  - Torsion scanning and custom OMEGA rules
- IEFF - Custom crystal force field
- Fast optimization of scoring of crystal structures
  - Wall clock time of hours
  - Fast entropy calculation
  - Higher levels of theory
- Parallelization reaching 100K processors
- Solubility prediction

Case study 1: O-acetamidobenzamide



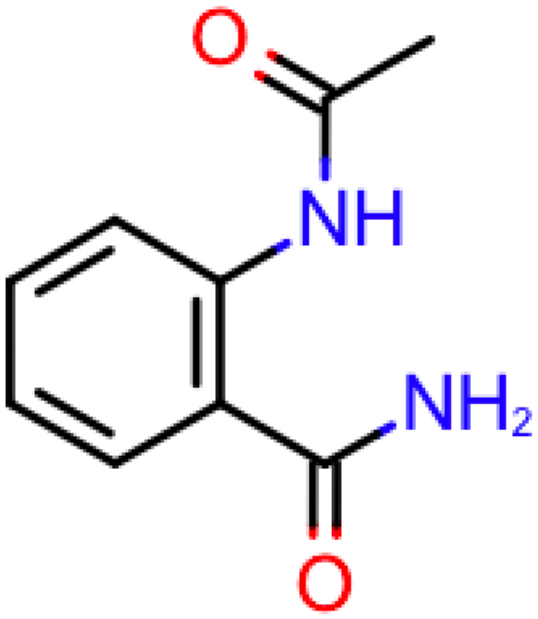
- # heavy atoms = 13
- # HBD = 2
- # HBA = 2
- *CCDC ID:*
  - ACBNZA (Z' = 1; sg 14)
  - ACBNZA01 (Z' = 1; sg 14)
  - ACBNZA02 (Z' = 1; sg 14)
  - ACBNZA03 (Z'= 1; sg 14)

rmsd20 = 0.15 A

rmsd20 = 0.08 A

ACBNZA = Hit1; ACBNZA01 = Hit2

O-acetamidobenzamide



Conformers

Hit1 ✅
Hit2 ❌

IEFF

Hit1 = 59 (0.25A)
Hit2 = No Hits

QM rescoring

Hit1 = 10 (0.26A)

Entropic correction

Hit1 = 12 (0.26A)

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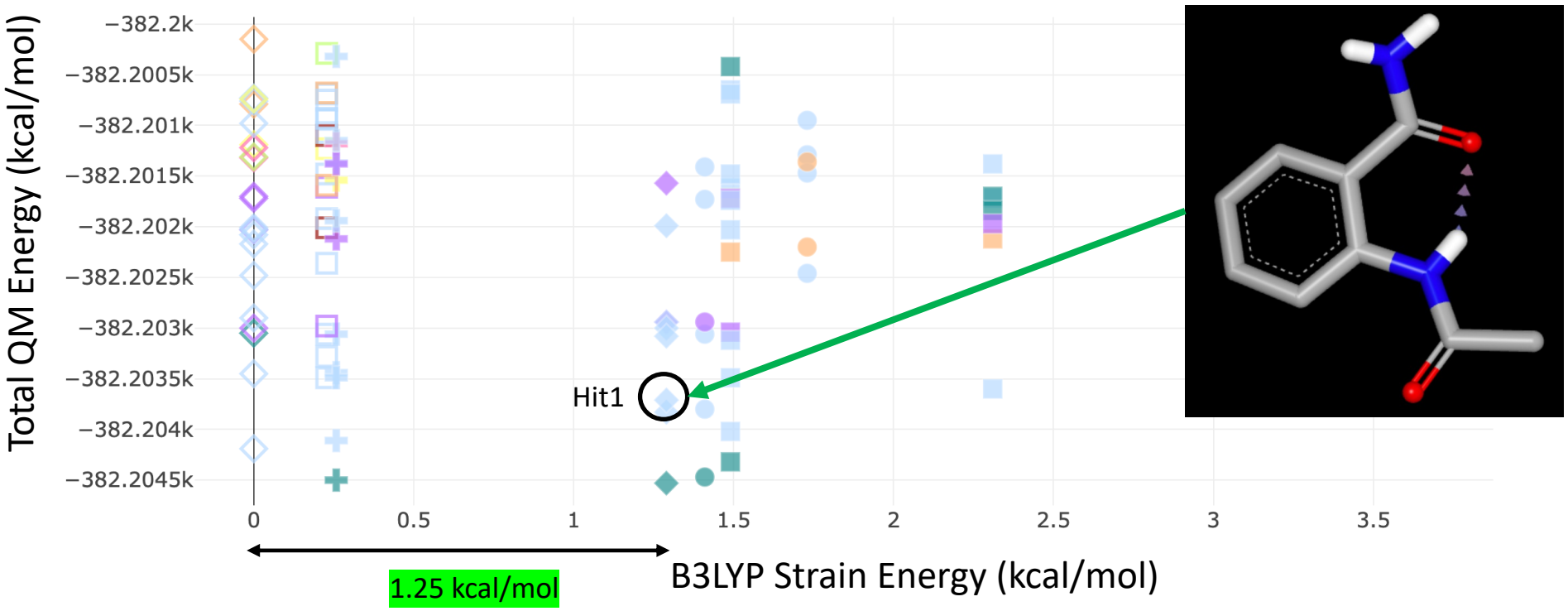
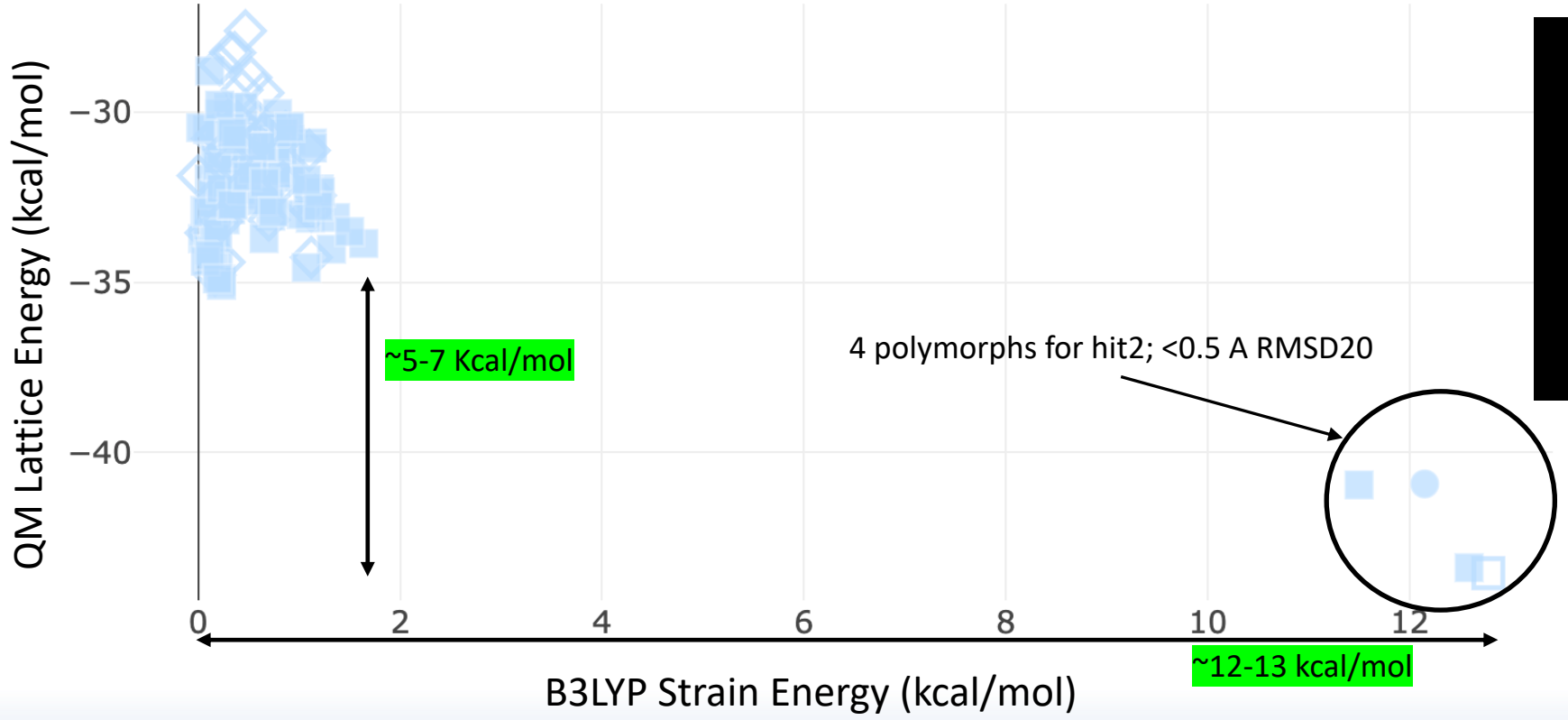
O-acetamidobenzamide: Conformer strain

