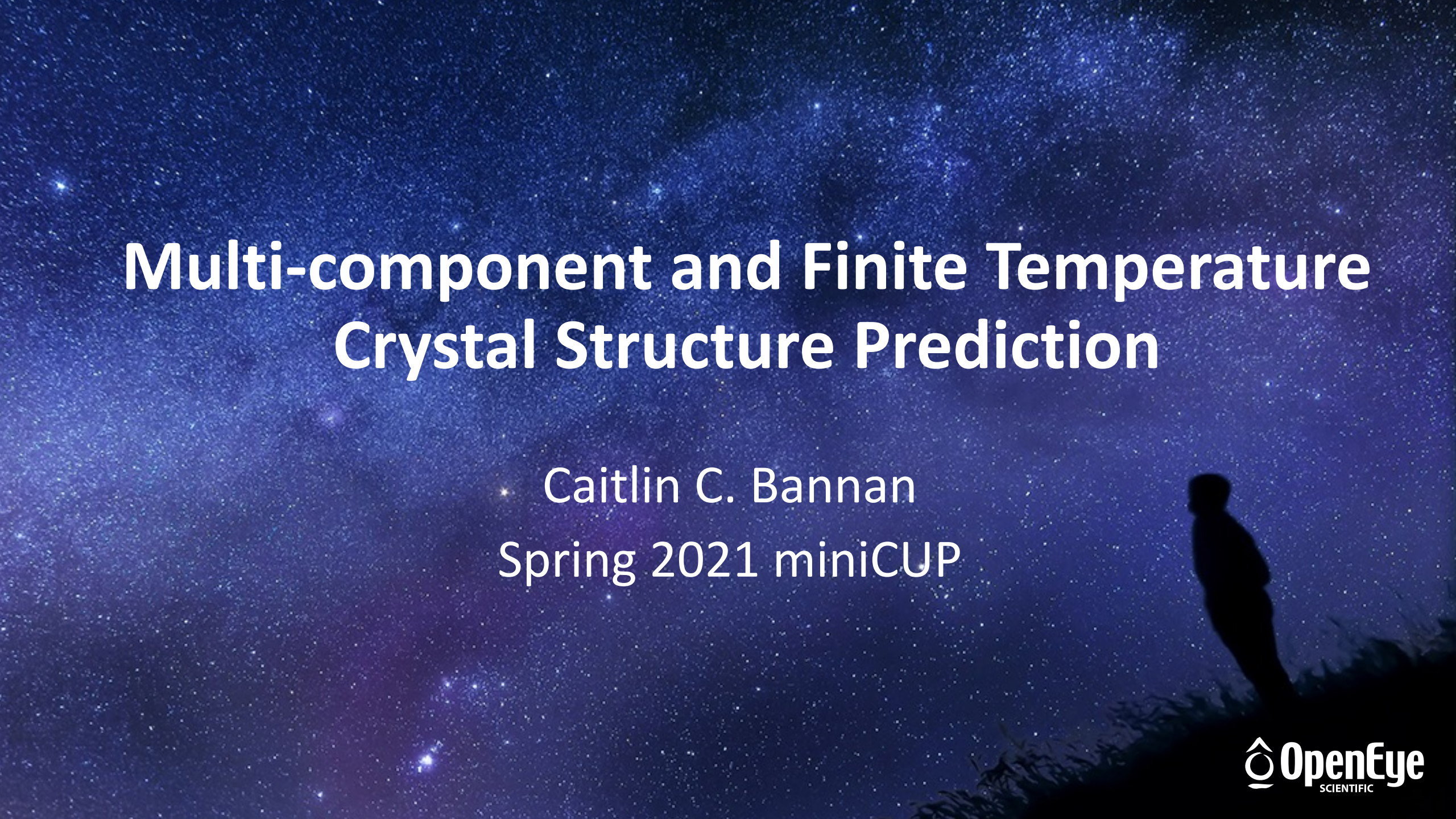
Multi-component and Finite Temperature Crystal Structure Prediction

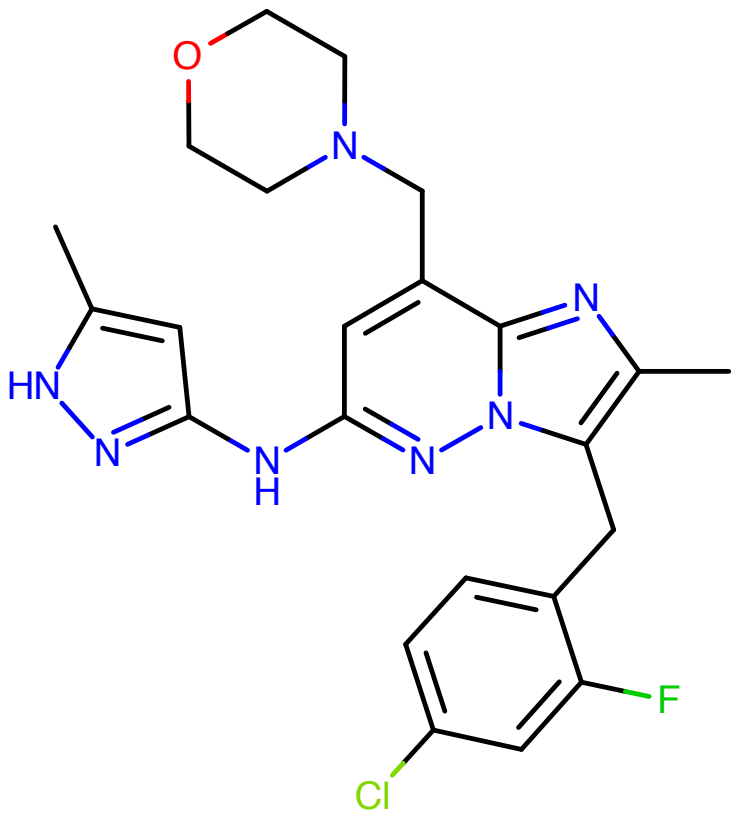
Caitlin C. Bannan

Spring 2021 miniCUP



OpenEye SCIENTIFIC

Complex Solid Form Landscape of Gandotinib



Braun et al. : Cryst. Growth Des. 2019, 19, 2947−2962

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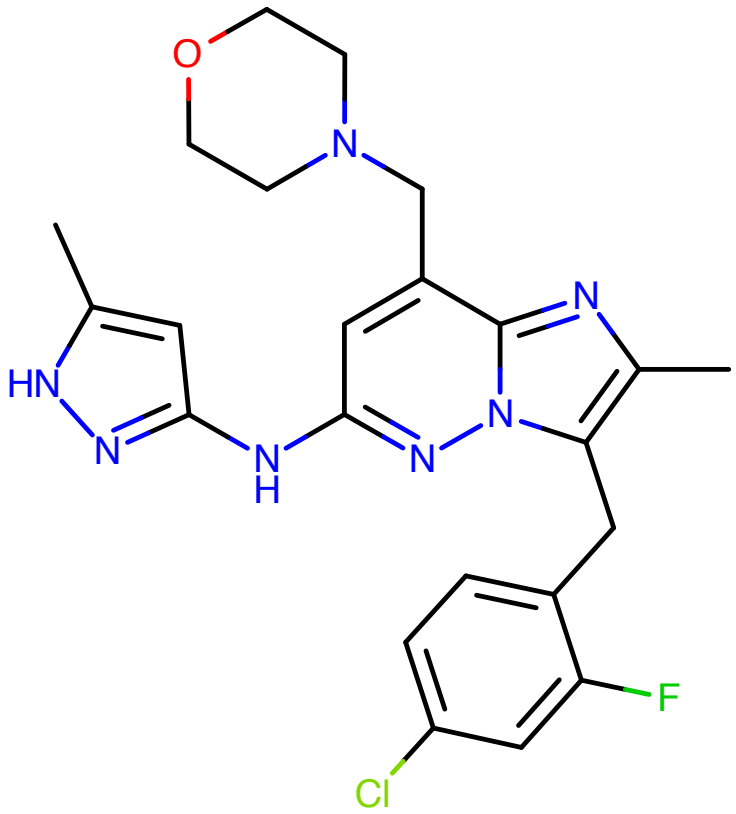

Solvates

Methanol
n-propanol
n-butanol
N-methyl-2-pyrrolidone

Braun et al. : Cryst. Growth Des. 2019, 19, 2947−2962

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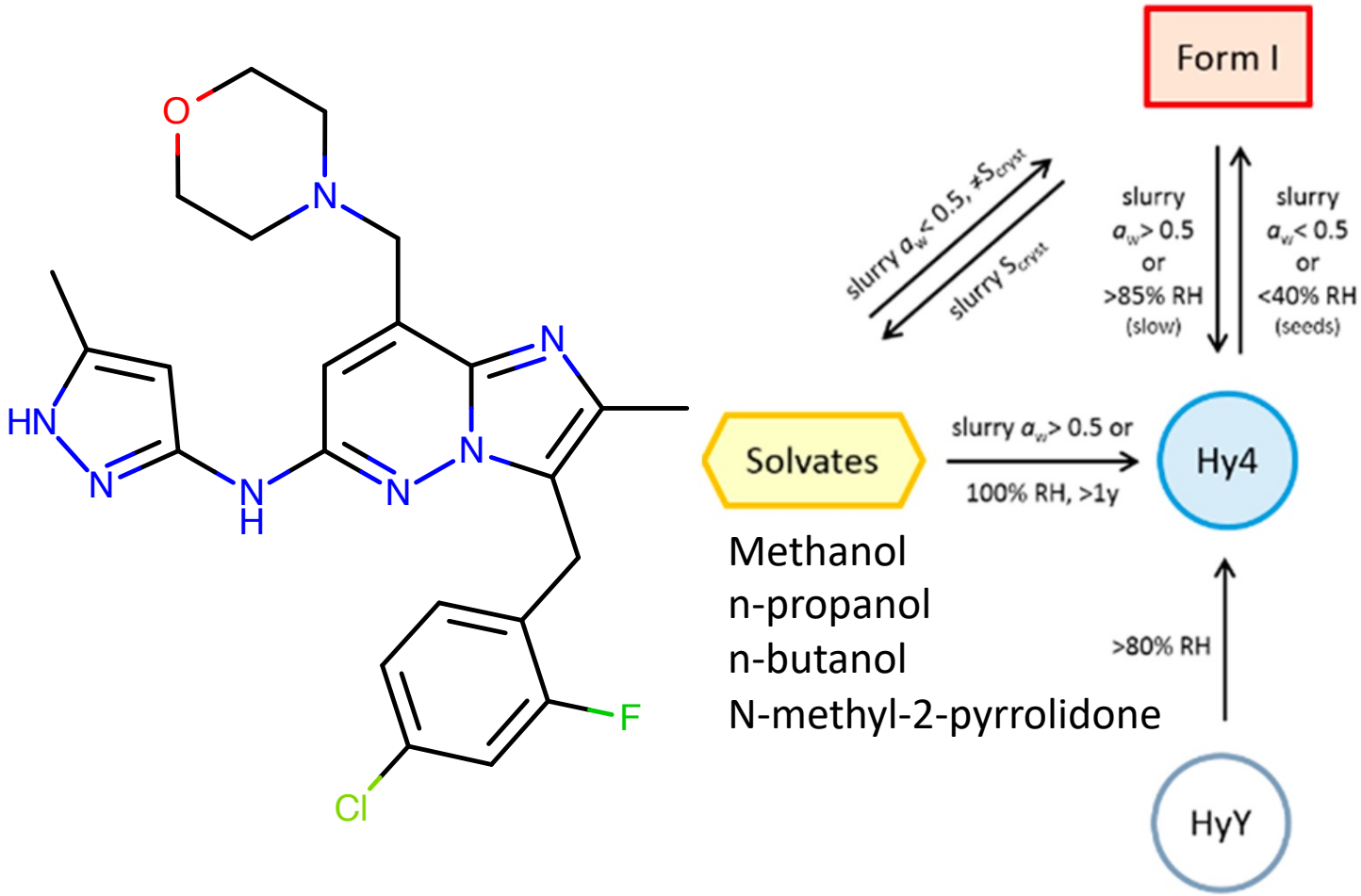

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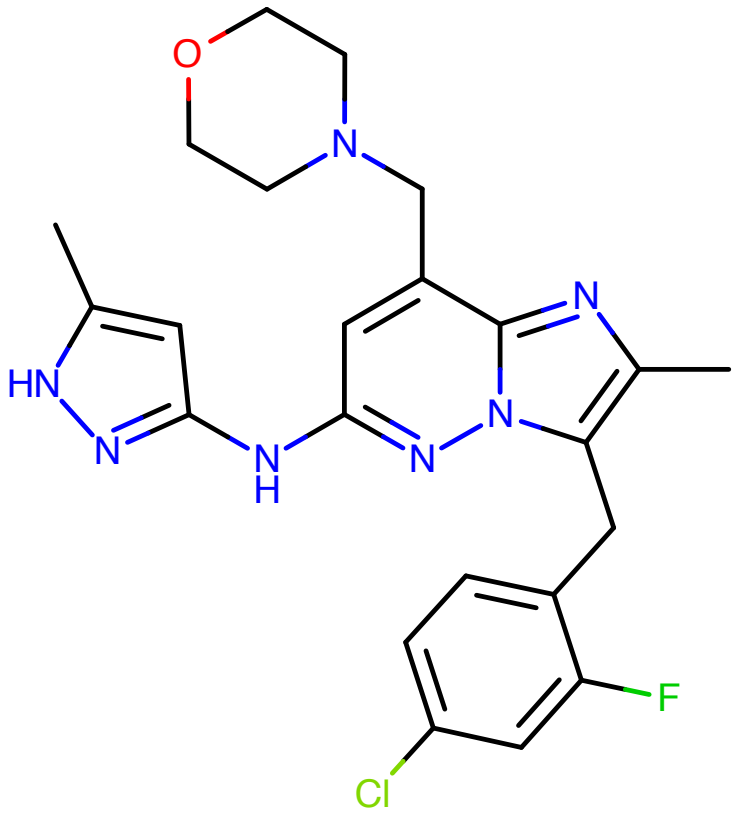

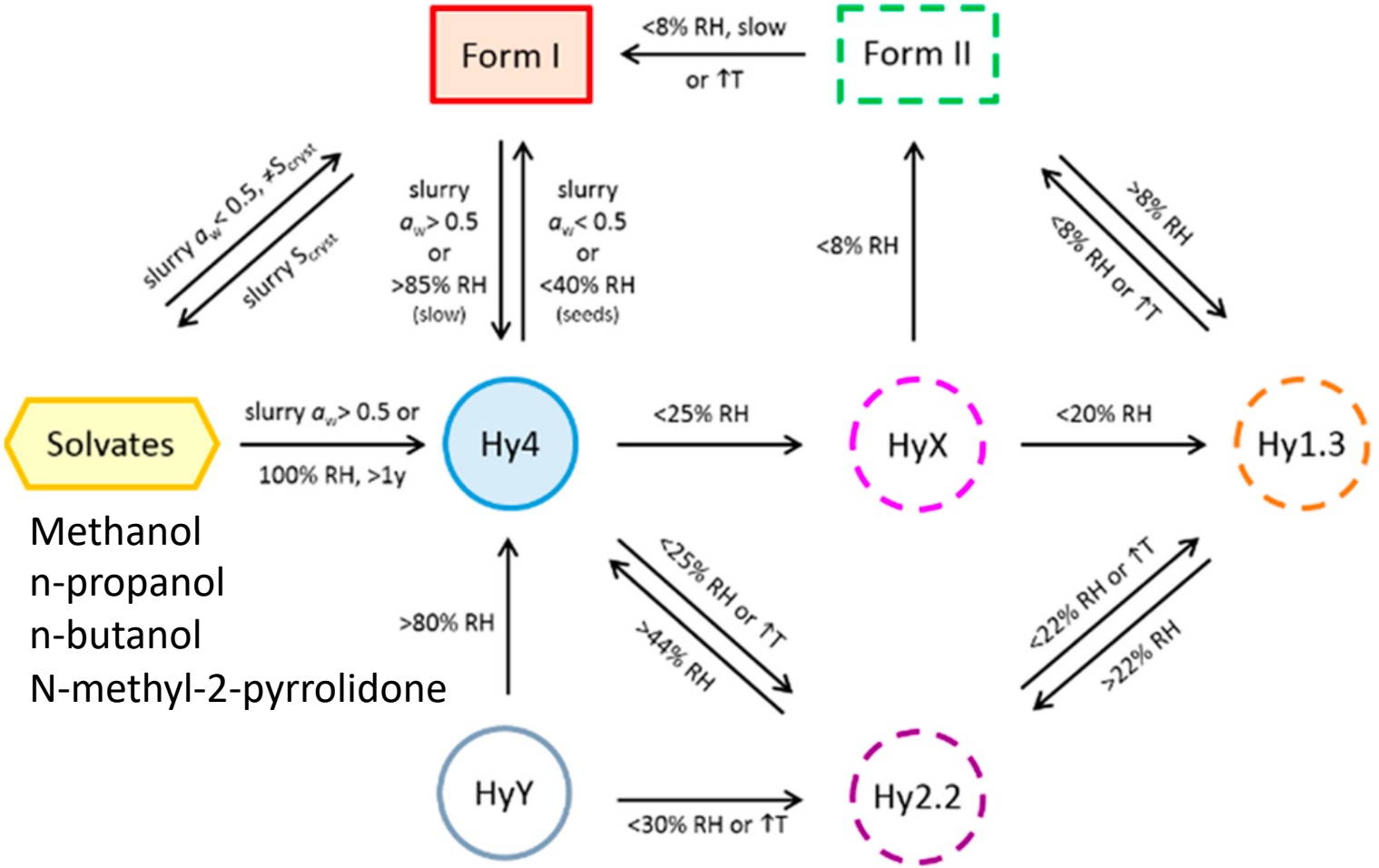

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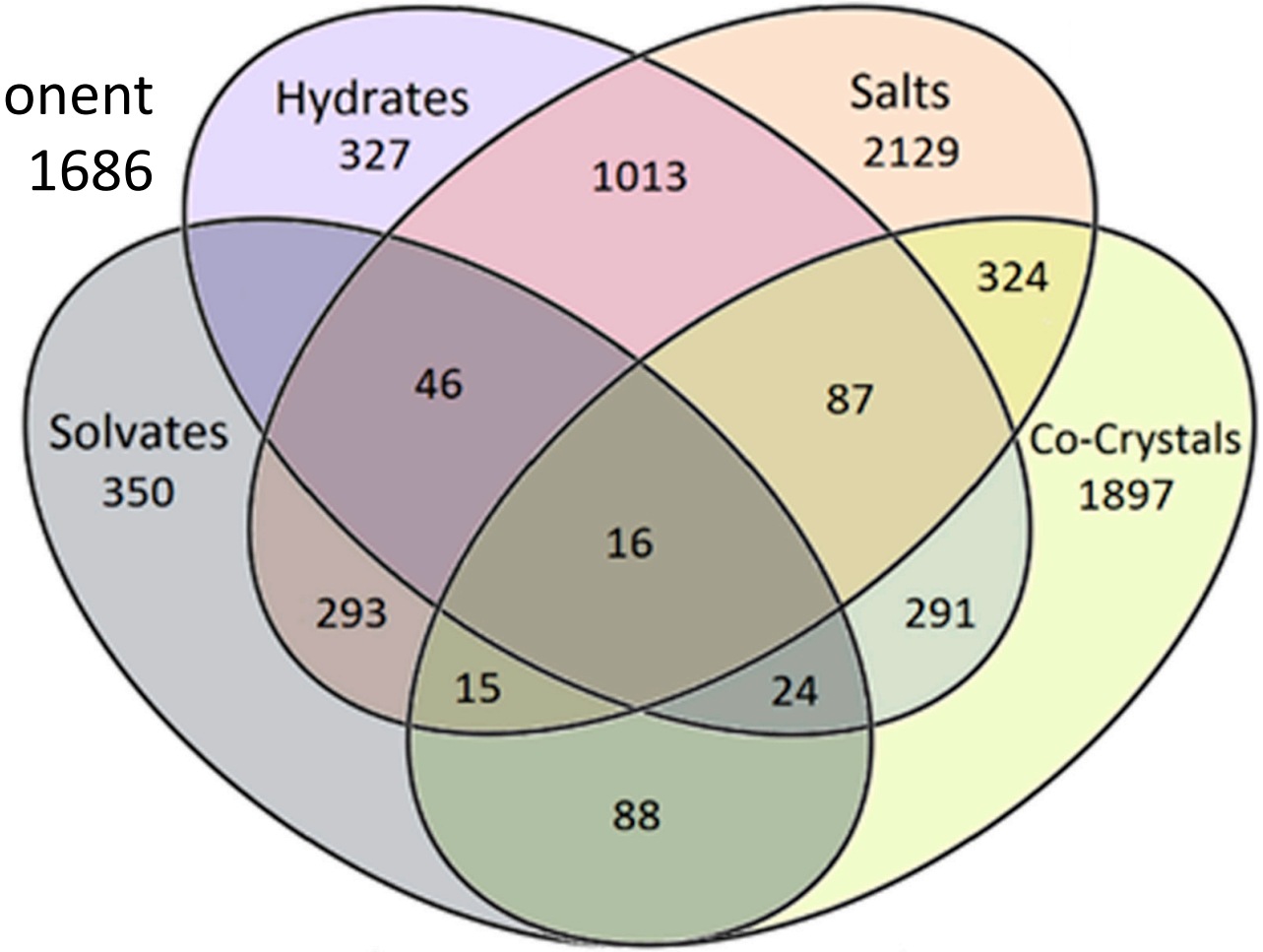
Most drug molecules crystals are multi-component

Single Component
1686



Brant et al.: J. Pharm. Sci. 2019, 108:5, 1655-1662

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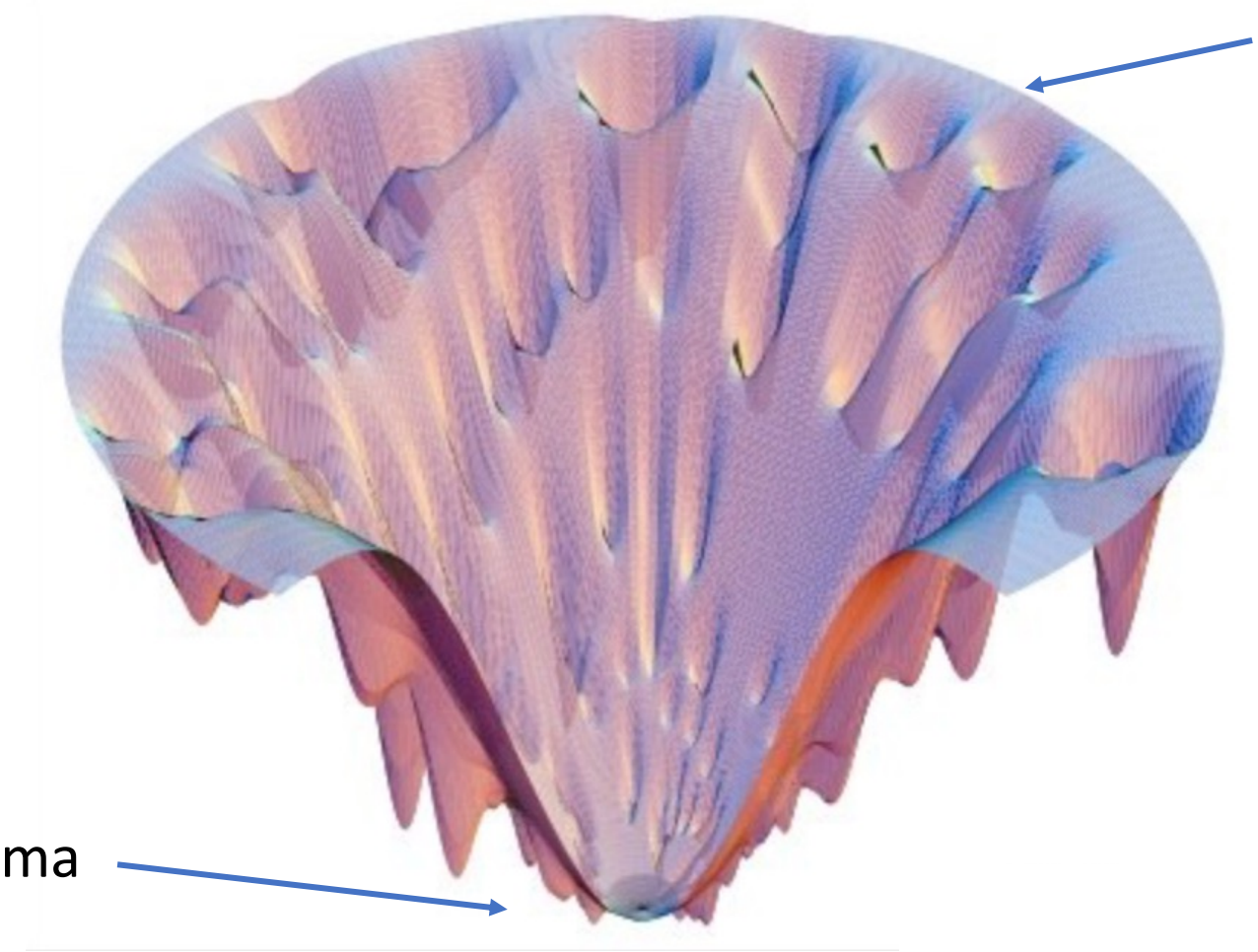
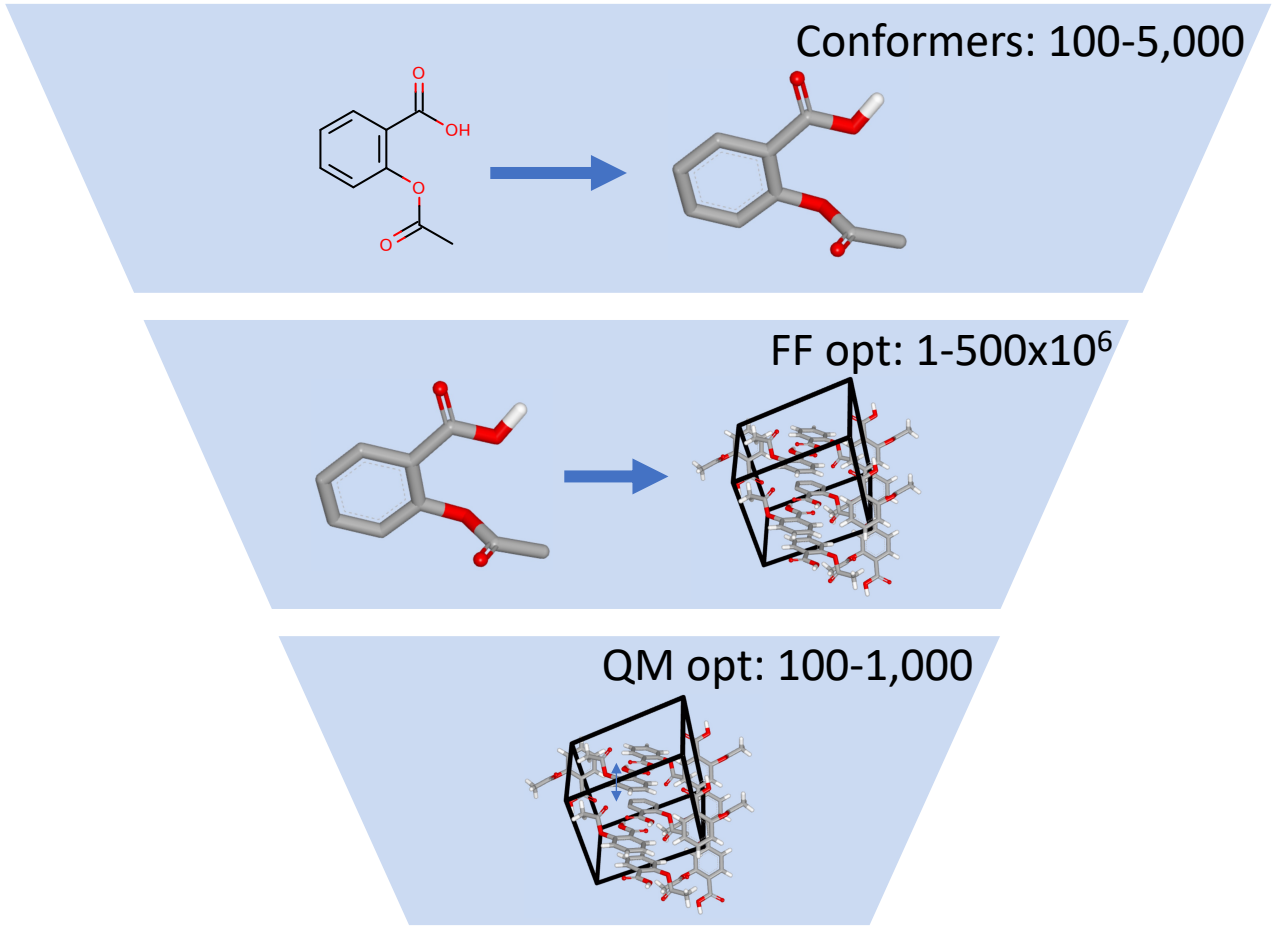
Goal: find all accessible local minima



