Solid forms affect physical properties of drugs

Crystal forms:

- Polymorphism
- Solvates, Hydrates, and Salts
- Co-crystals

Solid forms affect physical properties of drugs
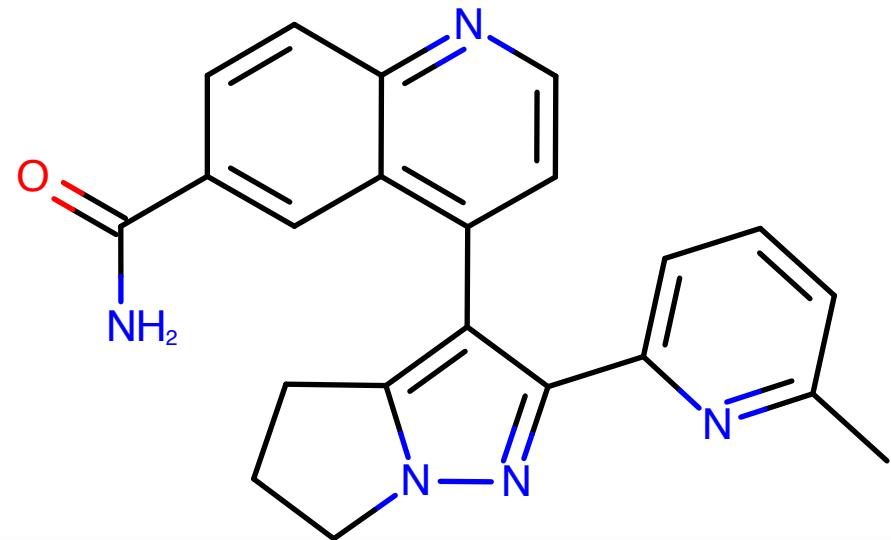
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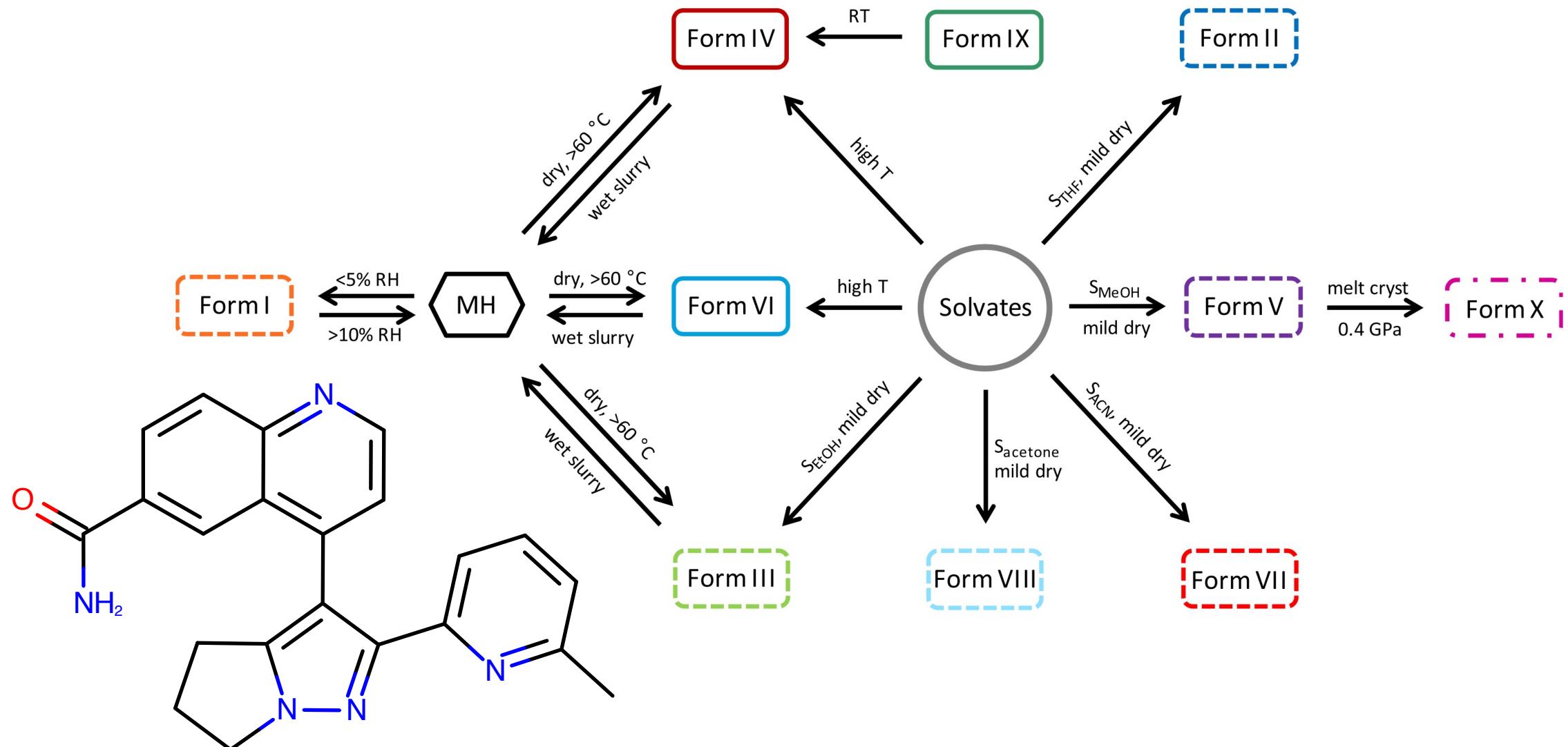
Physical properties:

- Solubility and dissolution
  - bioavailability
- Hardness, elasticity, and flow
  - Powder compaction
- Habit and morphology
  - Tableting performance
- Hygroscopicity (absorption of moisture)
  - Stability and shelf life
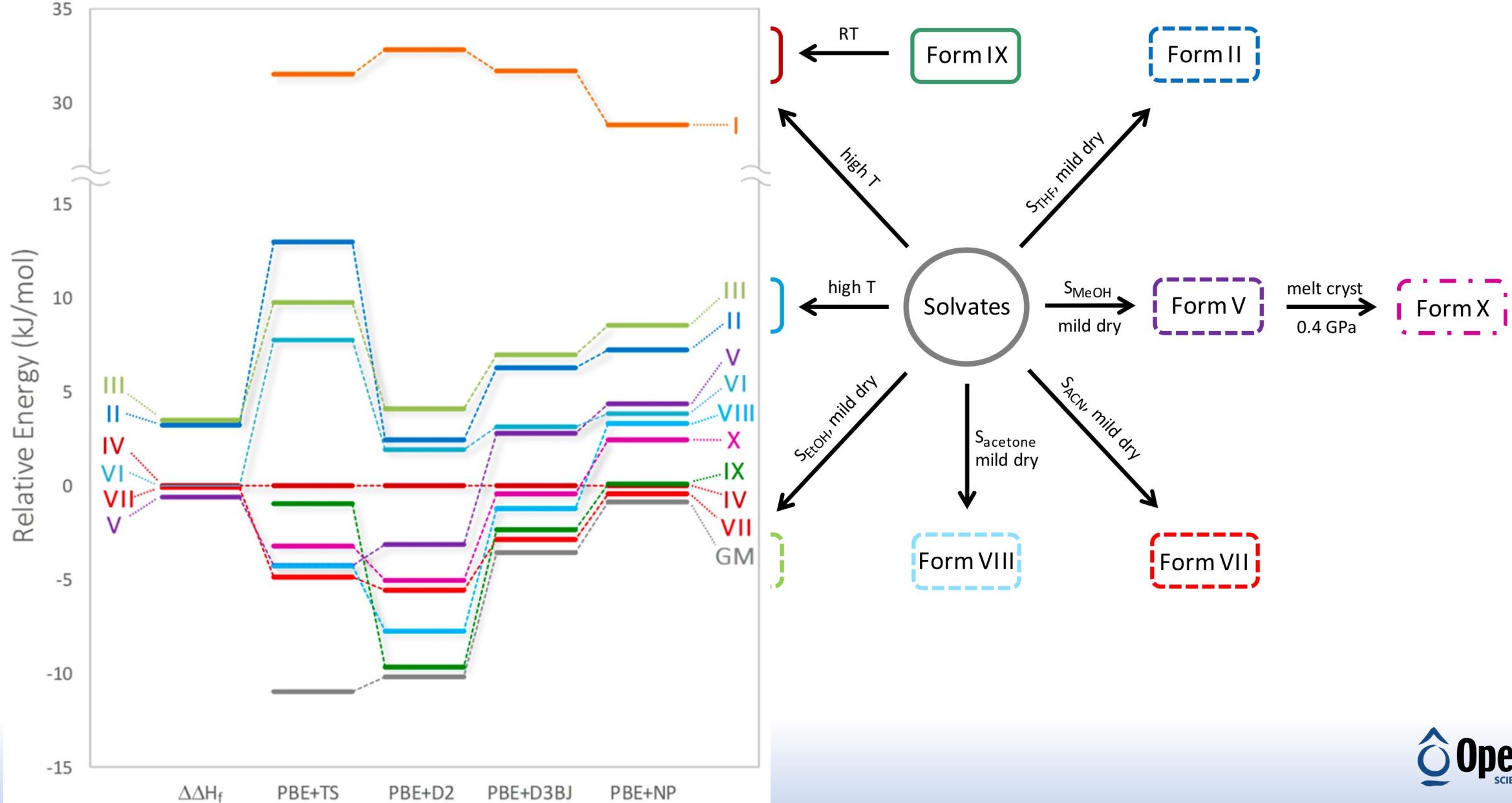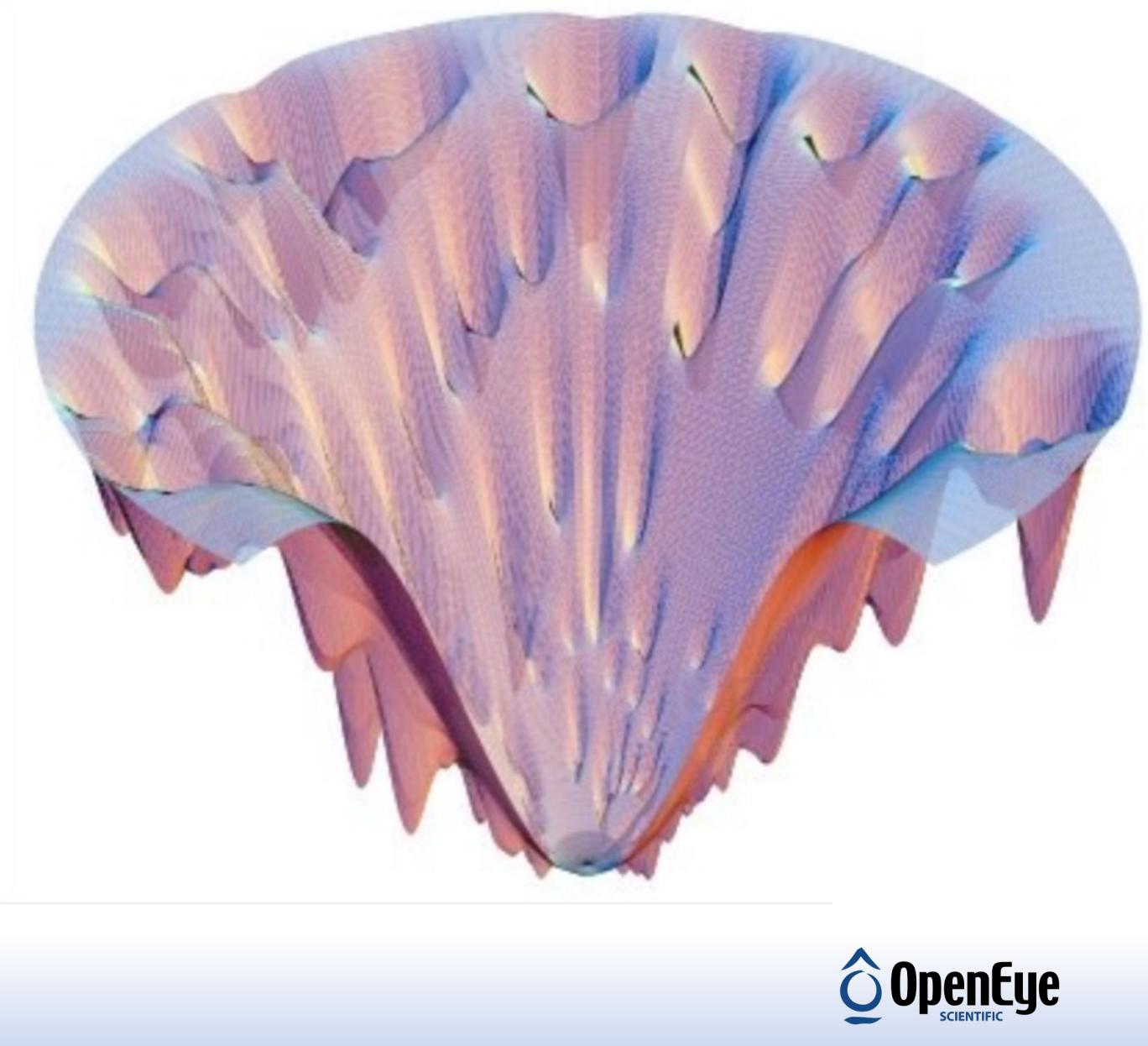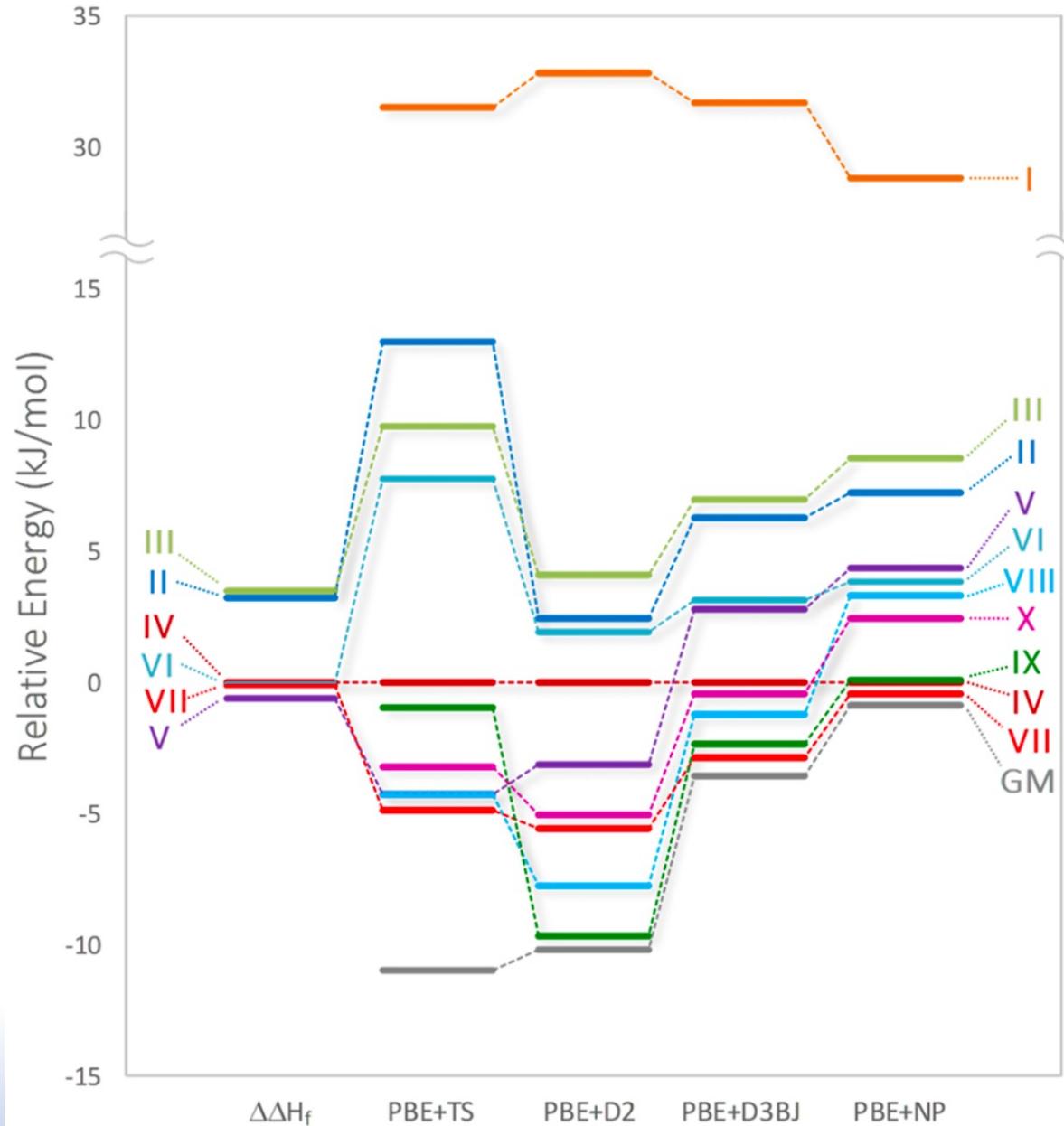
OpenEye
SCIENTIFIC