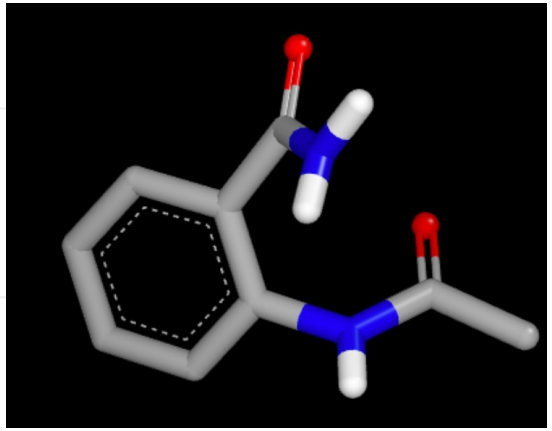
- Bioactive ligand conformations have strain energy under 5 kcal/mol
- Our CSP workflow uses 10 kcal/mol conformer strain cutoff



O-acetamidobenzamide: Hit2 conformer

- Hit2 conformer has a strain ~12 kcal/mol, outside our conformer energy window
- Hit2 polymorphs have lower lattice energy (i.e. more stable)





O-acetamidobenzamide: Lessons learnt

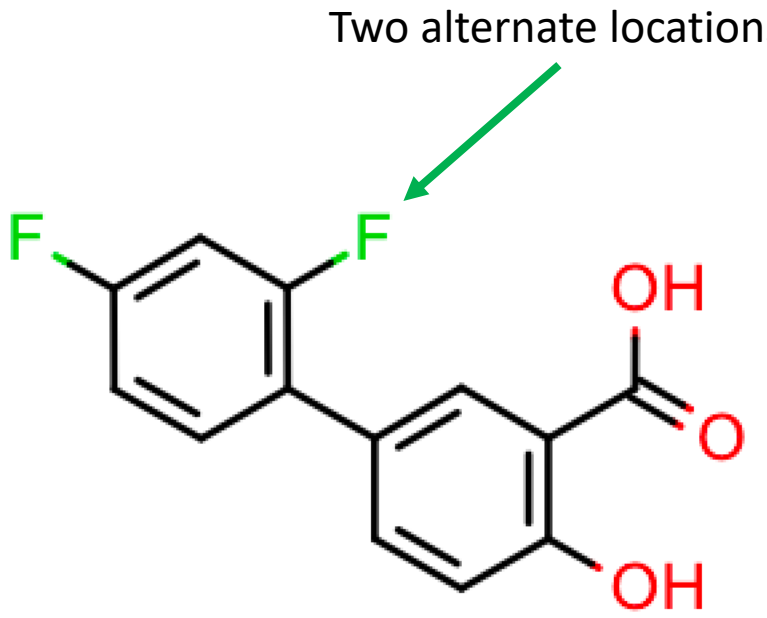
- Intramolecular hydrogen bonds
- Unusually high strain energy
- IEFF force field is not trained on highly strained conformers

Solution:

Estimate the intramolecular hydrogen bond energy and expand the conformer energy window.

Increase IEFF energy window

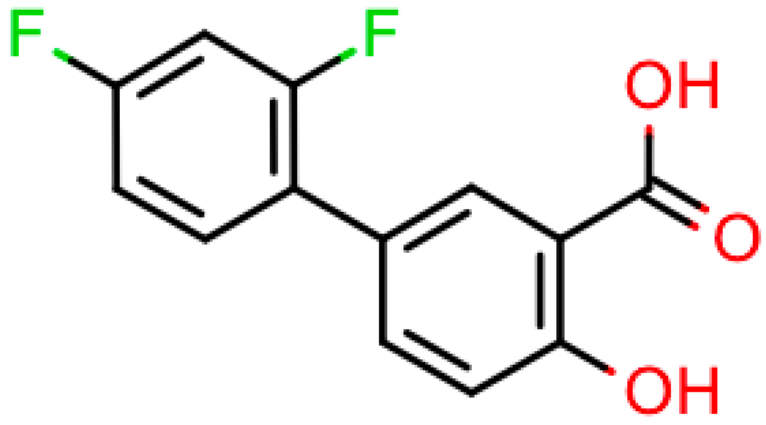
Case study 2: Diflunisal



- # heavy atoms = 18
- # HBD = 2
- # HBA = 5
- *CCDC ID:*
  - FAFWIS (Z’ = 1; sg 15)
  - FAFWIS01 (Z’ = 1; sg 2)
  - FAFWIS02 (Z’ = 2; sg 19)