Brief reminder of our protocol



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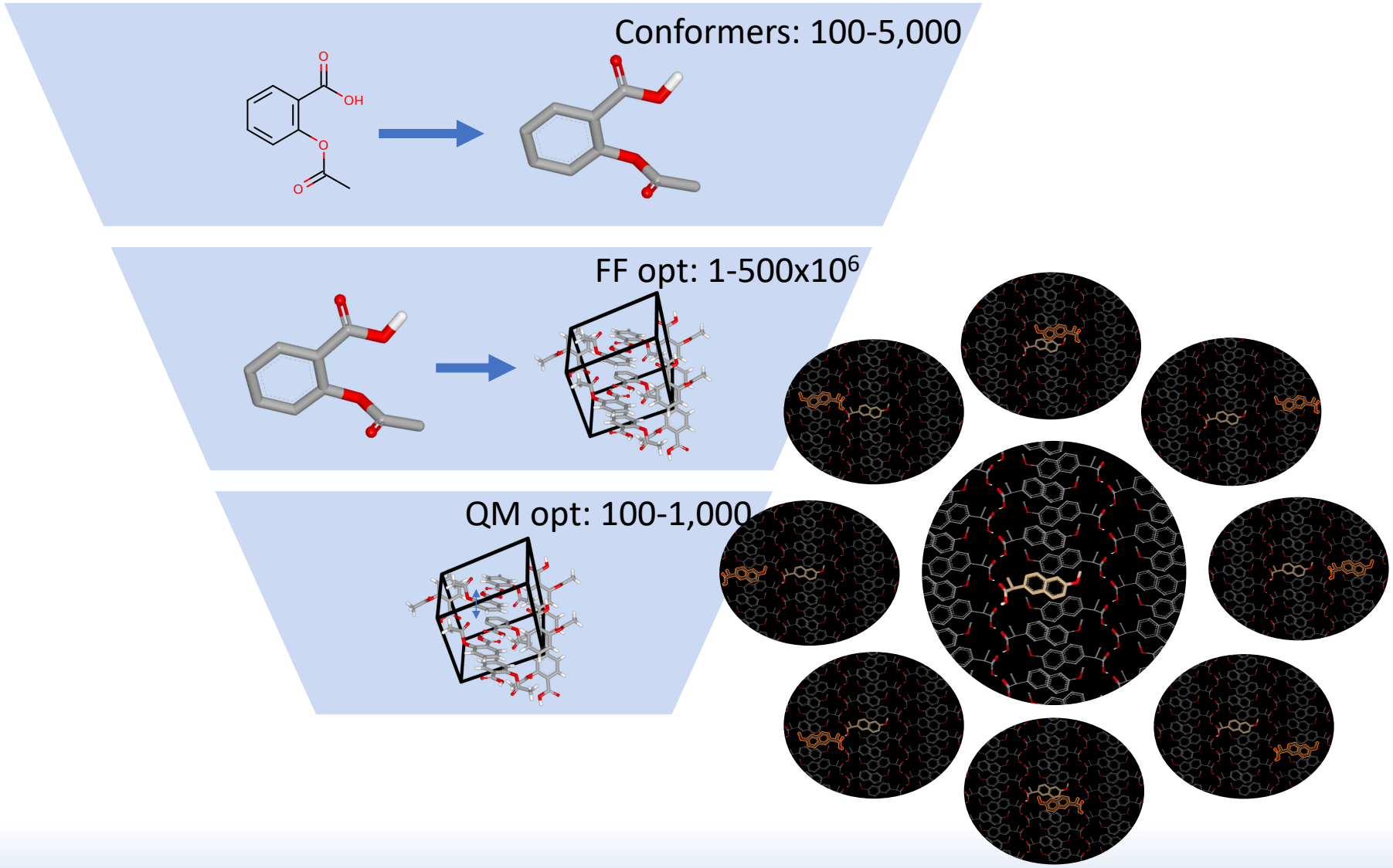

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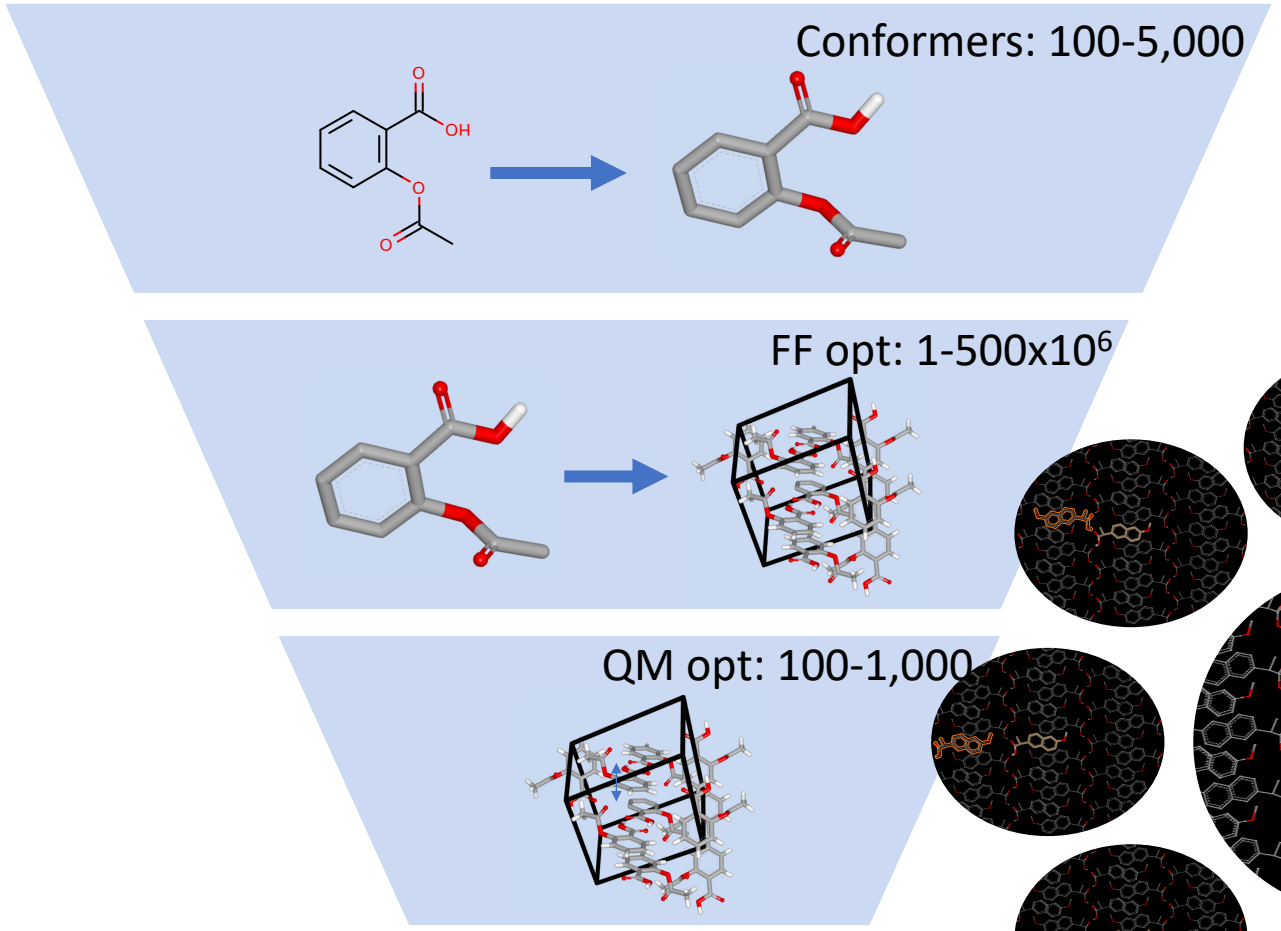
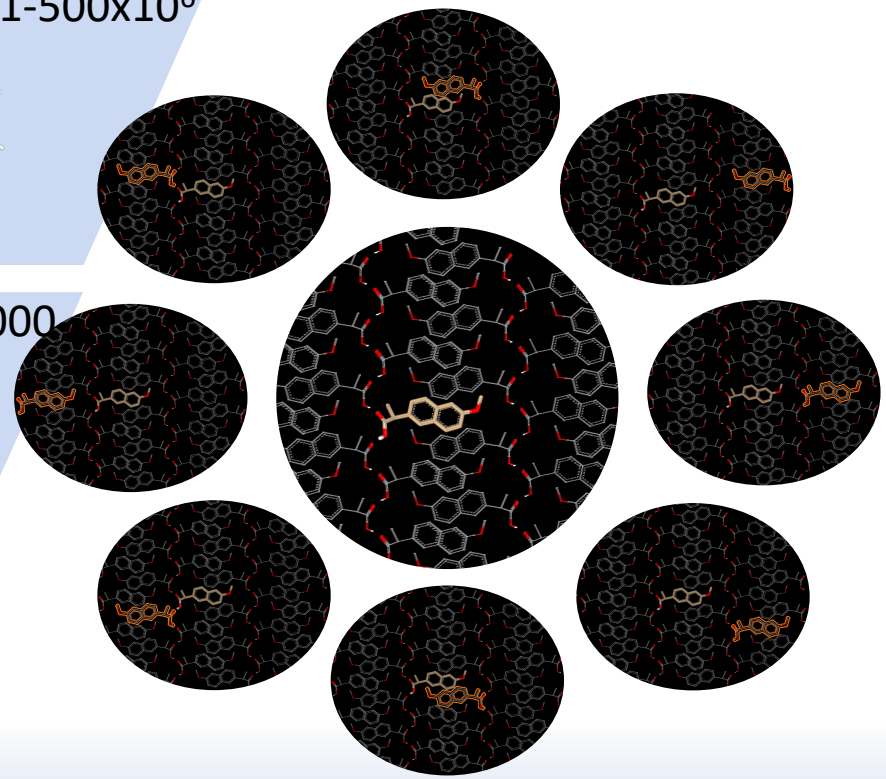


- Highly parallelizable (time for one dimer)



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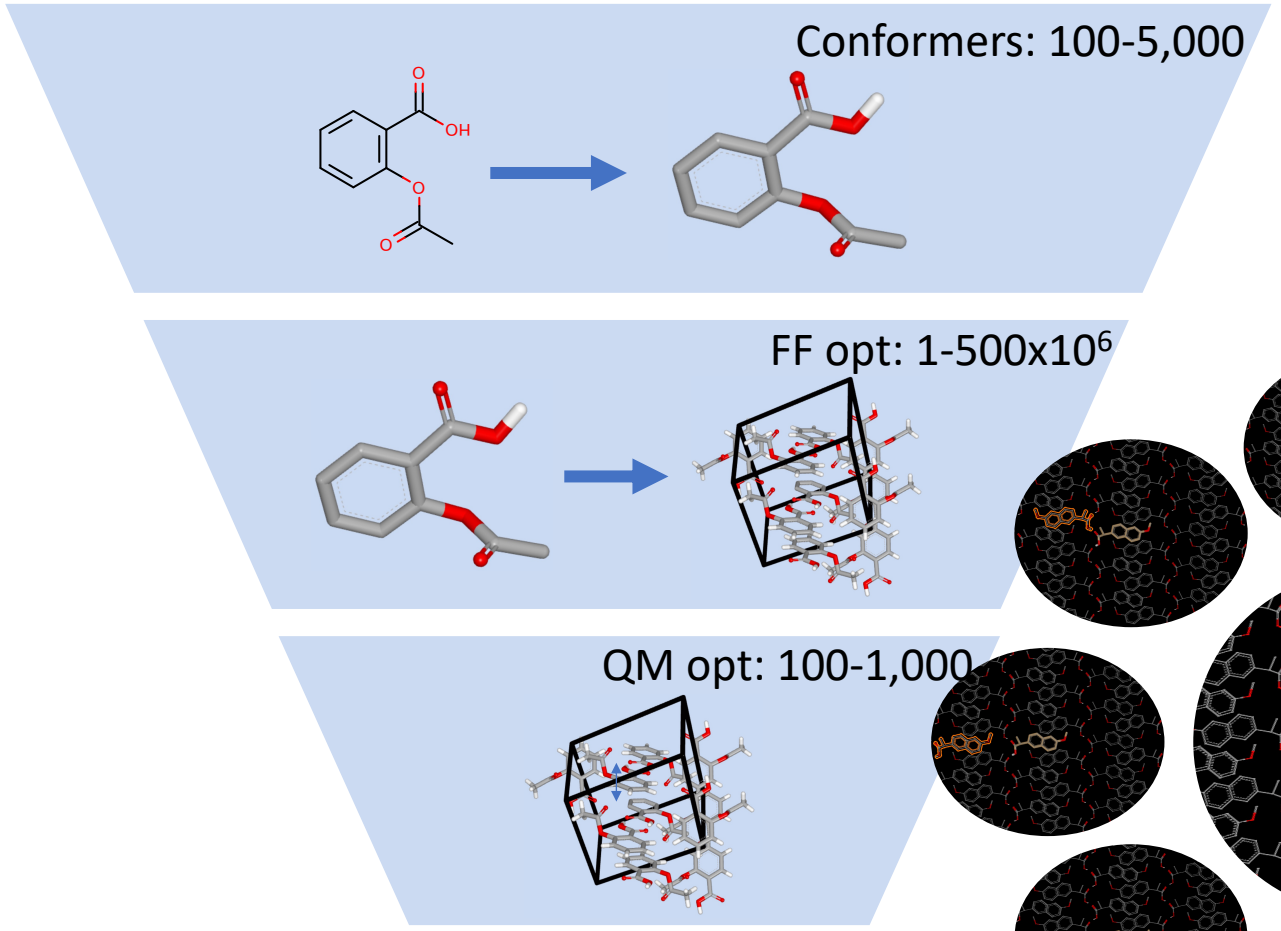
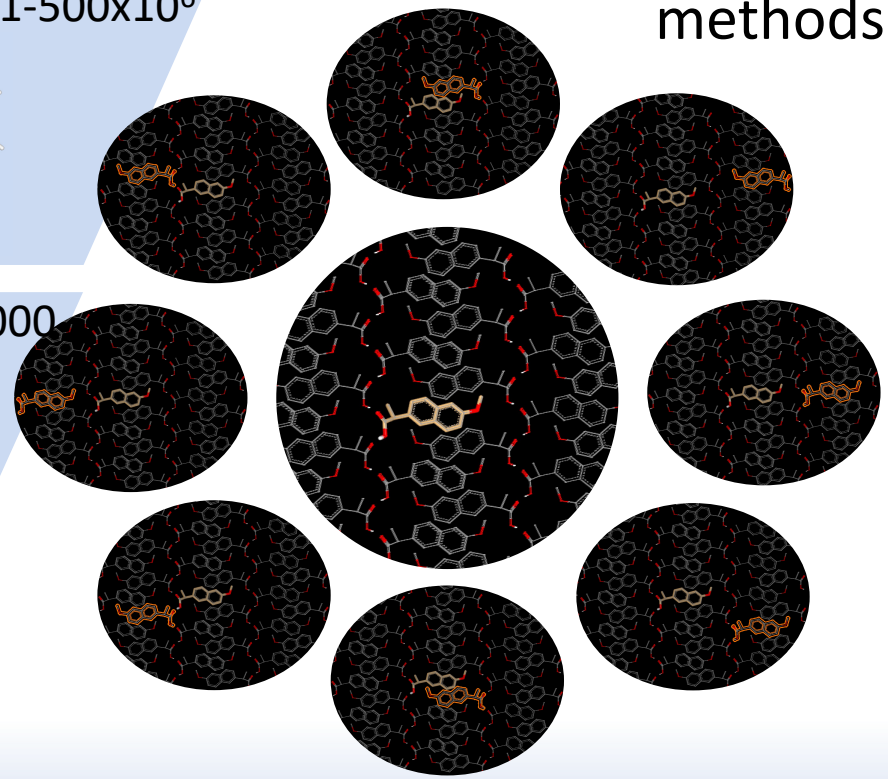


- Highly parallelizable (time for one dimer)
- Understand long range interaction
- Easily swap in more expensive methods



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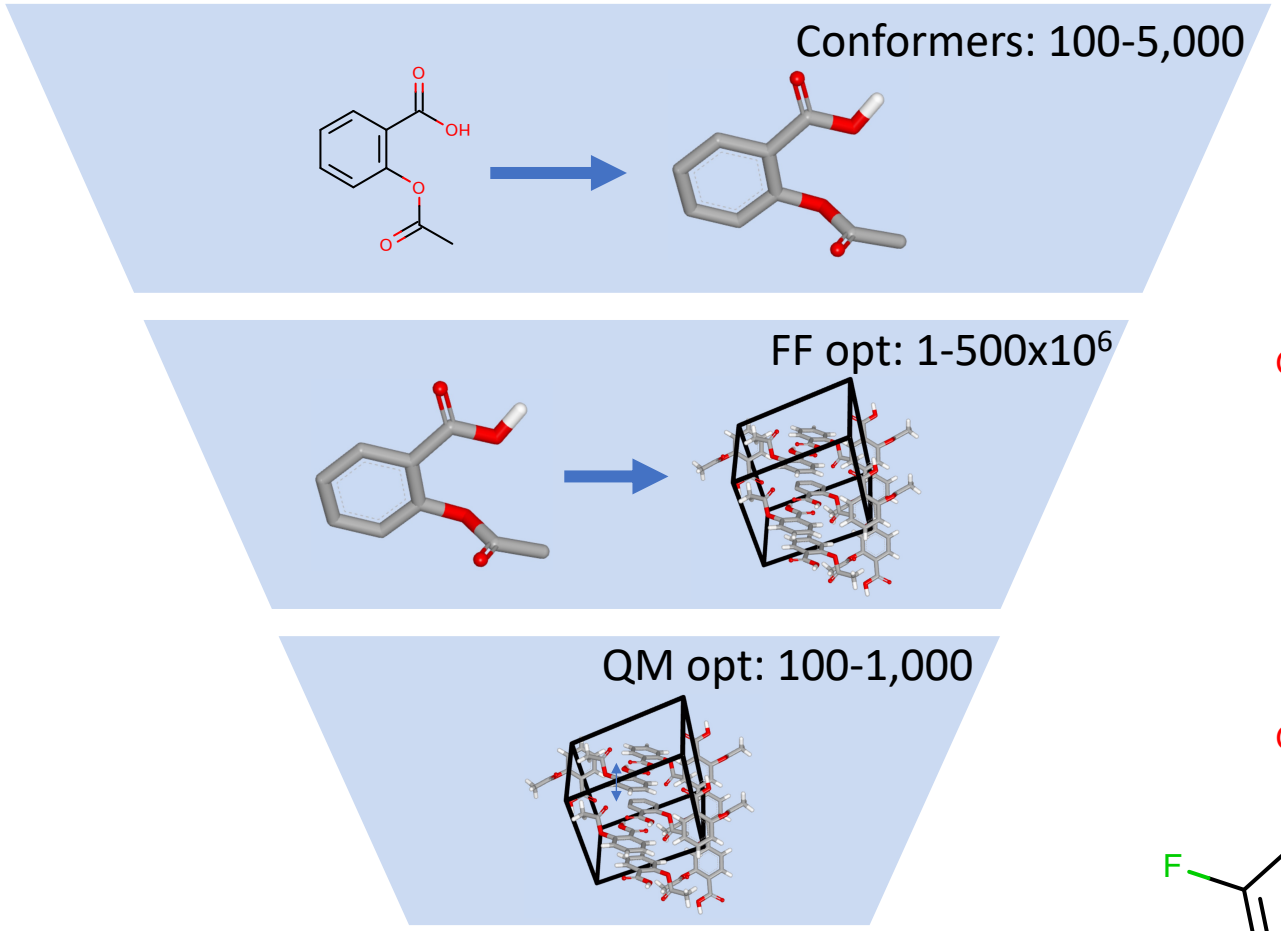
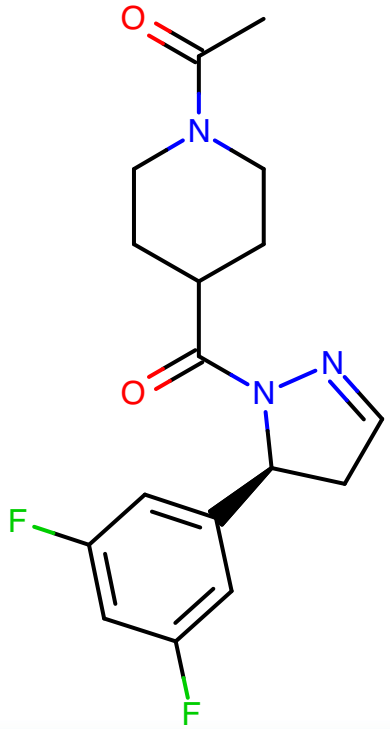
Successful blind challenges were successful





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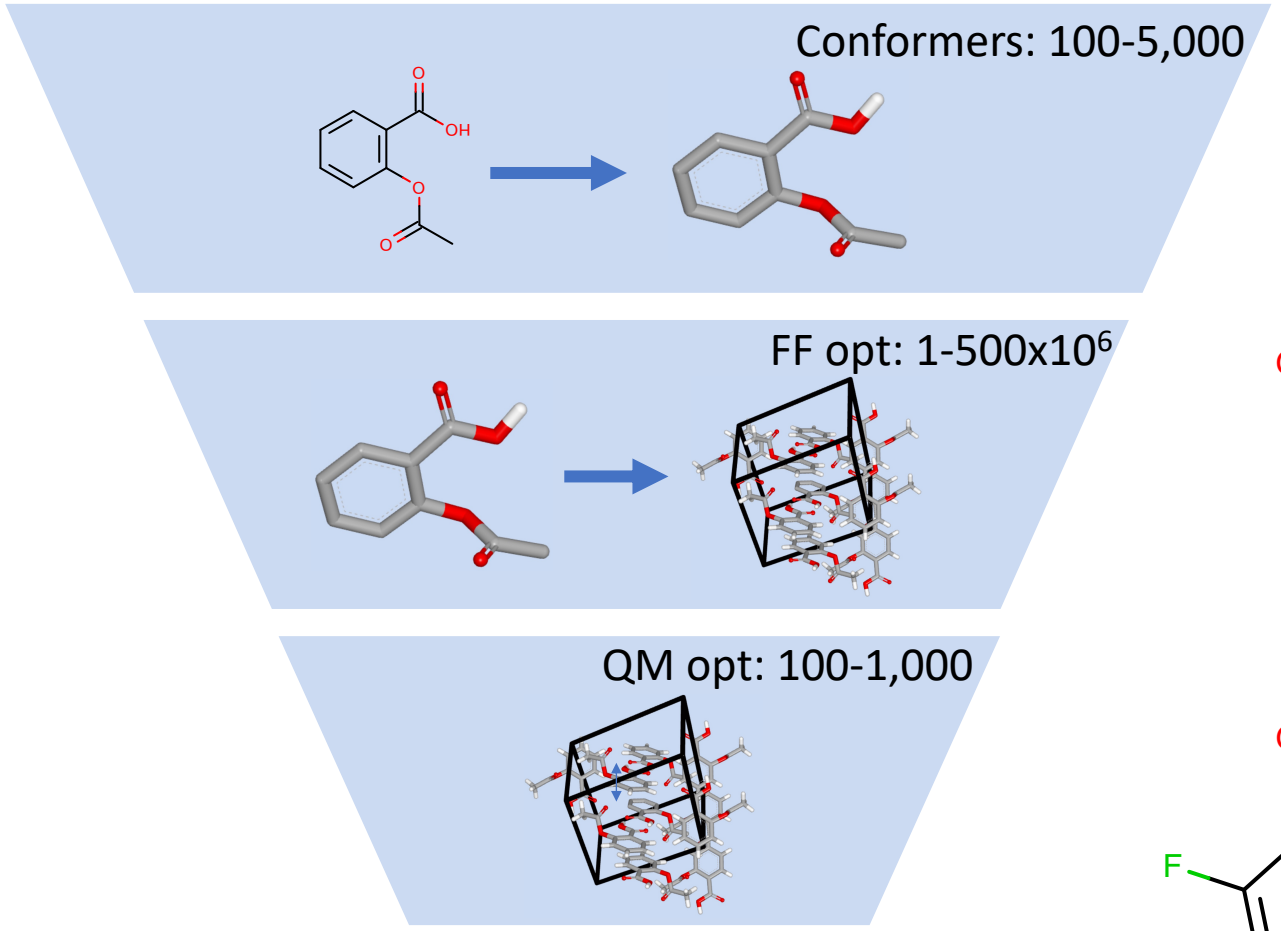

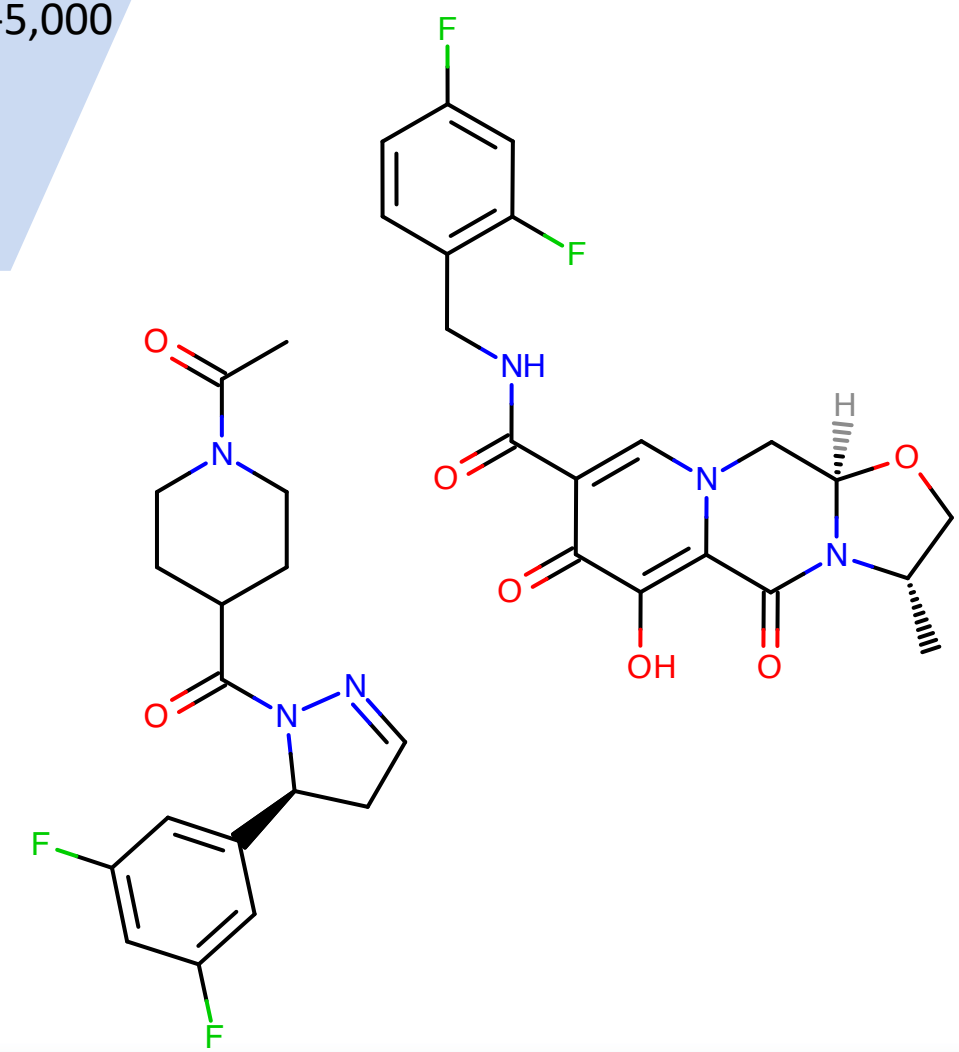

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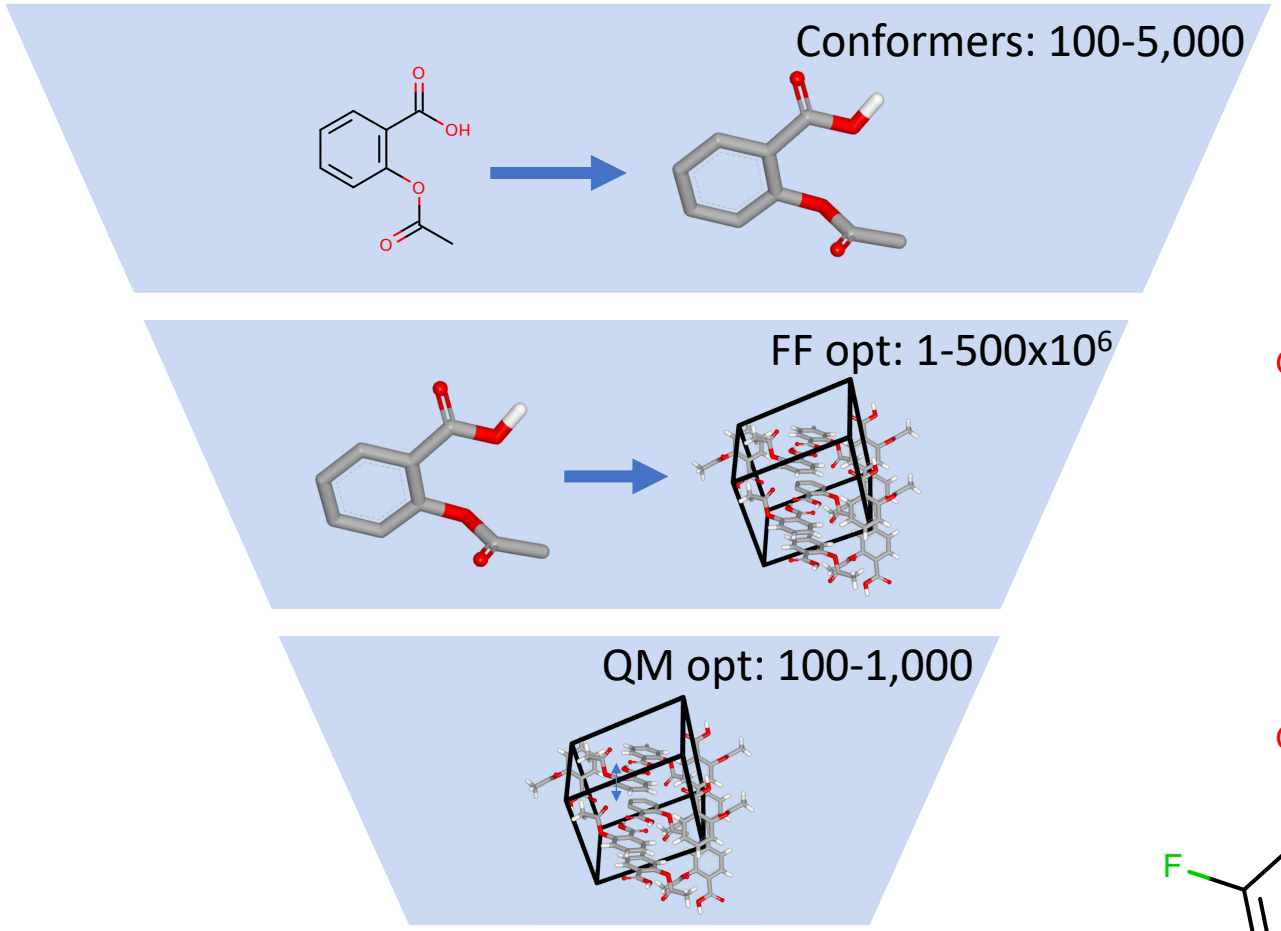
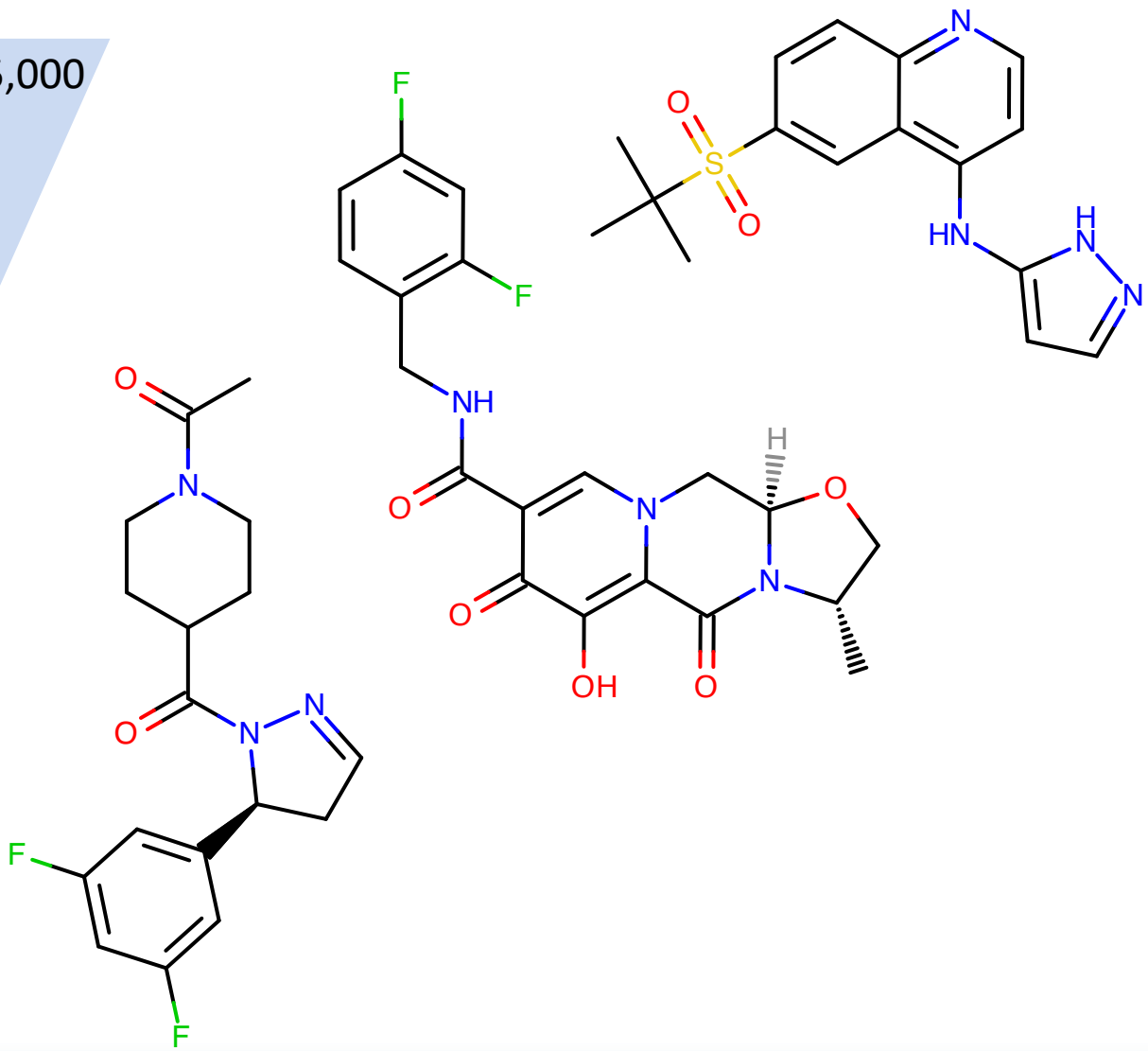