Complex Solid Form Landscape of Galunisertib

Braun et al. JACS. 2019, 19, 2947–2962

Complex Solid Form Landscape of Galunisertib

Braun et al. JACS. 2019, 19, 2947–2962
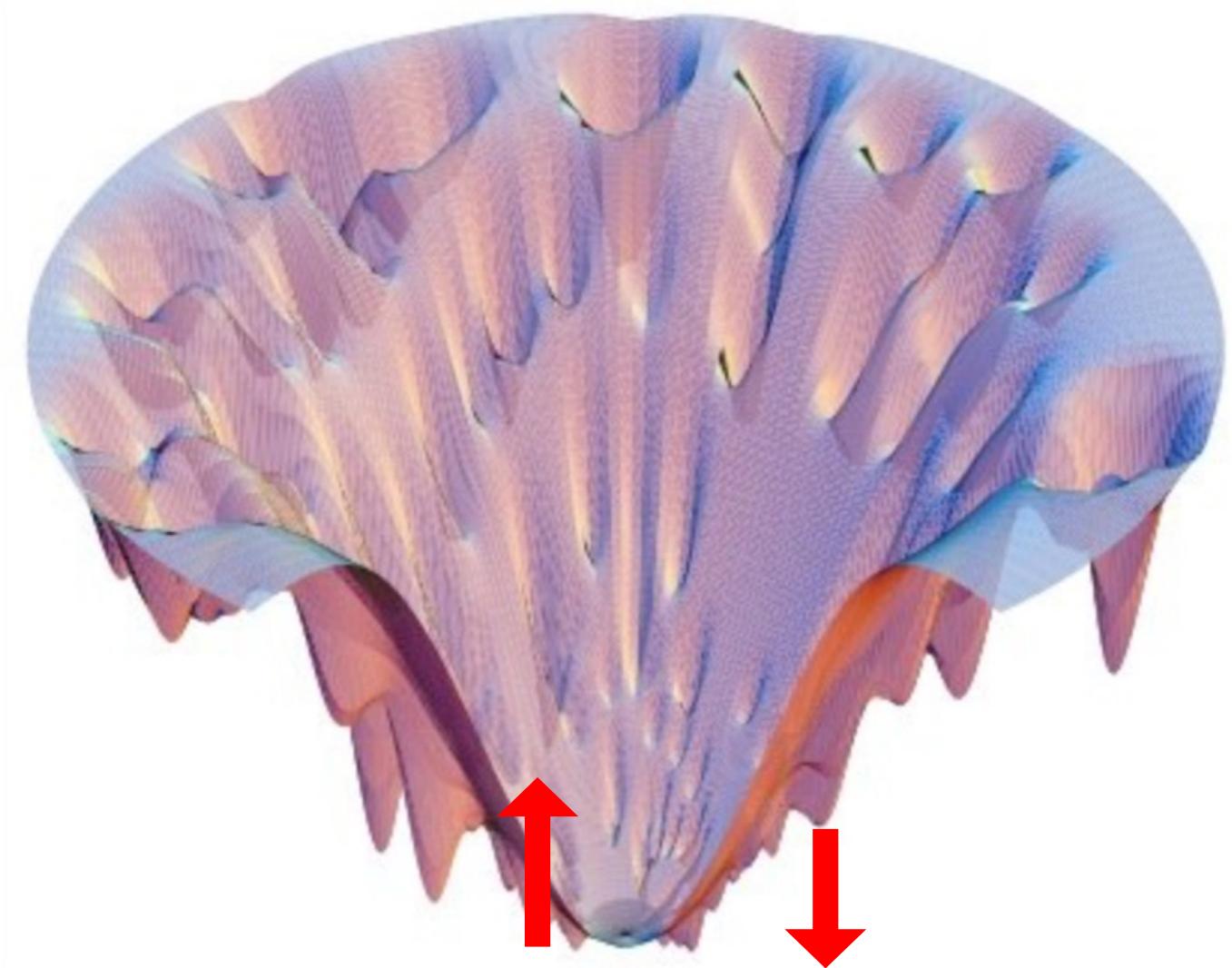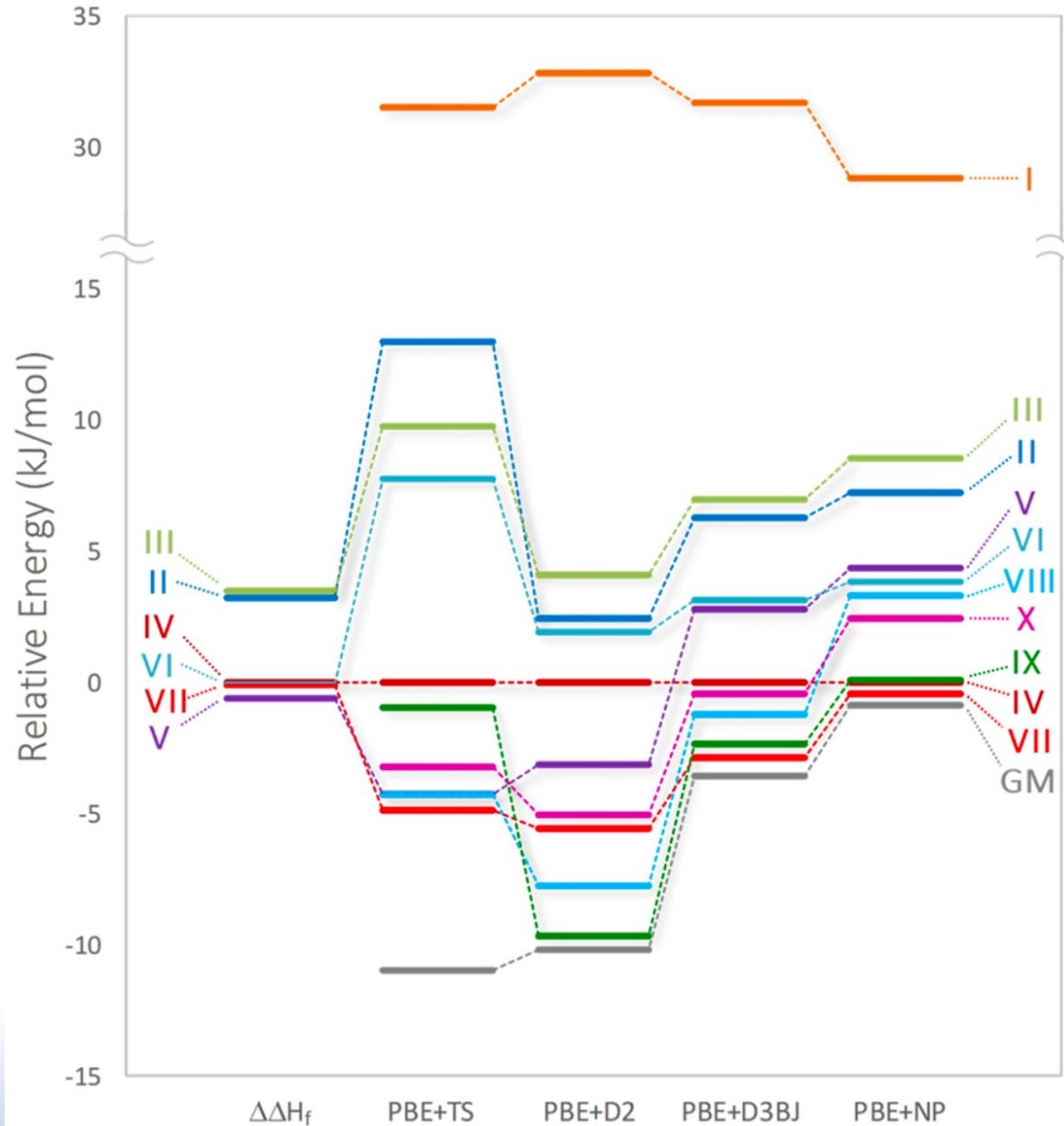
Complex Solid Form Landscape of Galunisertib

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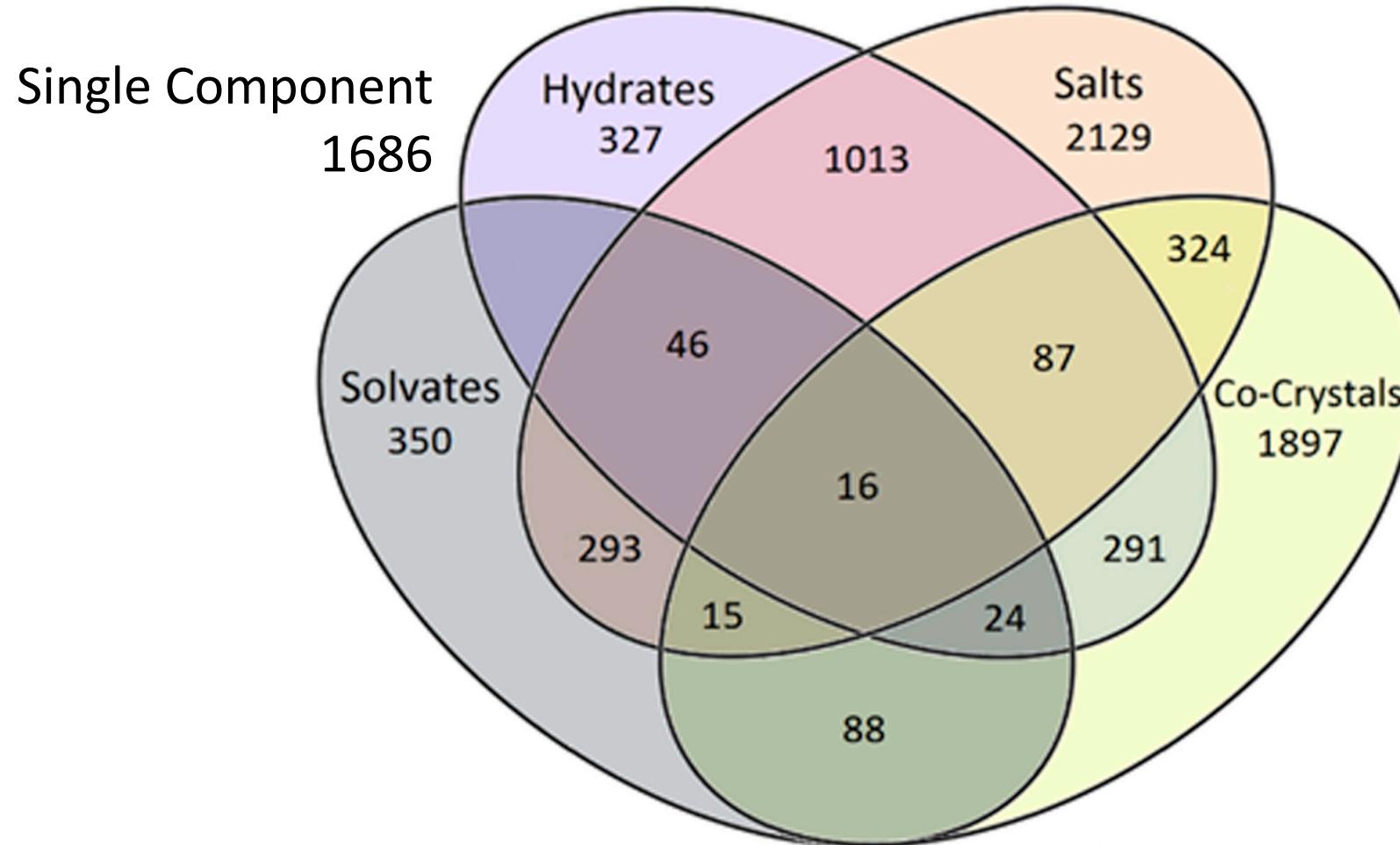
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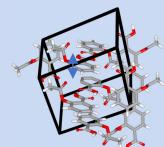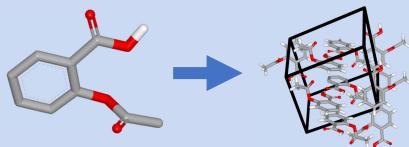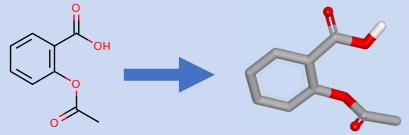
Relative rank will change
at finite temperatures
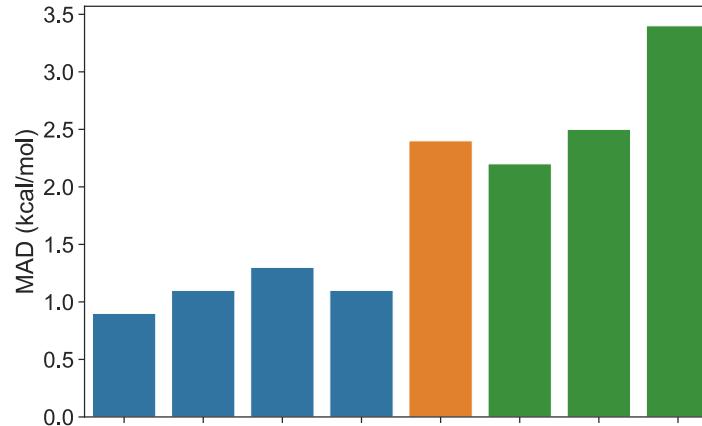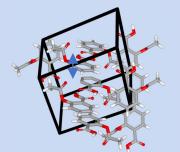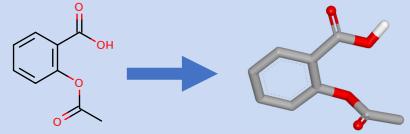
Most drug molecules crystals are multi-component

Single Component 1686

Hydrates 327

Salts 2129

1013

324

Solvates 350

46

87

Co-Crystals 1897

16

293

291

15

24

88

OpenEye
SCIENTIFIC
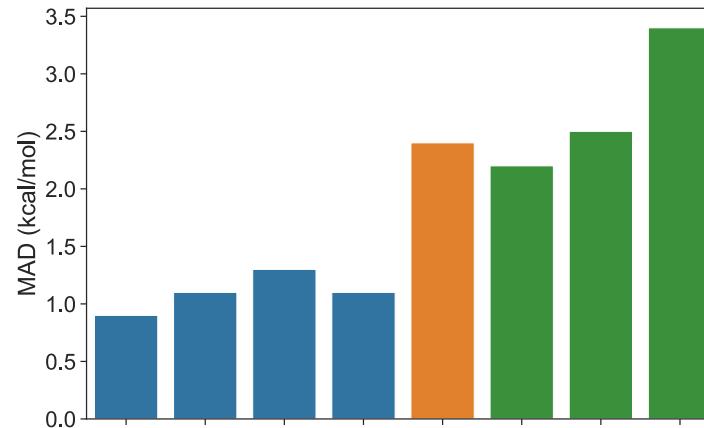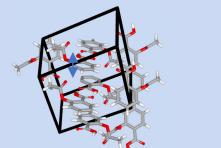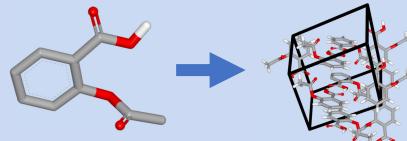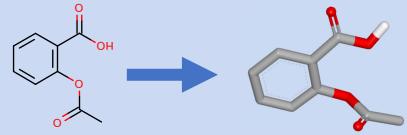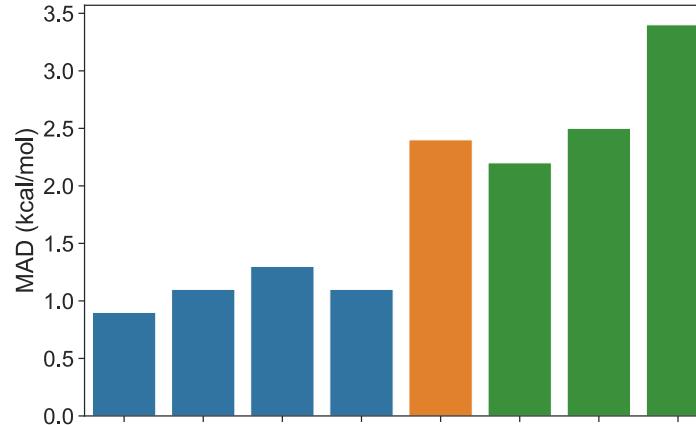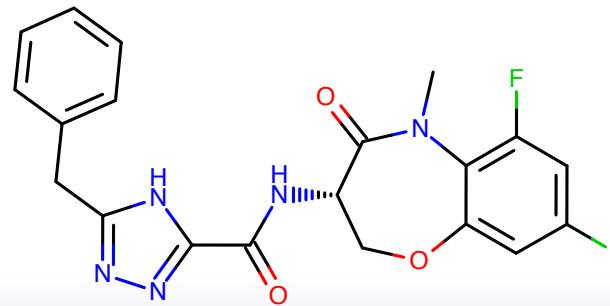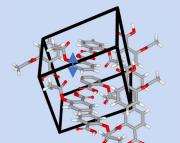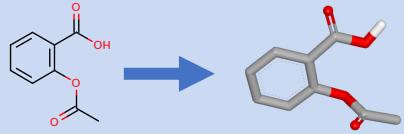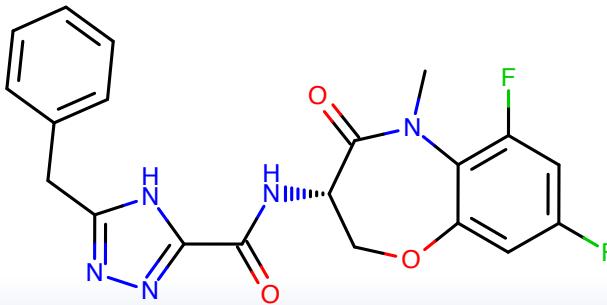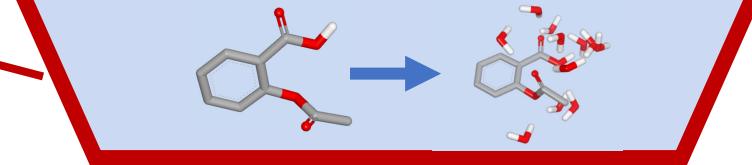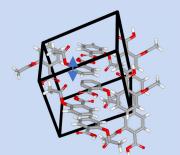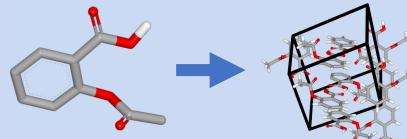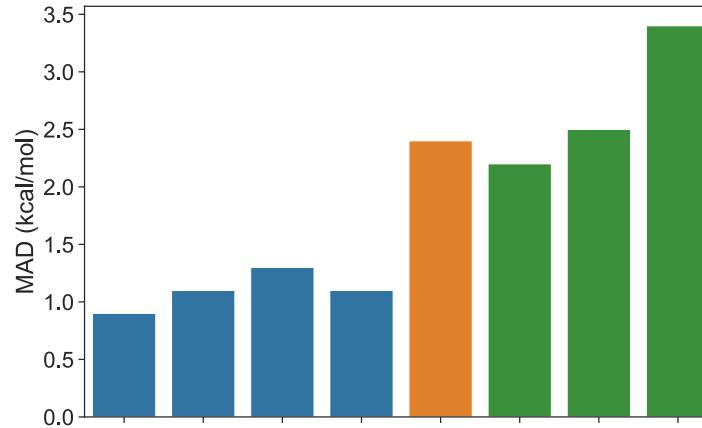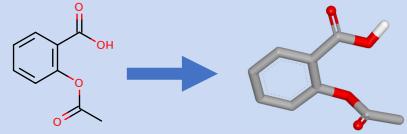
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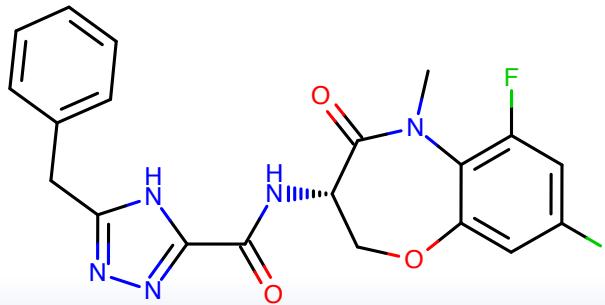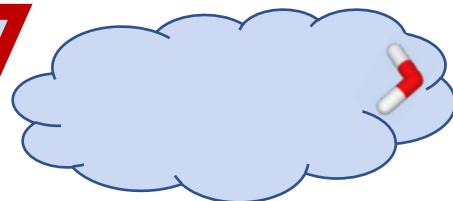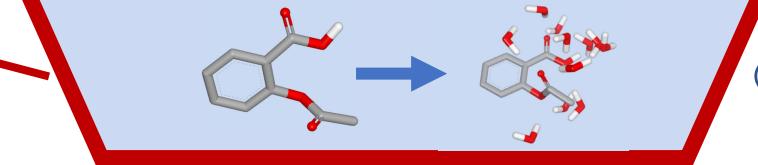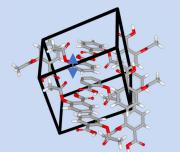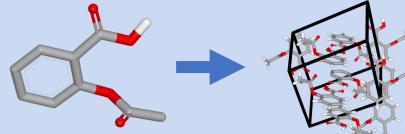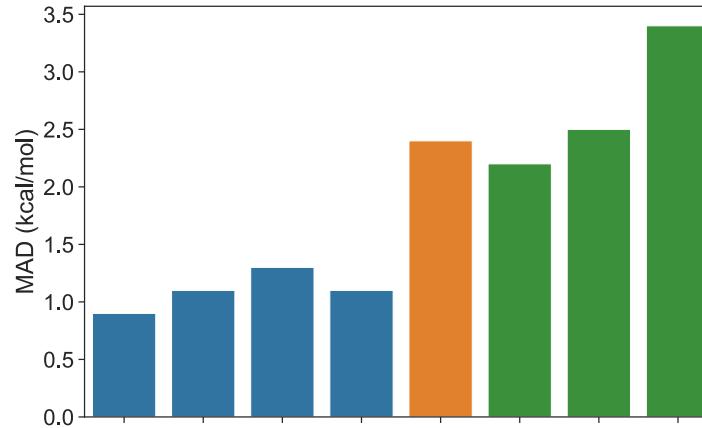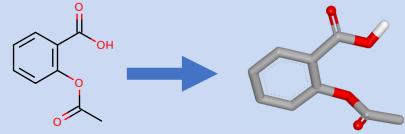
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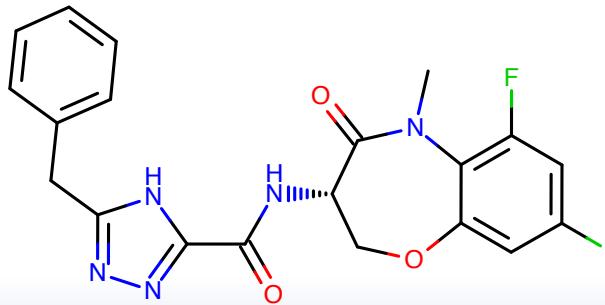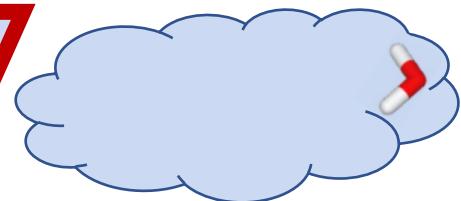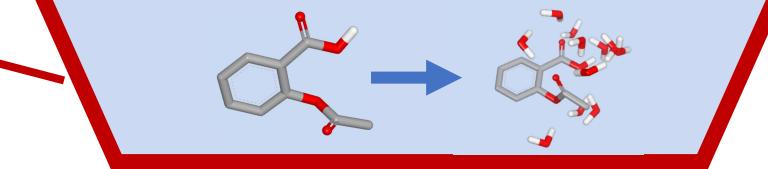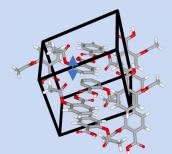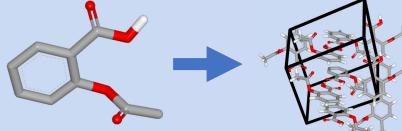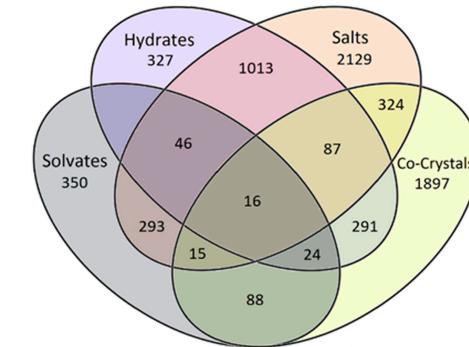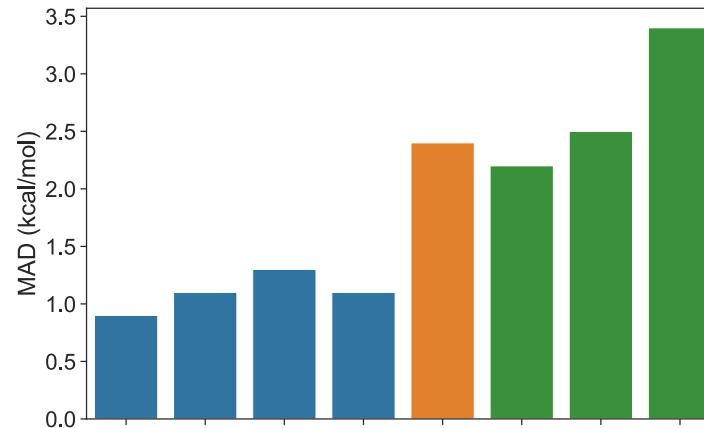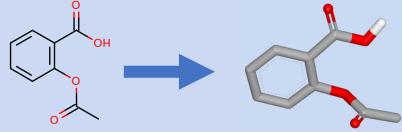
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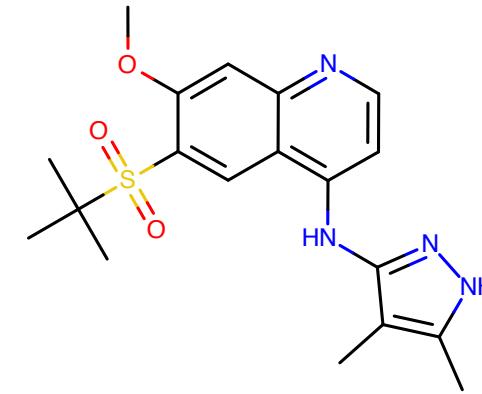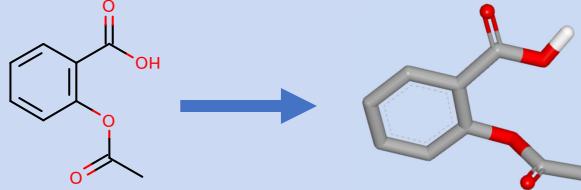
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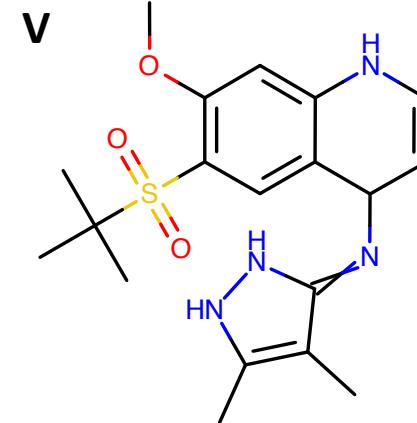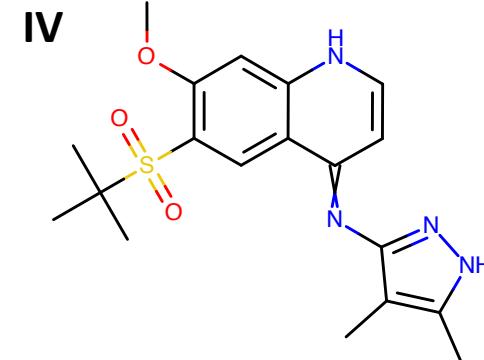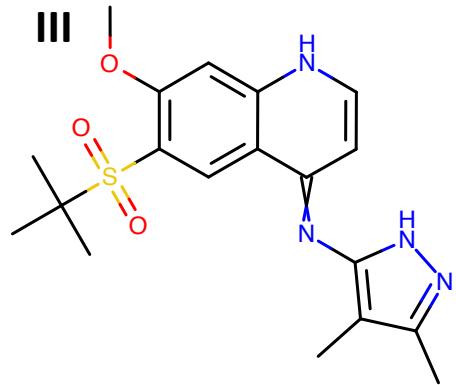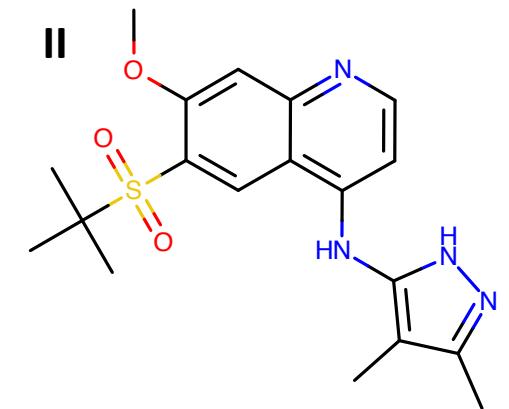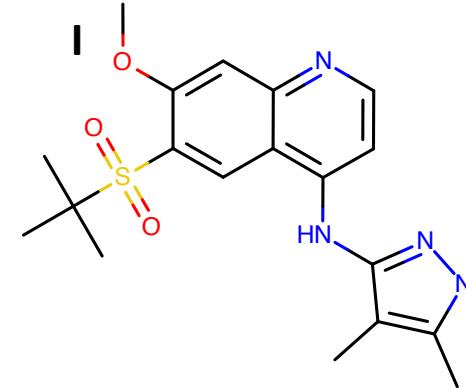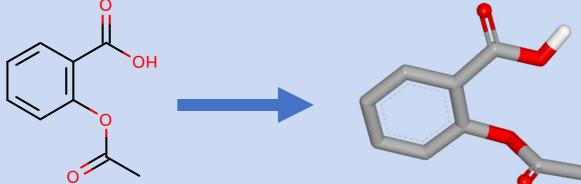
Outline