FAFWIS = Hit 1; FAFWIS01 = Hit 2

Diflunisal



Conformers

Hit1 ✅
Hit2 ✅

IEFF

Hit1 = No hits
Hit2 = 8 (0.35A)

QM rescoring

Hit2 = 20 (0.35A)

Entropic correction

Hit2 = 19 (0.35A)

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Diflunisal: Literature

GDCh Zuschriften Angewandte Chemie

Crystal Structure Prediction Hot Paper

Zitierweise: *Angew. Chem. Int. Ed.* **2020**, *59*, 20357–20360
Internationale Ausgabe: doi.org/10.1002/anie.202006939
Deutsche Ausgabe: doi.org/10.1002/ange.202006939

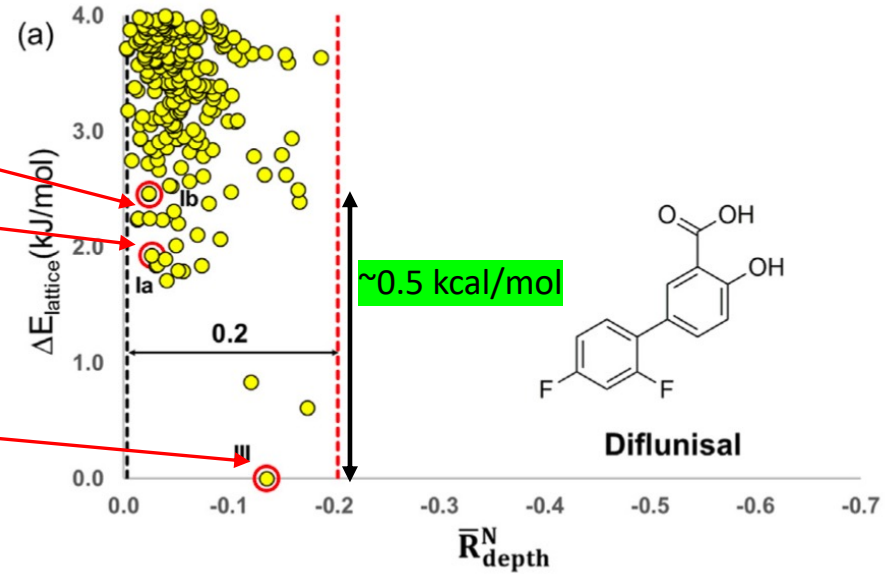
Transforming Computed Energy Landscapes into Experimental Realities: The Role of Structural Rugosity

*Riccardo Montis, Roger J. Davey, Sarah E. Wright, Grahame R. Woollam, and Aurora J. Cruz-Cabeza**

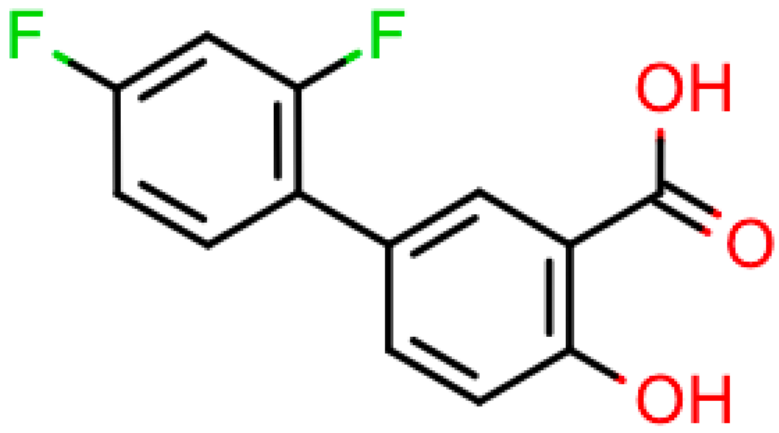
FAFWIS01 (Z'1, ALT2)

FAFWIS01 (Z'1, ALT1)

FAFWIS02 (Z'2)



Diflunisal: 10x more sampling



Conformers

Hit1 ✅
Hit2 ✅

IEFF

Hit1 = 438 (0.58A)
Hit2 = 8 (0.35A)

QM rescoring

Hit2 = 20 (0.35A)

Entropic correction

Hit2 = 19 (0.35A)

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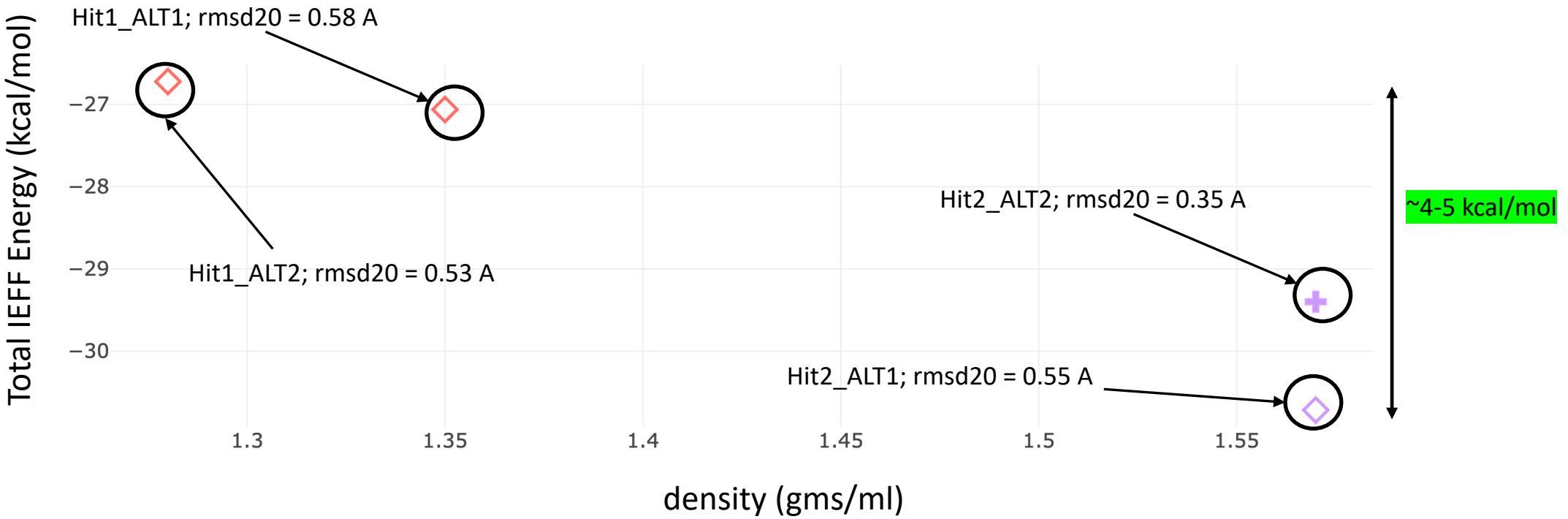
Diflunisal: Hit1 is consistently high in energy