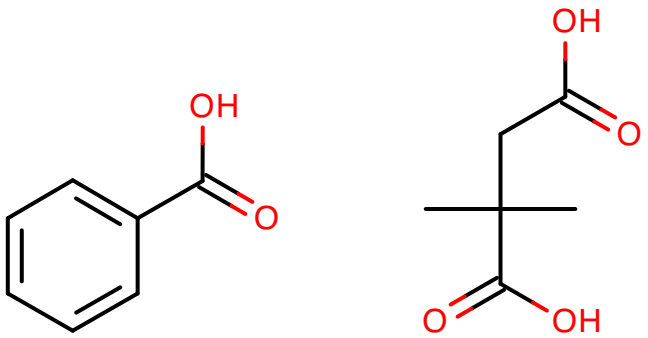
Outline for recent progress

Finite Temperature Correction

Monohydrate blind prediction

Outline for recent progress

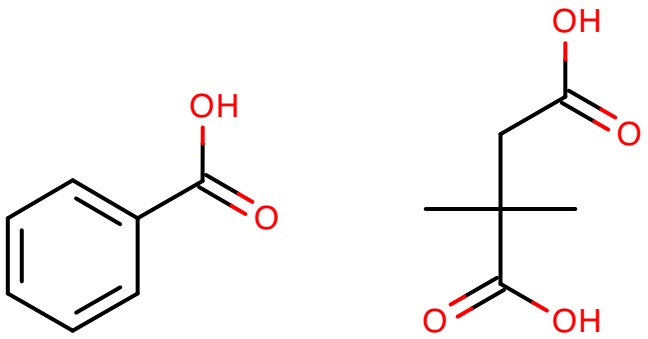
Finite Temperature Correction

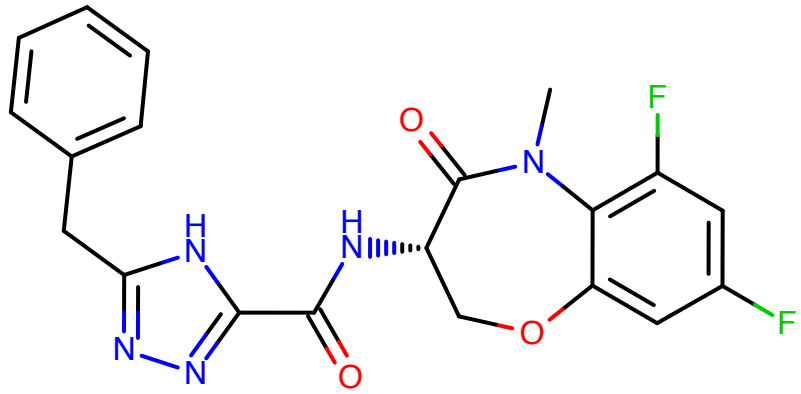


Monohydrate blind prediction

Outline for recent progress

Finite Temperature Correction





Monohydrate blind prediction

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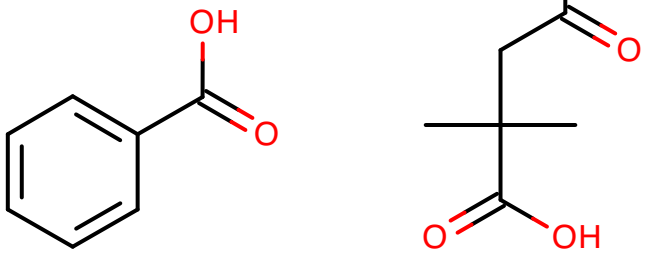
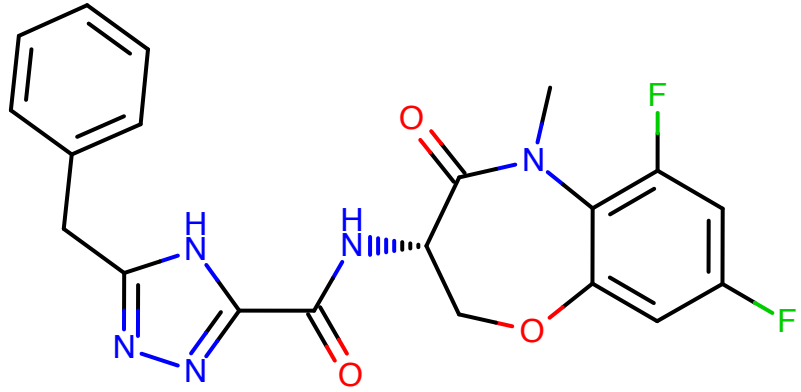
Outline for recent progress

Finite Temperature Correction





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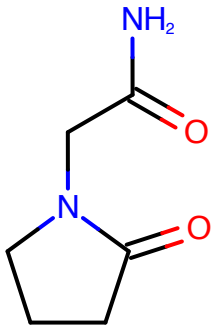

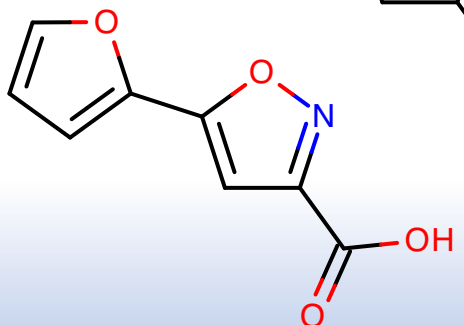

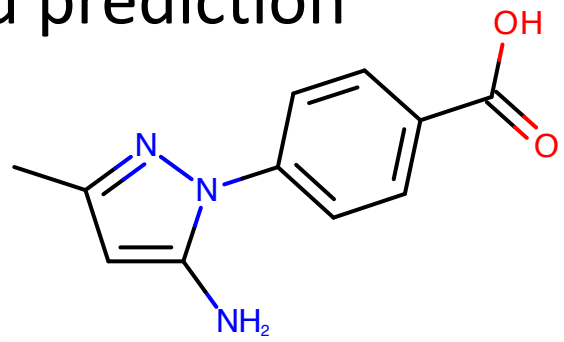

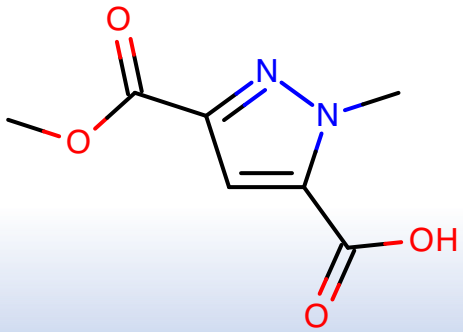

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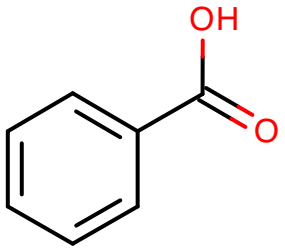

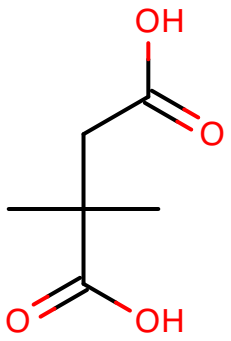

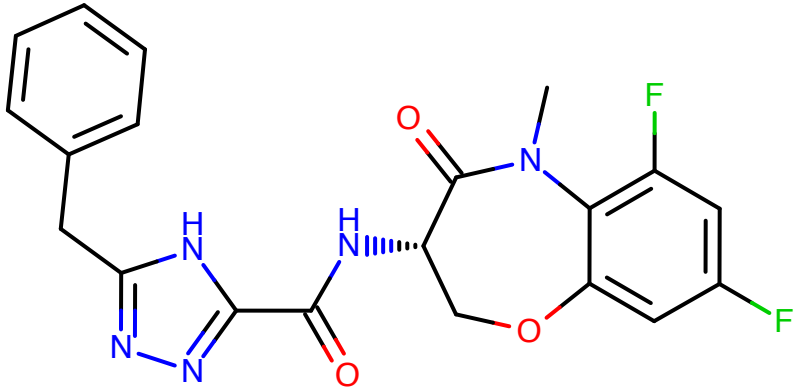

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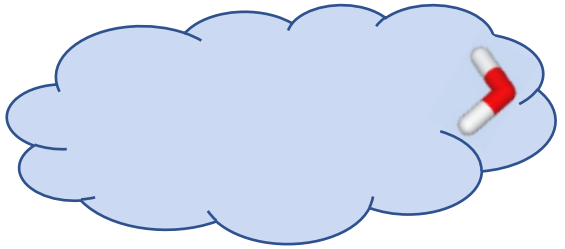

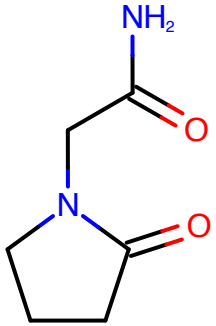

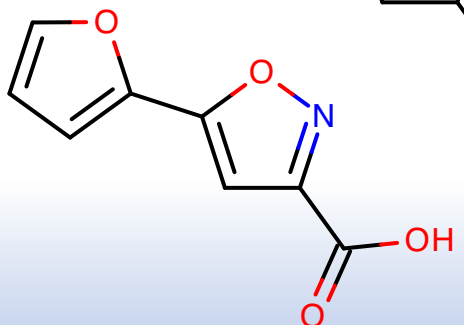

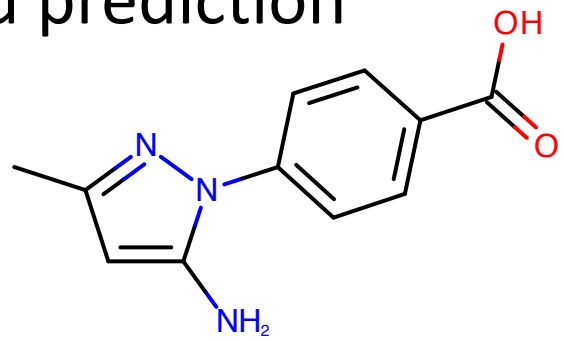

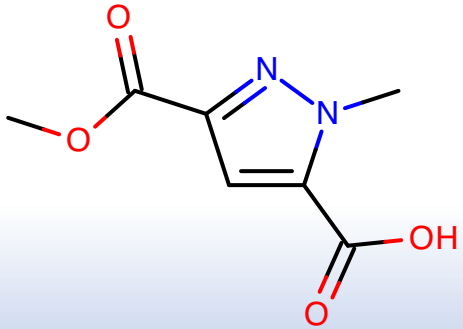

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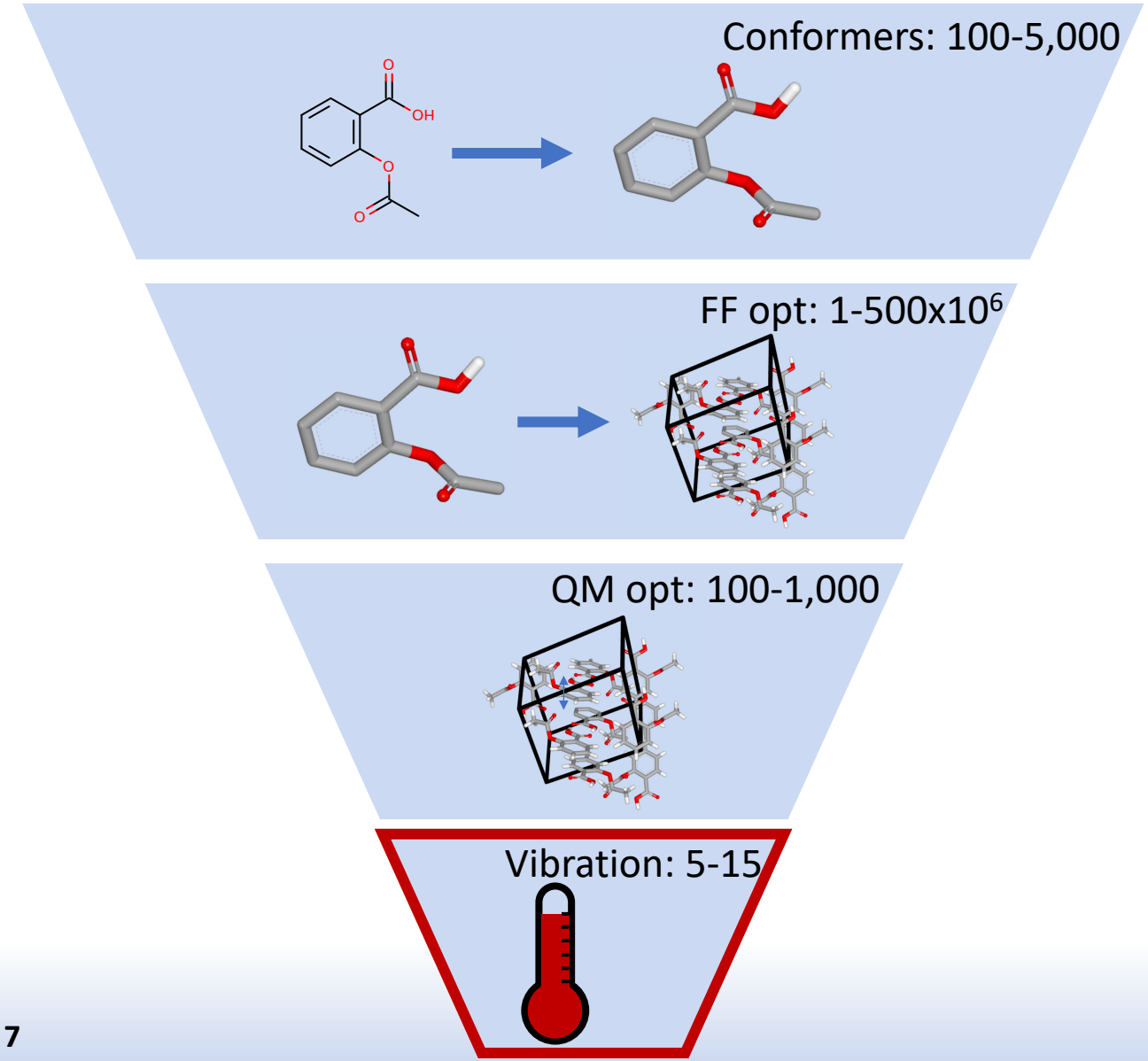
Evolving protocol now includes entropy calculations



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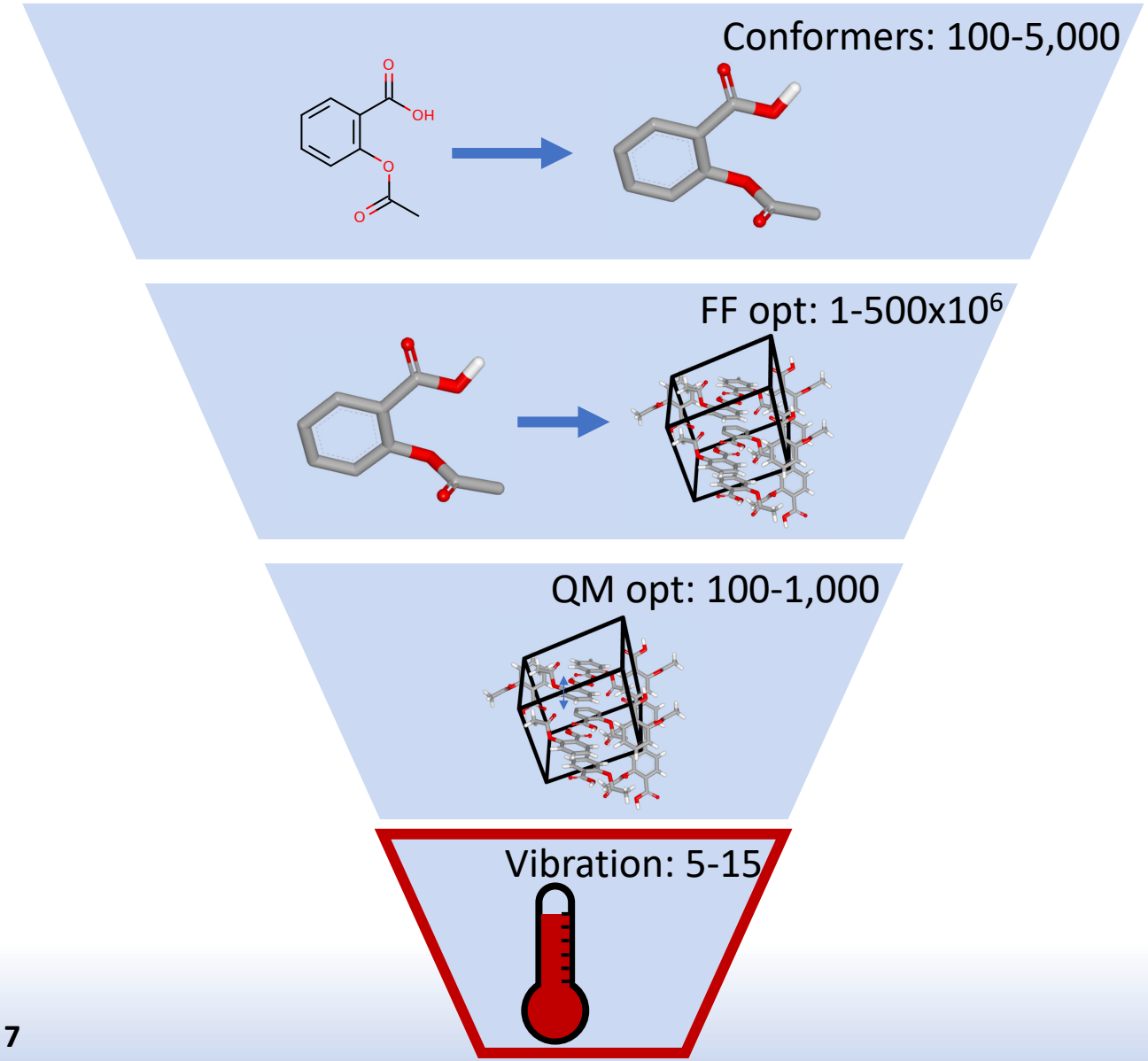

- Free energy of a crystal at finite temperature is due to vibrations
- Using a harmonic approximation, estimate entropy from the Hessian of the crystal

Harmonic approximation to finite temperature correction

- Vibrational contribution to free energy
- Third party software Phonopy

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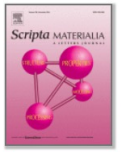
Scripta Materialia
Volume 108, November 2015, Pages 1-5



Viewpoint Paper

First principles phonon calculations in materials science

Atsushi Togo [a, b] ✉, Isao Tanaka [a, b, c] ✉

DOI:10.1016/j.scriptamat.2015.07.021

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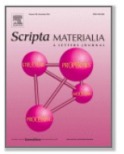

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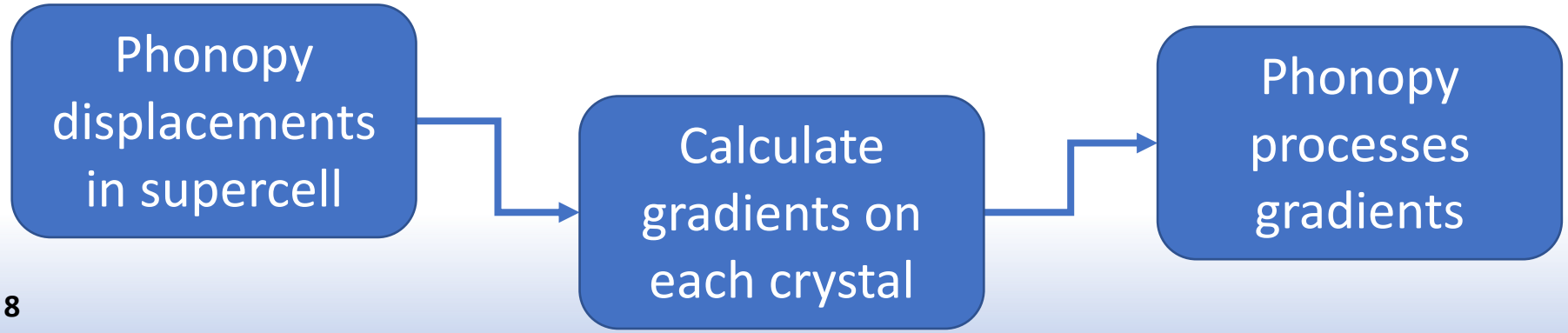

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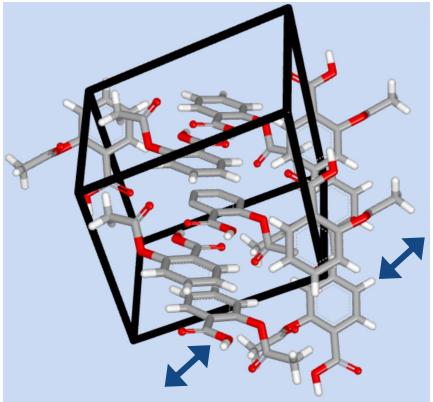

Phonopy displacements in supercell → Calculate gradients on each crystal → Phonopy processes gradients

Harmonic approximation to finite temperature correction

- Vibrational contribution to free energy
- Third party software Phonopy
- Computes finite difference Hessian to derive phonon internal energy and entropy
- Free energy at finite temperature (300K)

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Scripta Materialia
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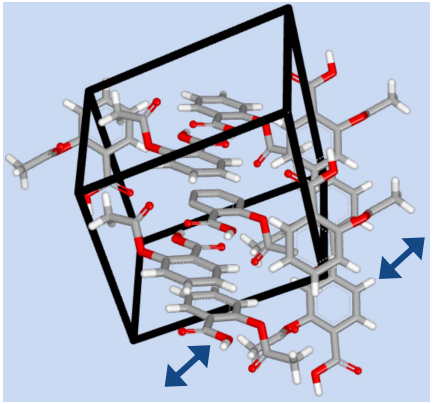

Phonopy displacements in supercell → Calculate gradients on each crystal → Phonopy processes gradients

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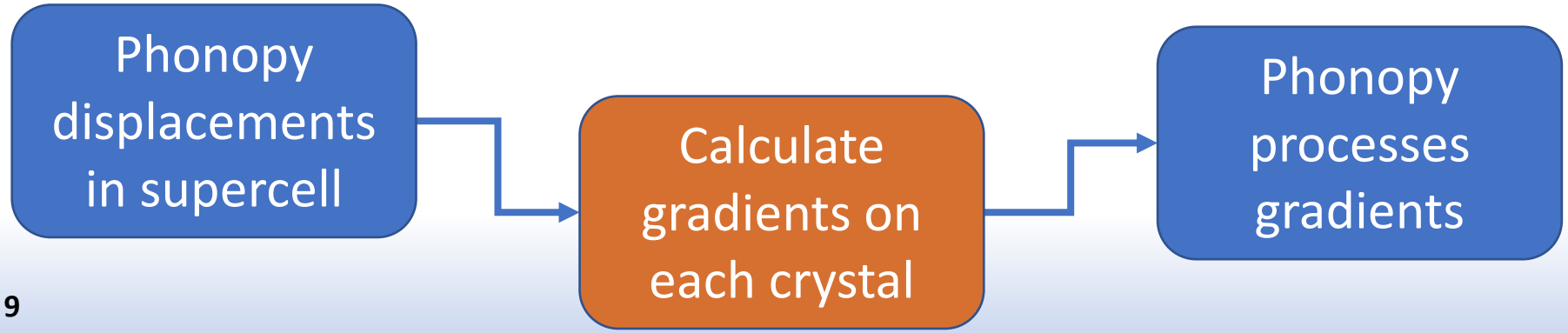
Compute gradients with FF or QM



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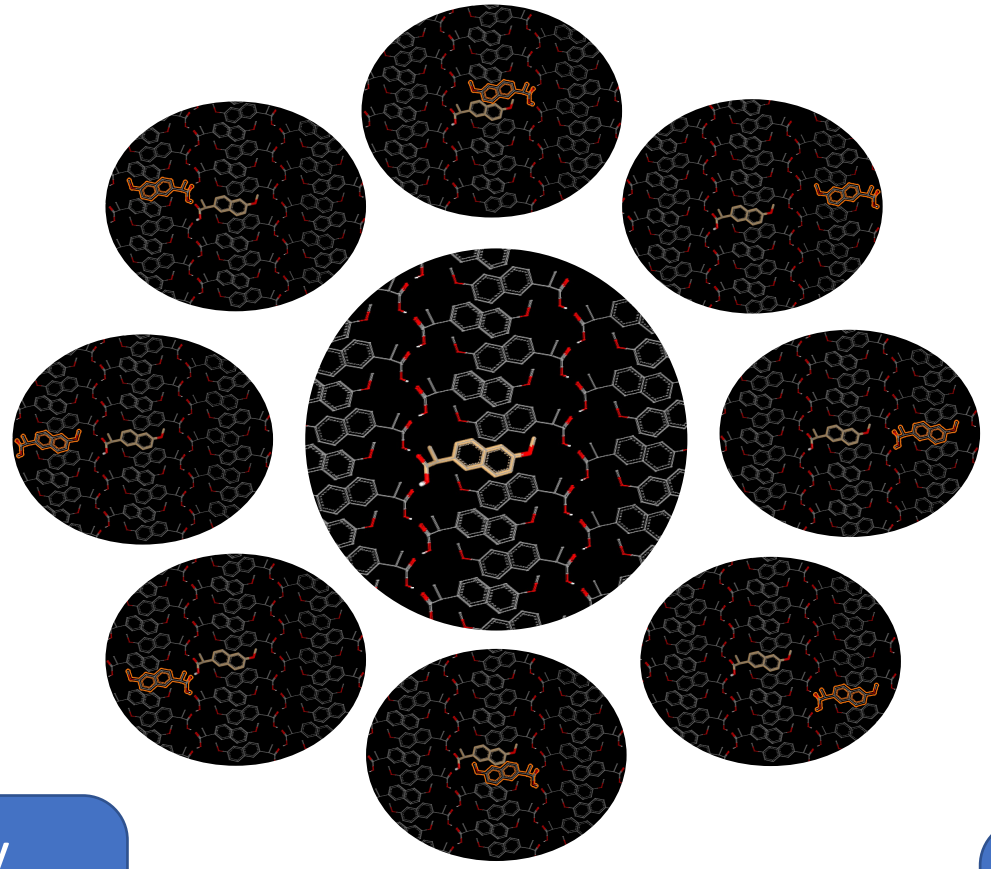
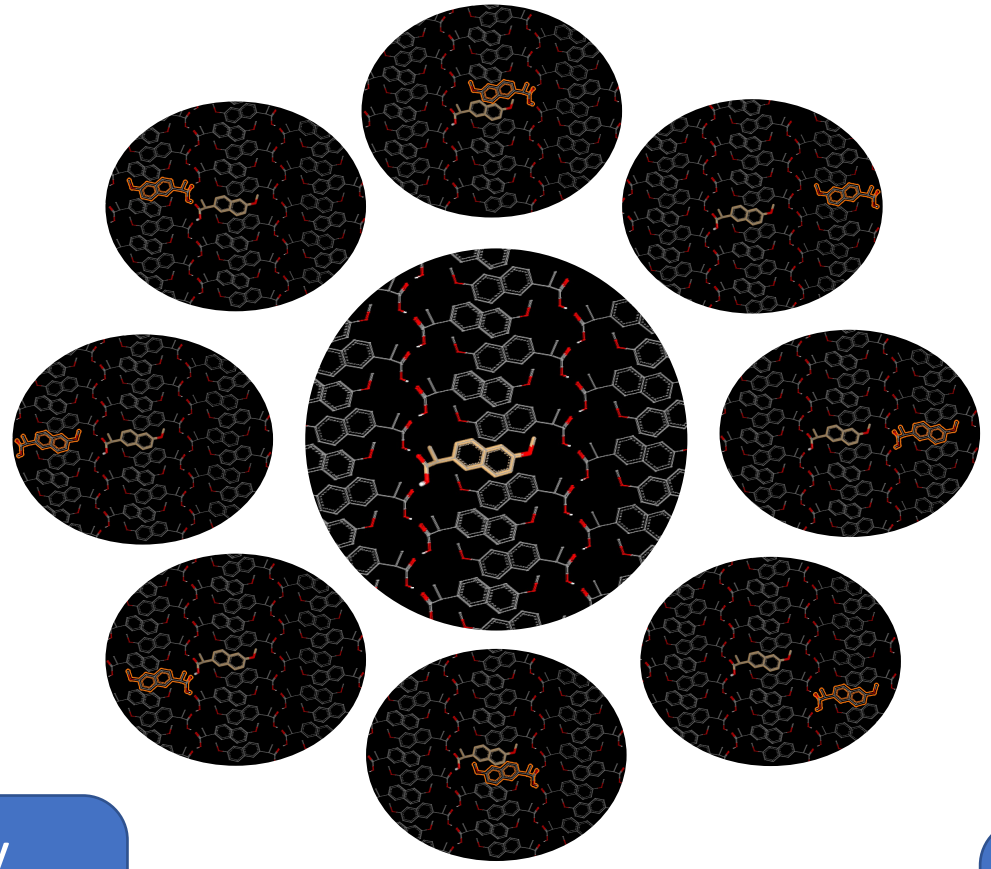