Outline

Outline

Protocol begins with dense conformer generation
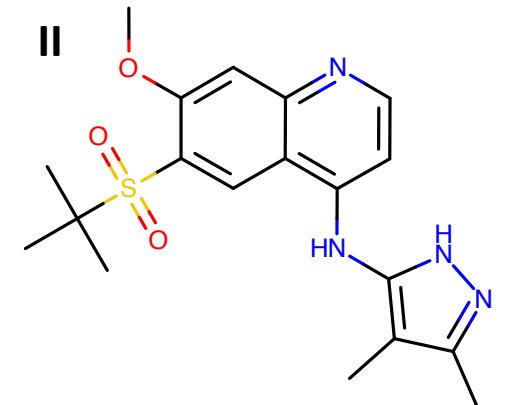
Protocol begins with dense conformer generation

Protocol begins with dense conformer generation

I

0.0 kcal/mol

II

1.54 kcal/mol

III
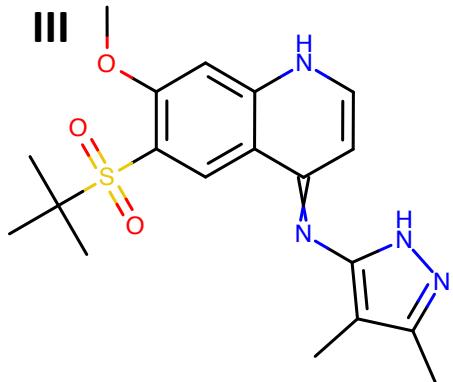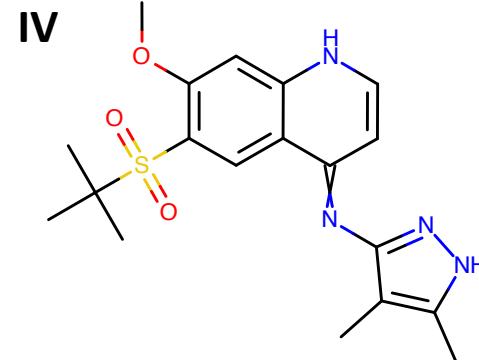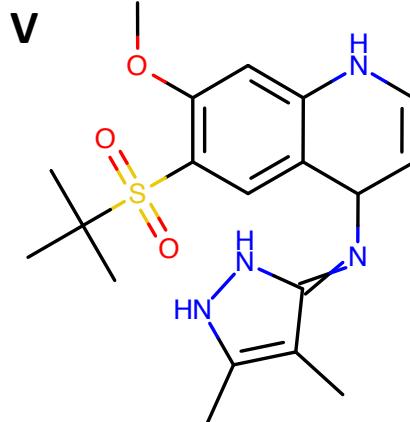
E: 9.04 kcal/mol
Z: 10.54 kcal/mol

IV
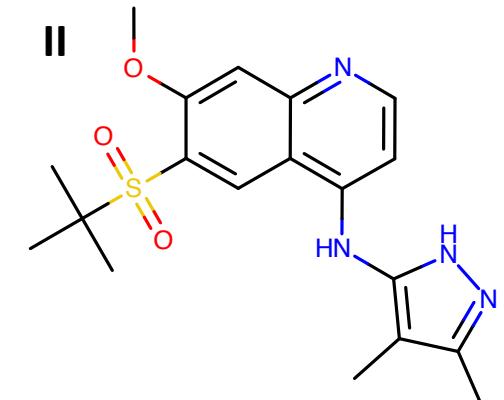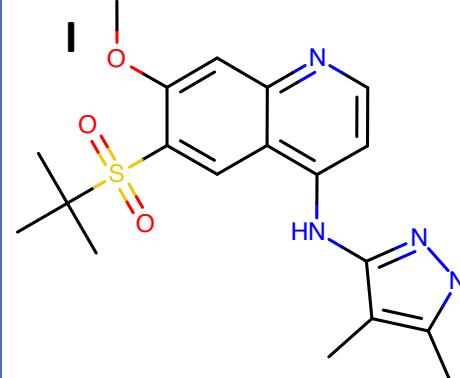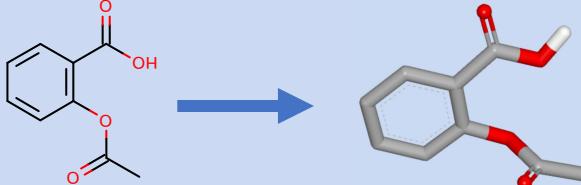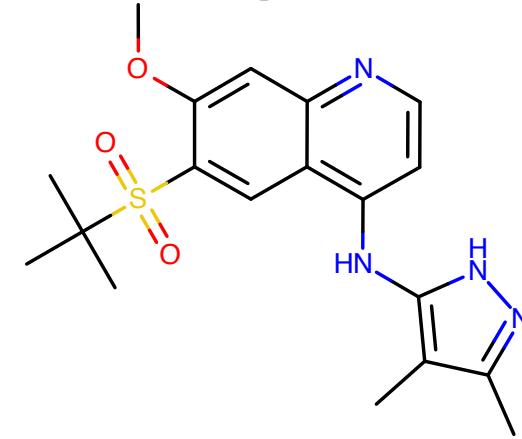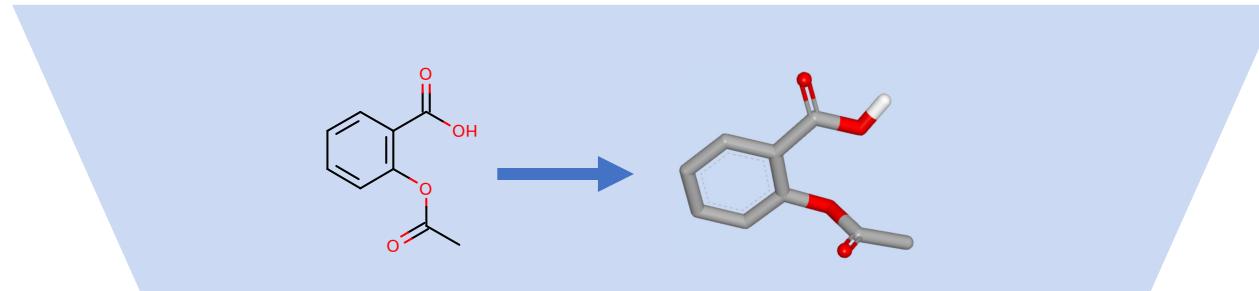
E: 9.05 kcal/mol
Z: 12.56 kcal/mol

V
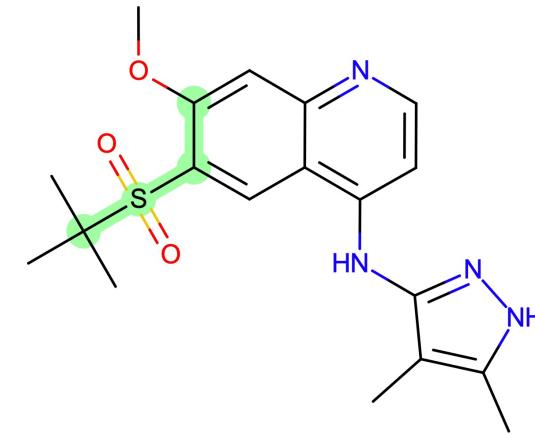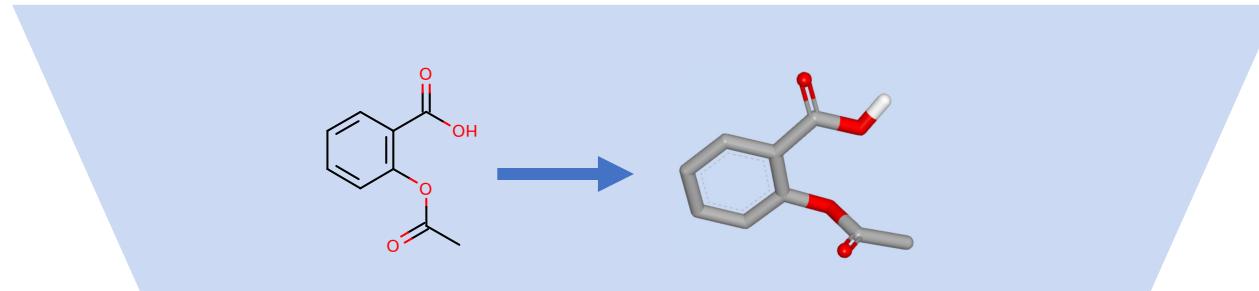
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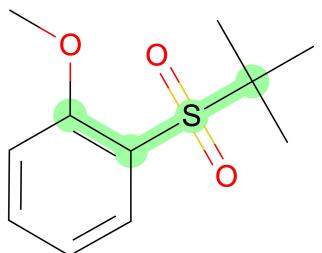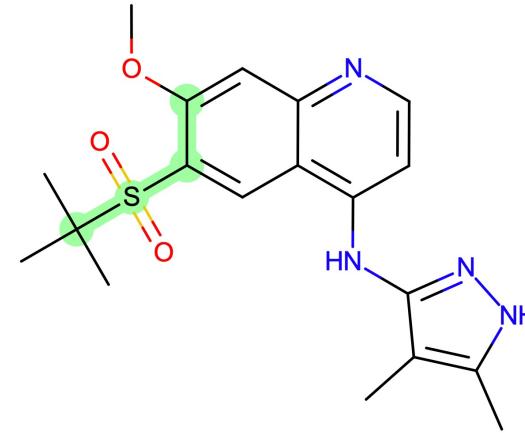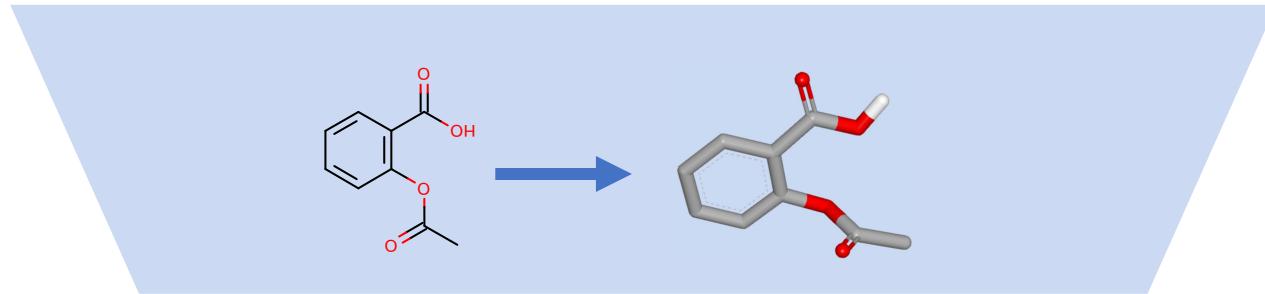
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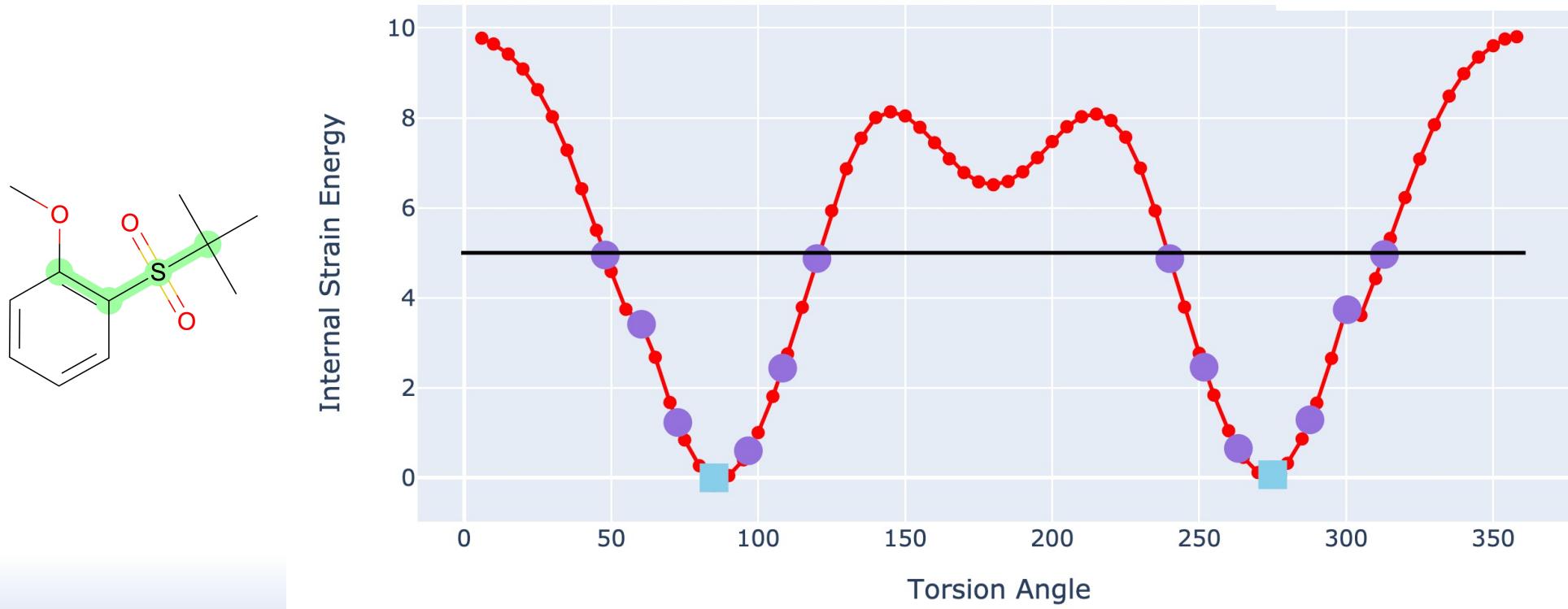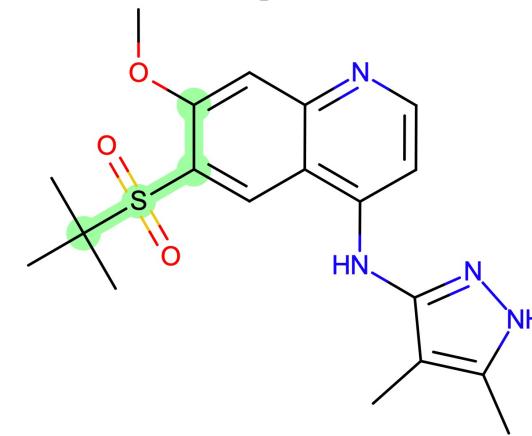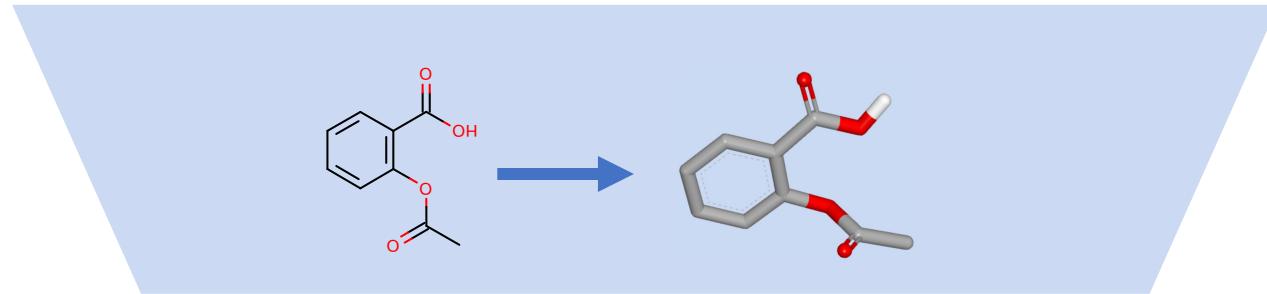
Protocol begins with dense conformer generation