- Hit1 is ~5 kcal/mol higher in energy than Hit2 in IEFF landscape
- Hit1 is ~4 kcal/mol higher in energy than Hit2 in QM landscape



Diflunisal: Questionable experimental data

The available nonsolvated crystal structure of diflunisal in the CCDC (ref 16; refcode, FAFWIS) was reported by Kim and Park.[10] Crystals of this form were grown at room temperature by slow evaporation of a solution of diflunisal in an acetone−water mixture. Crystals are monoclinic, space group $C2/c$ with unit cell dimensions $a = 34.666(6)$ Å, $b = 3.743(1)$ Å, $c = 20.737(1)$ Å, $\beta = 110.57(2)°$, and vol $= 2519.4(4)$ Å^3. The crystal packing for this structure, which is based on carboxylic acid dimers, is shown in Figure 1b. The simulated powder XRD pattern of this structure does not match any of the patterns reported in refs 12 or 15; hence, we have denoted it form V.

Cross, Wendy I., et al. "A whole output strategy for polymorph screening: Combining crystal structure prediction, graph set analysis, and targeted crystallization experiments in the case of diflunisal." *Crystal growth & design* 3.2 (2003): 151-158.

Diflunisal: Lessons learnt

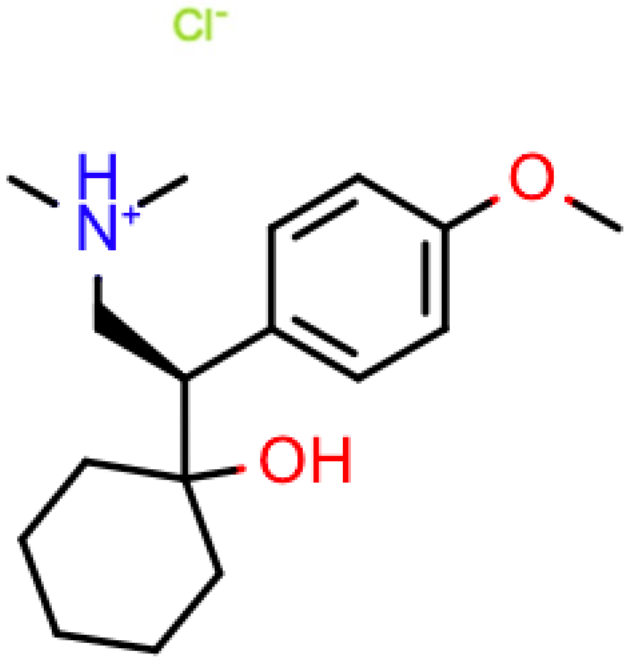
- Some conformers are difficult to pack
- Higher energy of experimental structure
- Inconsistency between experiments

Solution:

Increased sampling

Conformer-specific sampling convergence, e.g. Bayesian Bandits

Case study 3: Venlafaxine

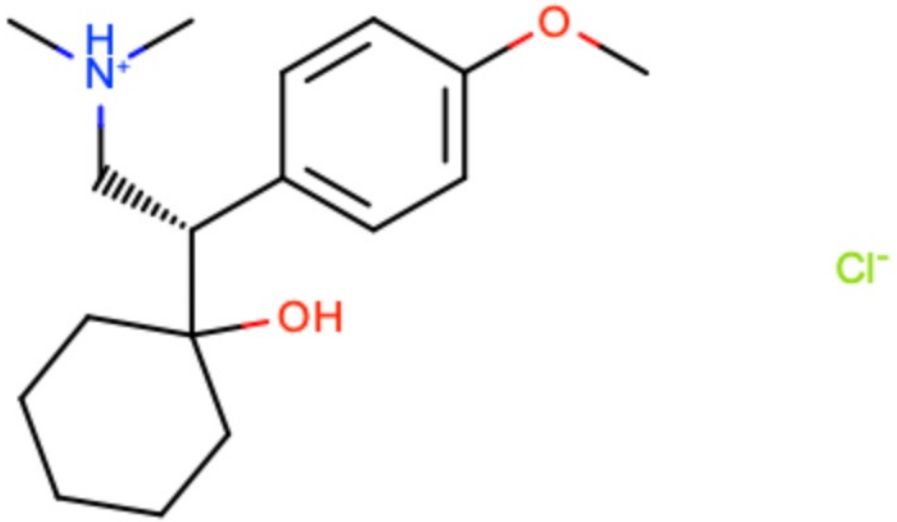


Venlafaxine

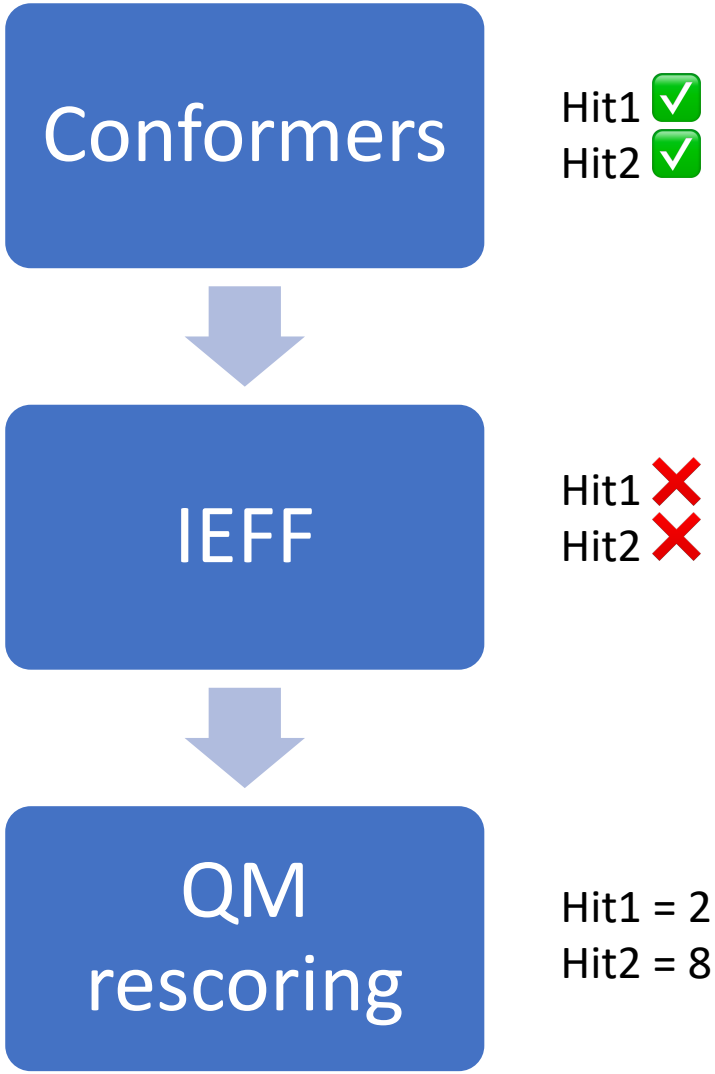
- # heavy atoms = 20
- # HBD = 1
- # HBA = 3
- *CCDC ID:*
  - WOBMUV (Z’ = 1; sg 29)
  - WOBMUV01 (Z’ = 1; sg 14)
  - WOBMUV02 (Z’ = 2; sg 14)