- Dimer expansion on each supercell
- Gradients can be computed with force fields or QM

Phonopy displacements in supercell → Calculate gradients on each crystal → Phonopy processes gradients

Compute gradients with FF or QM



- Dimer expansion on each supercell
- Gradients can be computed with force fields or QM
- Highly parallelizable
- Used prospectively

Phonopy displacements in supercell → Calculate gradients on each crystal → Phonopy processes gradients

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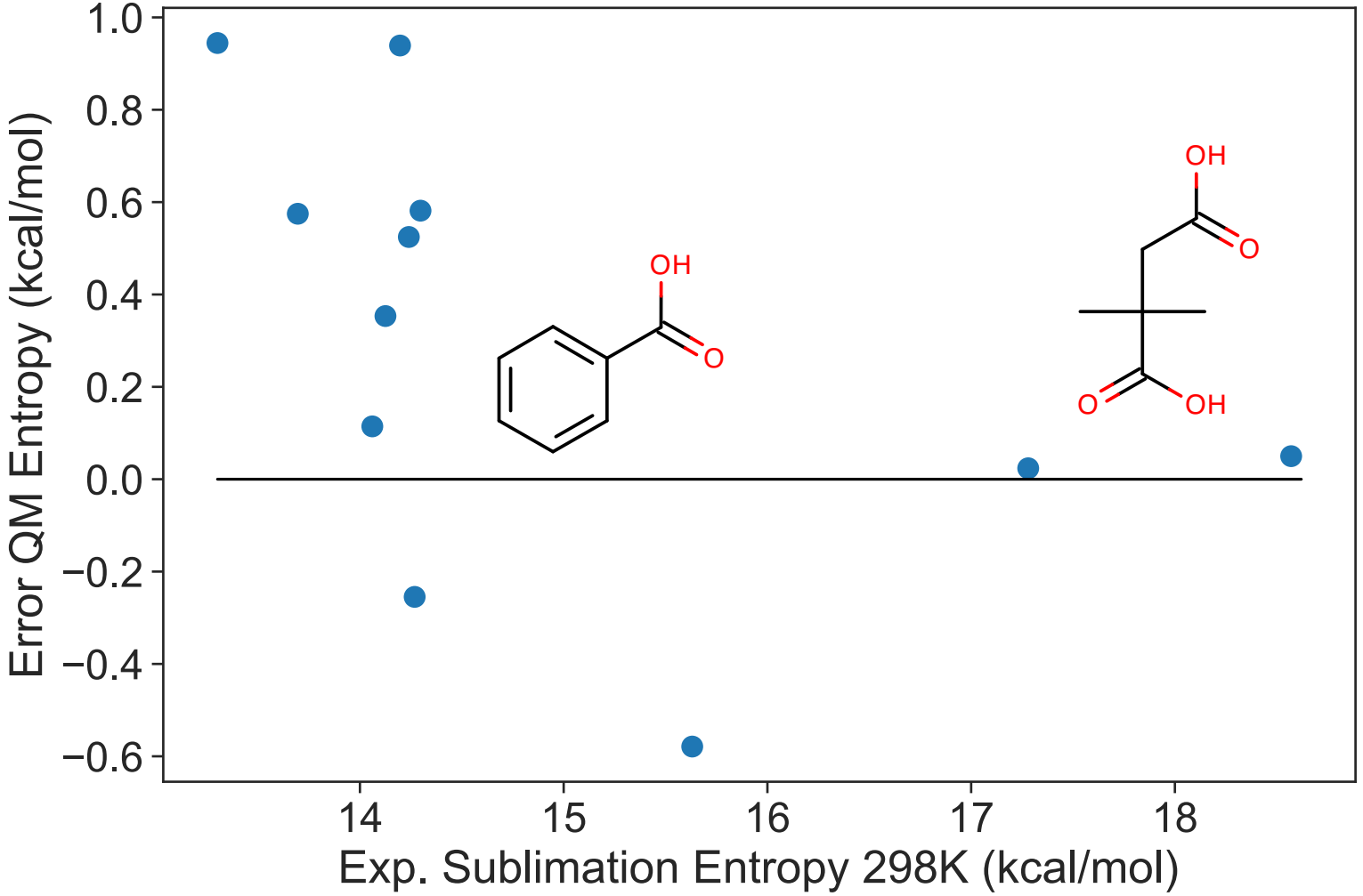
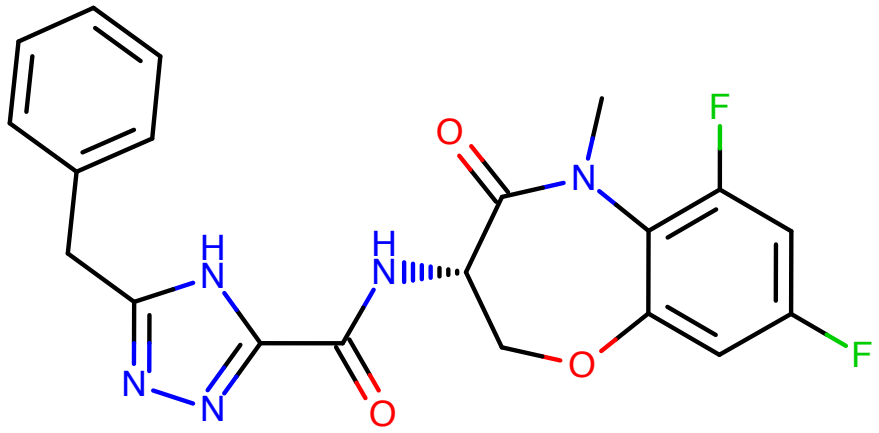
Compare to sublimation entropies



- Absolute sublimation entropies computed with HF3c
- Experimental sublimation entropies for crystals of carboxylic acids
- Plot error in predicted entropy

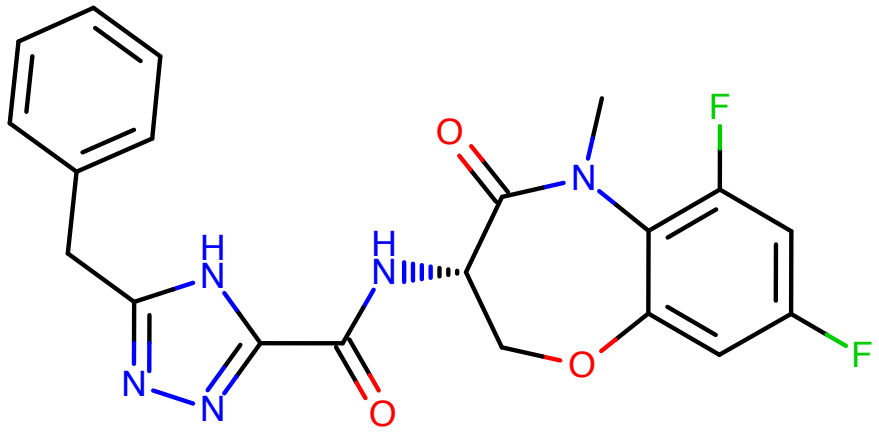
R^2 = 0.91 [0.71,0.98] Robust Error = 0.57 kcal/mol

Finite Temperature Correction in blind challenge



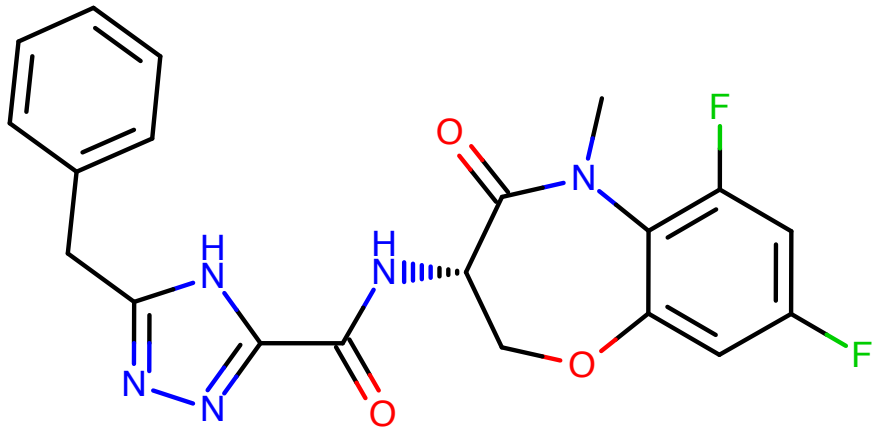
- Druglike molecule from GSK
  - 4 rotatable bonds and flexible ring
  - 3 tautomers

Finite Temperature Correction in blind challenge



- Druglike molecule from GSK
  - 4 rotatable bonds and flexible ring
  - 3 tautomers
- 2 Blind predictions start with QM enthalpy

Finite Temperature Correction in blind challenge



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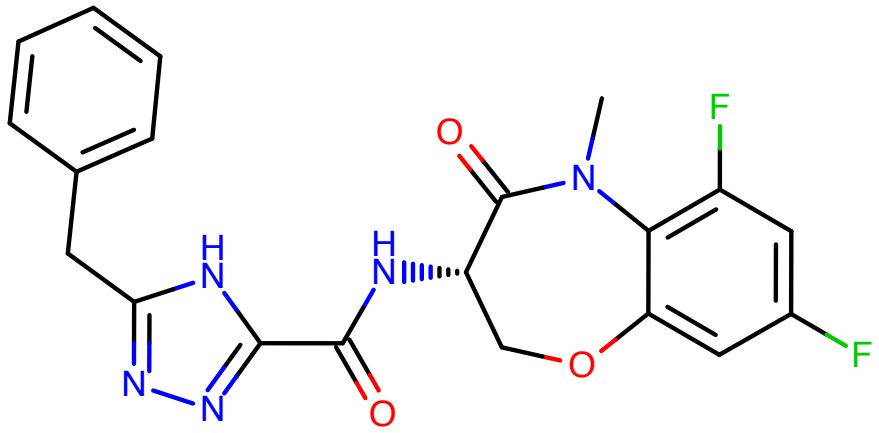
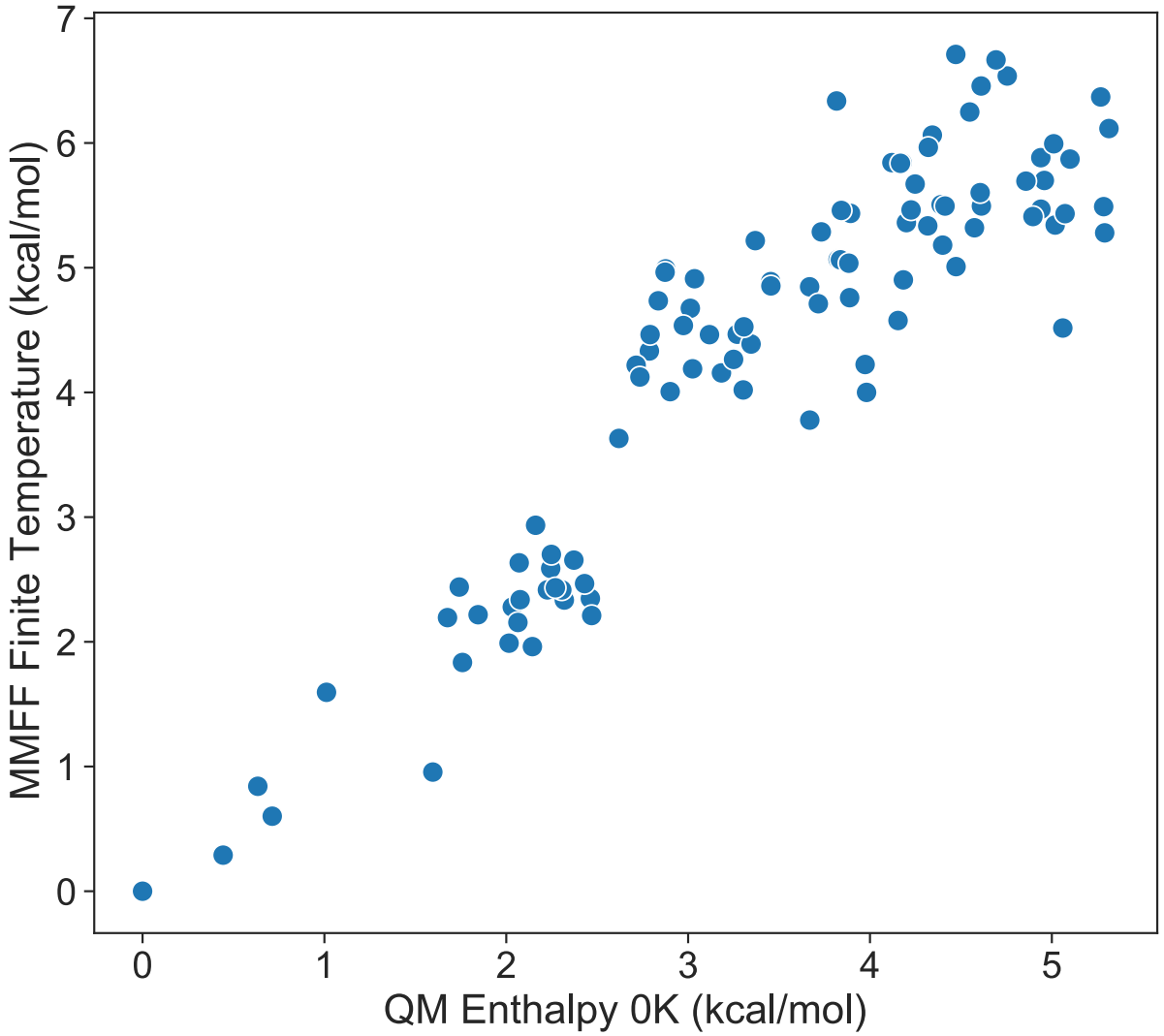
- 2 Blind predictions start with QM enthalpy
  - Force field finite temperature correction

Finite Temperature Correction in blind challenge

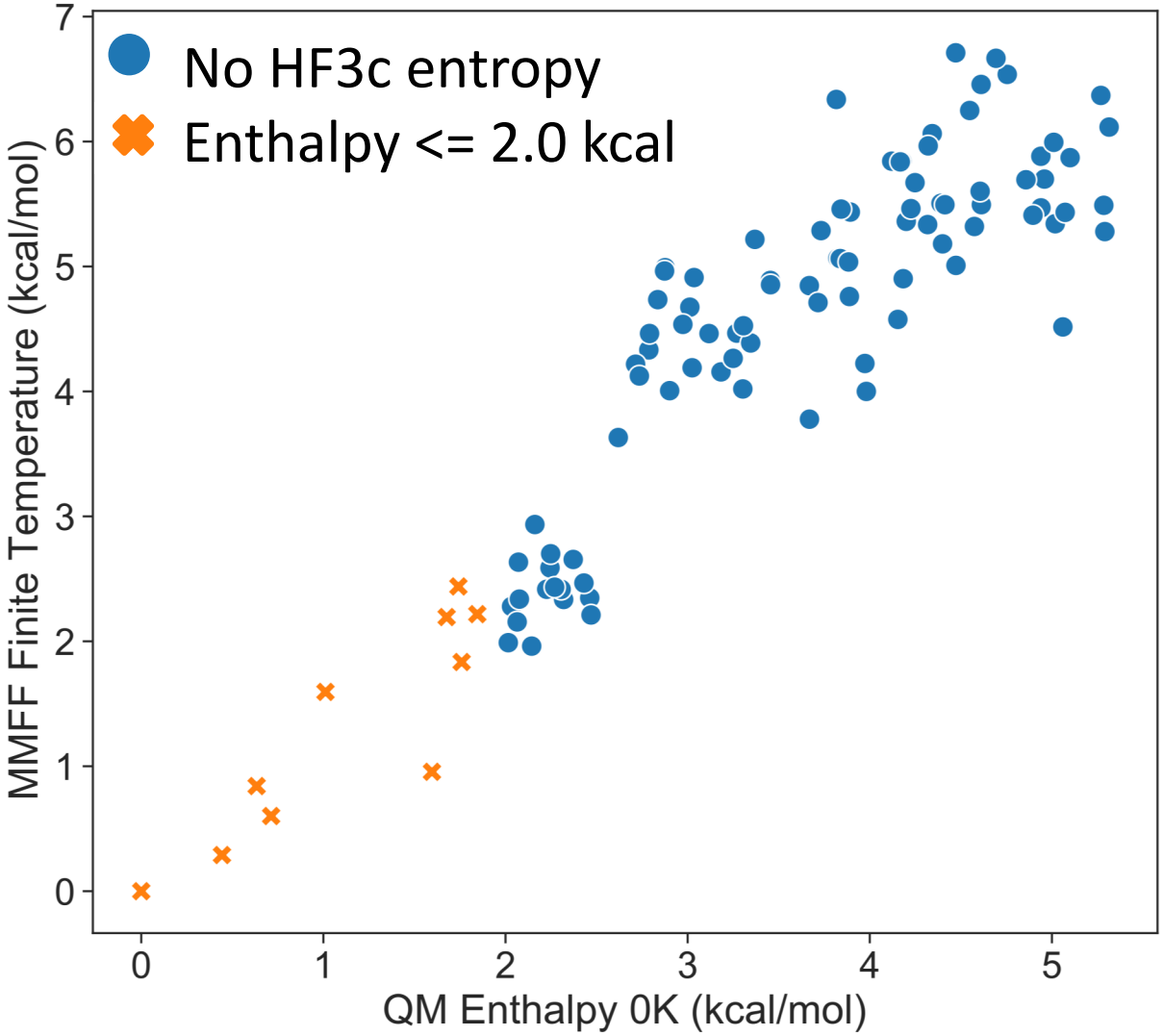


- Druglike molecule from GSK
  - 4 rotatable bonds and flexible ring
  - 3 tautomers
- 2 Blind predictions start with QM enthalpy
  - Force field finite temperature correction
  - Subset with QM finite temperature correction

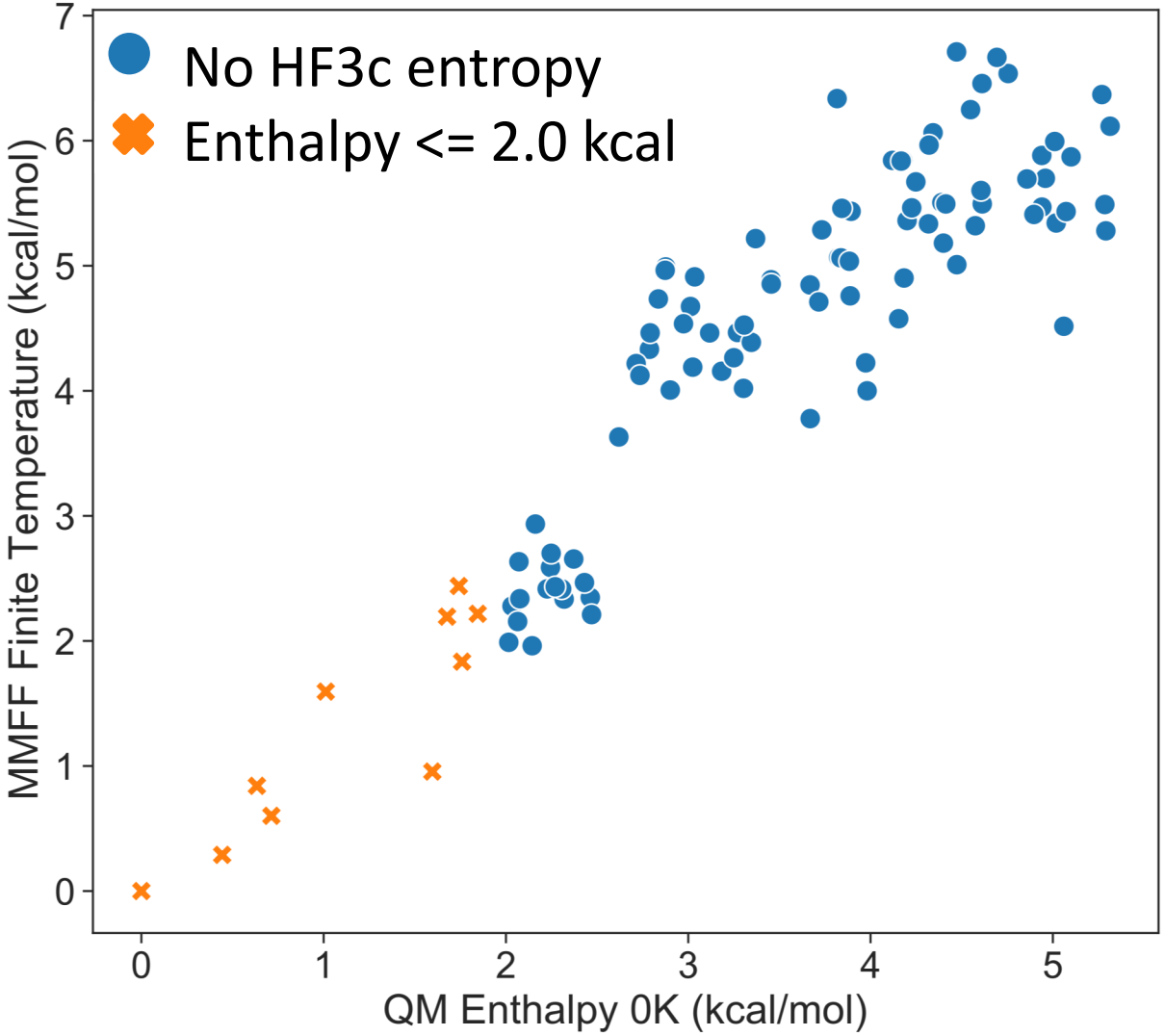
Ranks change with finite temperature corrections

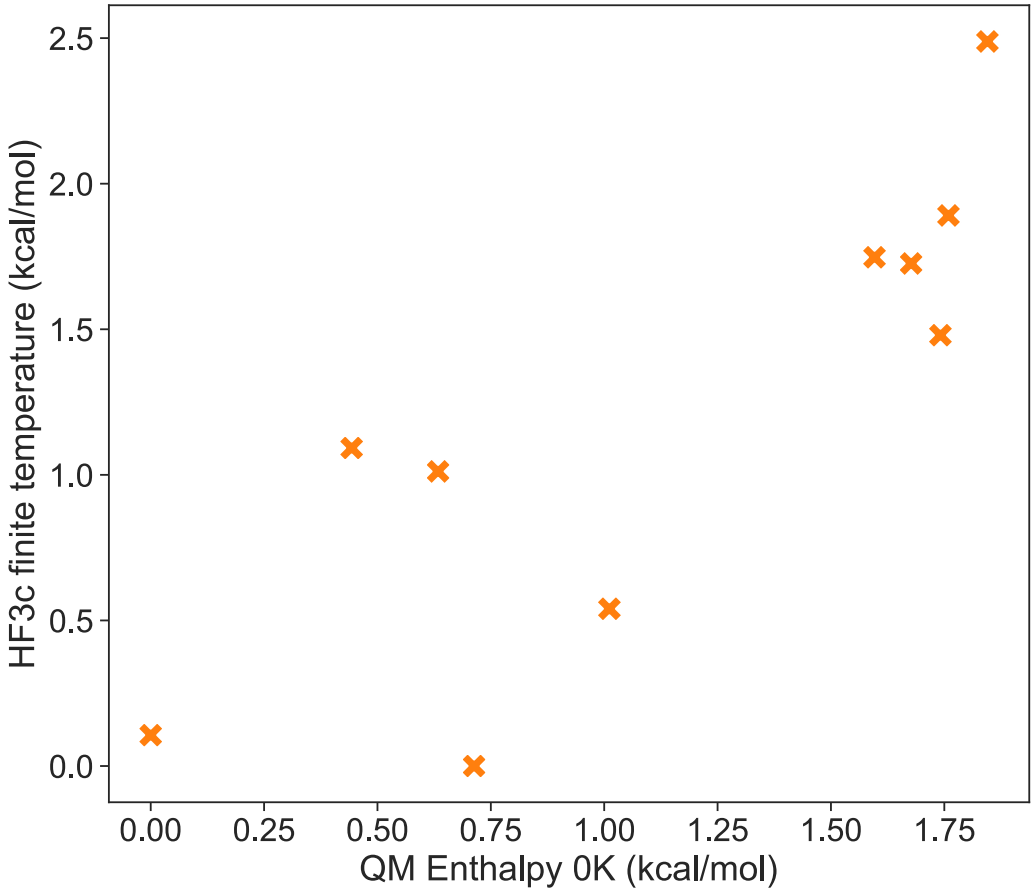


Ranks change with finite temperature corrections

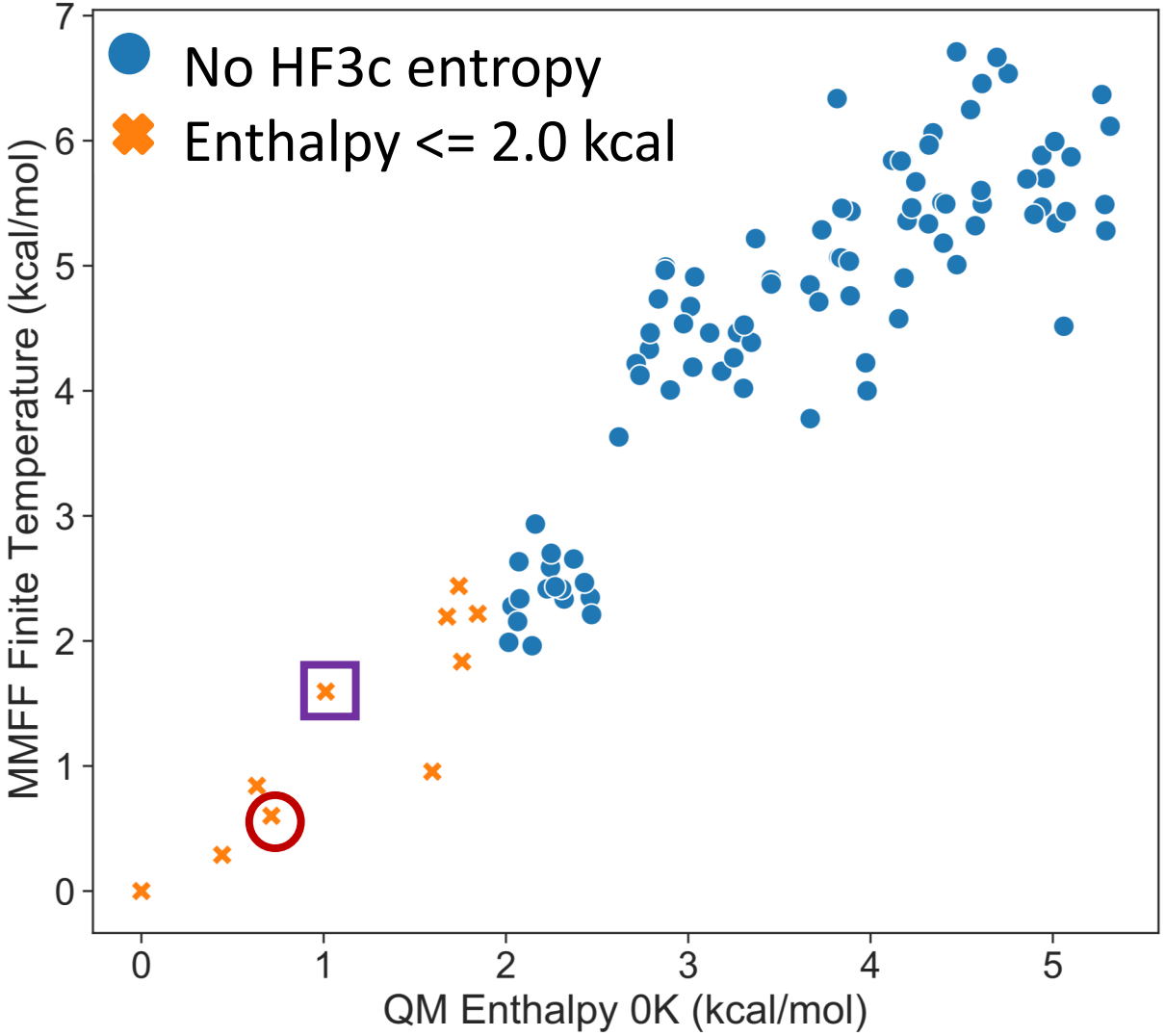


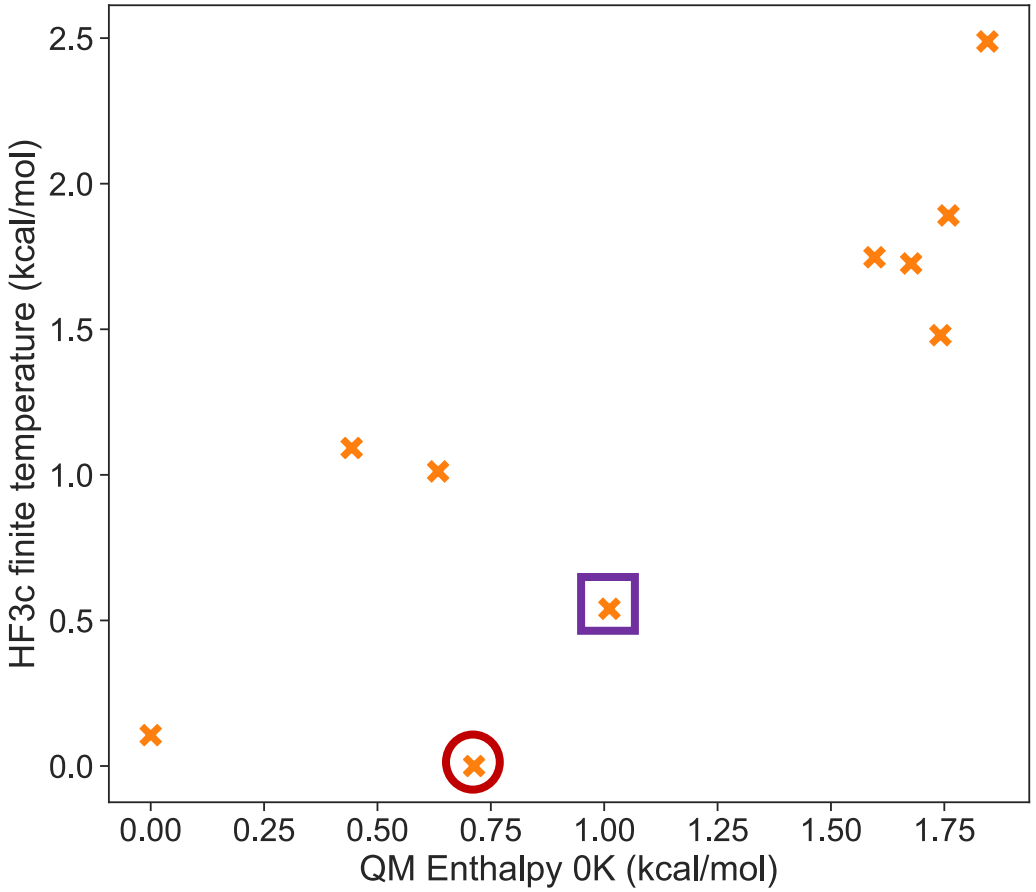
Ranks change with finite temperature corrections