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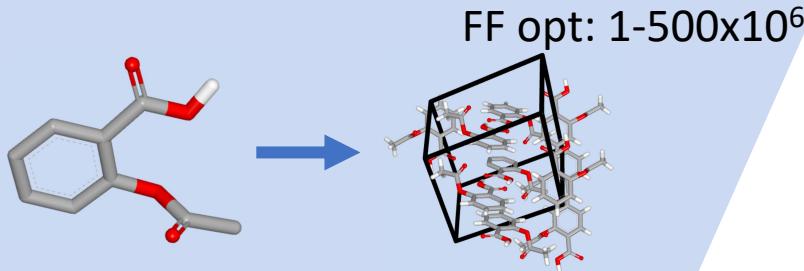
Protocol begins with dense conformer generation
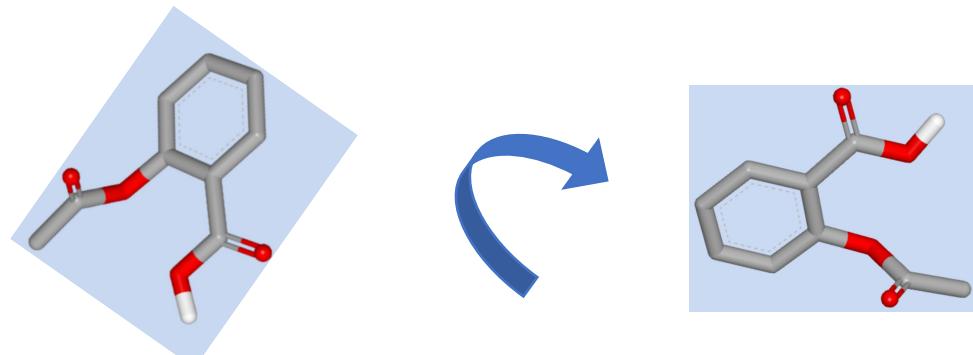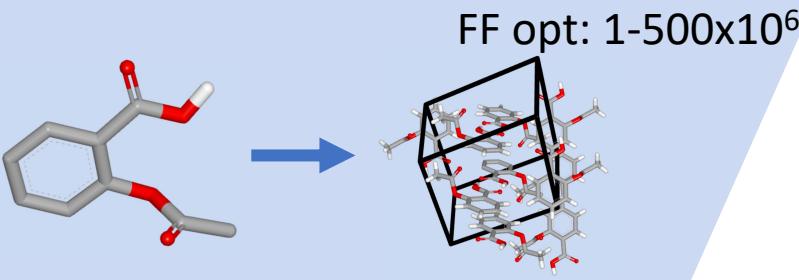
Protocol begins with dense conformer generation

Random packings optimized with multipole FF

Conformers: 100-5,000

FF opt: $1\text{-}500\text{x}10^6$

Random packings optimized with multipole FF

Conformers: 100-5,000

FF opt: $1\text{-}500\text{x}10^6$

OpenEye
SCIENTIFIC

Random packings optimized with multipole FF

Conformers: 100-5,000

FF opt: $1\text{-}500\text{x}10^{6}$

OpenEye
SCIENTIFIC

Random packings optimized with multipole FF

Conformers: 100-5,000

FF opt: $1\text{-}500\times10^6$
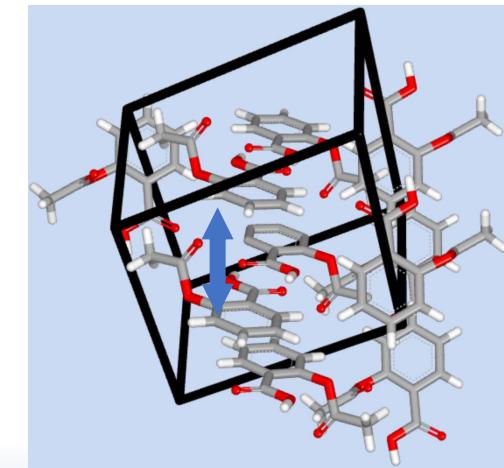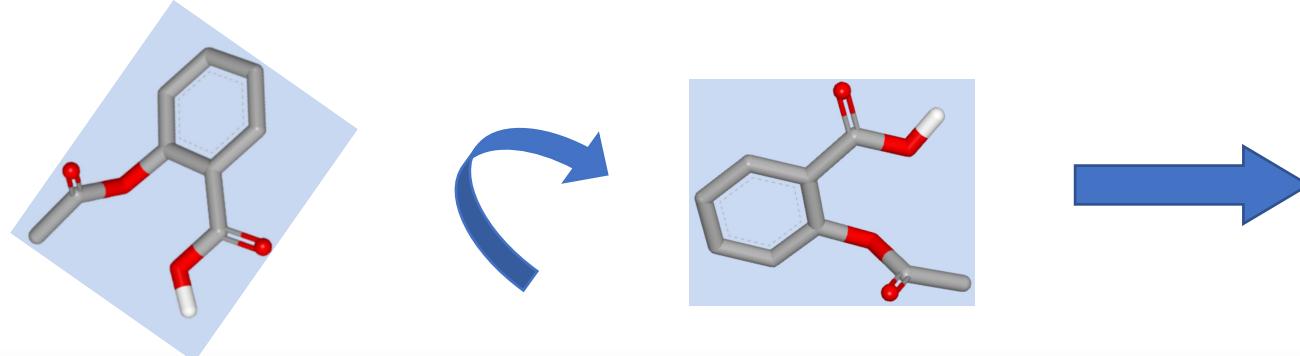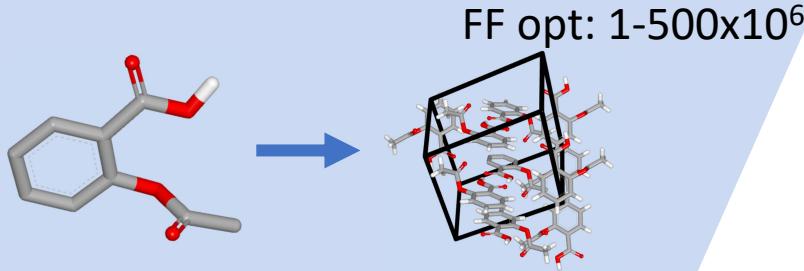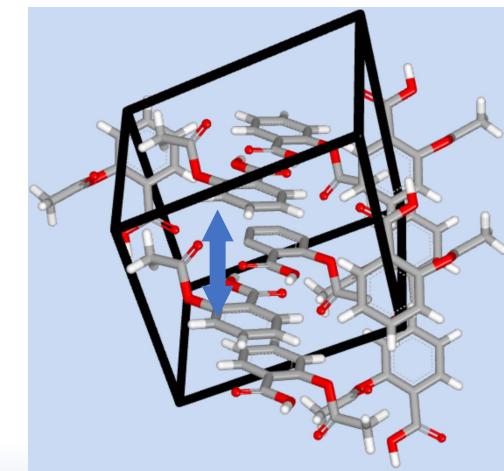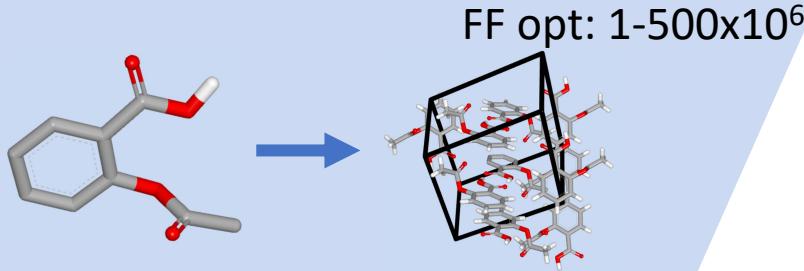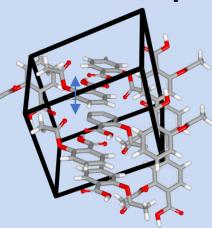
- Intermolecular potentials
- Stone multipoles
- VdW terms by atom types (mostly elemental)
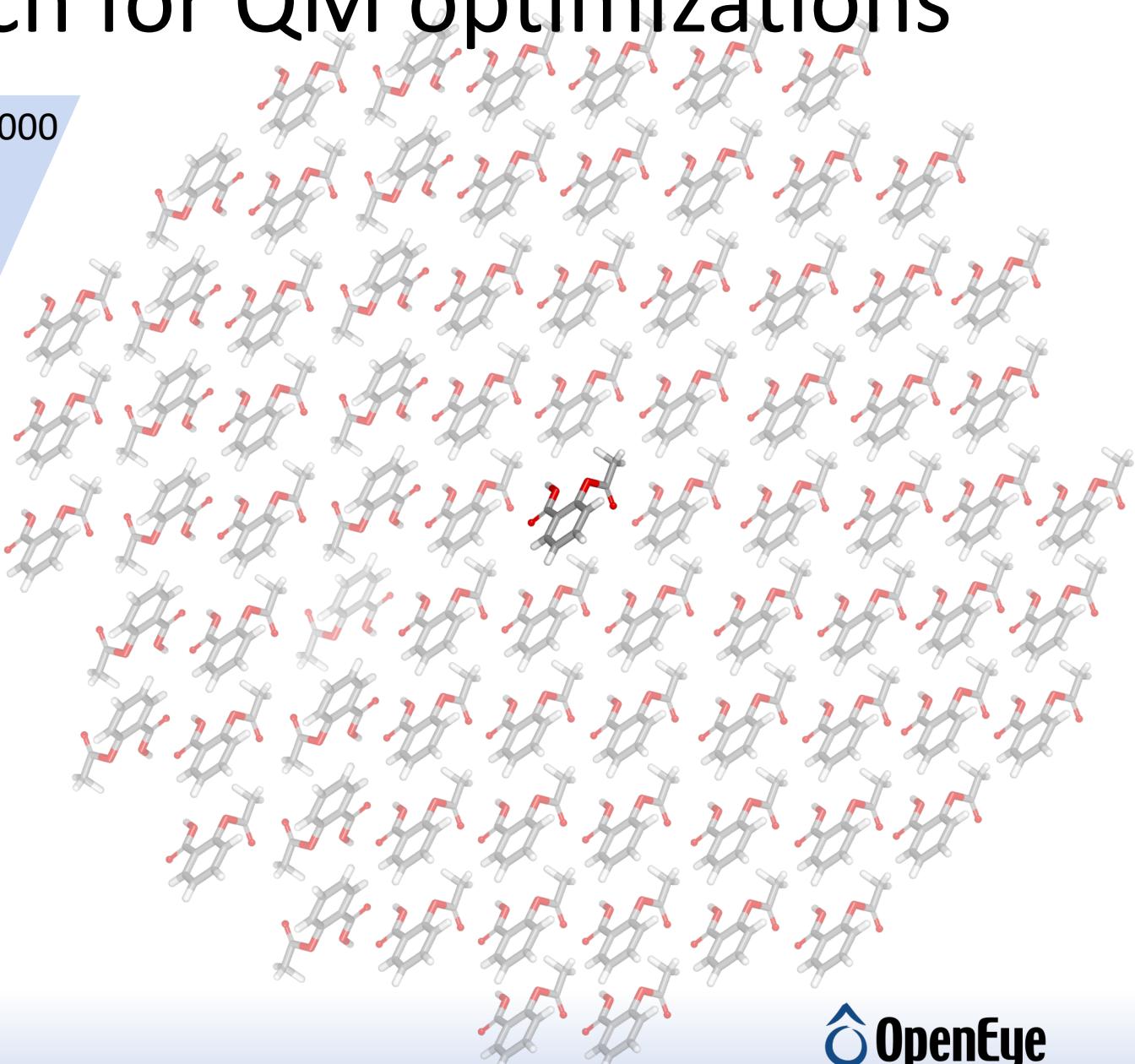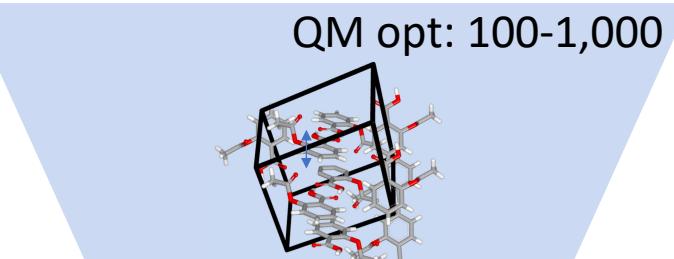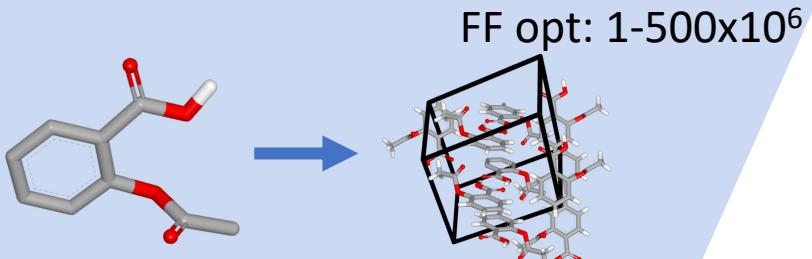
Dimer expansion approach for QM optimizations
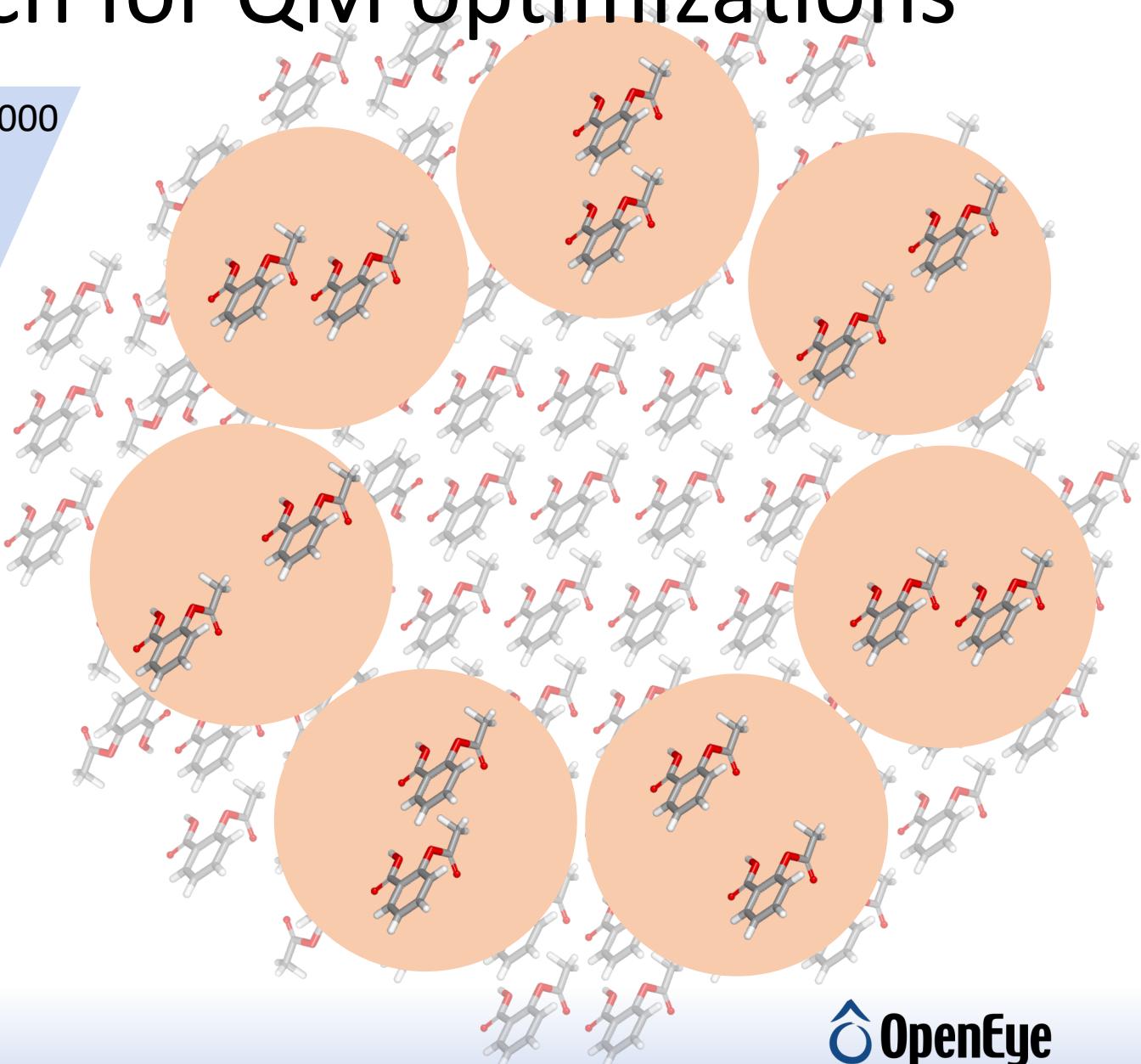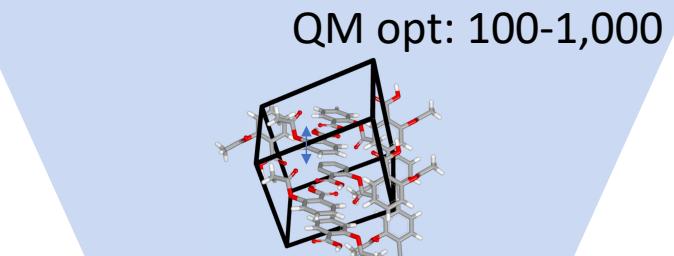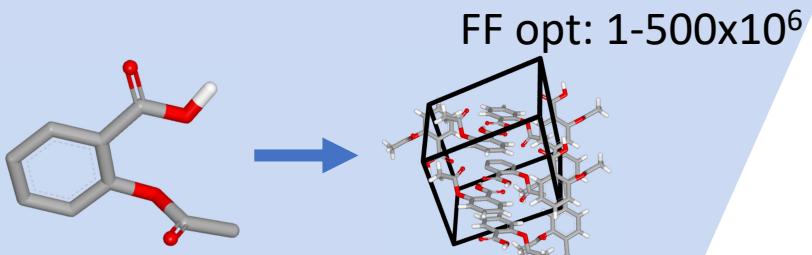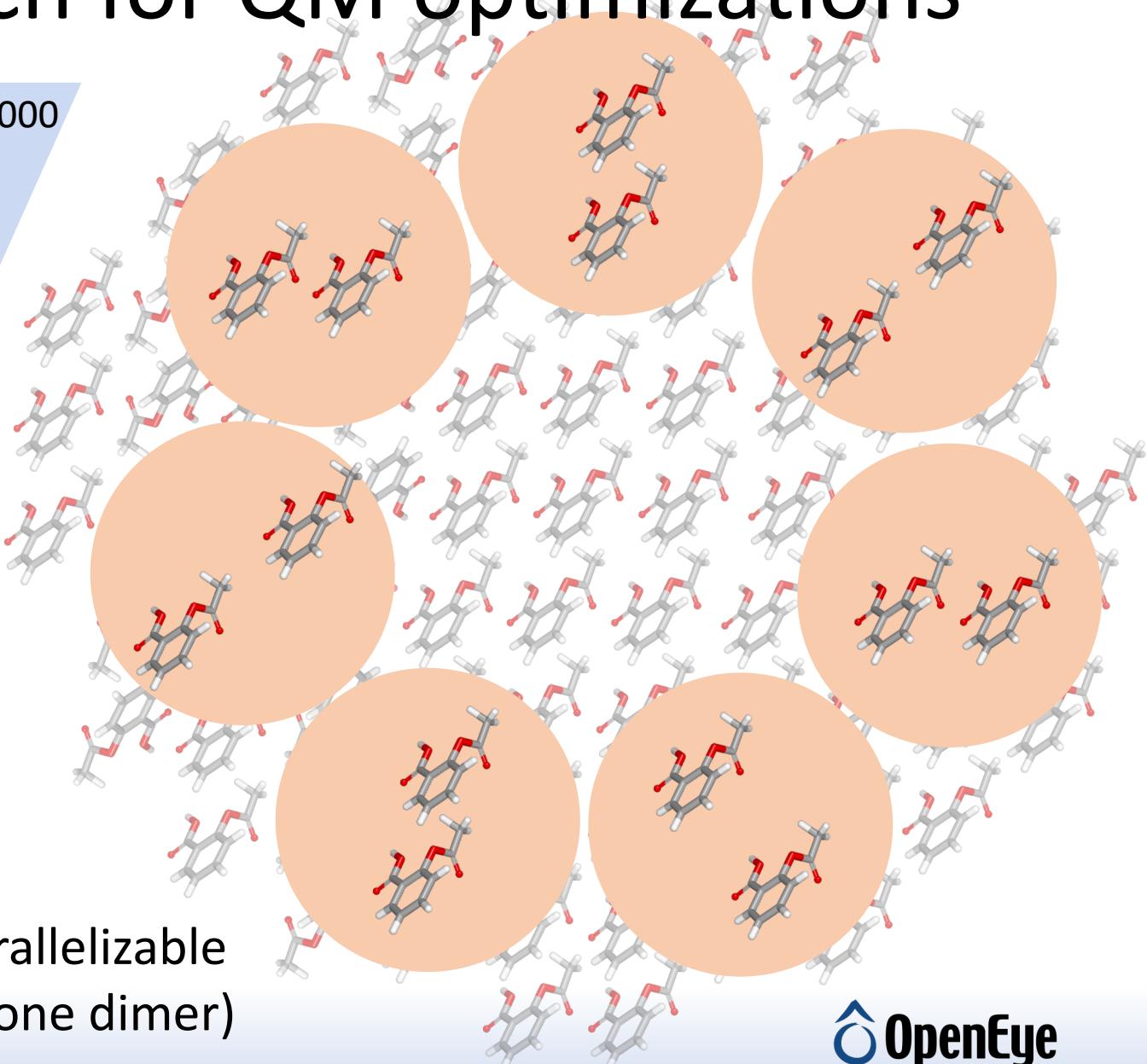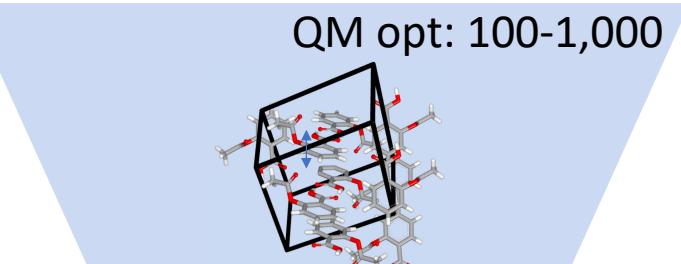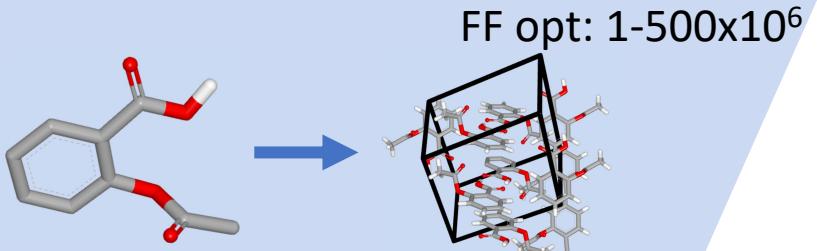
Conformers: 100-5,000