WOBMUV = Hit 1; WOBMUV01 = Hit 2

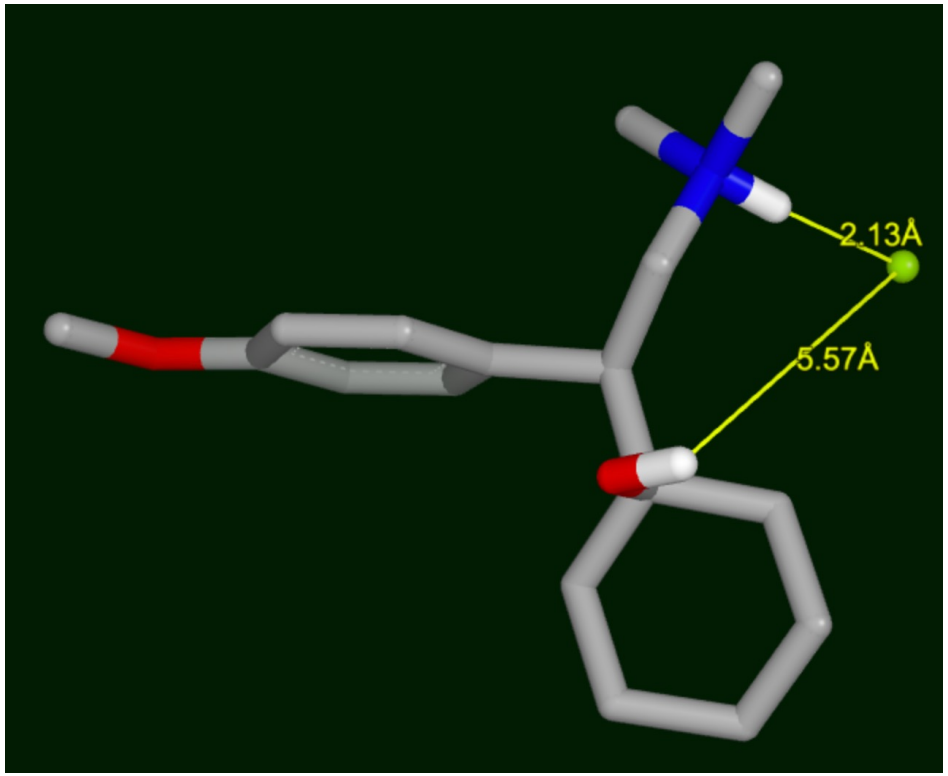
Venlafaxine



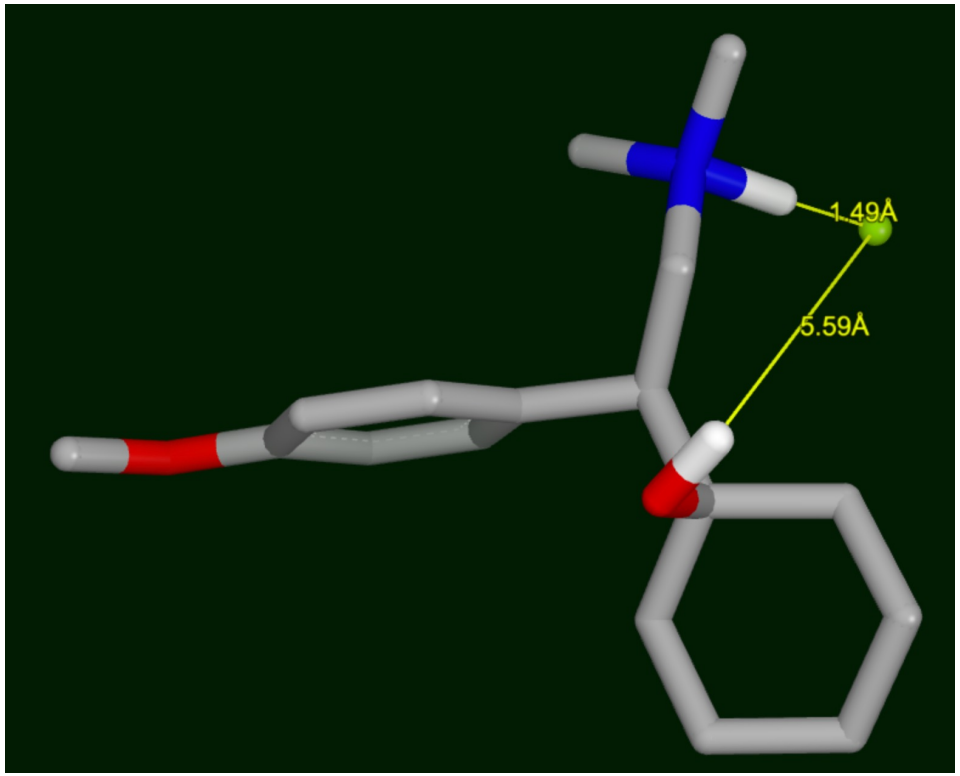
Venlafaxine hits with IEFF energy were >25 kcal/mol above global minima