Ranks change with finite temperature corrections

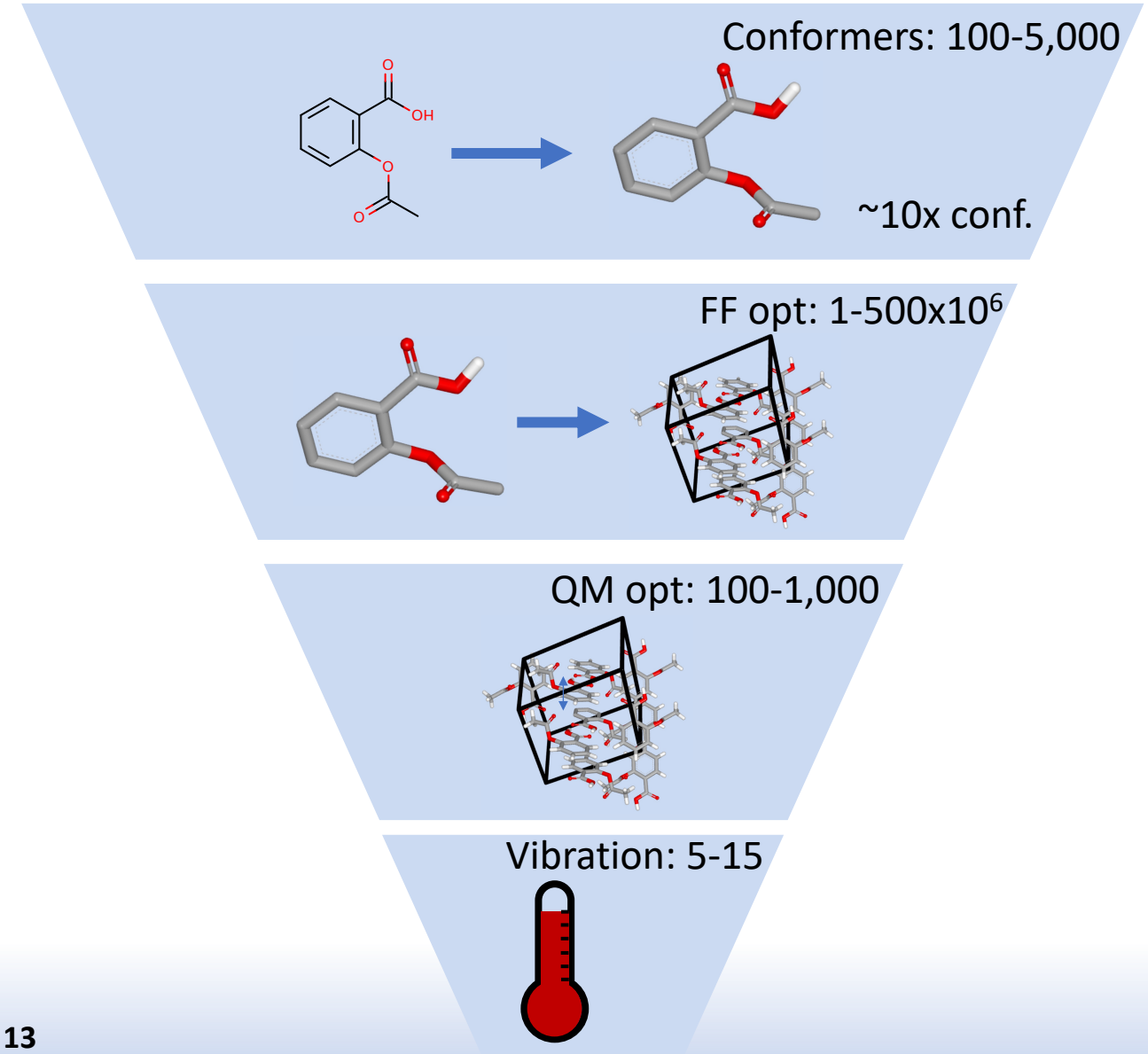




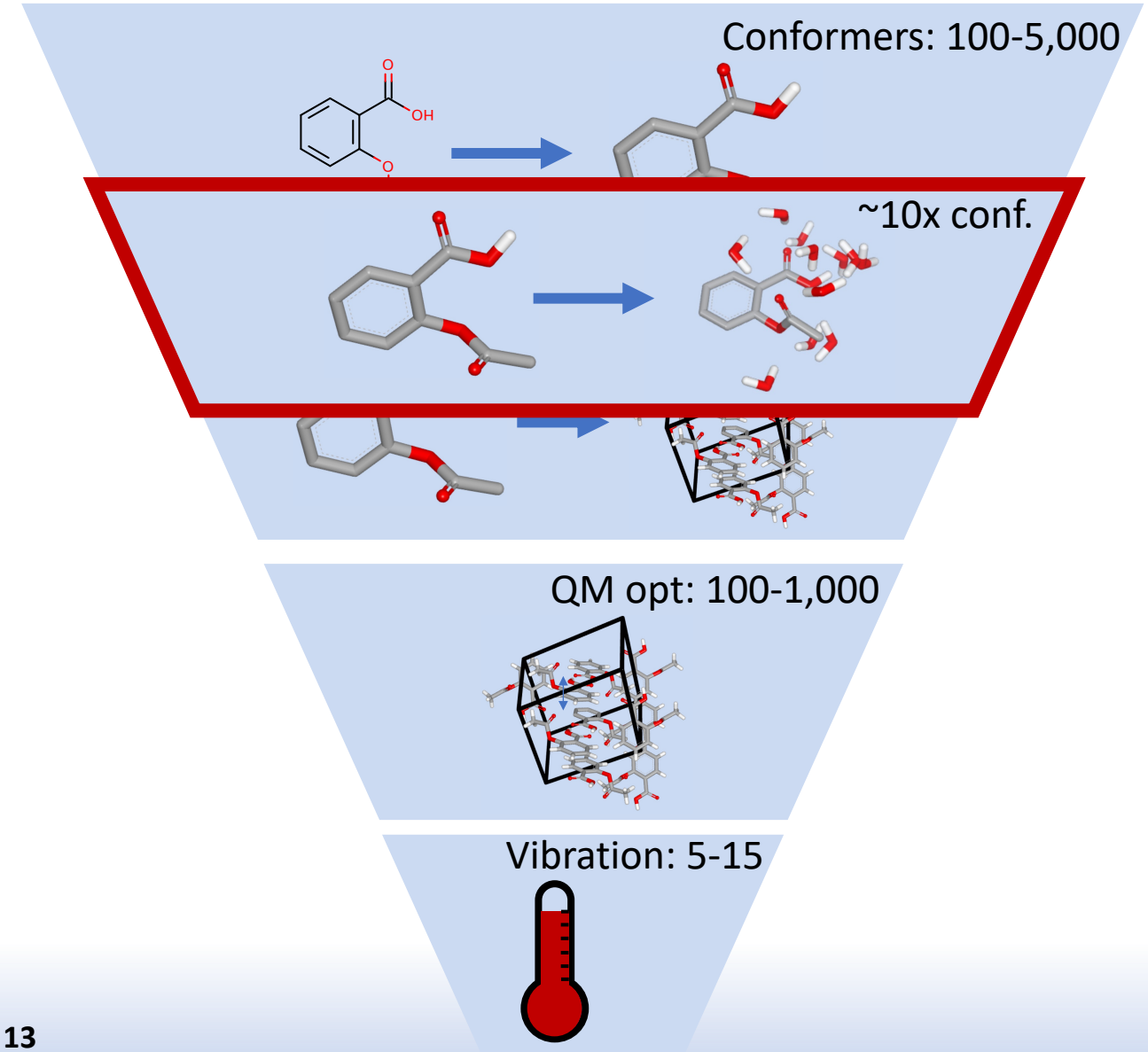
Hit 1: RMSD20 = 0.16

Hit 2: RMSD20 = 0.23

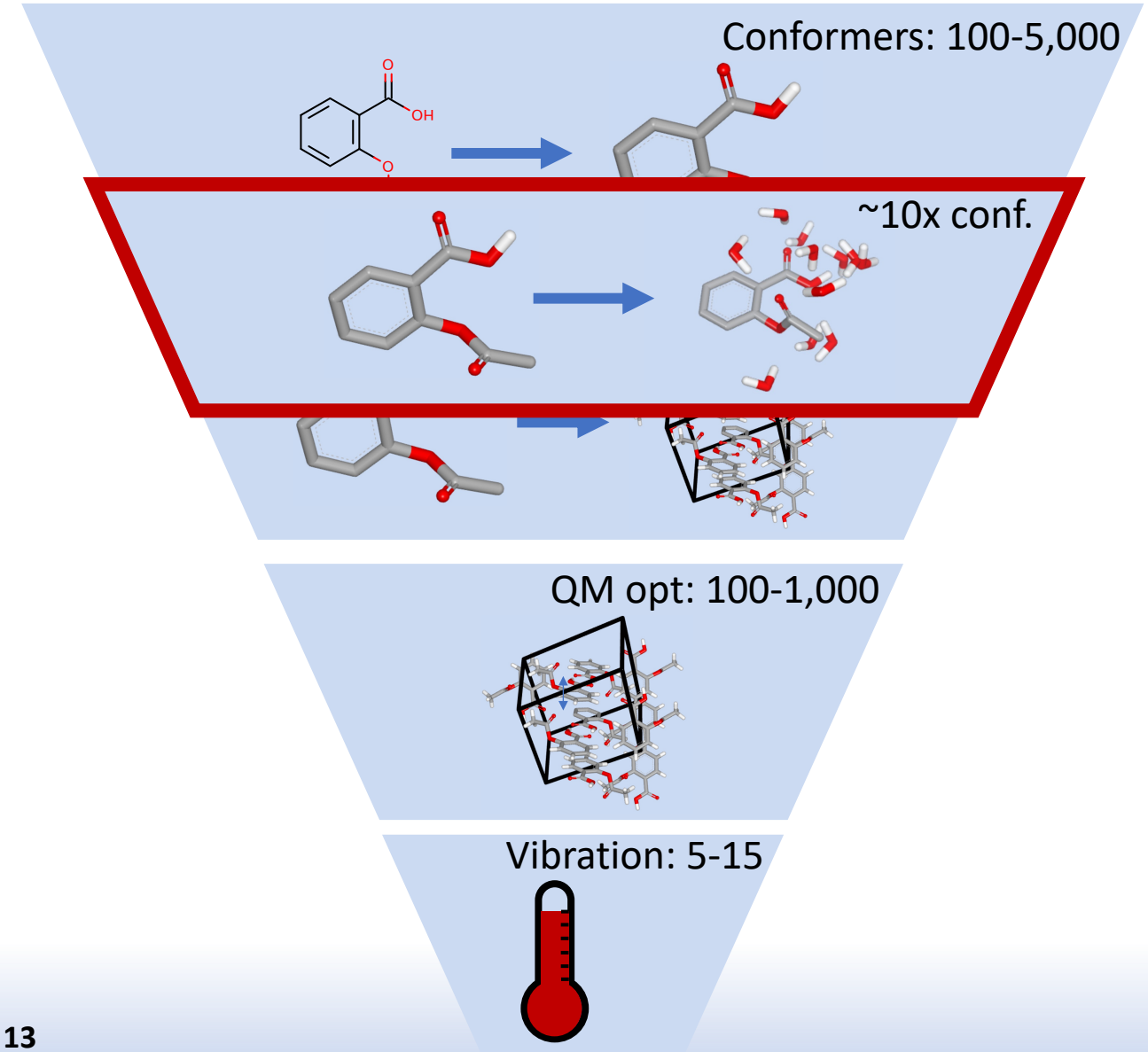
Monohydrate first multi-components crystal prediction



Monohydrate first multi-components crystal prediction



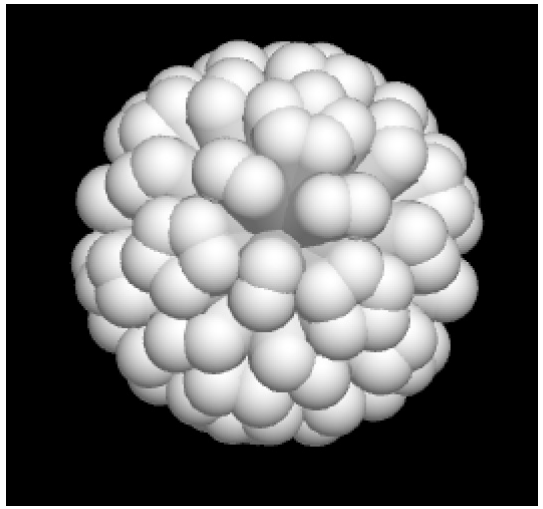
Monohydrate first multi-components crystal prediction



- Sample waters around all conformers
- Pack molecule-water dimers as a single asymmetric unit

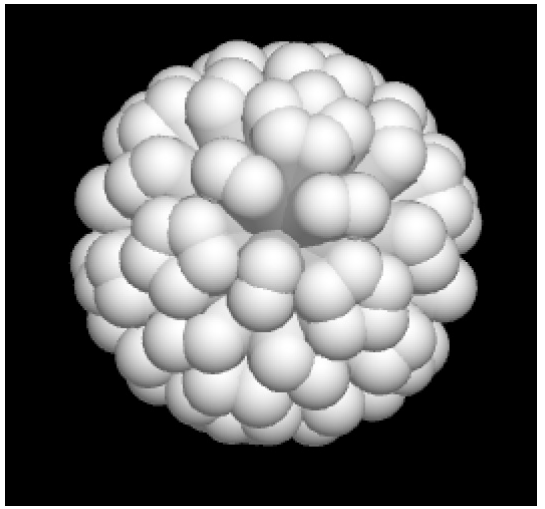
Sample water positions around all donors and acceptors

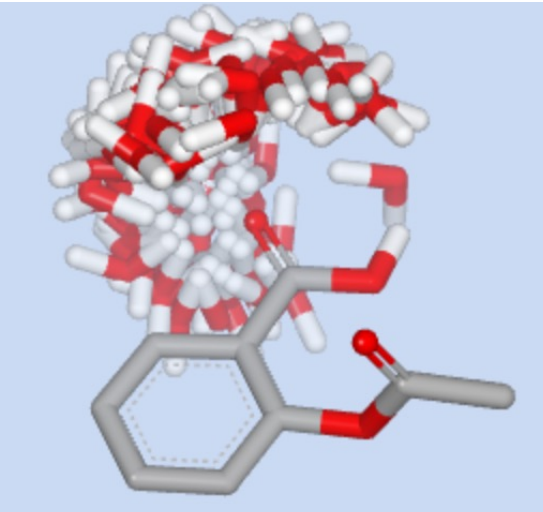
- Generate a set of 60 rotated waters
- Build a grid around each donor and acceptor



Sample water positions around all donors and acceptors

- Generate a set of 60 rotated waters
- Build a grid around each donor and acceptor
- Evaluate interaction energies using multipole FF
  - Keep waters within a set energy range
  - Deduplicate remaining waters





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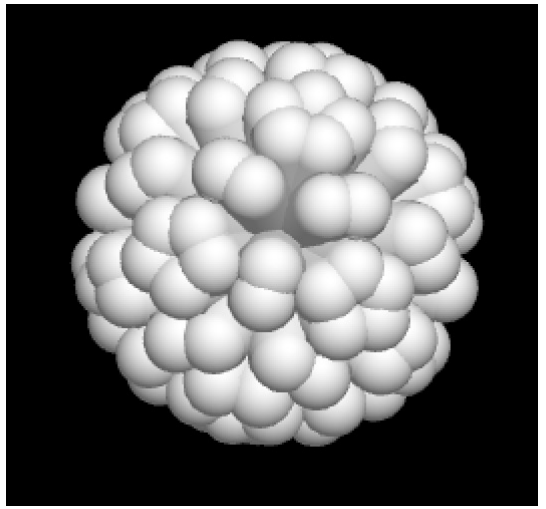
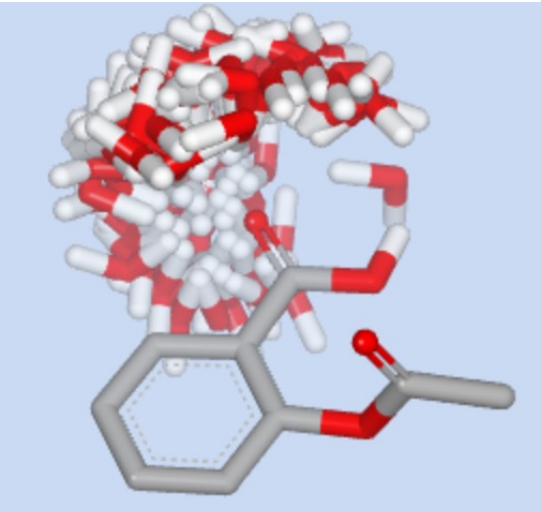
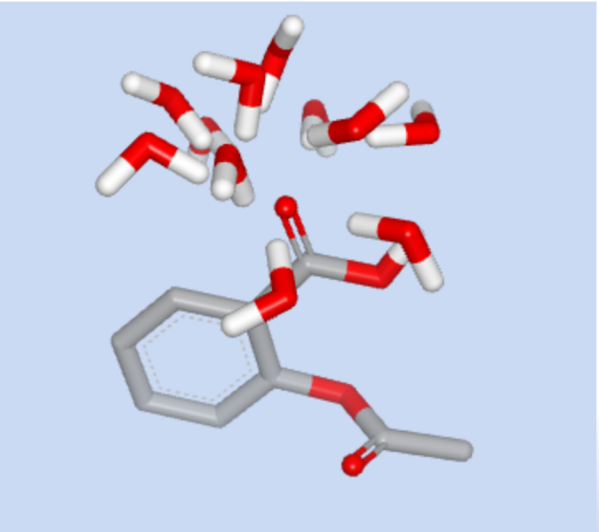
Sample water positions around all donors and acceptors

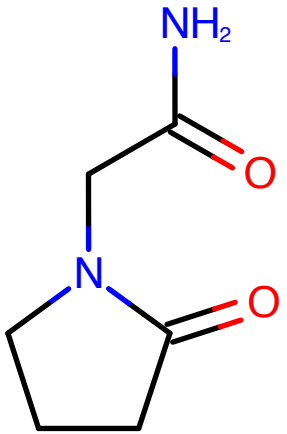


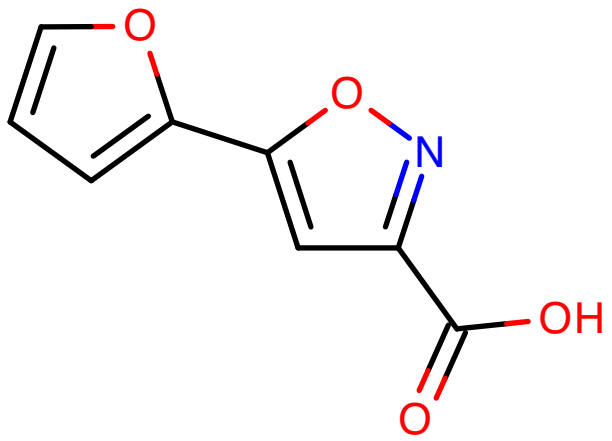
- Generate a set of 60 rotated waters
- Build a grid around each donor and acceptor
- Evaluate interaction energies using multipole FF
  - Keep waters within a set energy range
  - Deduplicate remaining waters
- Apply MinMax selection algorithm to pick ‘N’ most diverse water sites



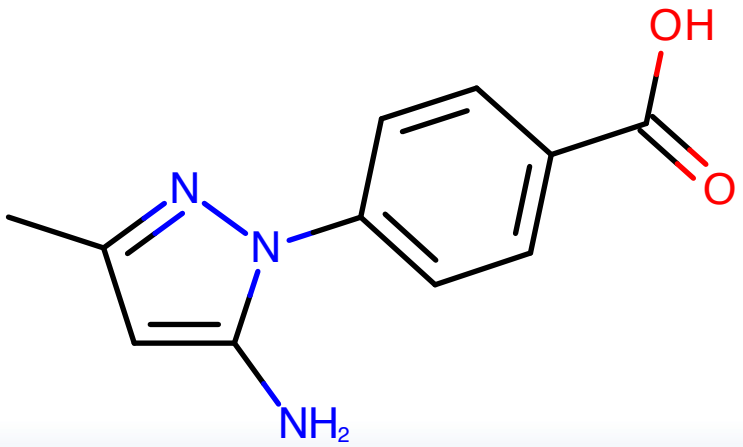


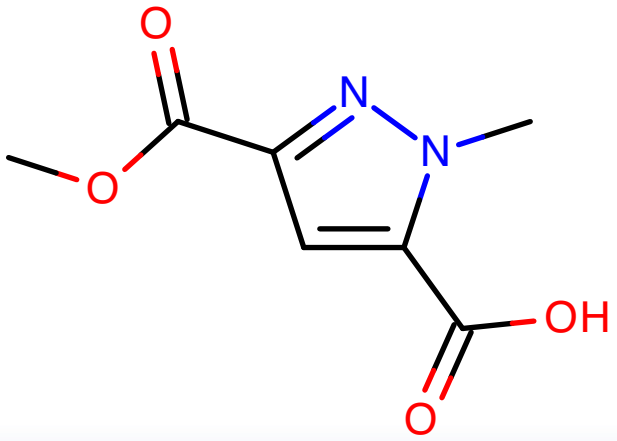
How many waters per site?



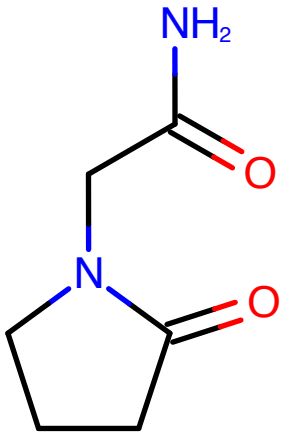


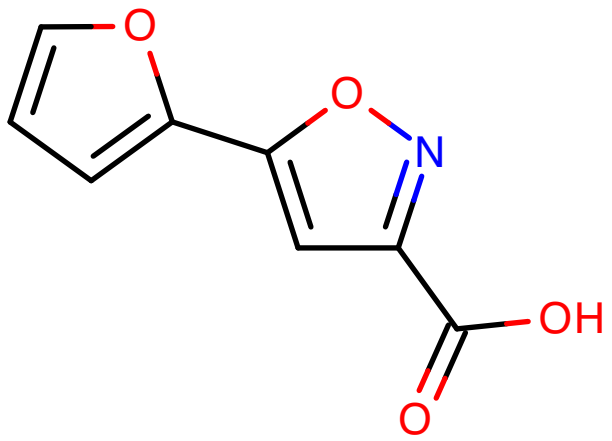
Check dimer and FF crystal opt.





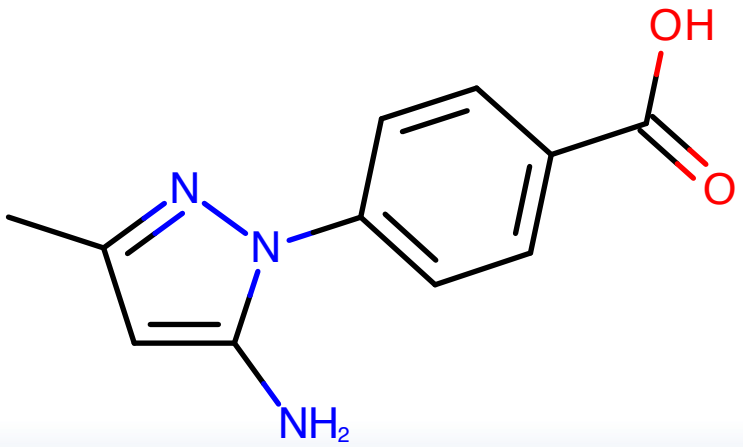
How many waters per site?

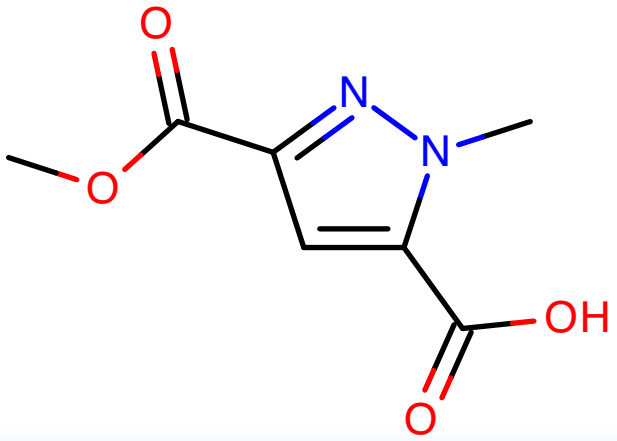




Check dimer and FF crystal opt.

1. Experimental conformer: N=10?





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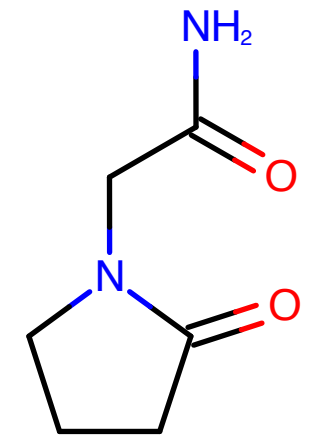
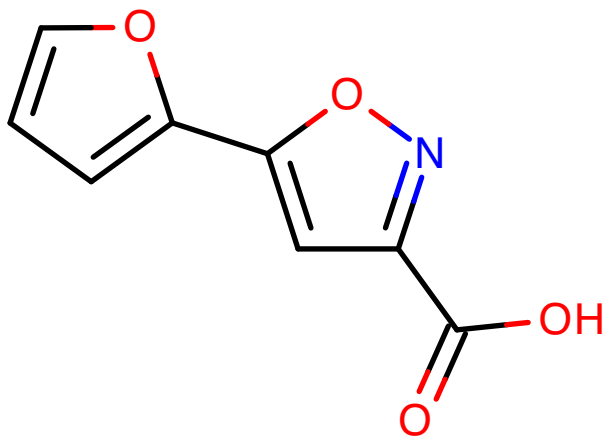
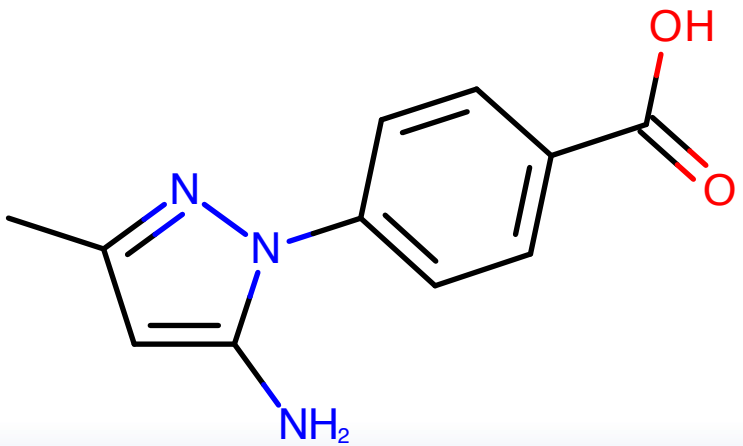
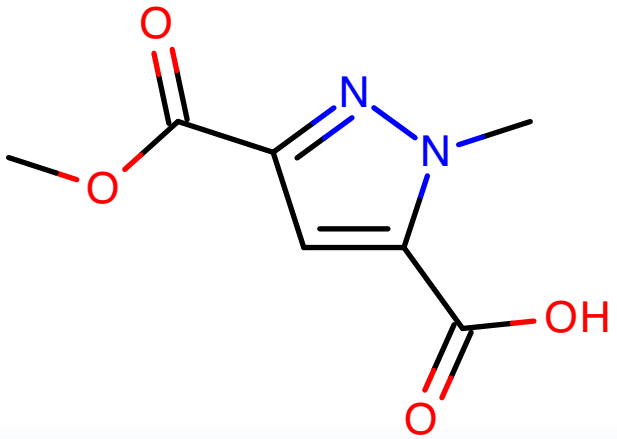
How many waters per site?