FF opt: $1\text{-}500\text{x}10^6$

QM opt: 100-1,000

Dimer expansion approach for QM optimizations

Conformers: 100-5,000

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Dimer expansion approach for QM optimizations

Conformers: 100-5,000

FF opt: 1-500x10^6

QM opt: 100-1,000

Highly parallelizable
(time for one dimer)

OpenEye
SCIENTIFIC

Dimer expansion approach for QM optimizations

Conformers: 100-5,000

FF opt: $1\text{-}500\times10^6$

QM opt: 100-1,000

6Å

12Å

OpenEye
SCIENTIFIC

Dimer expansion approach for QM optimizations

Conformers: 100-5,000

FF opt: $1\text{-}500\text{x}10^6$

QM opt: 100-1,000

Short Range (DFT)

6Å

Mid-range (HF3c)

12Å

Long Range (IEFF)

OpenEye
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Dimer expansion approach for QM optimizations

Conformers: 100-5,000

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QM opt: 100-1,000

Short Range (DFT)

6Å

Mid-range (HF3c)

12Å

Long Range (IEFF)

- Understand long range interaction
- Easily swap in more expensive methods

OpenEye
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Reference set for evaluating CSP energies

Reference set for evaluating CSP energies

Experimental datasets:

• 21 crystal structure benchmark for non-covalent interactions (c21)
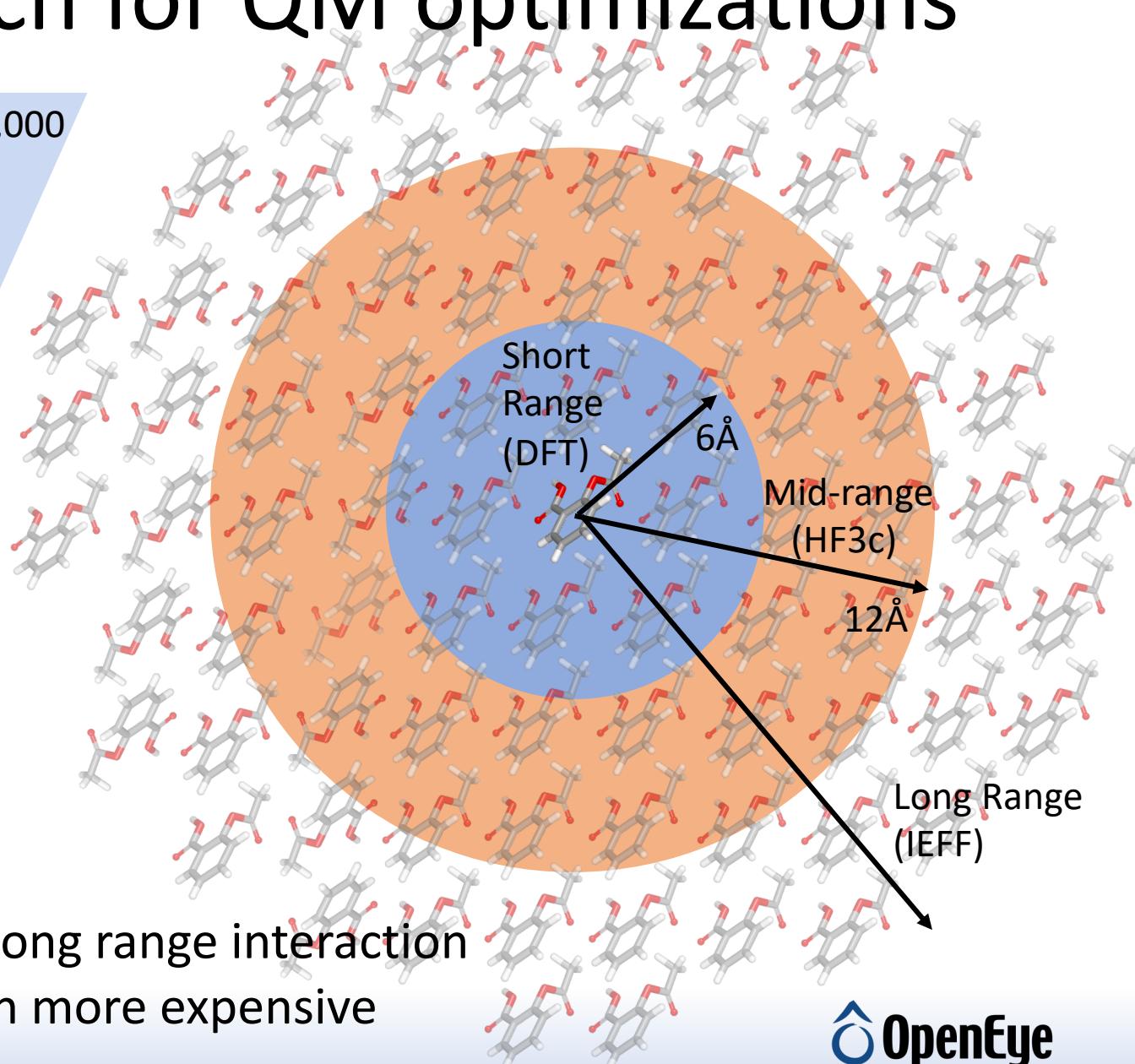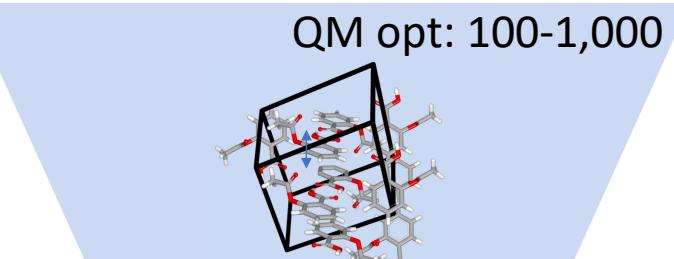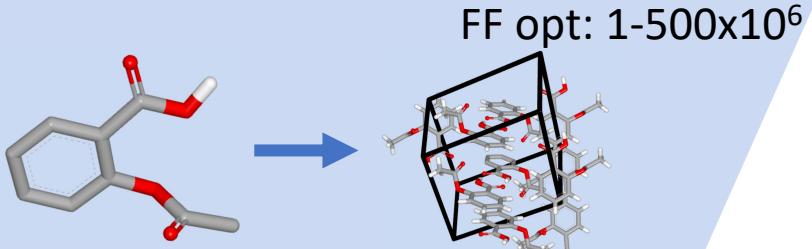
• Sublimation enthalpies measured for all

Reference set for evaluating CSP energies
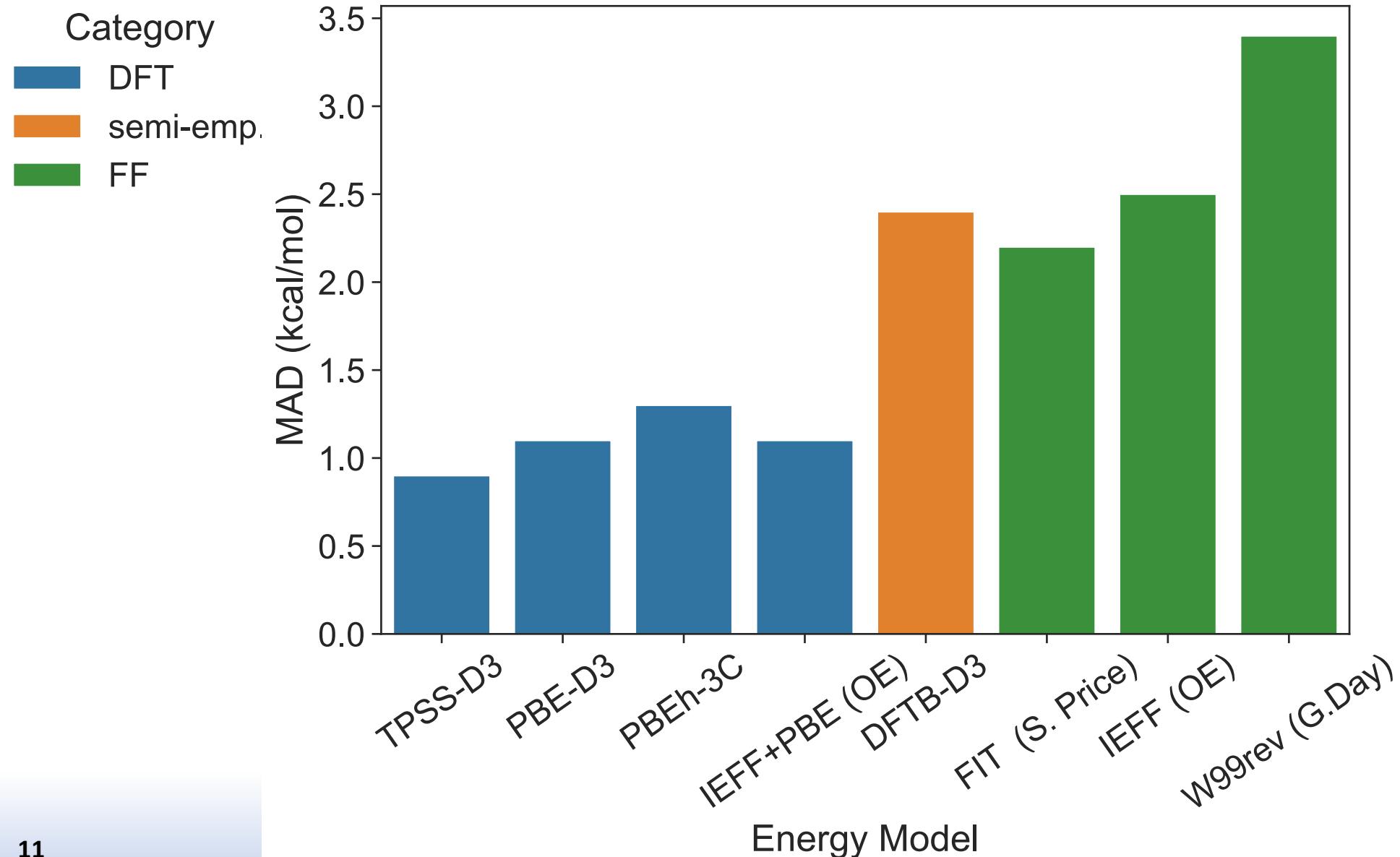
Experimental datasets:

- 21 crystal structure benchmark for non-covalent interactions (c21)
- Sublimation enthalpies measured for all
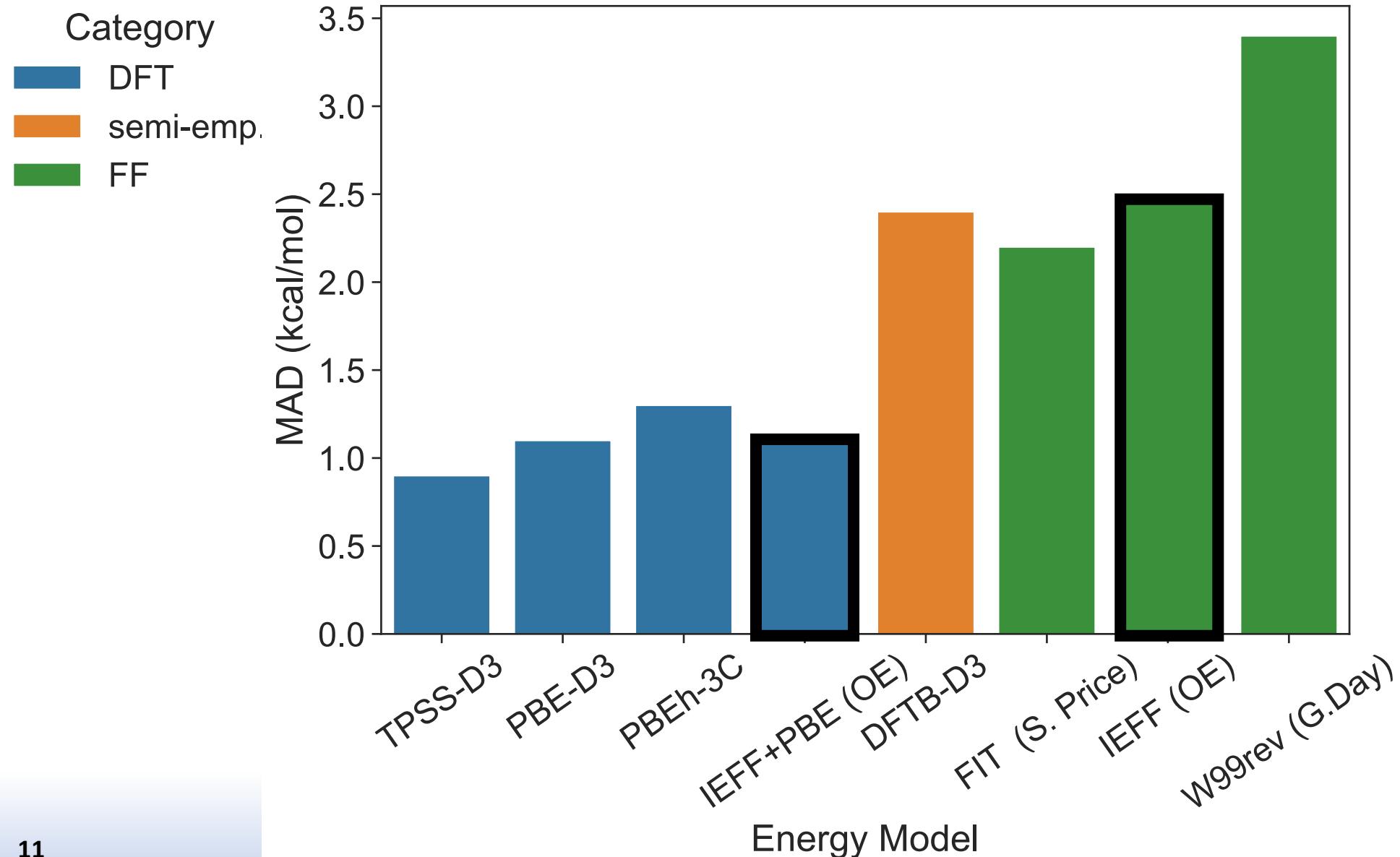
Calculated enthalpies and computational time

- Force field
- Semi-empirical
- DFT
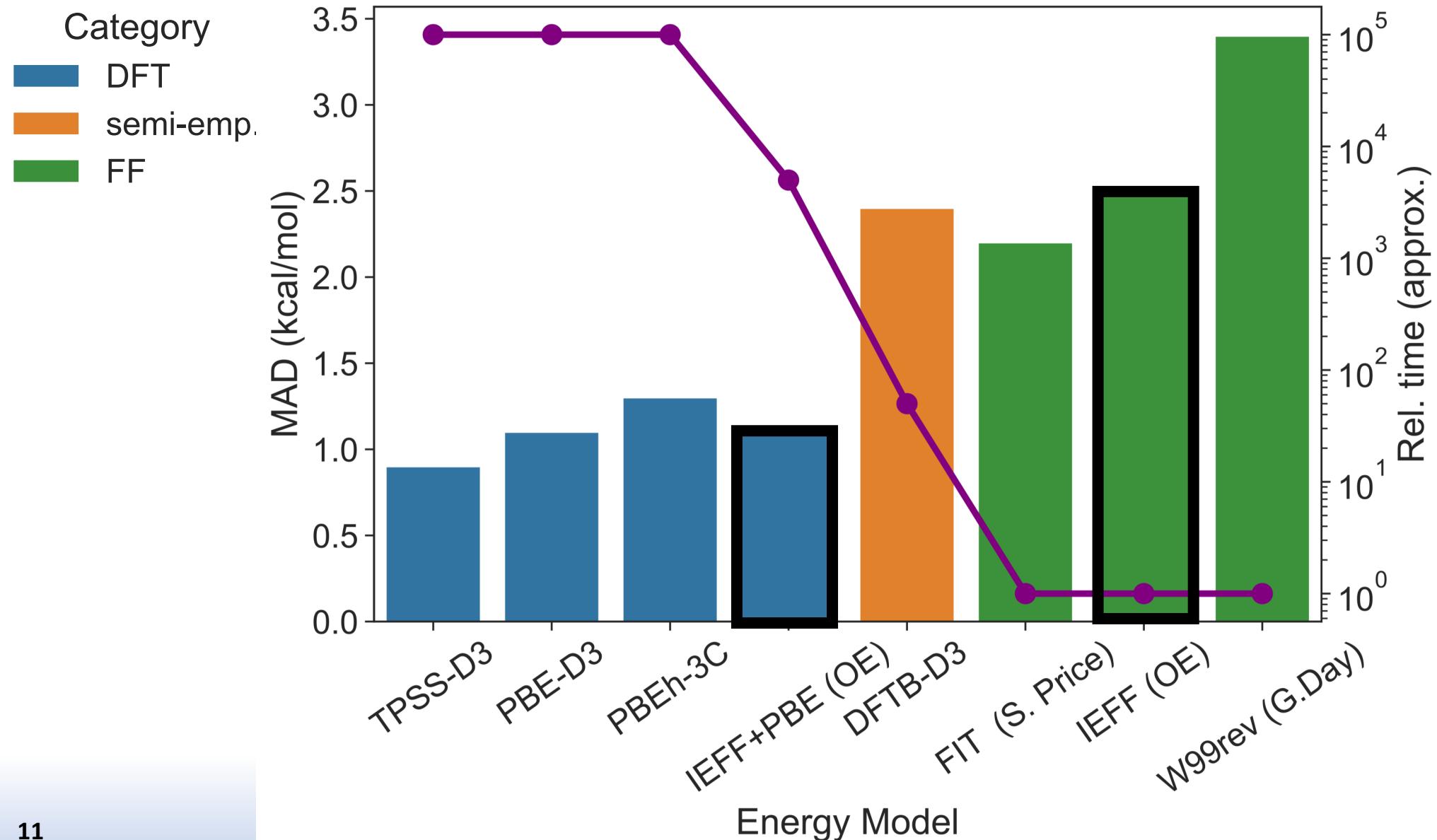
Reference set for evaluating CSP energies