Venlafaxine: Anions need large basis sets



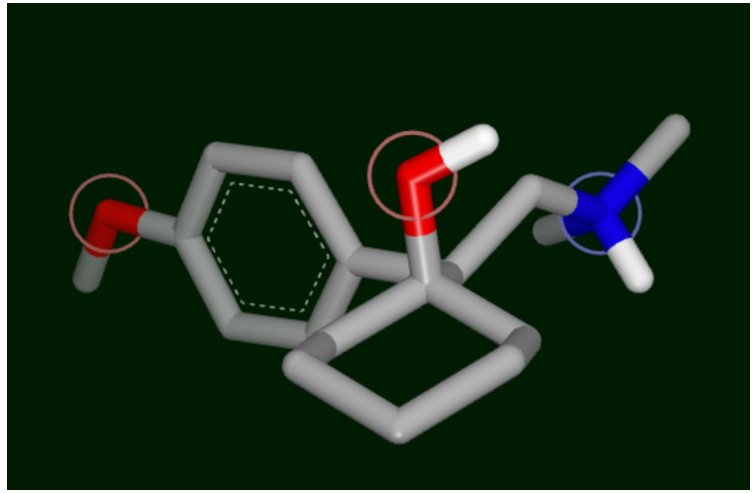
Experimental



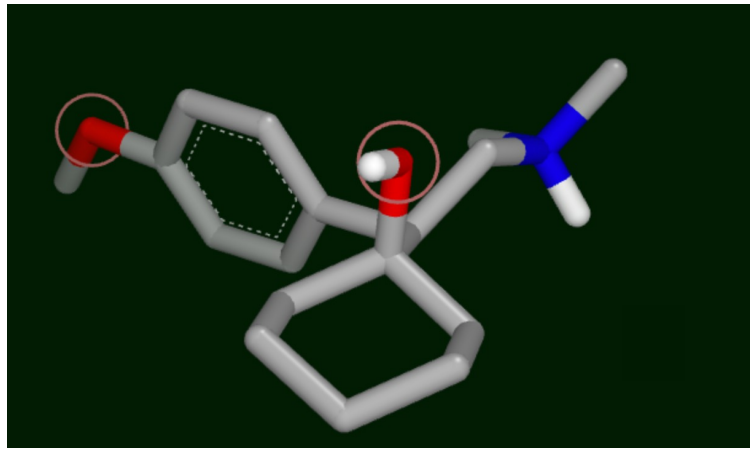
B3LYP-D3/6-31G*

Dimer closest to experimental structure has a strain energy ~10kcal/mol

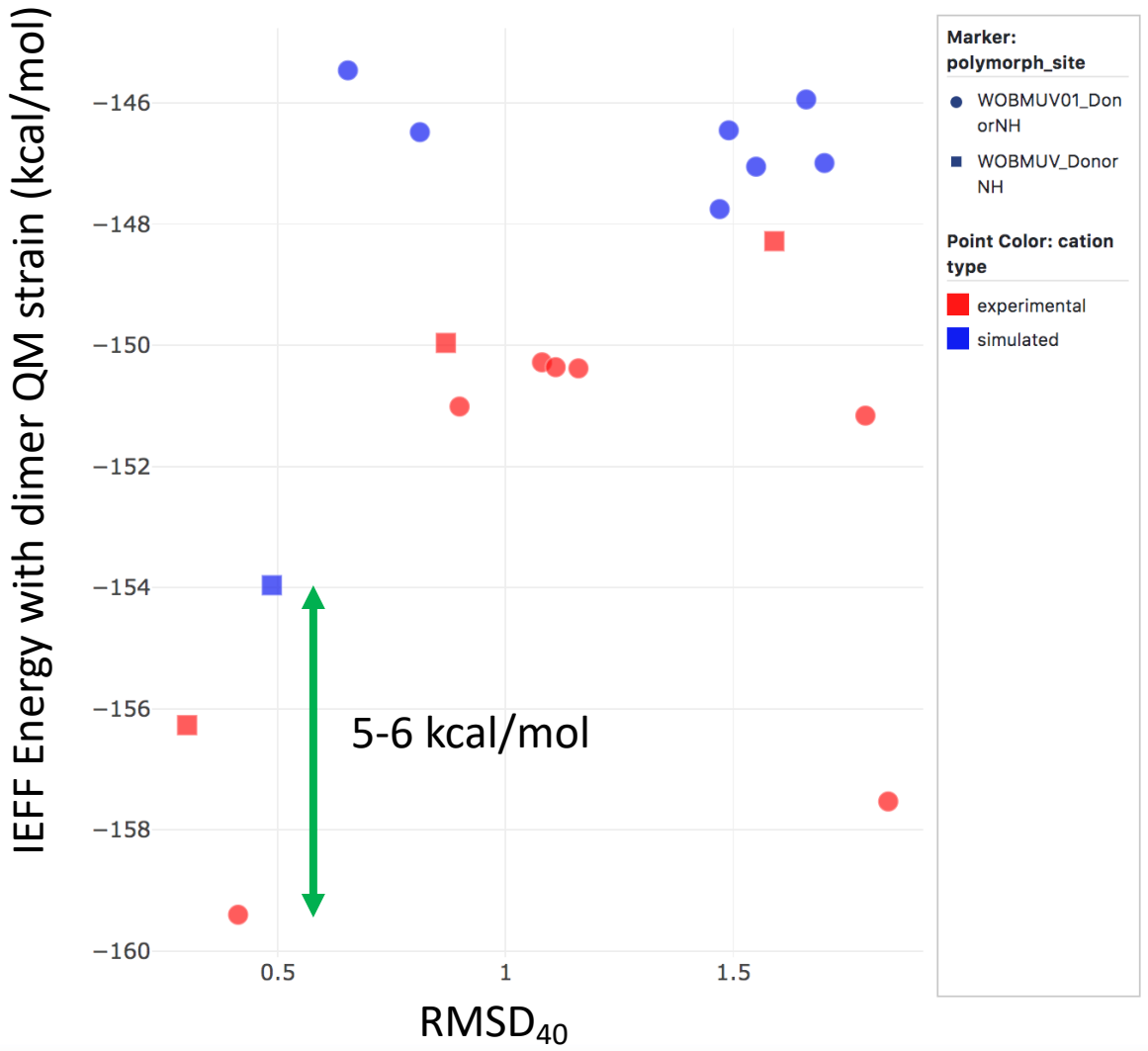
Venlafaxine: Hydroxyl orientation



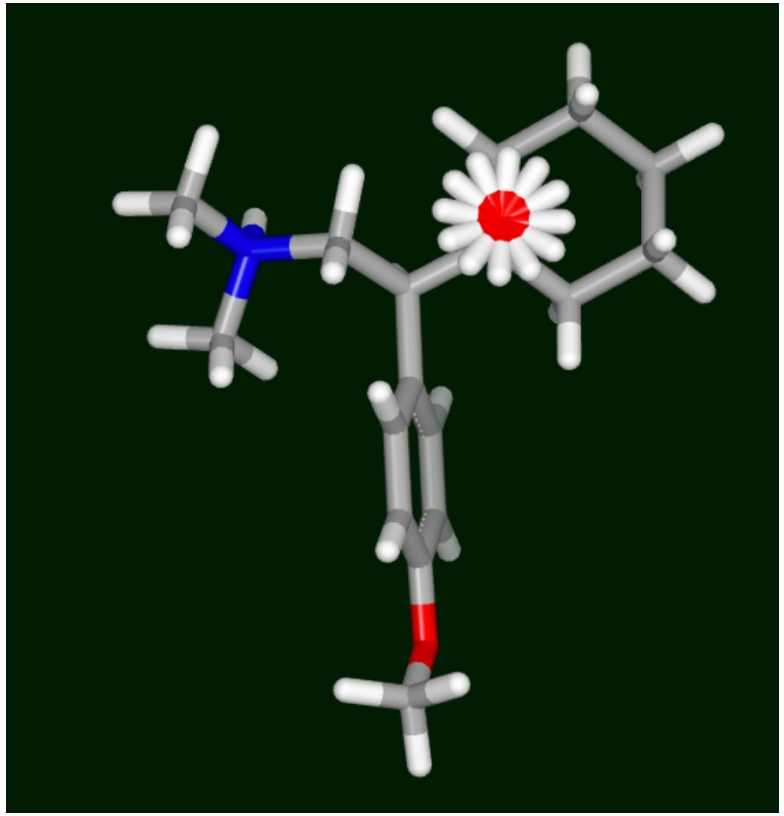
Experimental



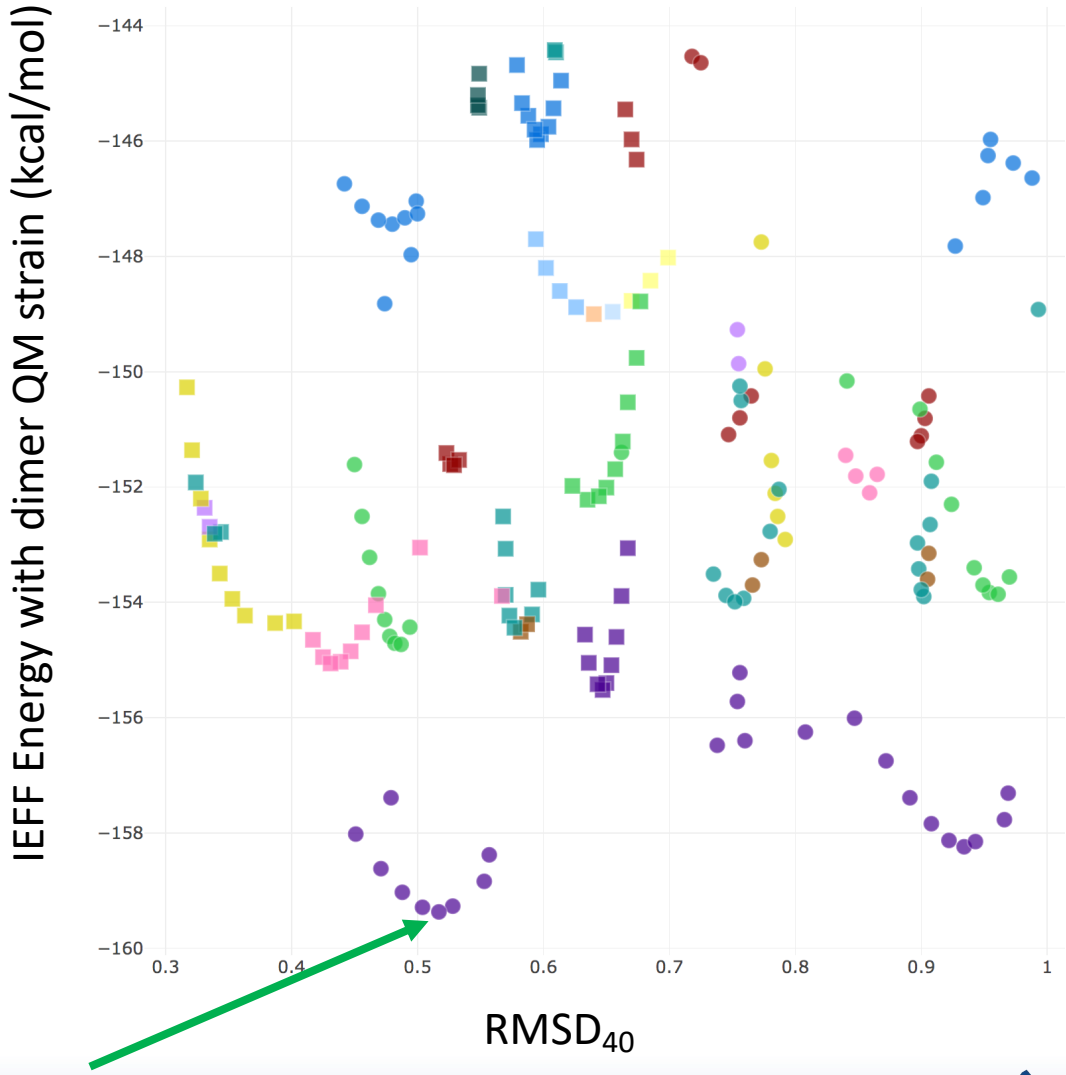
Closest dimer



Venlafaxine: Hydroxyl orientation



Enhanced hydroxyl sampling



Best packing has same energy as experimental structure

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Venlafaxine: Lessons learnt

- Anions need large basis sets
- Subtle changes in Salt/Hydroxyl geometry affects the energetics significantly
- Ions are not a significantly part of FF development

Solution:

Larger basis sets for salts

Multi-stage hydroxyl sampling

Lessons learnt

- **O-acetamidobenzamide**
  - Unusually high strain energy
  - Intramolecular hydrogen bonds
- **Diflunisal**
  - Some conformers are difficult to pack
  - Higher energy of experimental structure
  - Inconsistency between experiments
- **Venlafaxine**
  - Ion placement and strain energy can add more noise to the total energies
  - Hydroxyl orientation can have a significant impact
    - Multi-level hydroxyl sampling

CSP Capabilities: Now and Future

- Crystal forms
  - Z’ = 1 (pure)
  - Monohydrate
  - Salts
- Properties
  - Solubility

- Growth potential
  - Z’=2
  - Di-, tri-, and poly-hydrates
  - Solvent screening
  - Cocrystal screening
- Crystal growth and kinetics
- Properties
  - Morphology
  - Hygroscopicity (water absorption)
  - Compressibility