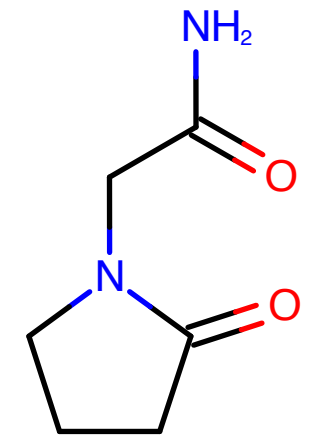


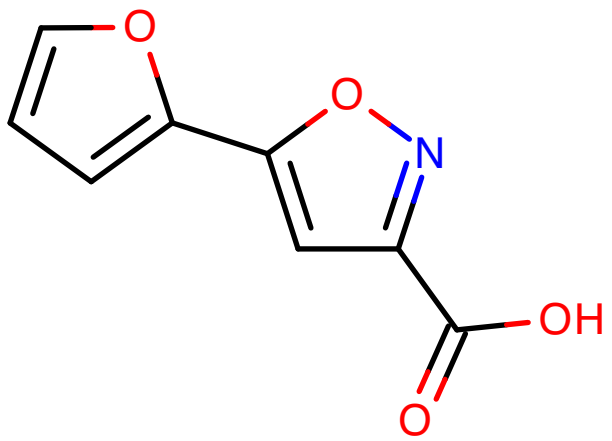


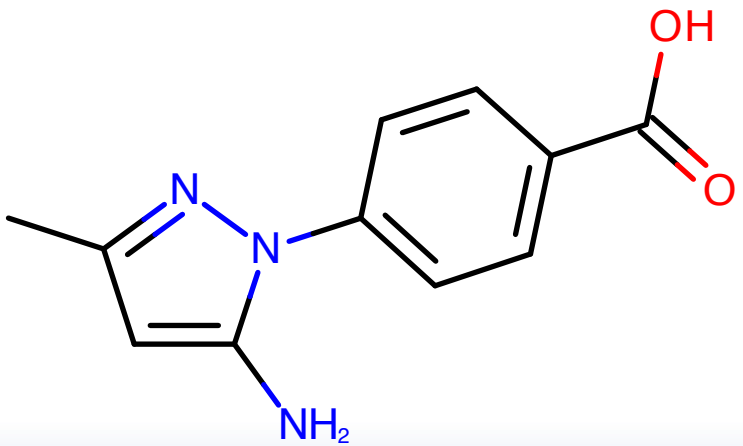
Check dimer and FF crystal opt.

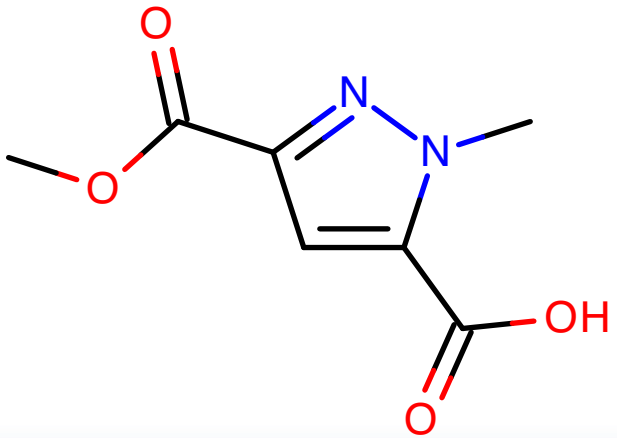
1. Experimental conformer: N=10?

How many waters per site?





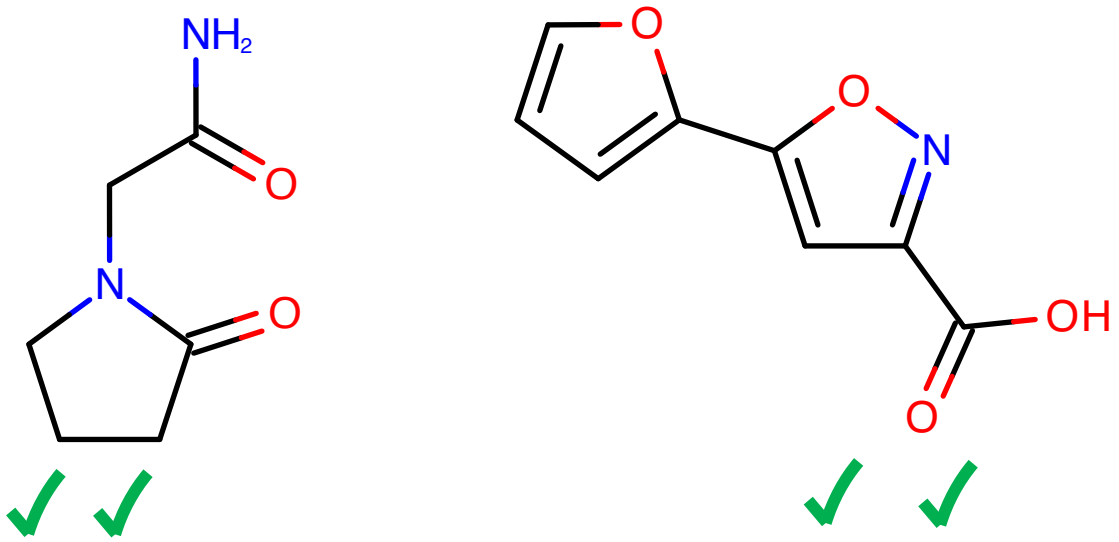




Check dimer and FF crystal opt.

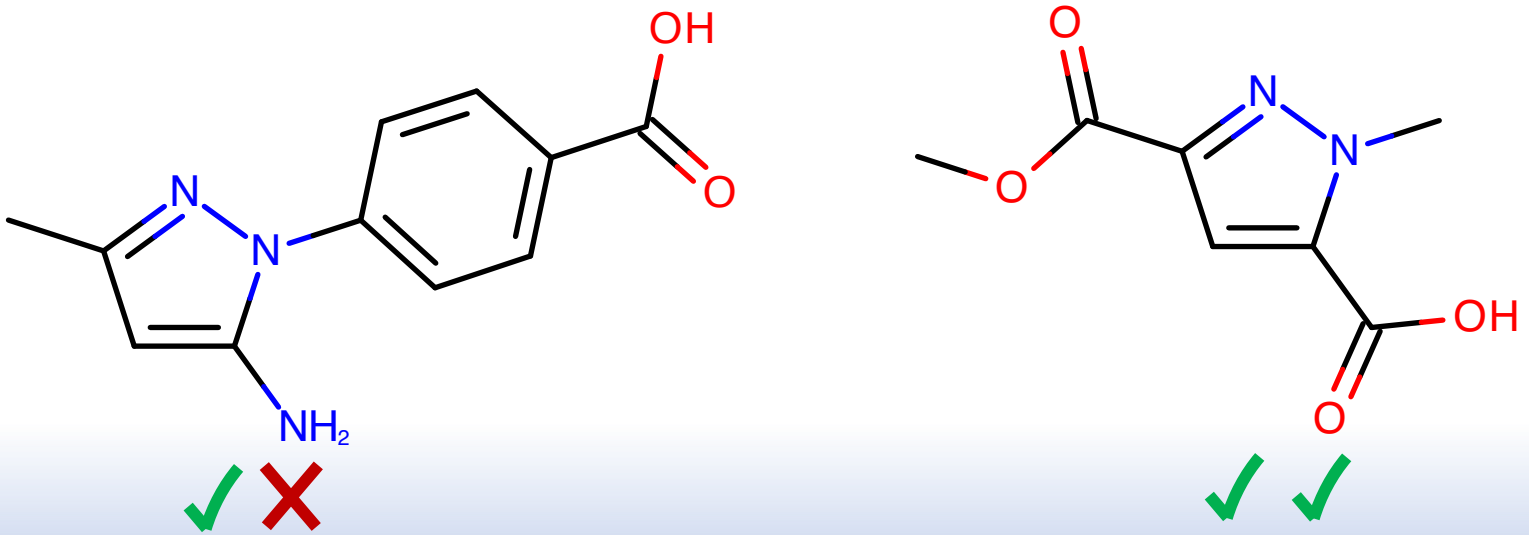
1. Experimental conformer: N=10?
2. Generated Conformers
   a. N=10?

How many waters per site?



Check dimer and FF crystal opt.

1. Experimental conformer: N=10?
2. Generated Conformers
   a. N=10?



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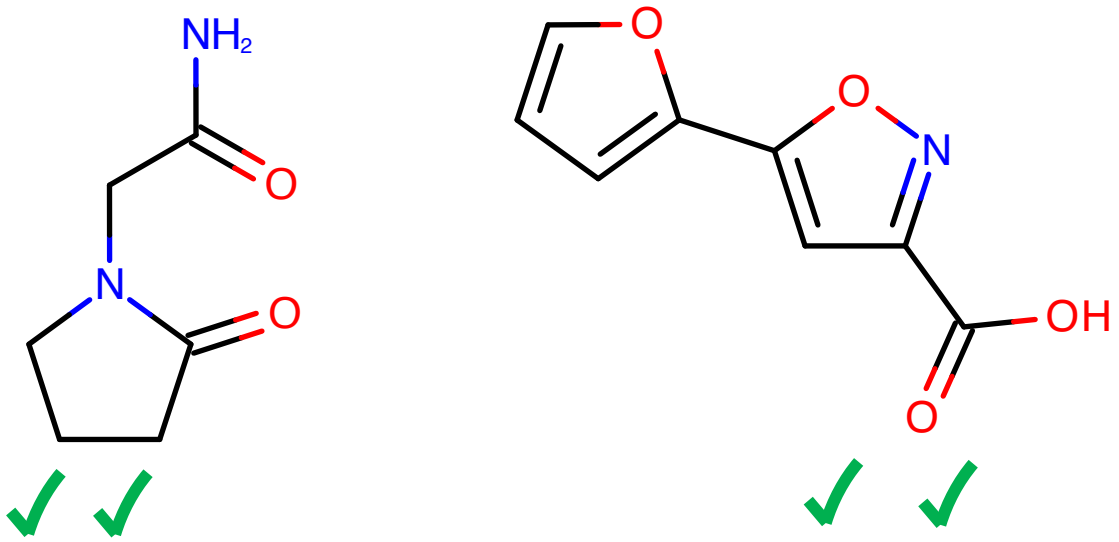
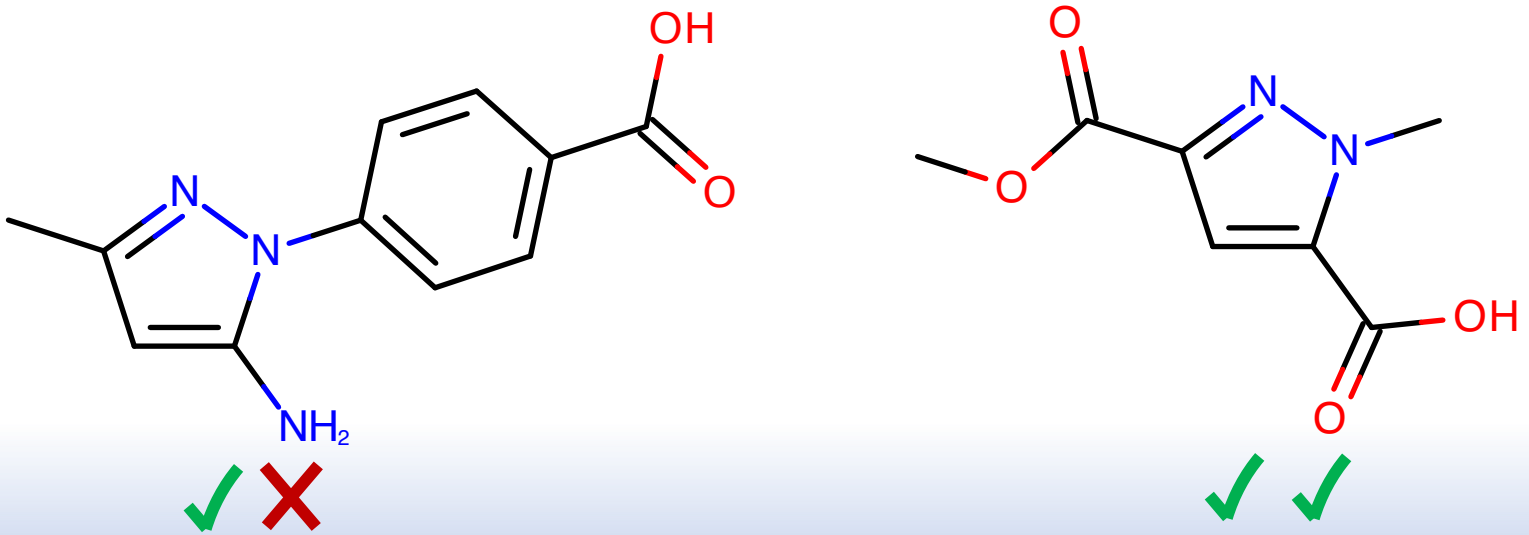
How many waters per site?



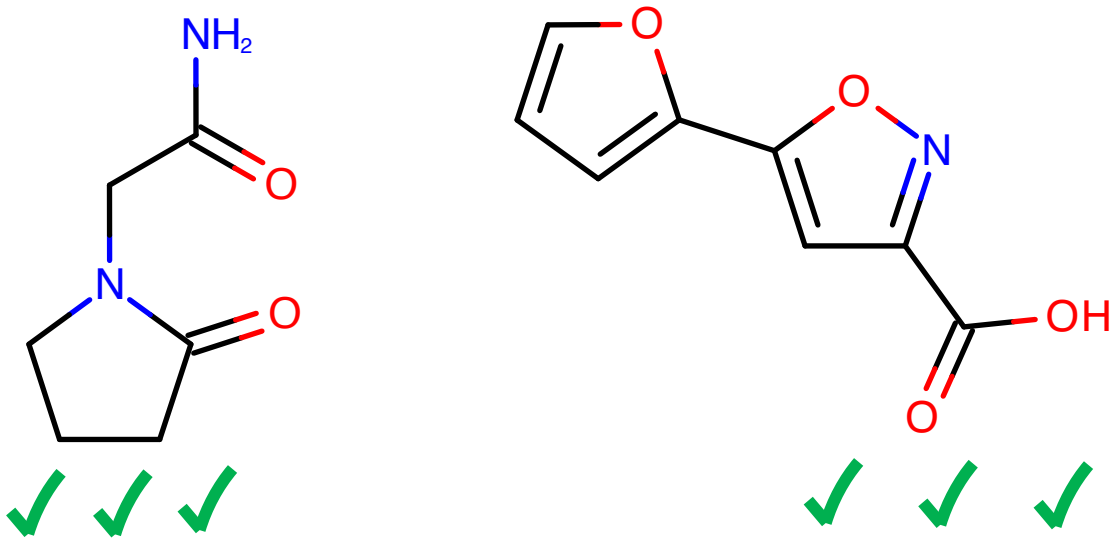
Check dimer and FF crystal opt.

1. Experimental conformer: N=10?
2. Generated Conformers
   a. N=10?
   b. N=15?



OpenEye SCIENTIFIC

How many waters per site?



Check dimer and FF crystal opt.

1. Experimental conformer: N=10?
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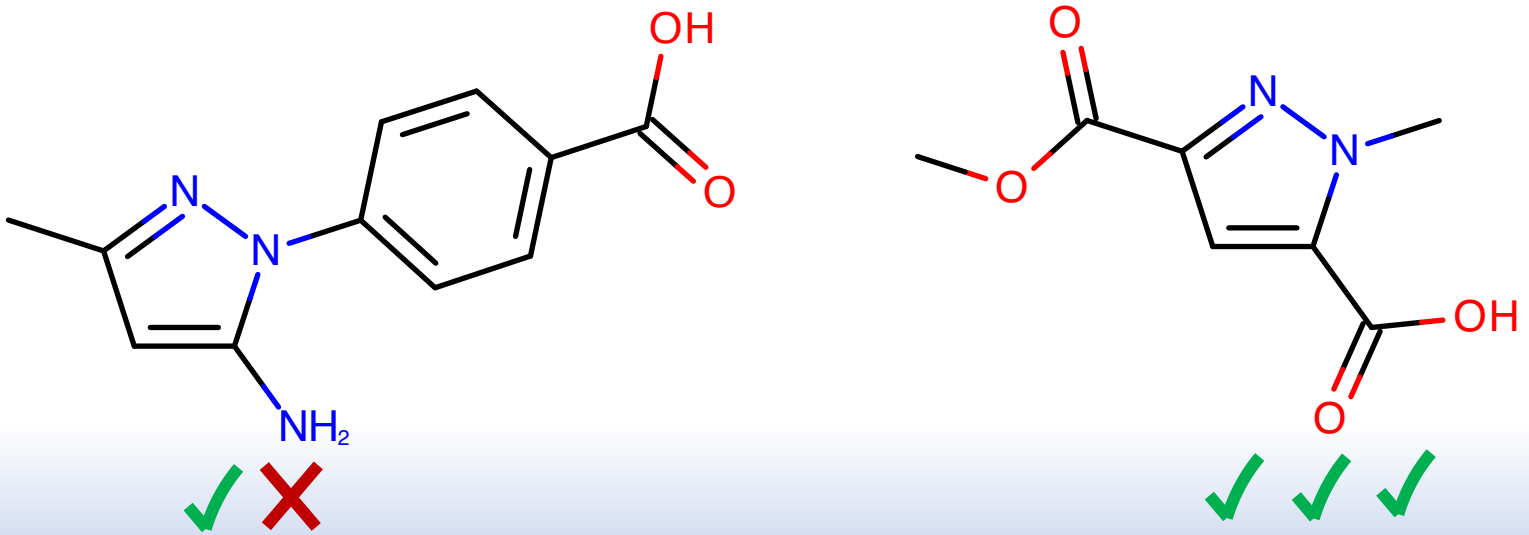
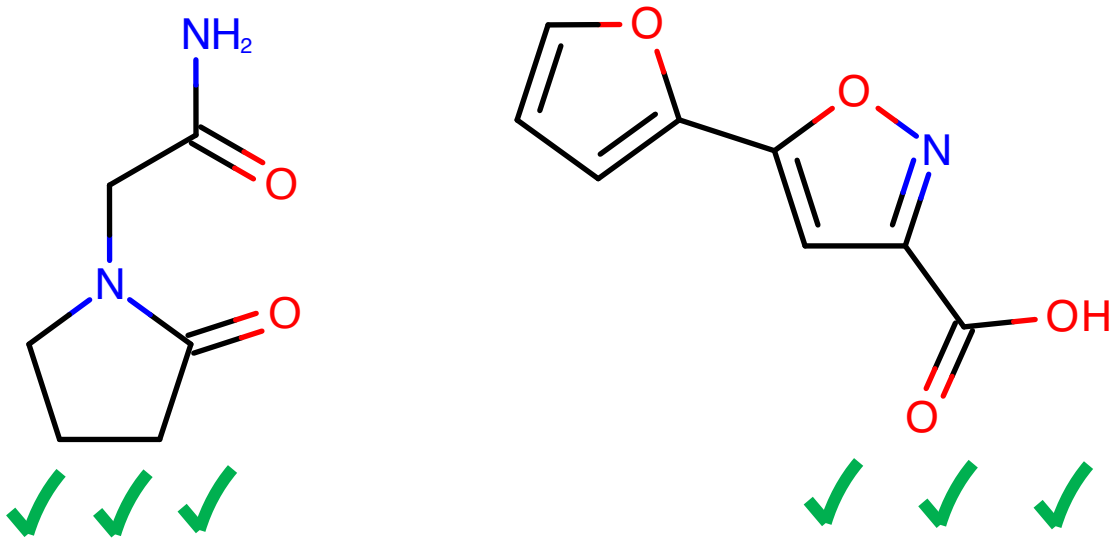
   a. N=10?
   b. N=15?



OpenEye SCIENTIFIC

How many waters per site?



Check dimer and FF crystal opt.

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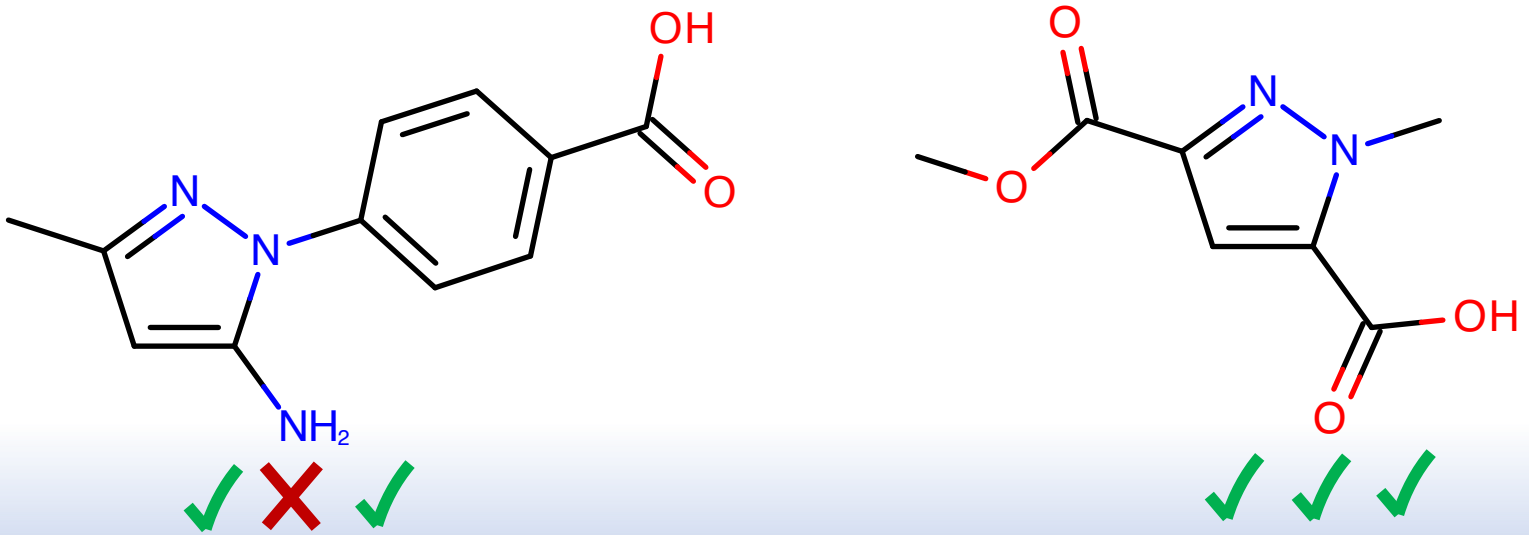

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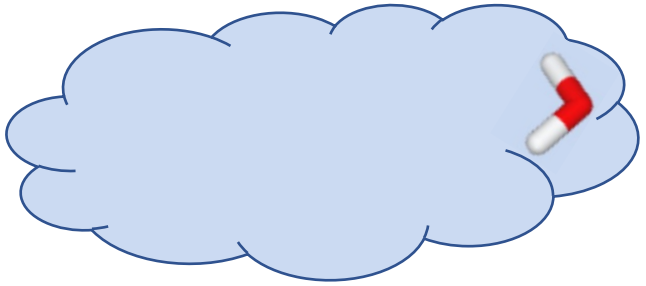
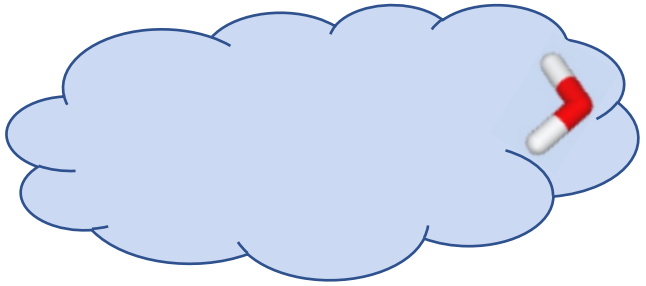
One monohydrate blind challenge so far



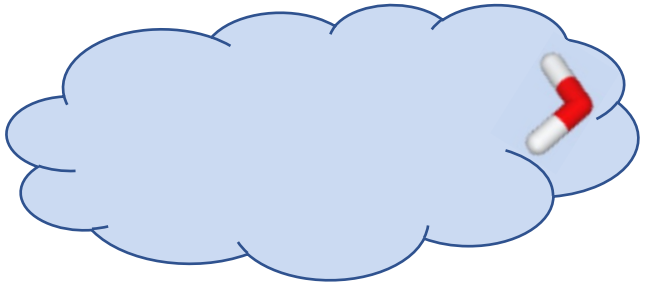
- 1H-bond donor, 5 acceptors

One monohydrate blind challenge so far



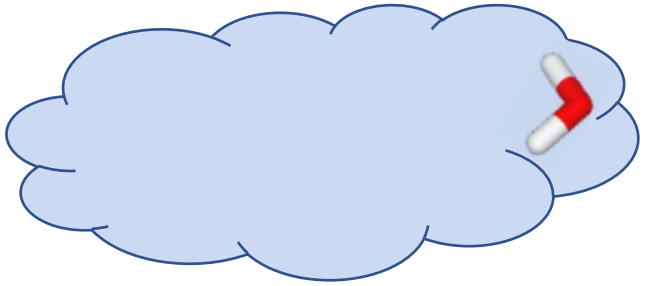
- 1H-bond donor, 5 acceptors
- 100 conformers at 0.5A

One monohydrate blind challenge so far



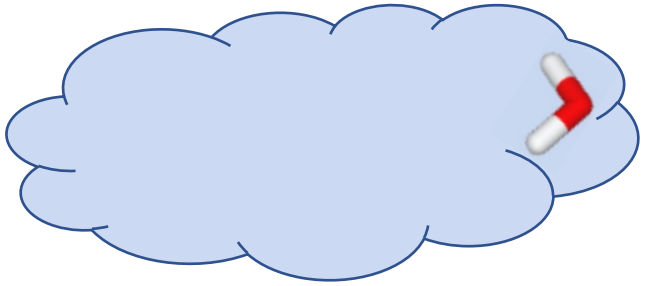
- 1H-bond donor, 5 acceptors
- 100 conformers at 0.5A
- 15 waters/site → 9,000 dimers

One monohydrate blind challenge so far



- 1H-bond donor, 5 acceptors
- 100 conformers at 0.5A
- 15 waters/site → 9,000 dimers
- Change ‘N’ waters by site

One monohydrate blind challenge so far



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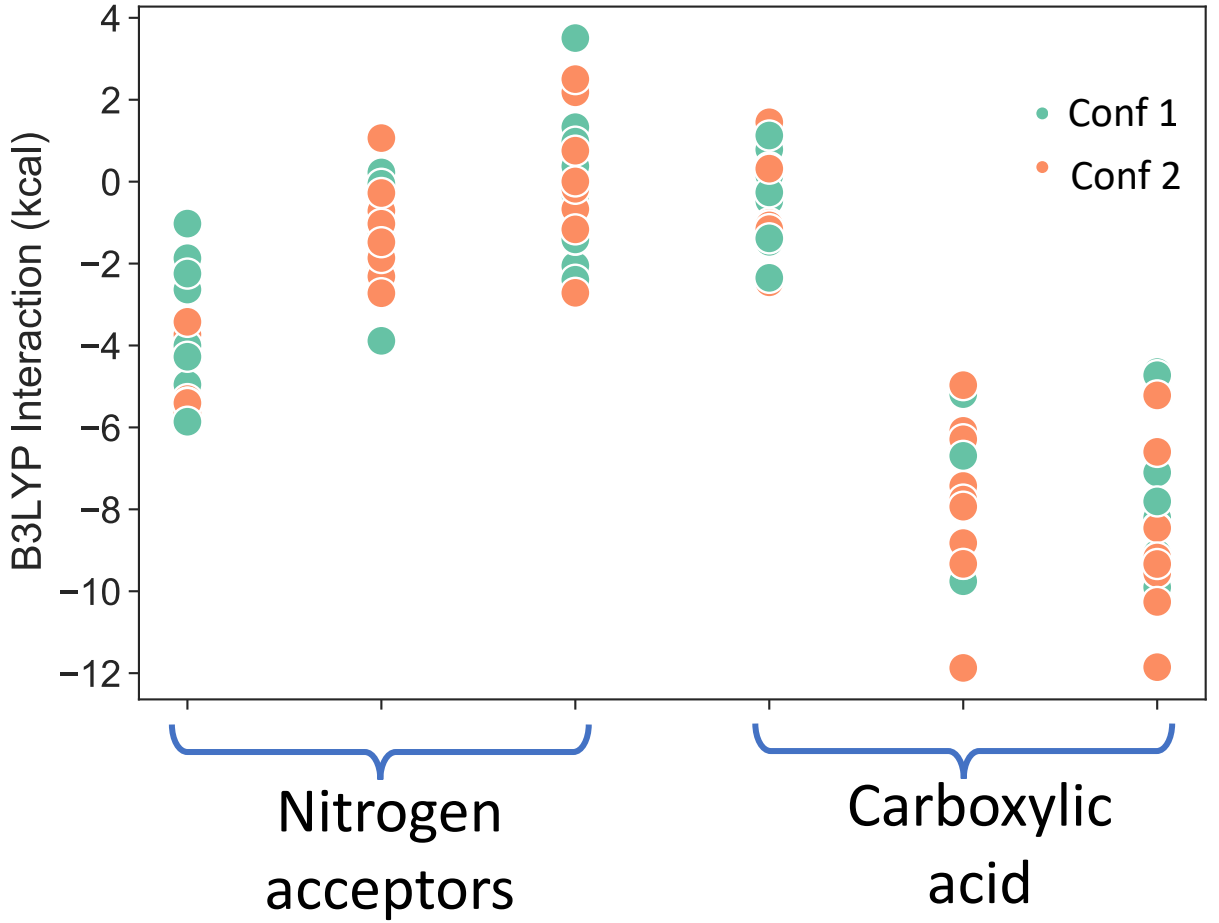
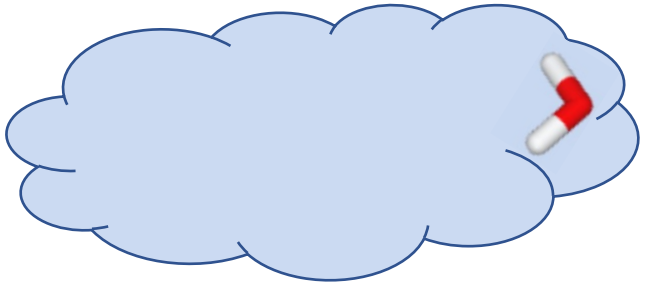
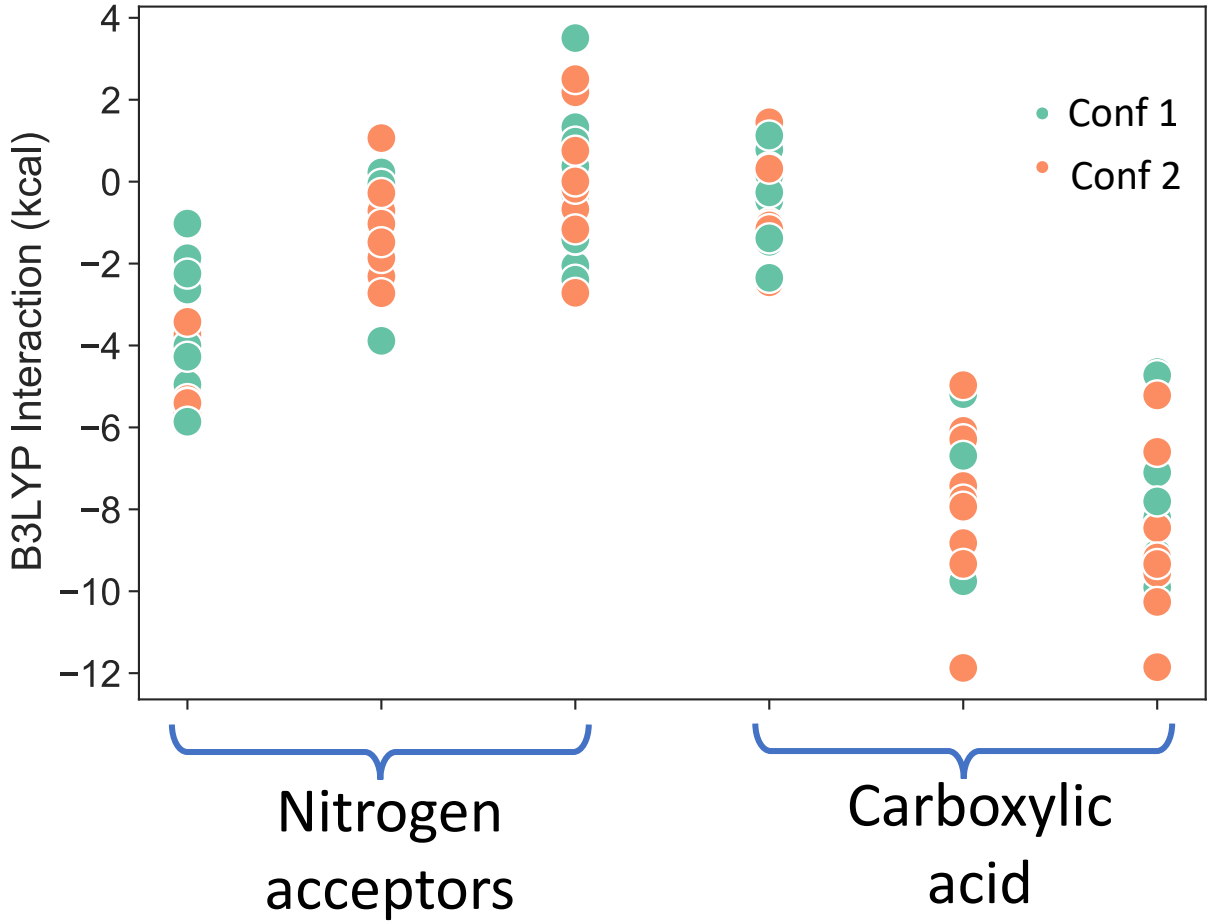