Reference set for evaluating CSP energies
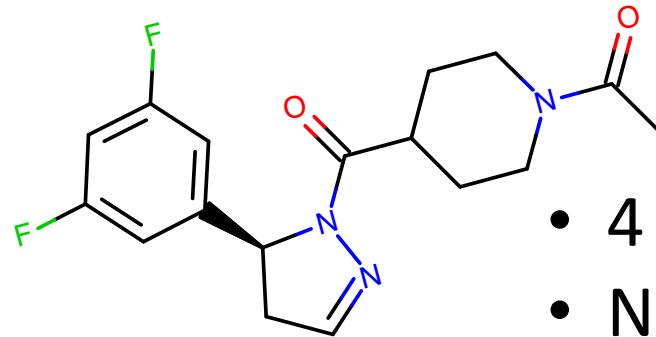
Reference set for evaluating CSP energies
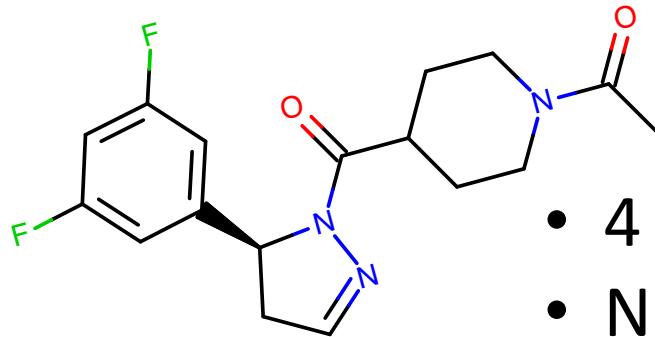
GSK collaboration on blind challenges

GSK collaboration on blind challenges
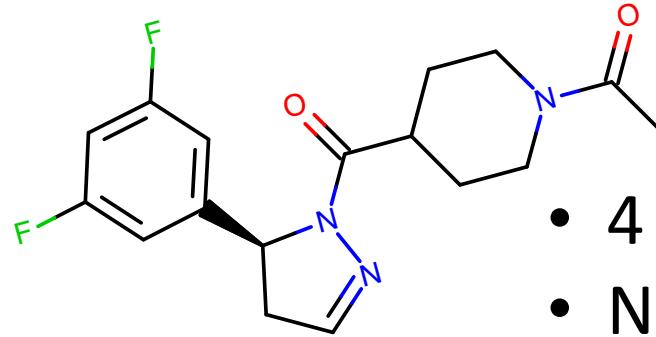
- 4 rotatable bonds
- No hydrogen bonding

GSK collaboration on blind challenges
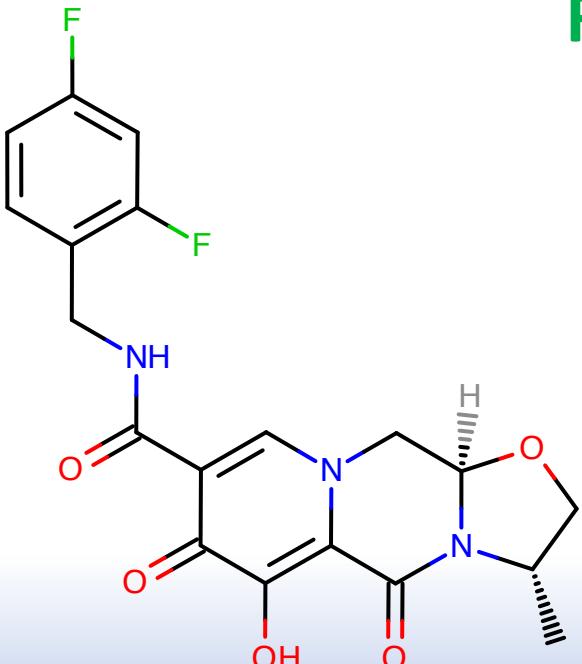
- 4 rotatable bonds
- No hydrogen bonding
- **RMS_20 = 0.18 A**
  Rank = 1

GSK collaboration on blind challenges
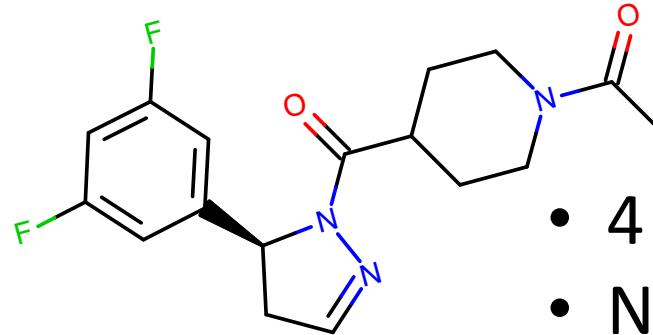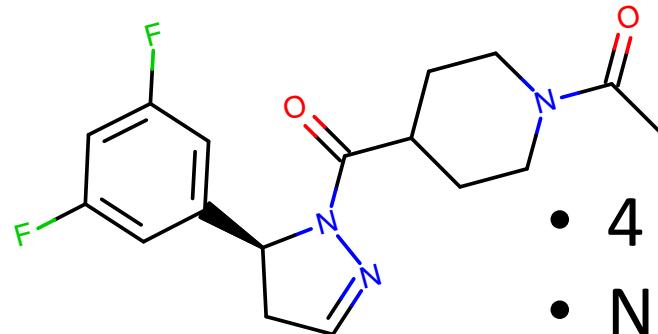
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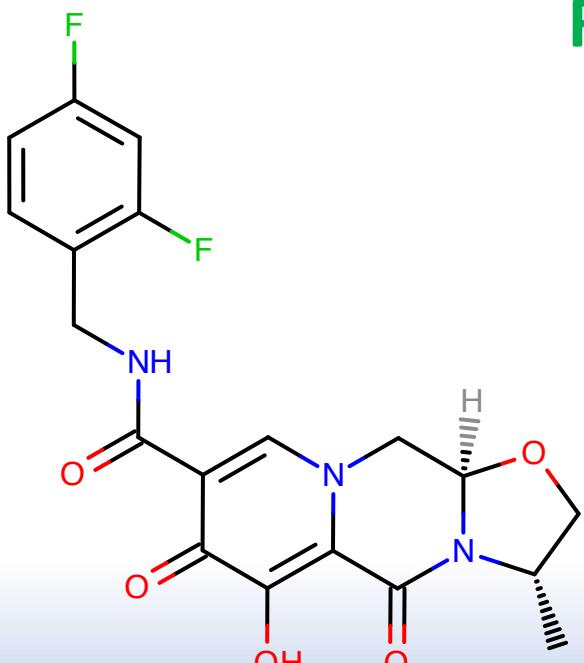
- 4 rotatable bonds
- 2 donors, 7 donors

GSK collaboration on blind challenges

- 4 rotatable bonds
- No hydrogen bonding
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- 4 rotatable bonds
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OpenEye
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GSK collaboration on blind challenges

- 4 rotatable bonds
- No hydrogen bonding
- **RMS_20 = 0.18 A**
Rank = 1

- 5 rotatable bonds
- 2 donors, 7 donors

- 4 rotatable bonds
- 2 donors, 7 donors
- **RMS_20 = 0.18 A**
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OpenEye
SCIENTIFIC

GSK collaboration on blind challenges

- 4 rotatable bonds
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- 5 rotatable bonds
- 2 donors, 7 donors
- 2 tautomers

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OpenEye
SCIENTIFIC

GSK collaboration on blind challenges

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- 5 rotatable bonds
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- "Rare space group"

- 4 rotatable bonds
- 2 donors, 7 donors
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OpenEye
SCIENTIFIC
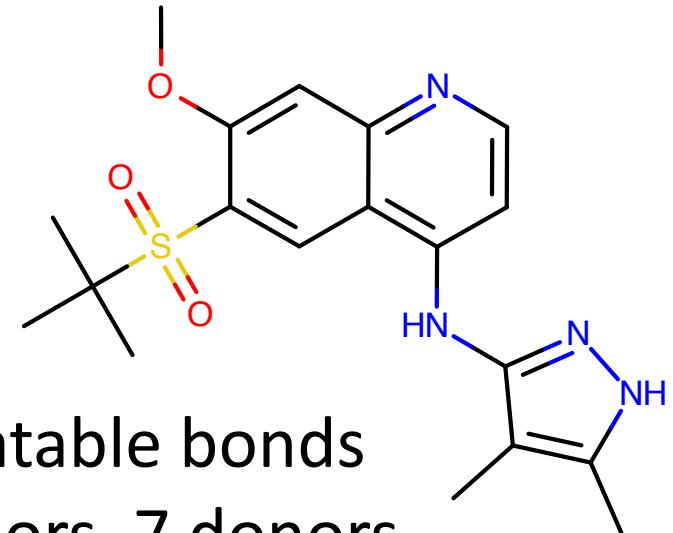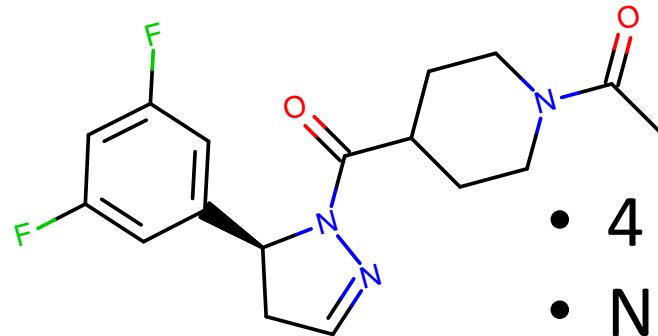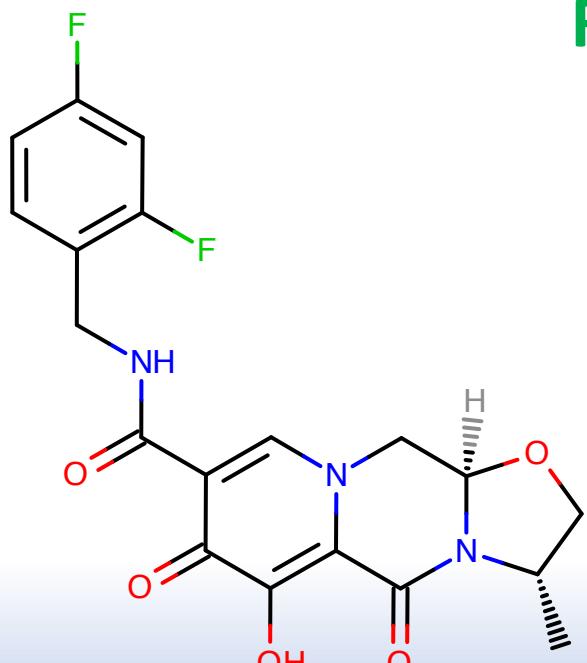
GSK collaboration on blind challenges

- 4 rotatable bonds
- No hydrogen bonding
- **RMS_20 = 0.18 A**
Rank = 1

- 4 rotatable bonds
- 2 donors, 7 donors
- **RMS_20 = 0.18 A**
Rank = 1

- 5 rotatable bonds
- 2 donors, 7 donors
- 2 tautomers
- "Rare space group"
- **RMS_20 = 0.16 A**
Rank = 1

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Evolving protocol now includes entropy calculations

Conformers: 100-5,000

FF opt: $1\text{-}500\text{x}10^{6}$
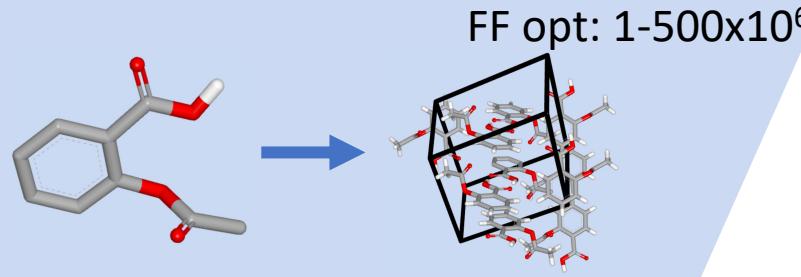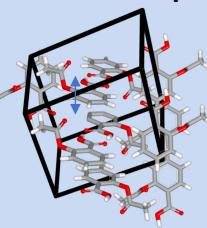
QM opt: 100-1,000

Evolving protocol now includes entropy calculations
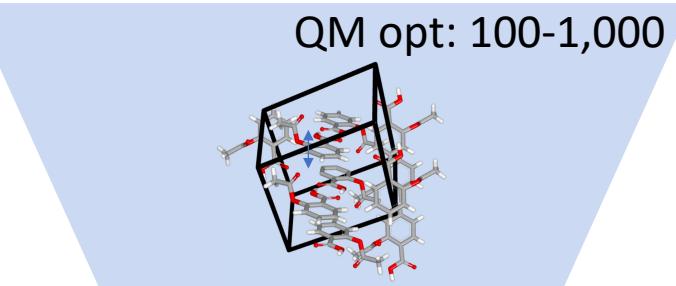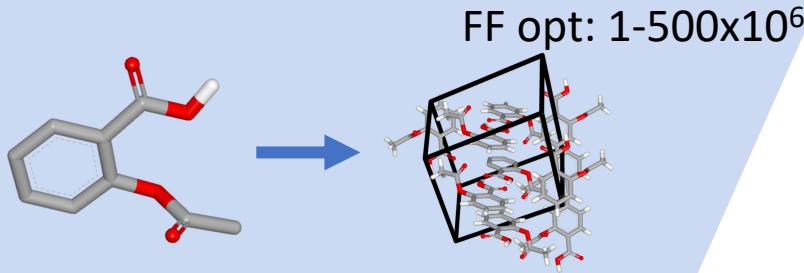
Conformers: 100-5,000

FF opt: $1\text{-}500\text{x}10^{6}$

QM opt: 100-1,000

Vibration: 5-15

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SCIENTIFIC

Evolving protocol now includes entropy calculations

Conformers: 100-5,000

FF opt: $1-500 \times 10^6$

QM opt: 100-1,000

Vibration: 5-15

- 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

Harmonic approximation to finite temperature correction

- Vibrational contribution to free energy
- Third party software Phonopy

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

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

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Harmonic approximation to finite temperature correction

- Vibrational contribution to free energy
- Third party software Phonopy

First principles phonon calculations in materials science

Atsushi Togo [a, b] ✉, Isao Tanaka [a, b, c] 👤 ✉
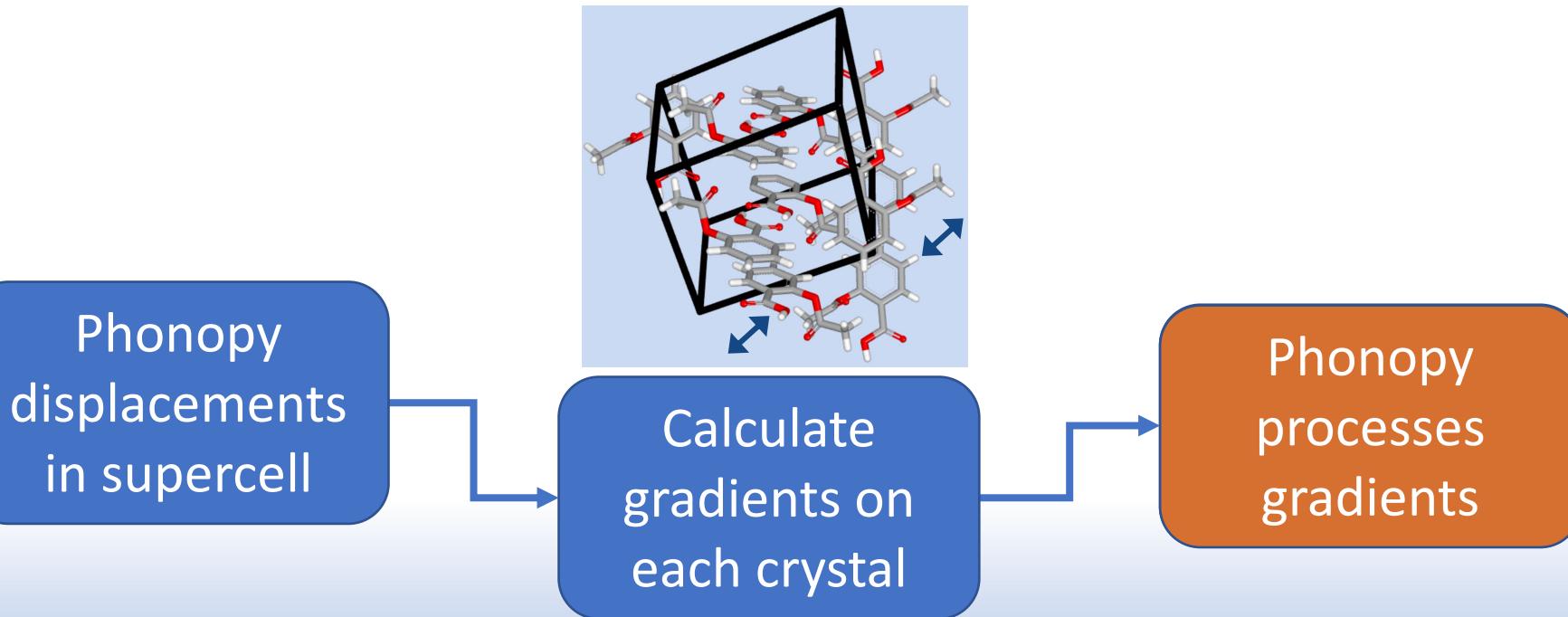
Phonopy displacements in supercell → Calculate gradients on each crystal → Phonopy processes gradients

14

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)

Phonopy displacements in supercell

Calculate gradients on each crystal

Phonopy processes gradients

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Compute gradients with FF or QM