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Antibody Discovery Suite

Formulations Suite

Third Par Softwar

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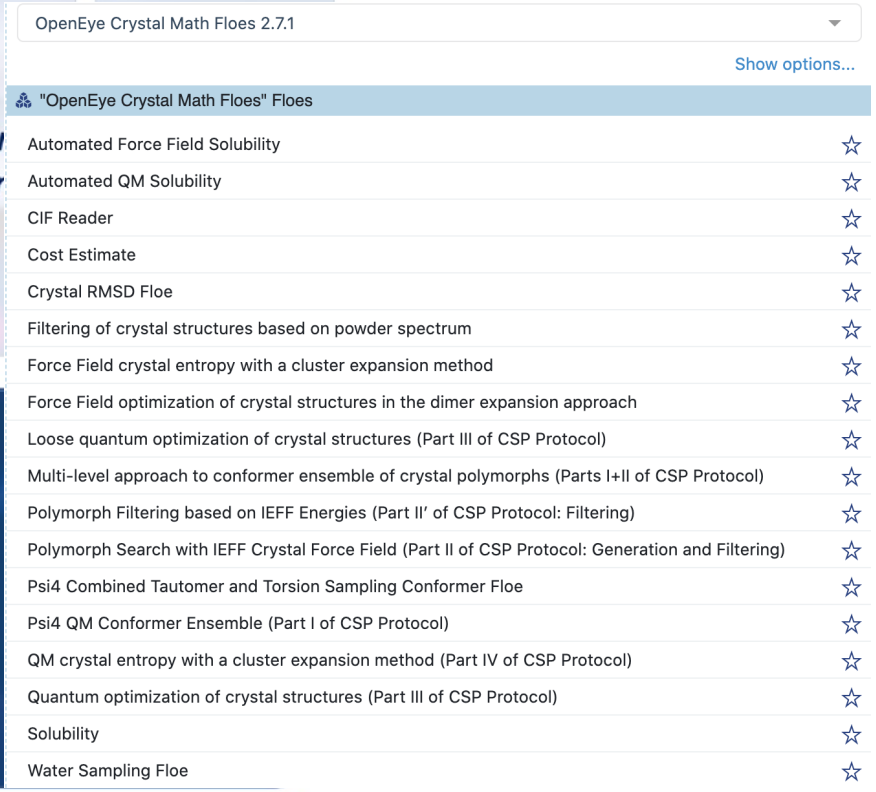
orion®

Crystal Math Floes 2.7.1



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CSP Posters

- **“Crystal structure prediction: Road-map, road-ways, and road-bumps”** by Varsha Jain, OpenEye

- **“OpenEye’s Orion Formulations Suite”** by Hari Muddana, OpenEye

Poster Session, CUP Day 2

Acknowledgements

Grigory

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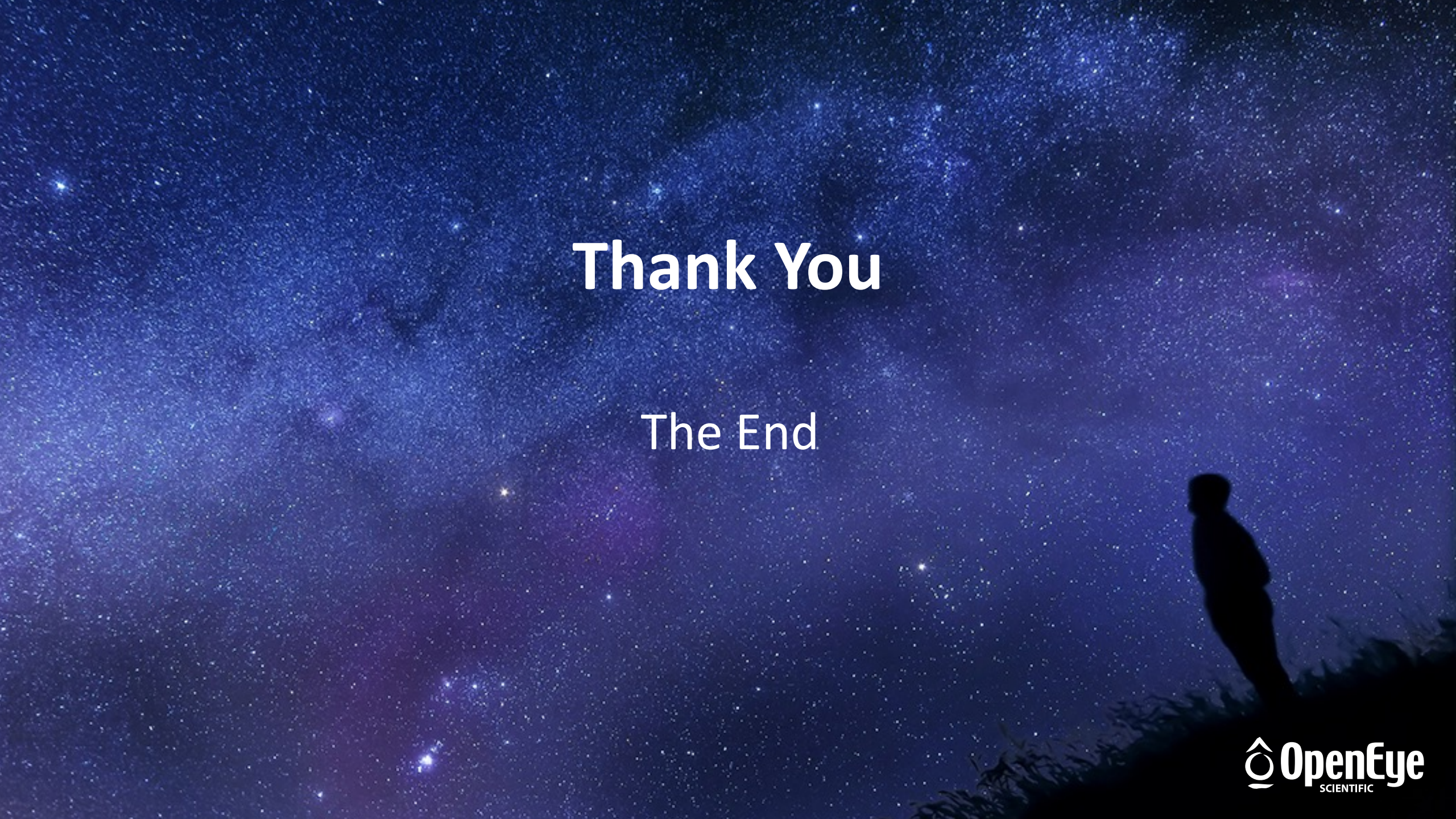
Tom

Geoff

Ant


Thank You
The End
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