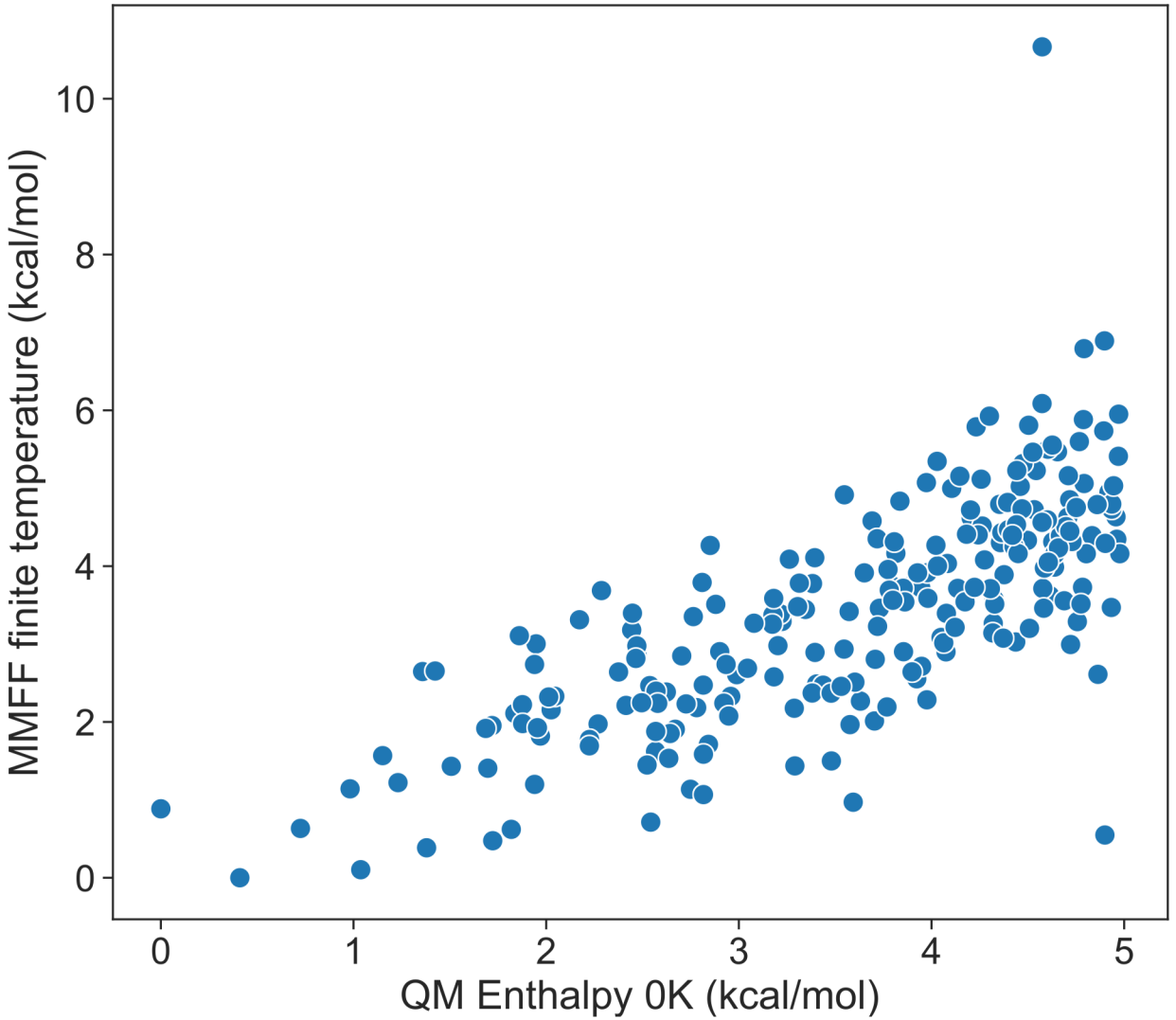
One monohydrate blind challenge so far



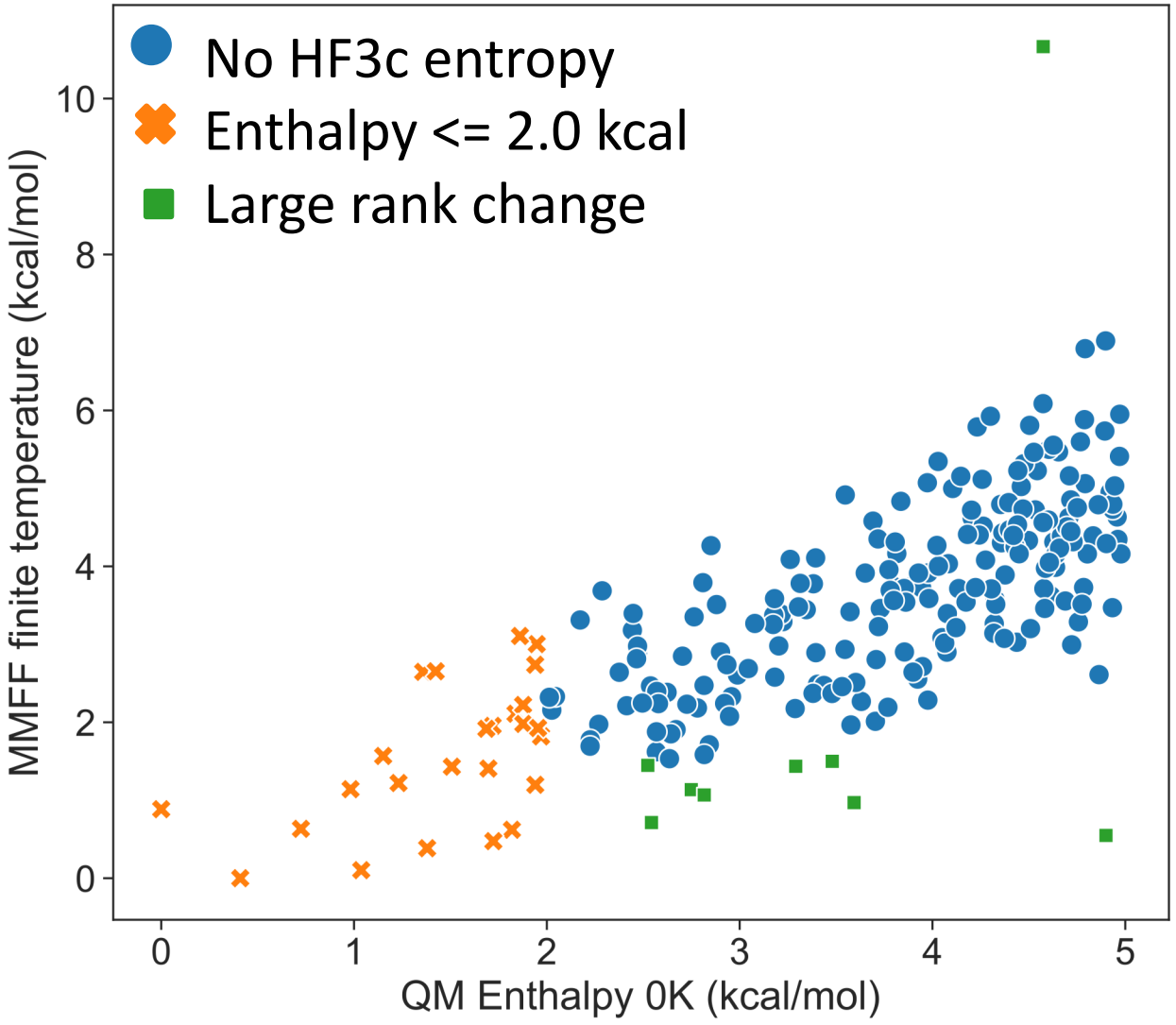


- 1H-bond donor, 5 acceptors
- 100 conformers at 0.5A
- 15 waters/site → 9,000 dimers
- Change ‘N’ waters by site
- Submit MMFF and QM finite temperature predictions

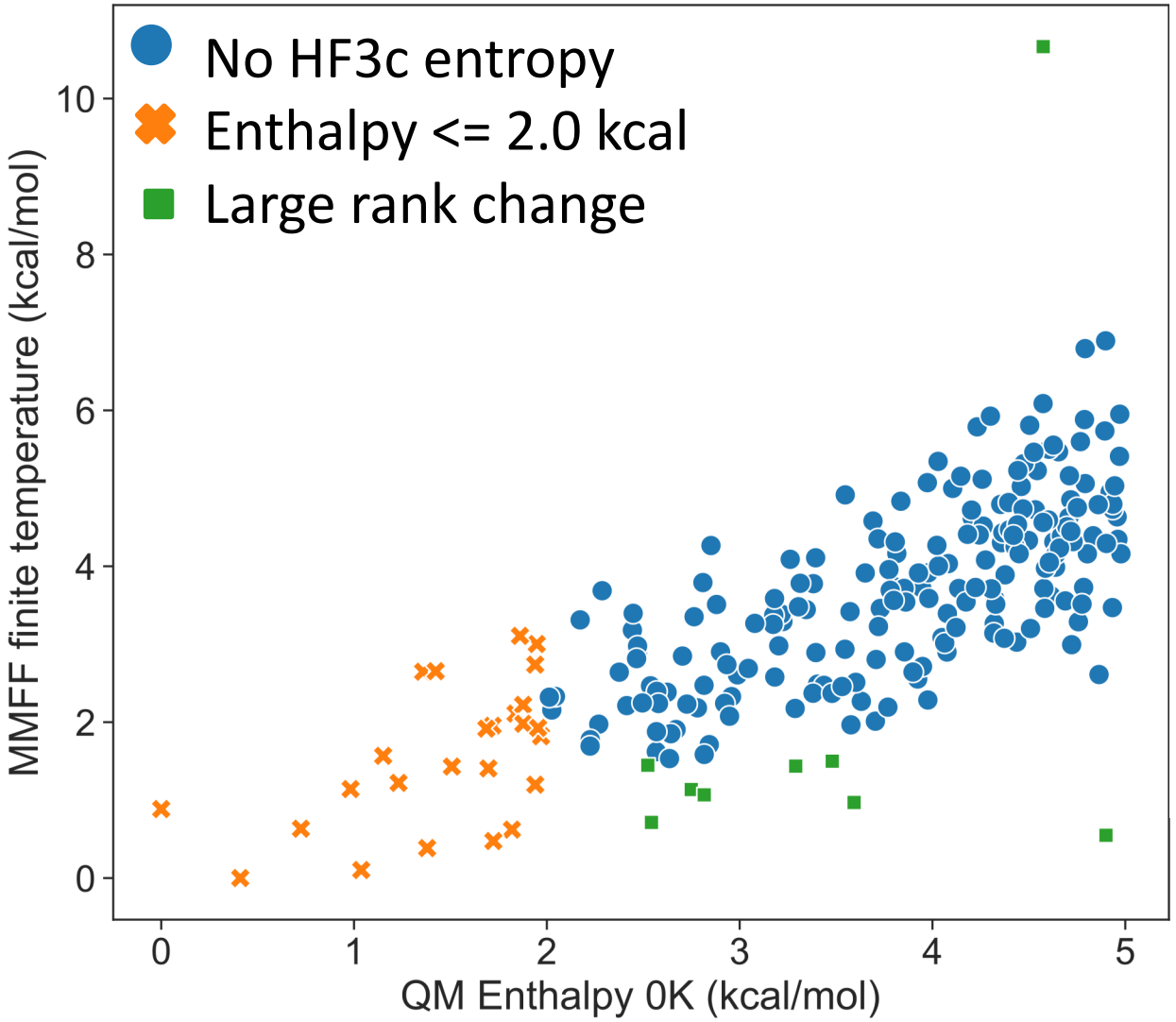
Final monohydrate predictions

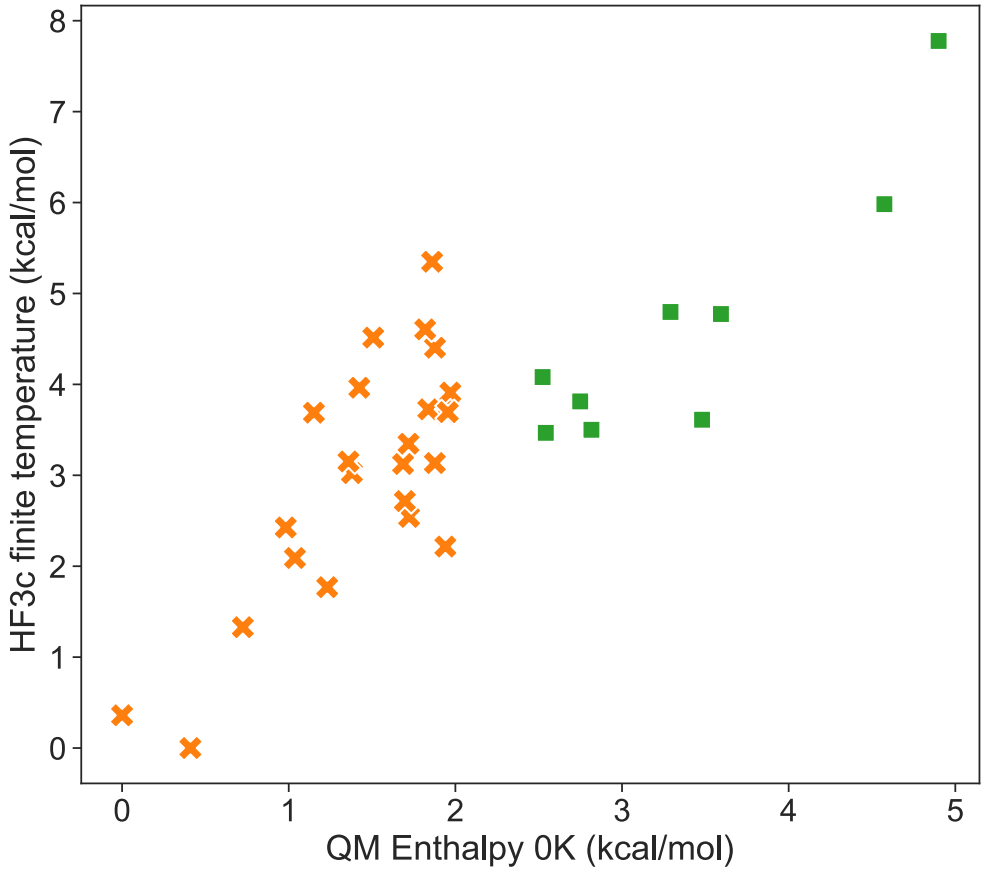


Final monohydrate predictions

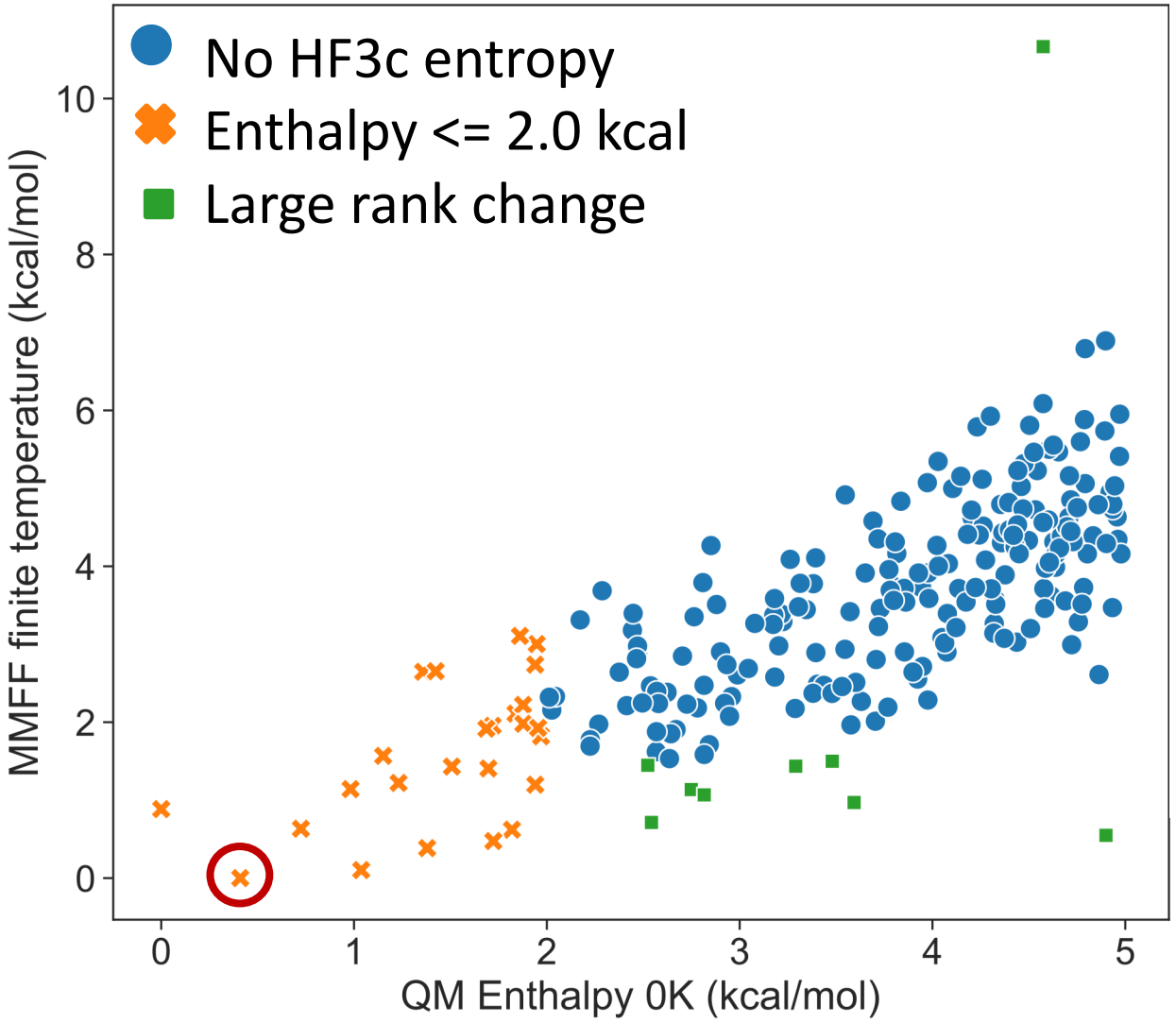


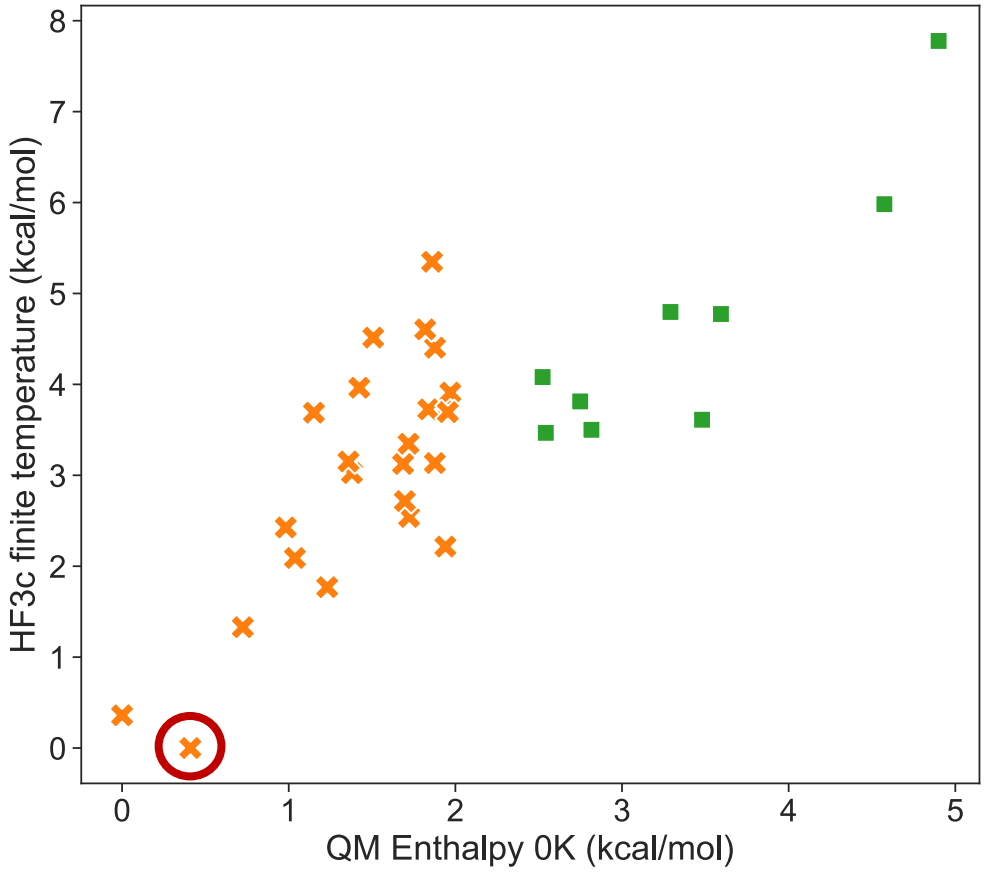
Final monohydrate predictions





Final monohydrate predictions

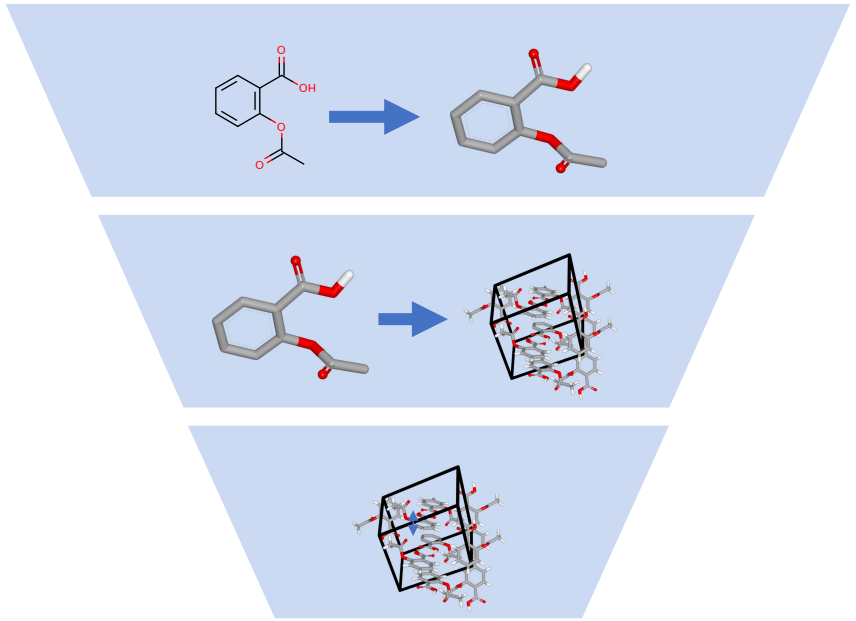




Hit RMSD40 = 0.47A

Summary

Summary



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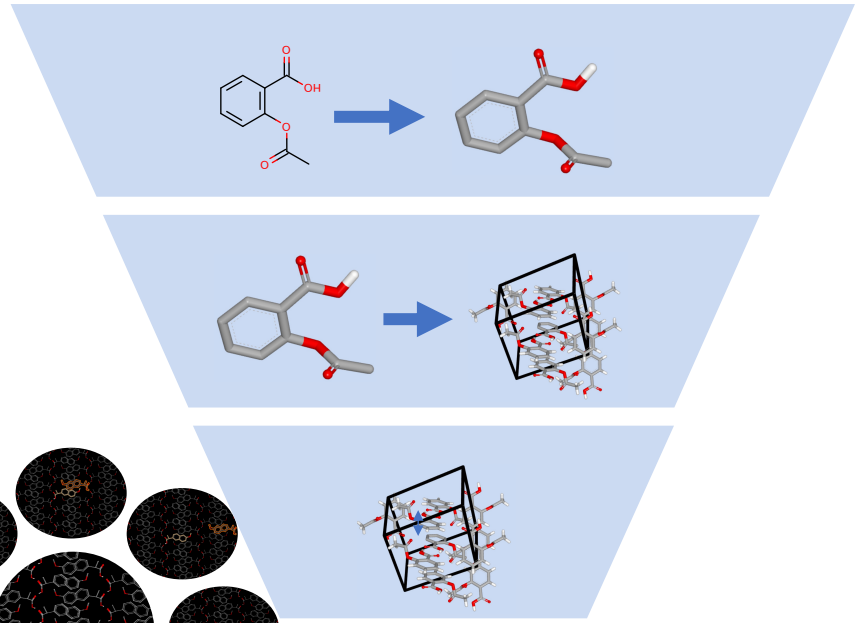

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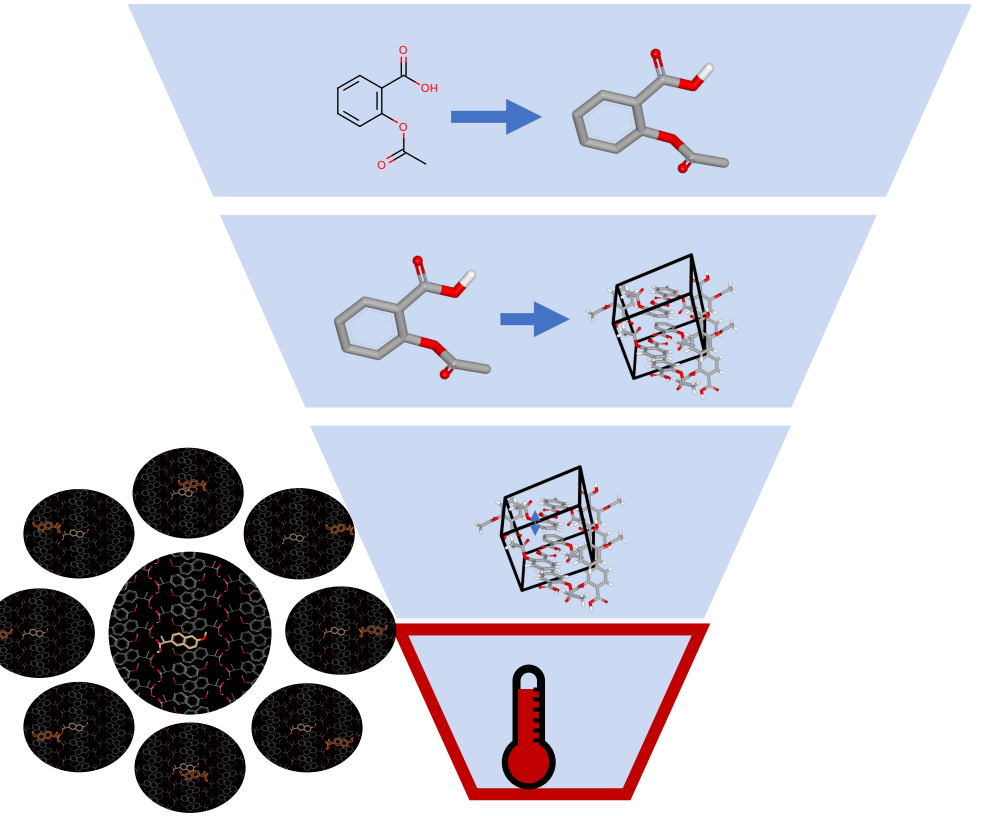
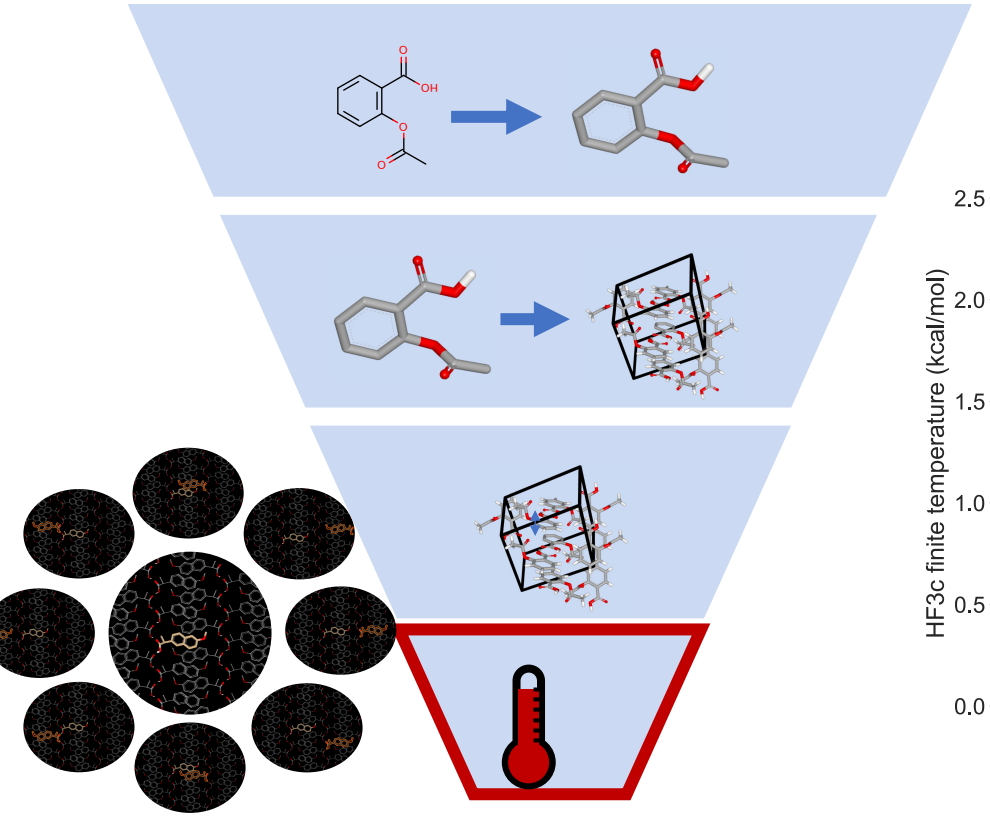