- 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

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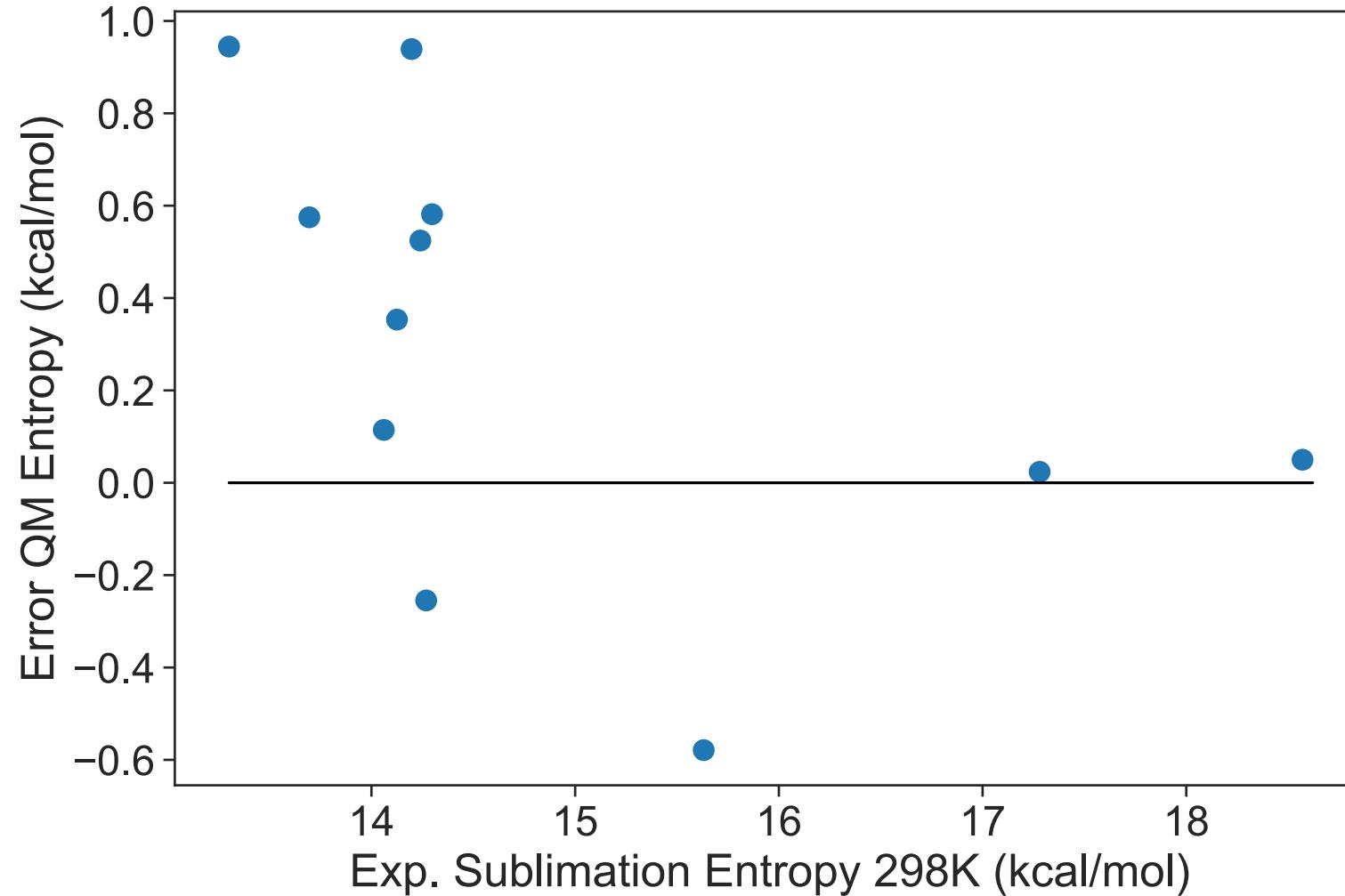
Compute gradients with FF or QM
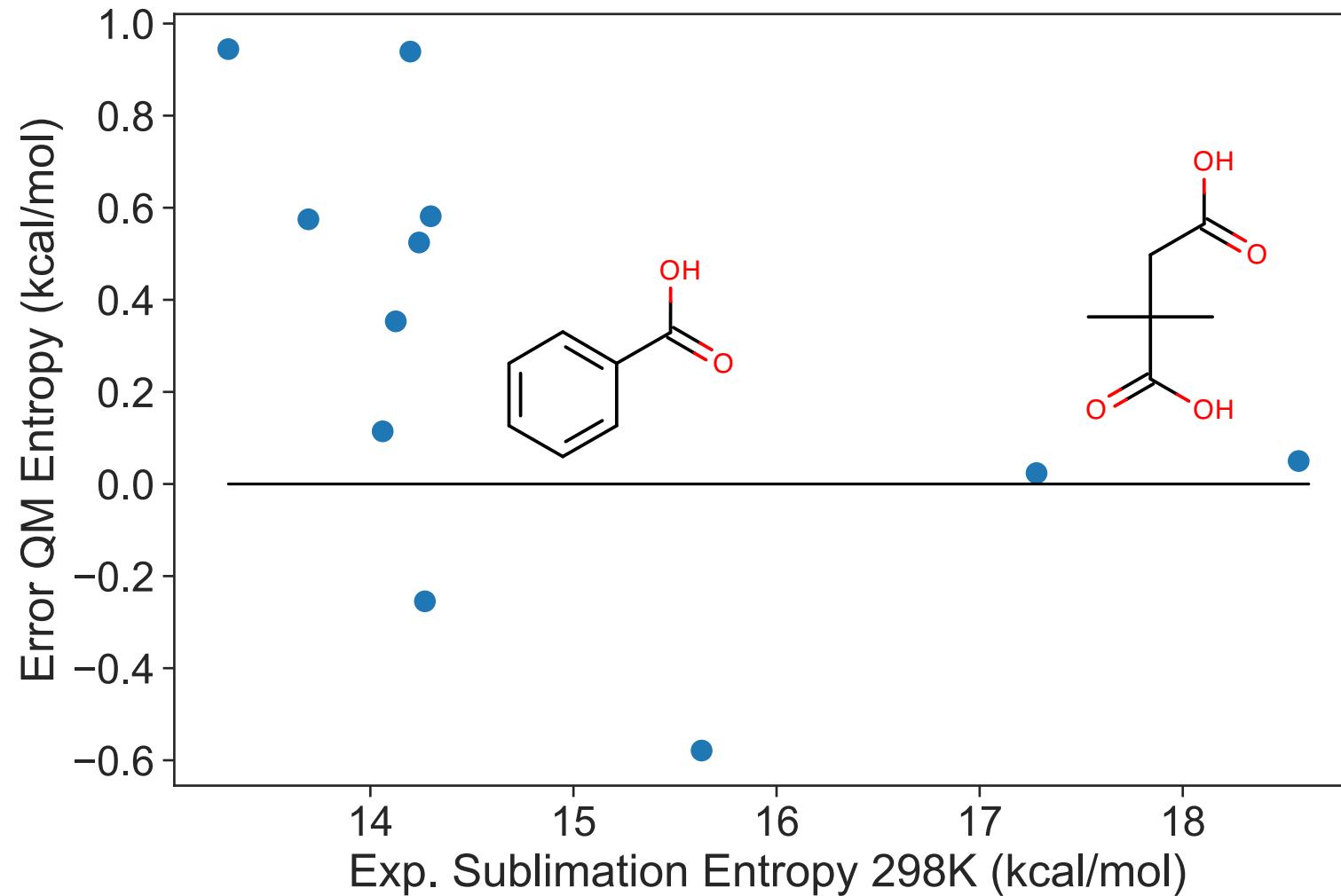
- Dimer expansion on each supercell
- Gradients can be computed with force fields or QM
- Highly parallelizable
- Used prospectively
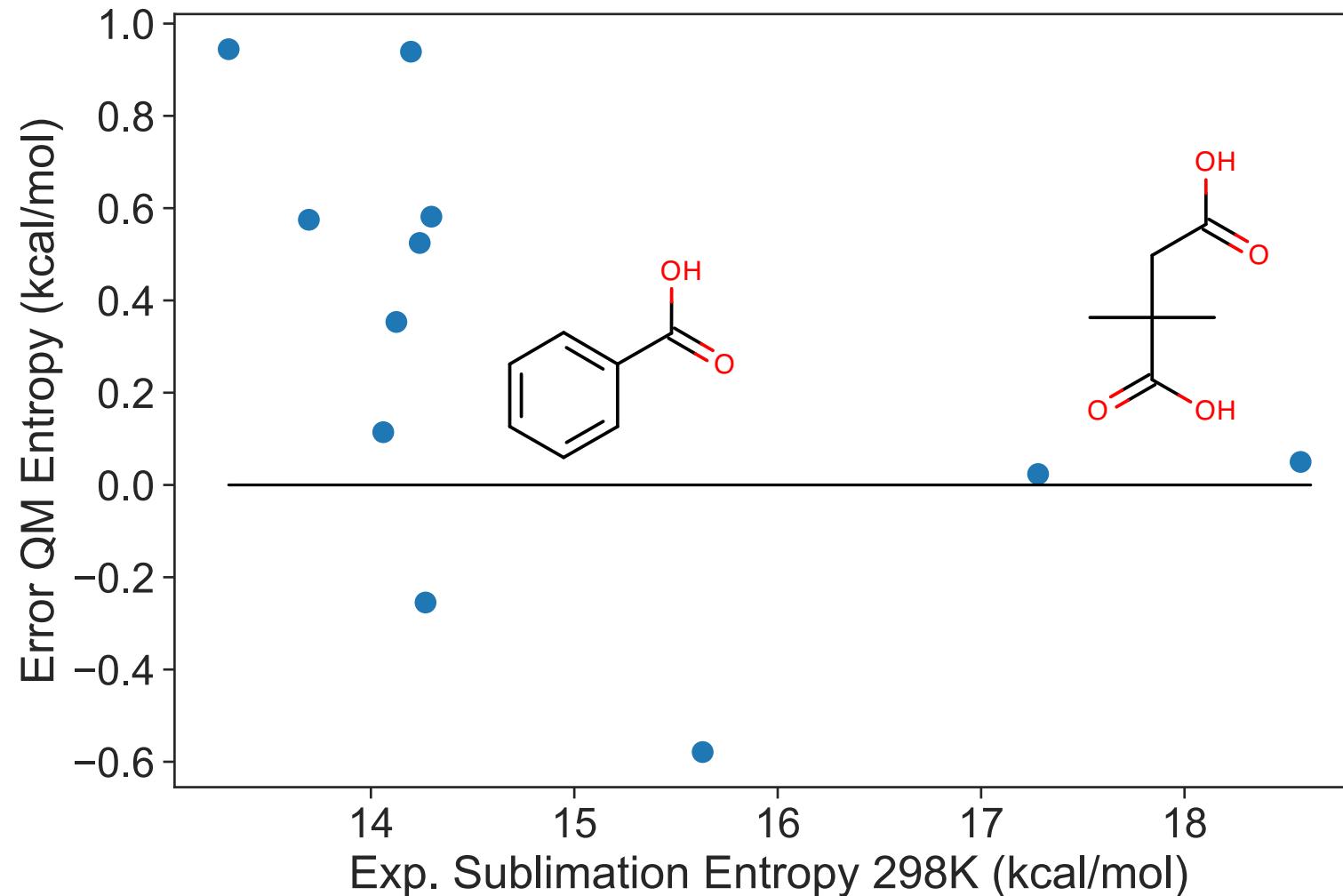
Phonopy displacements in supercell → Calculate gradients on each crystal → Phonopy processes gradients

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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

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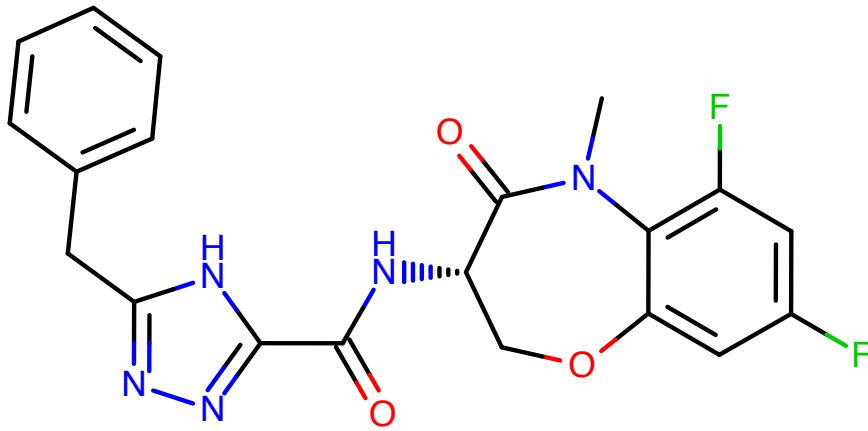
$R^2 = 0.91 \, [0.71, 0.98]$ Robust Error = 0.57 kcal/mol

# Finite Temperature Correction in blind challenge
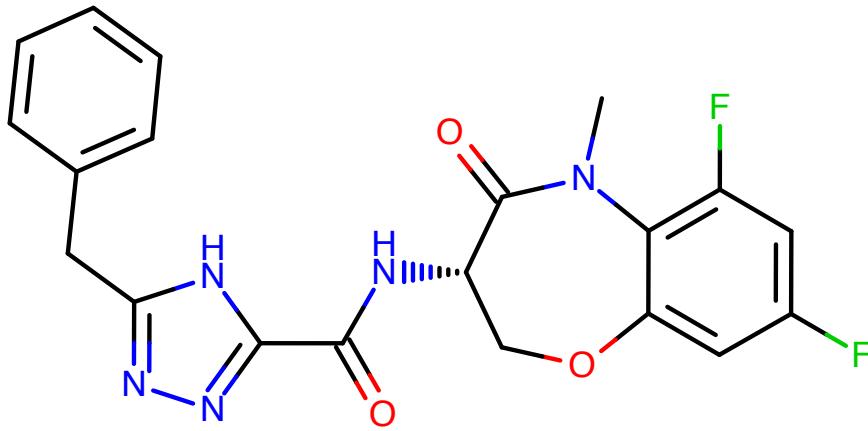
- Druglike molecule from GSK
  - 4 rotatable bonds and flexible ring
  - 3 tautomers

# Finite Temperature Correction in blind challenge
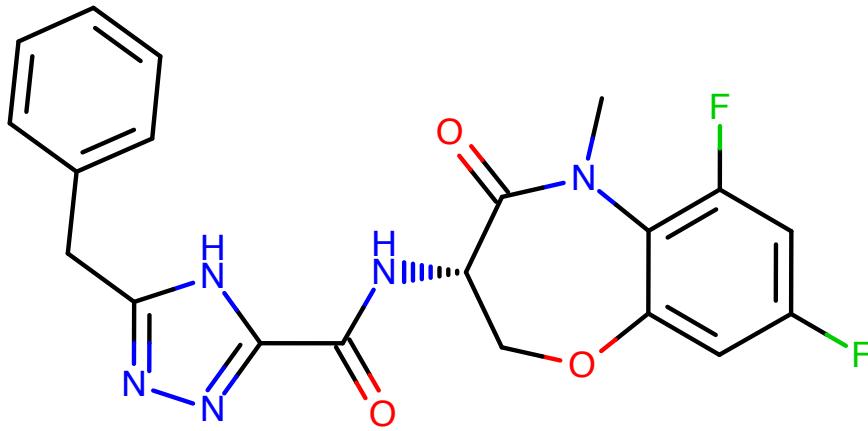
- Druglike molecule from GSK
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  - 3 tautomers
- 2 Blind predictions start with QM enthalpy

# Finite Temperature Correction in blind challenge
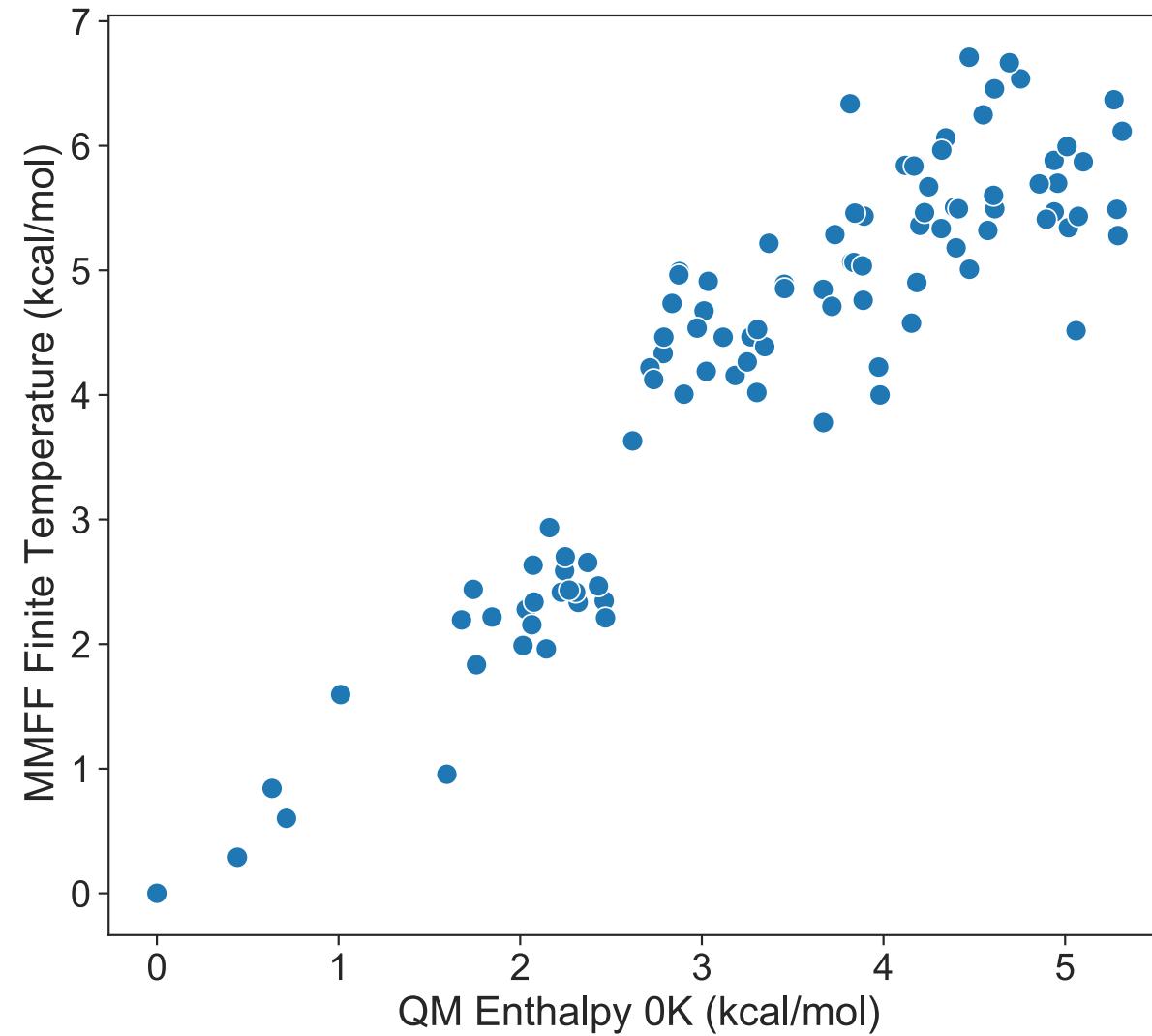
- Druglike molecule from GSK
  - 4 rotatable bonds and flexible ring
  - 3 tautomers
- 2 Blind predictions start with QM enthalpy
  - Force field finite temperature correction