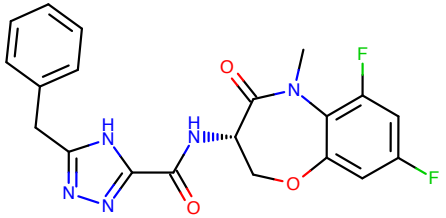
Phonopy displacements in supercell

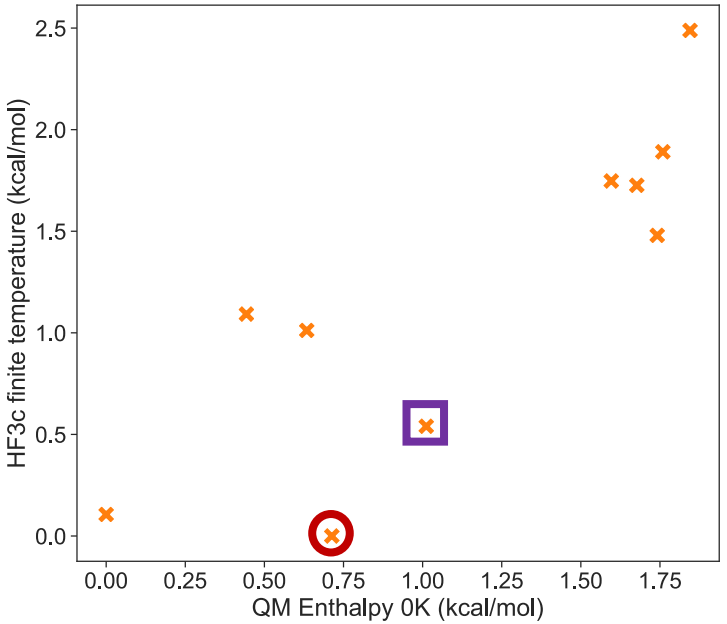
Calculate gradients on each crystal

Phonopy processes gradients

Summary







Phonopy displacements in supercell

Calculate gradients on each crystal

Phonopy processes gradients

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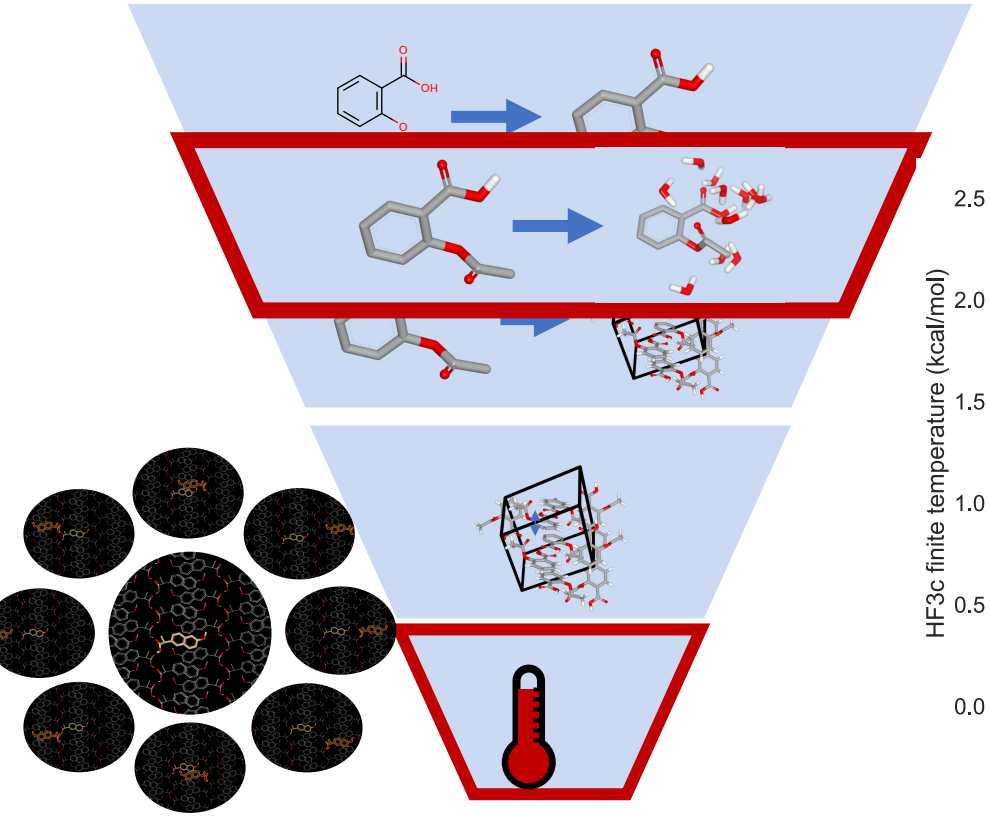
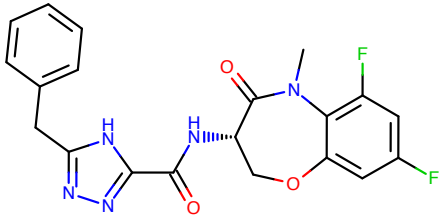
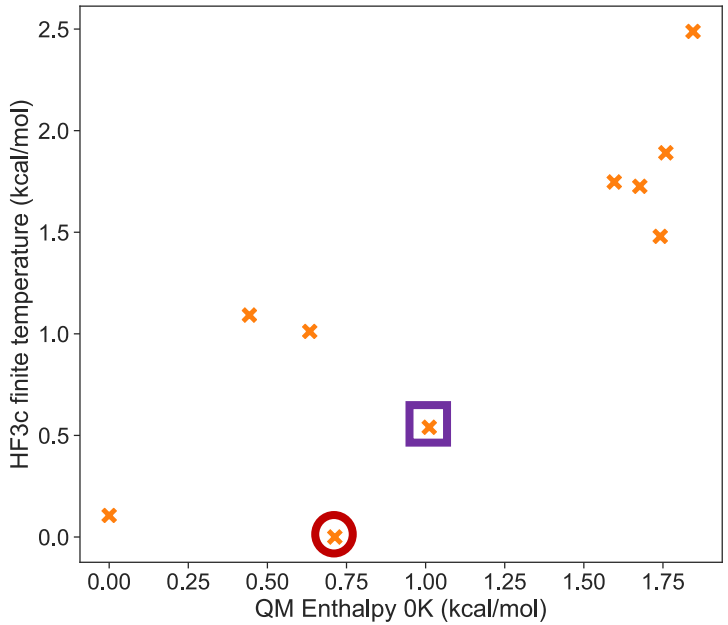
Summary







Phonopy displacements in supercell → Calculate gradients on each crystal → Phonopy processes gradients

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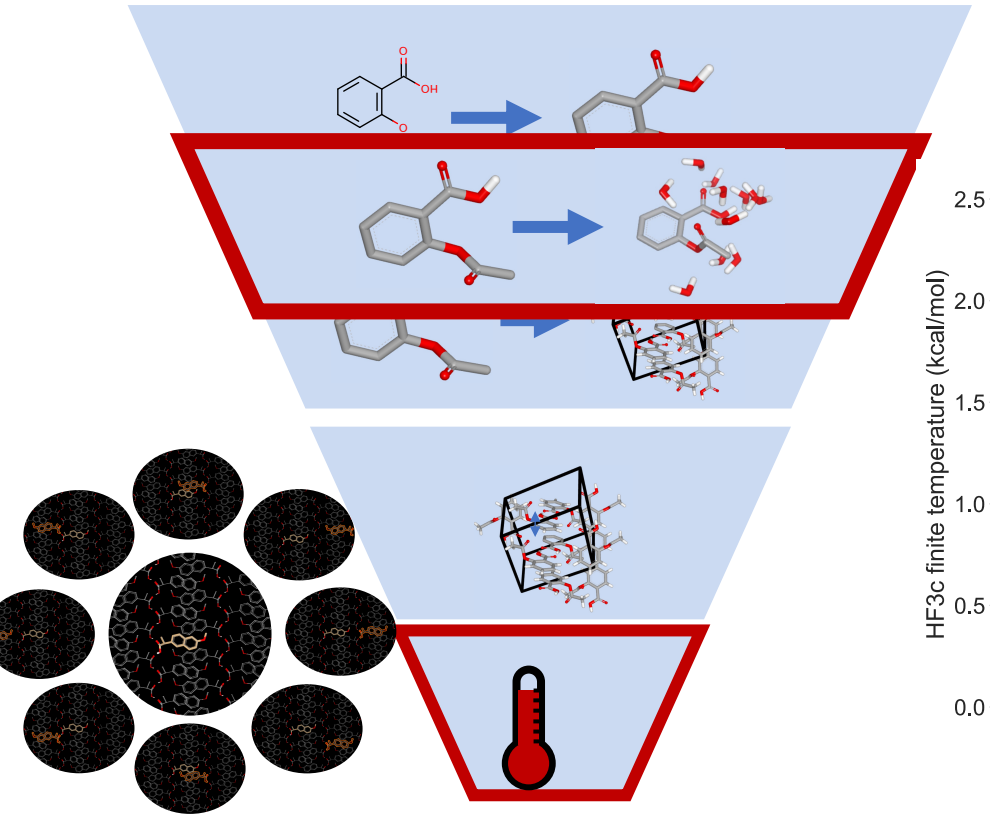
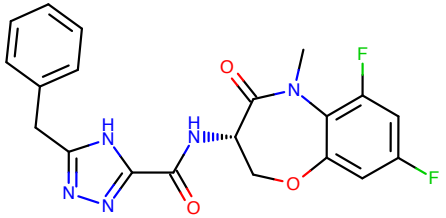
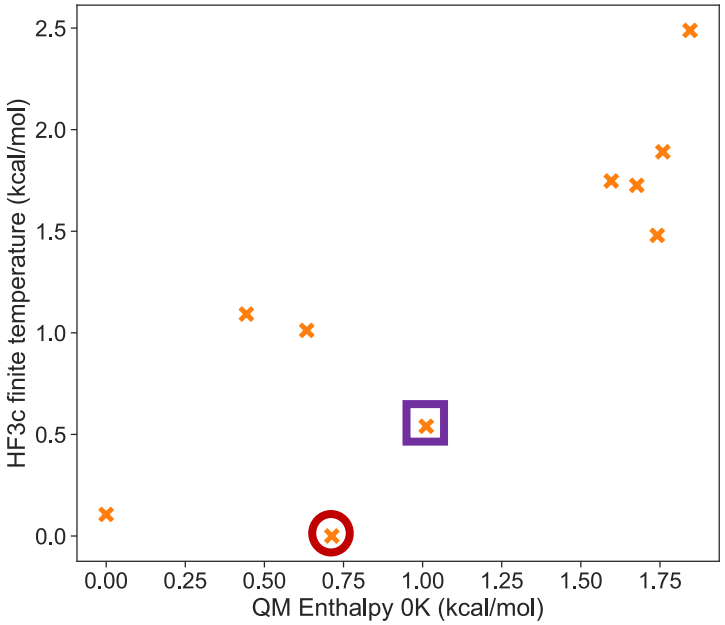
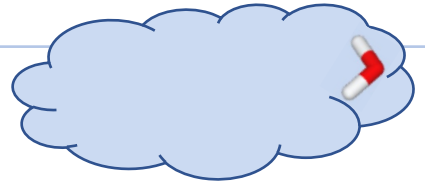
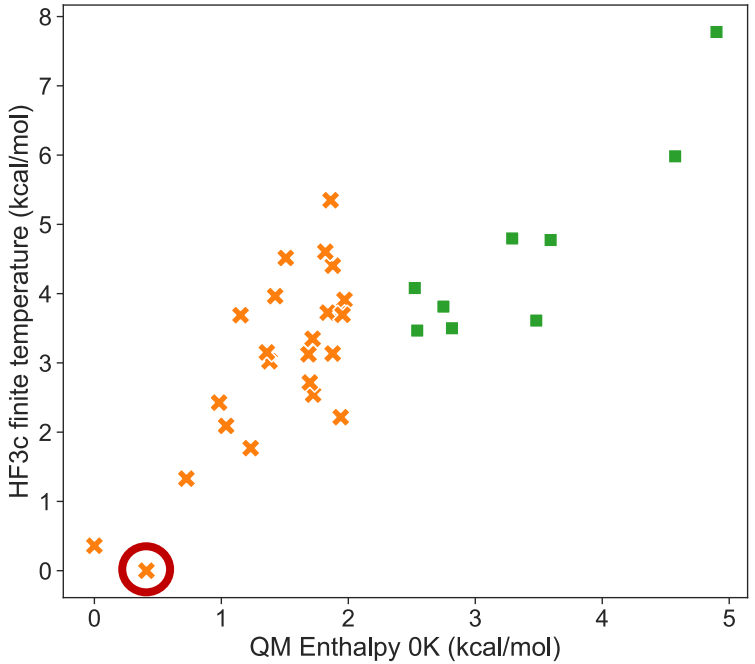
Summary





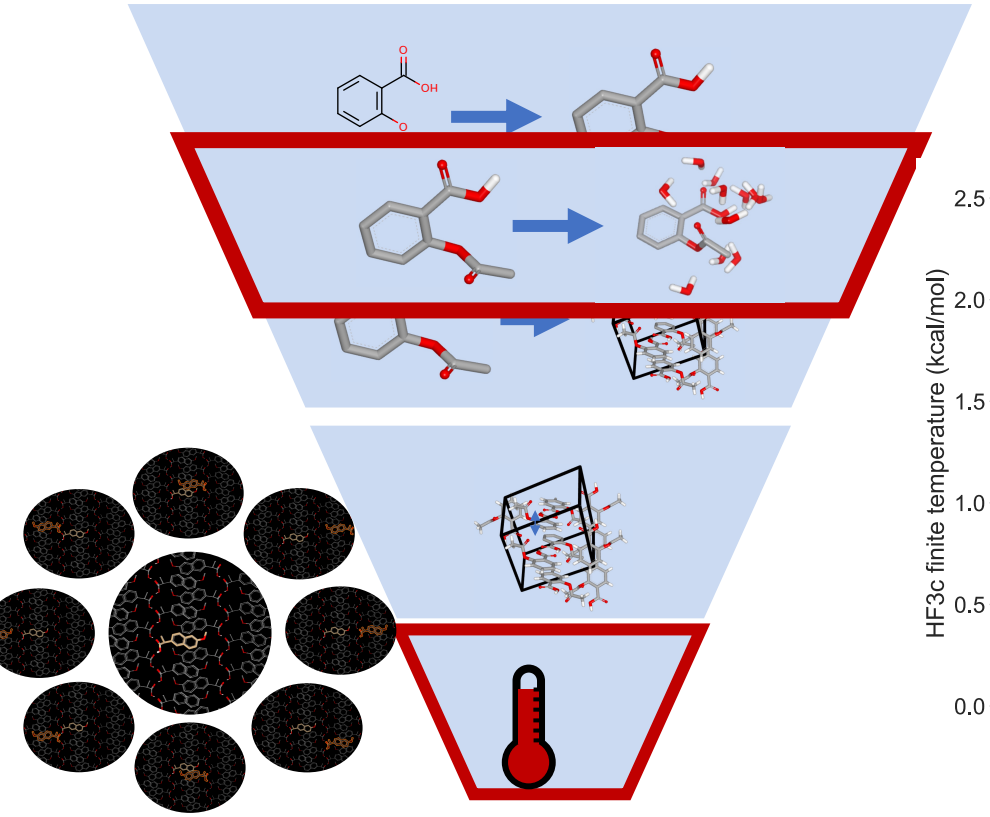


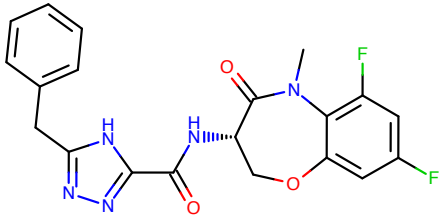


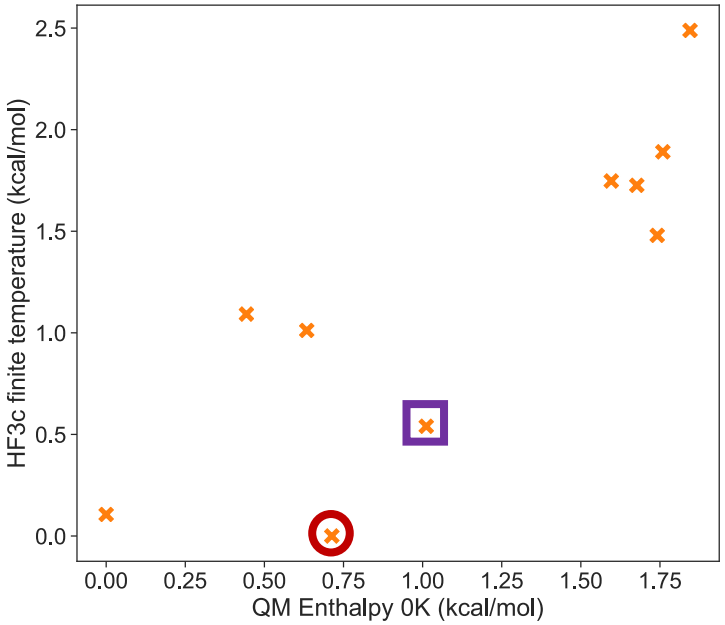


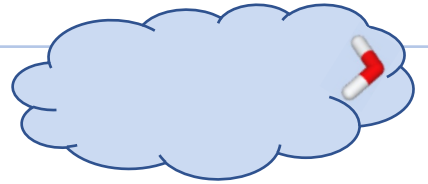
Phonopy displacements in supercell → Calculate gradients on each crystal → Phonopy processes gradients

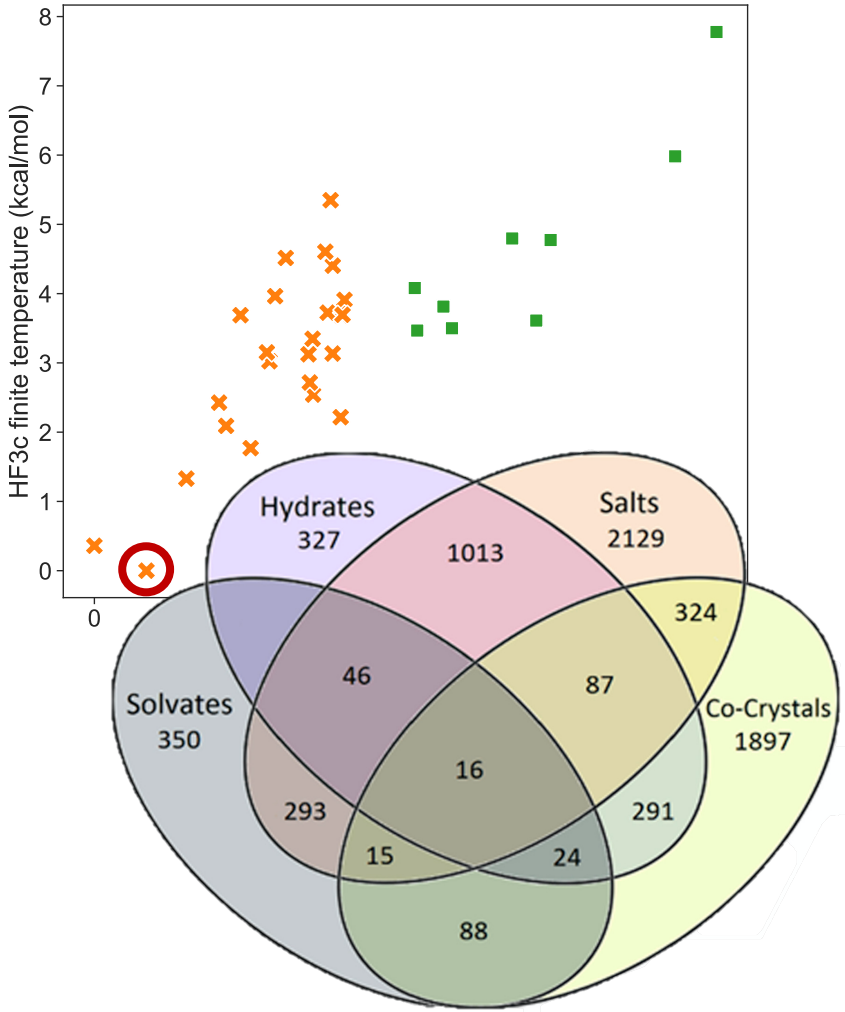
Summary





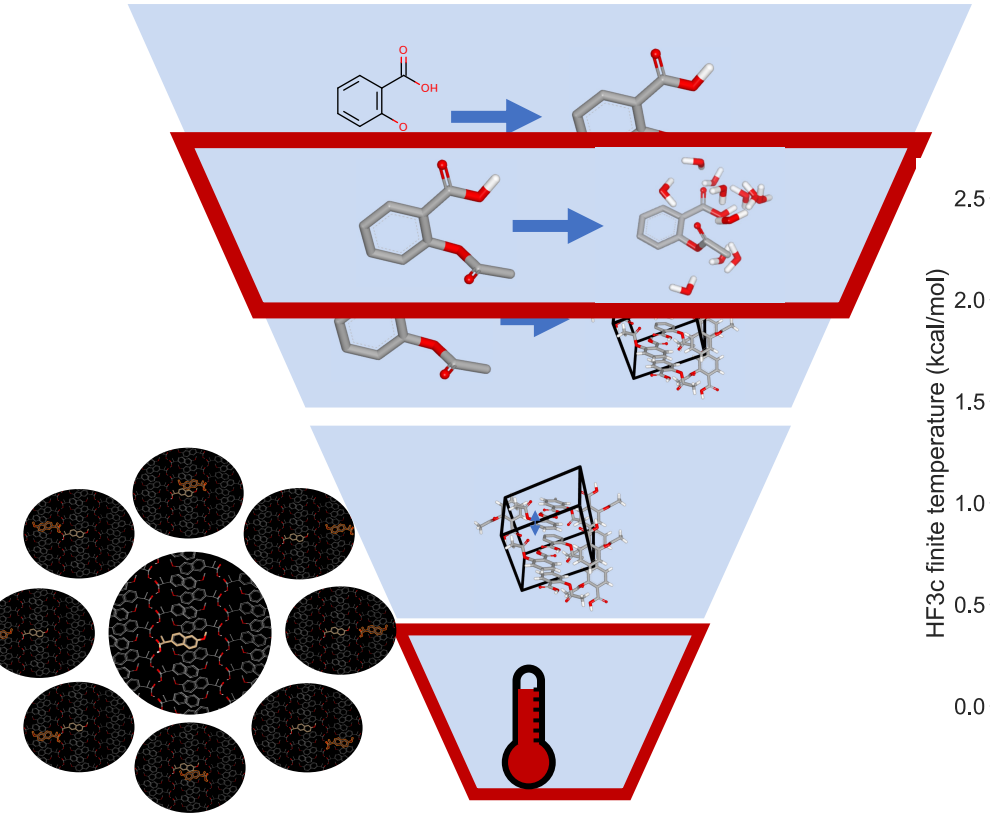


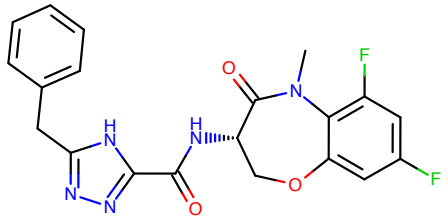


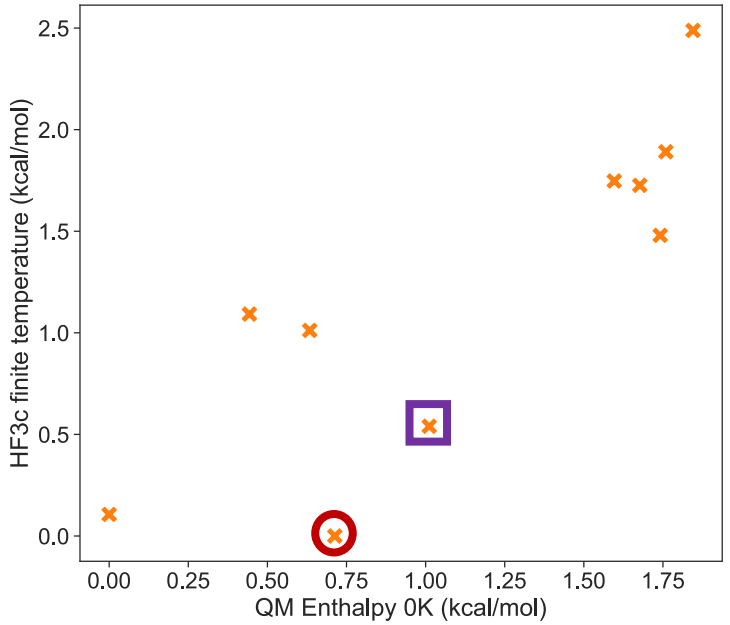


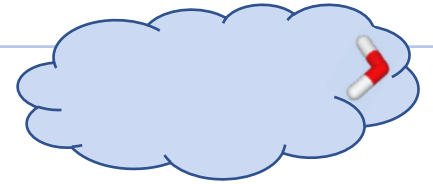
Phonopy displacements in supercell → Calculate gradients on each crystal → Phonopy processes gradients

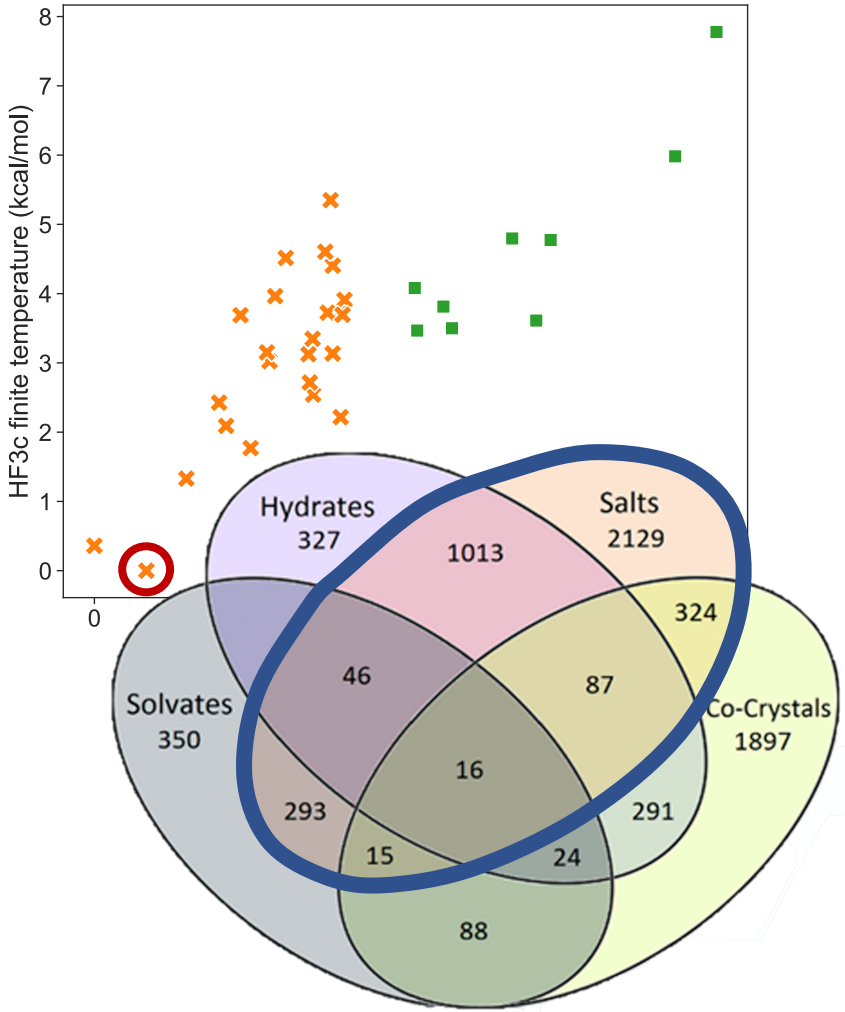
Summary











Phonopy displacements in supercell → Calculate gradients on each crystal → Phonopy processes gradients

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Thank You
The End
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