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Finite Temperature Correction in blind challenge
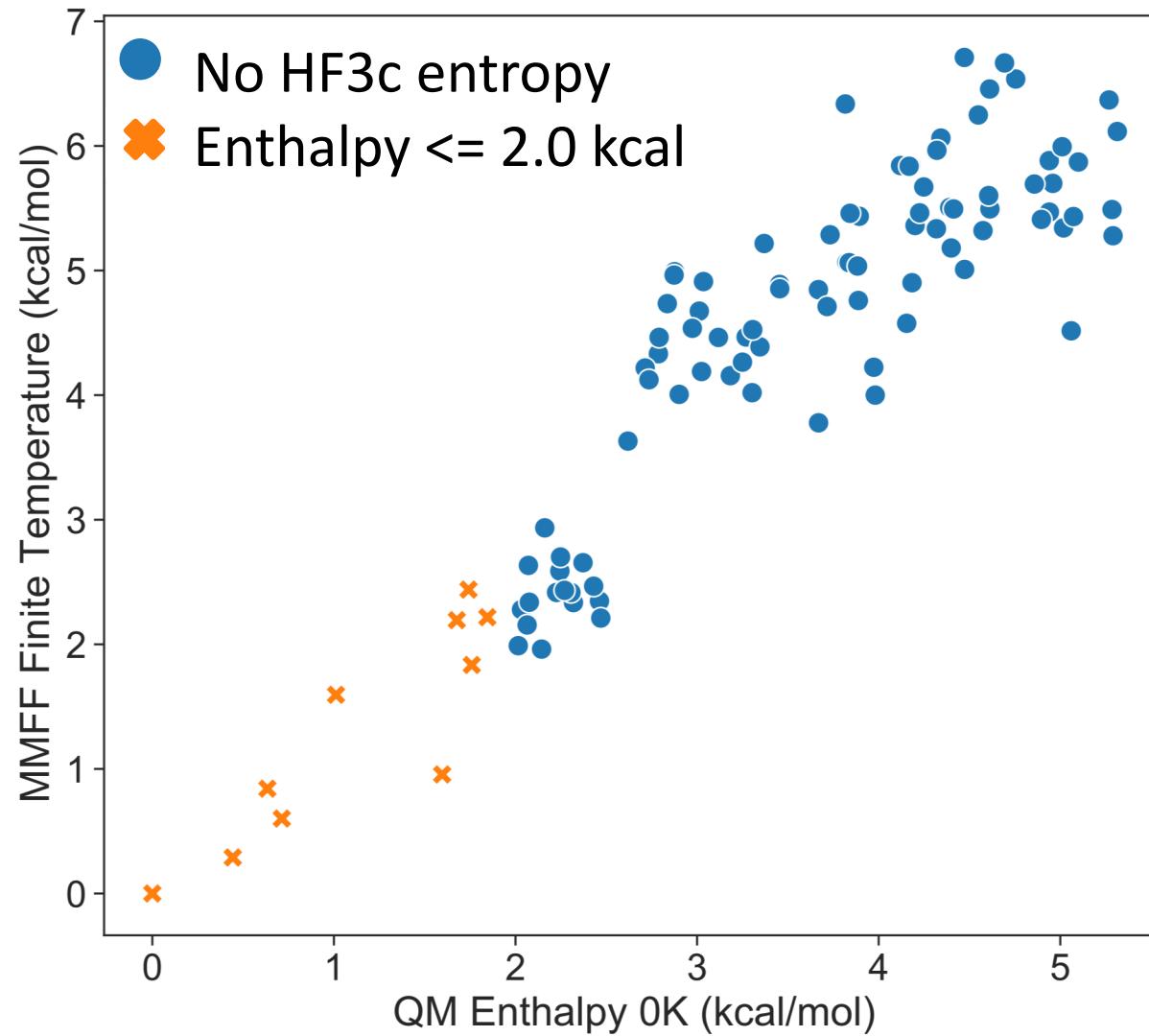
- Druglike molecule from GSK
  - 4 rotatable bonds and flexible ring
  - 3 tautomers
- 2 Blind predictions start with QM enthalpy
  - Force field finite temperature correction
 - Subset with QM finite temperature correction
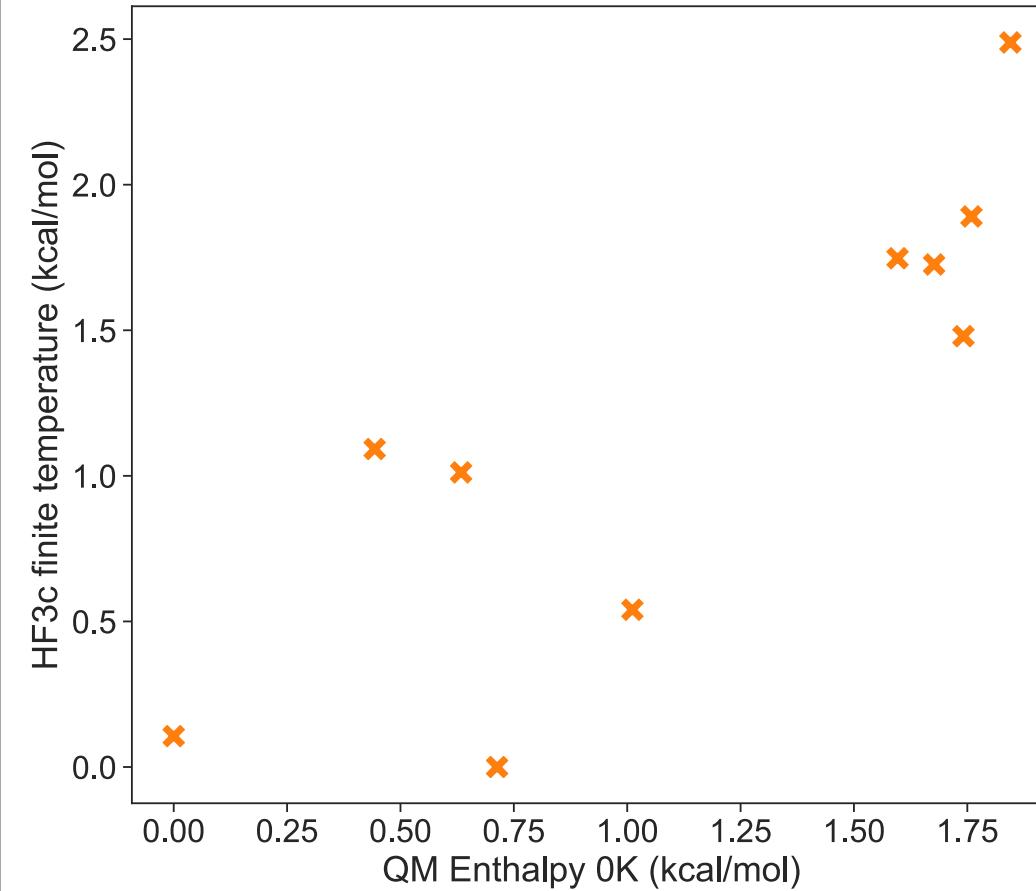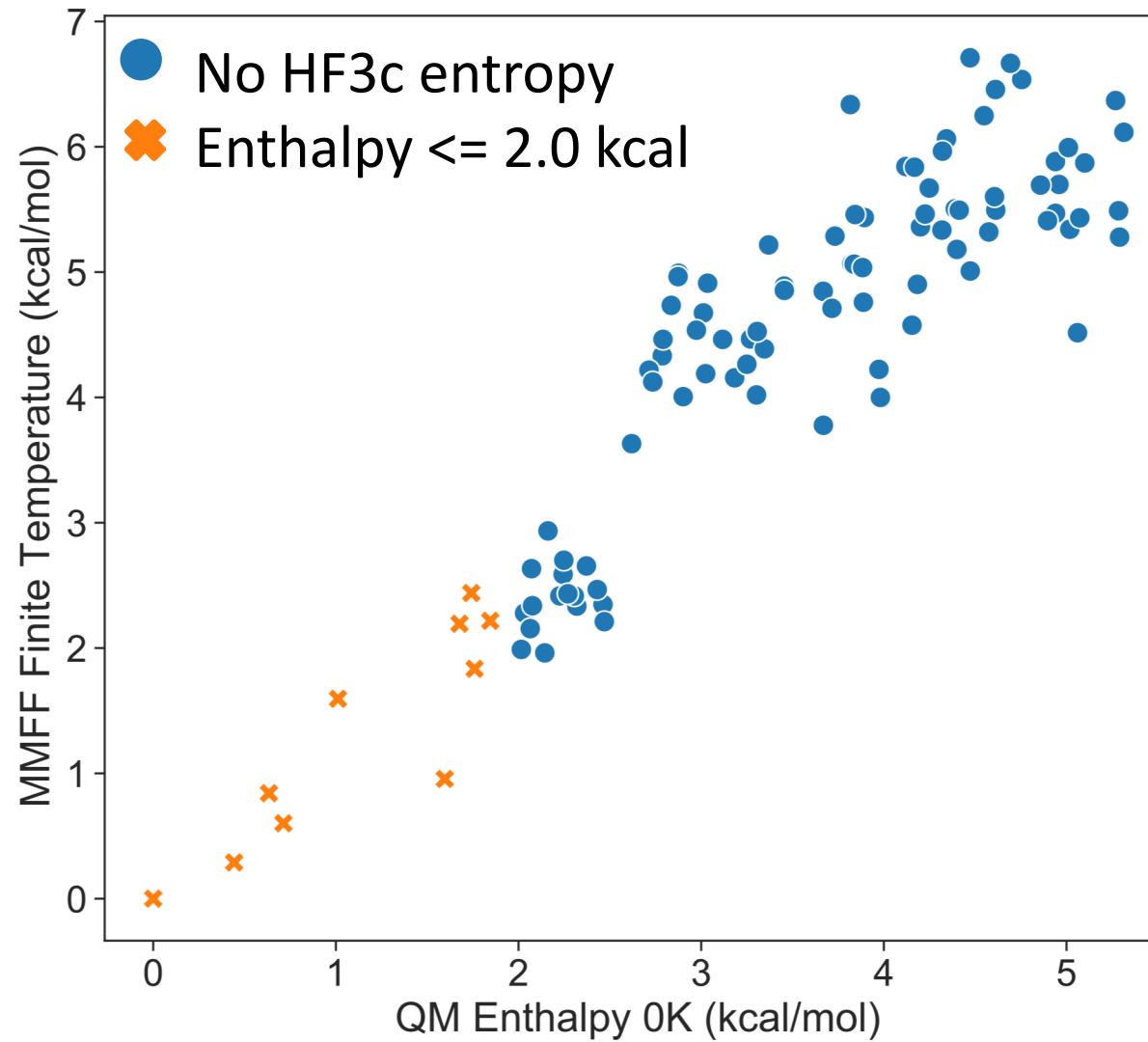
Ranks change with finite temperature corrections
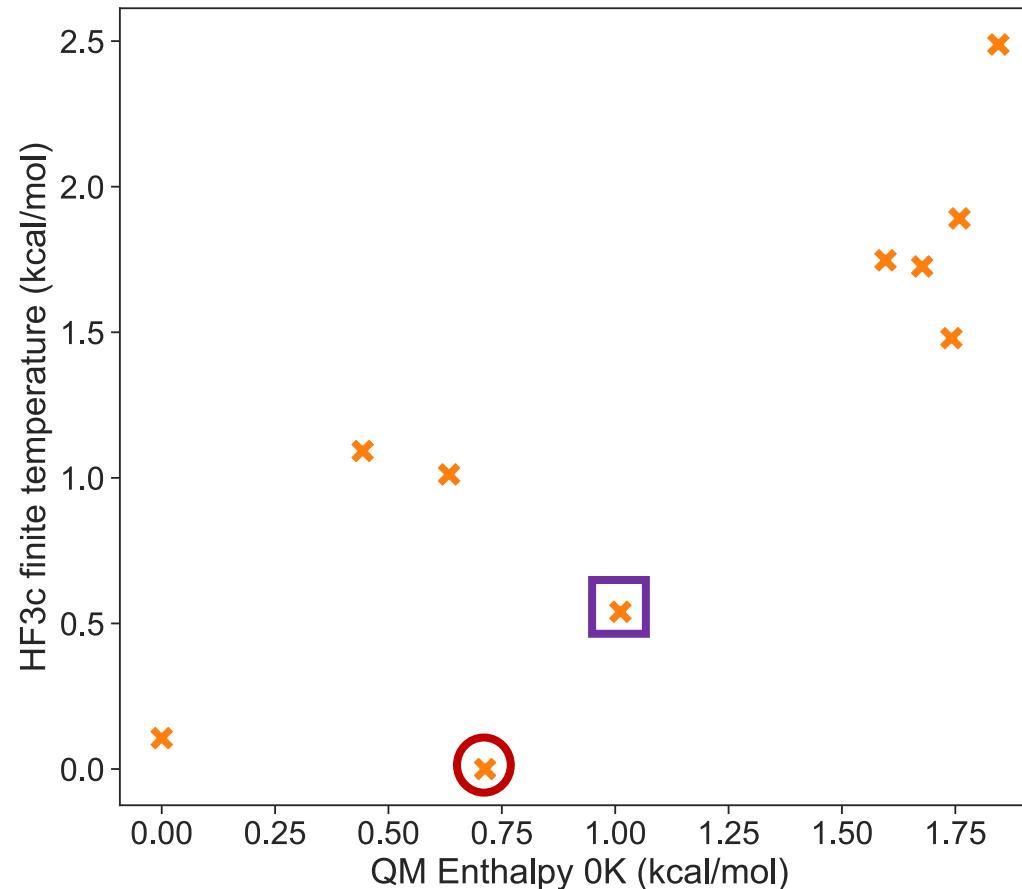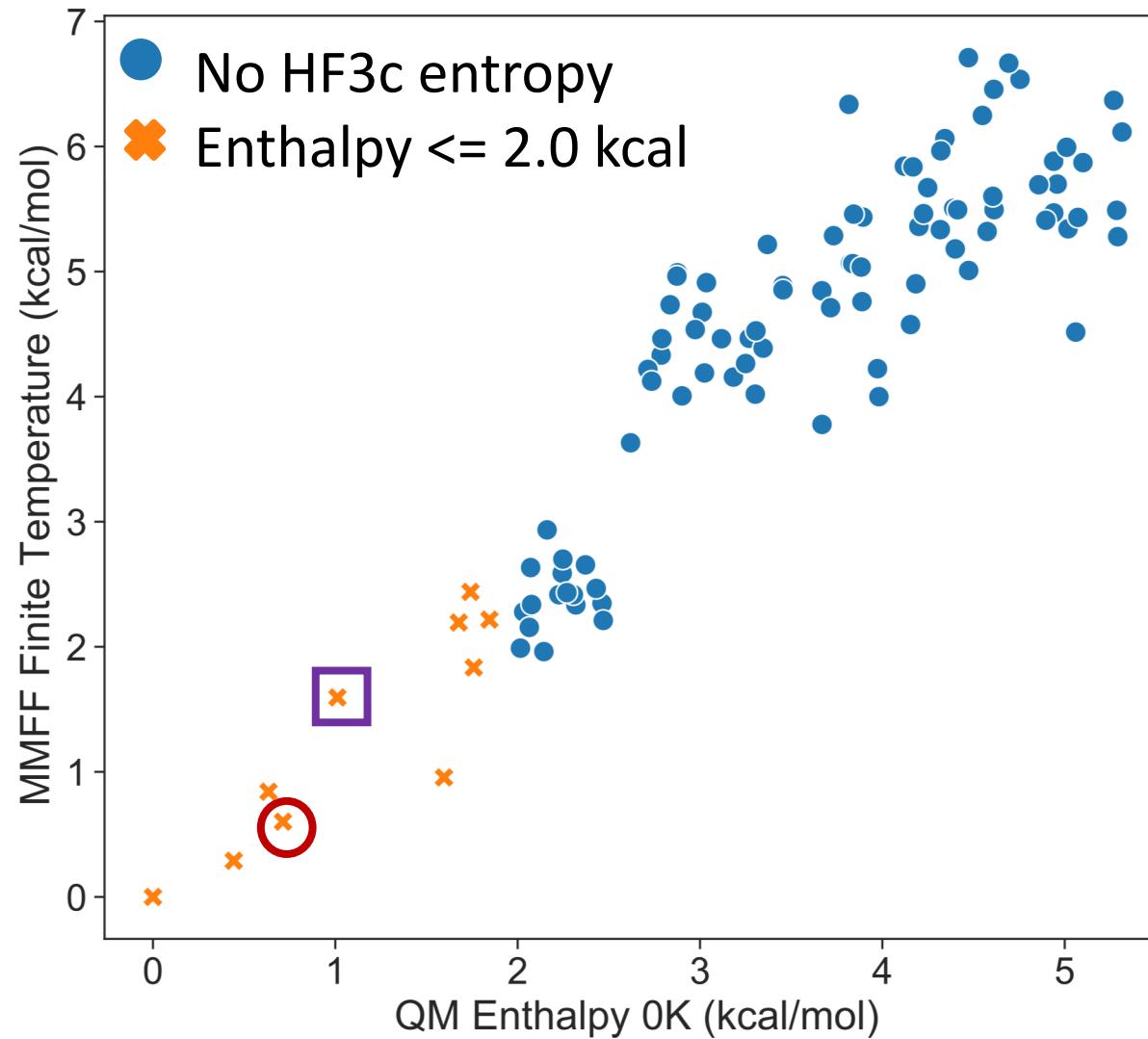
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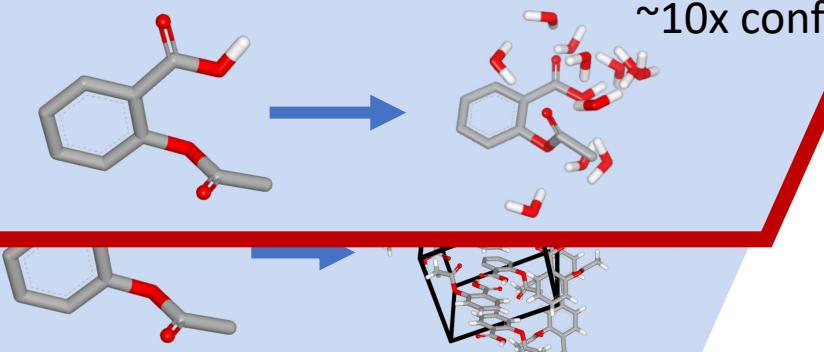
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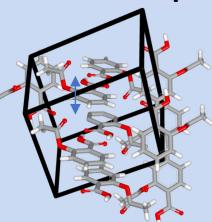
Hit 1: RMSD20 = 0.16   Hit 2: RMSD20 = 0.23

Monohydrate first multi-components crystal prediction
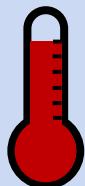
- Sample waters around all conformers
- Pack molecule-water dimers as a single asymmetric unit
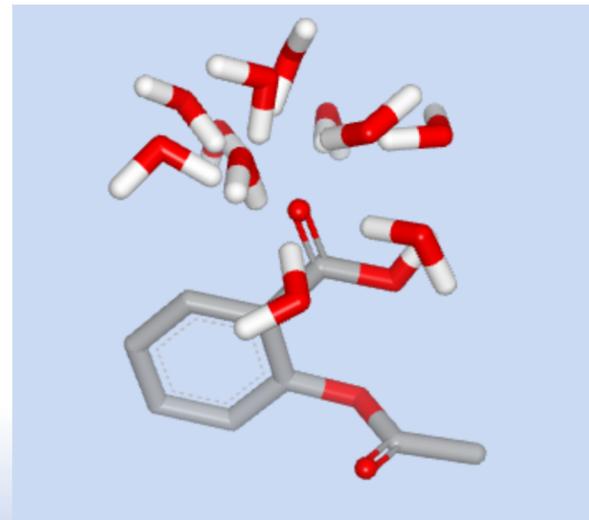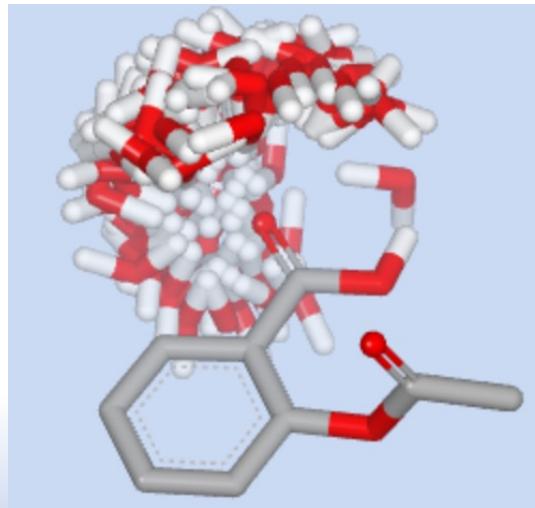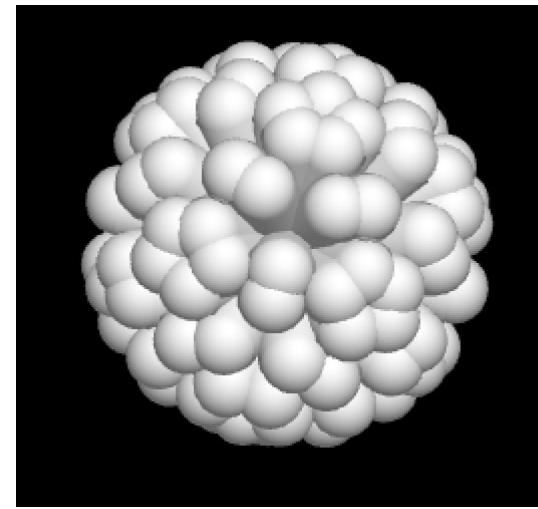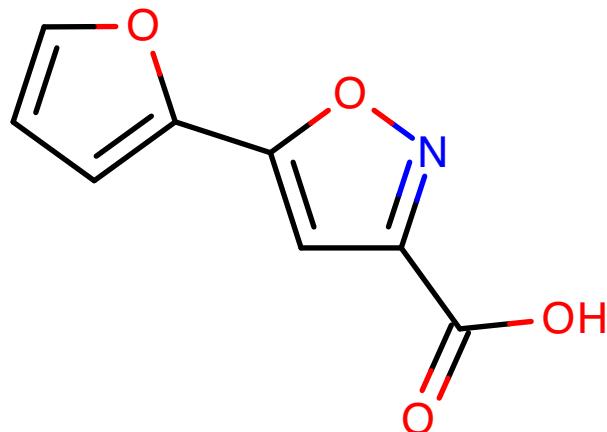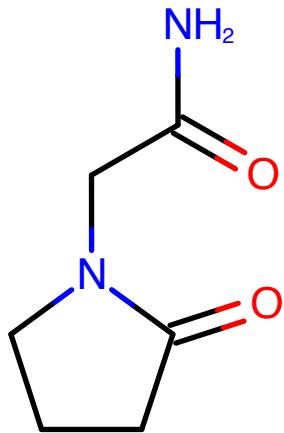
Sample water positions around all donors and acceptors
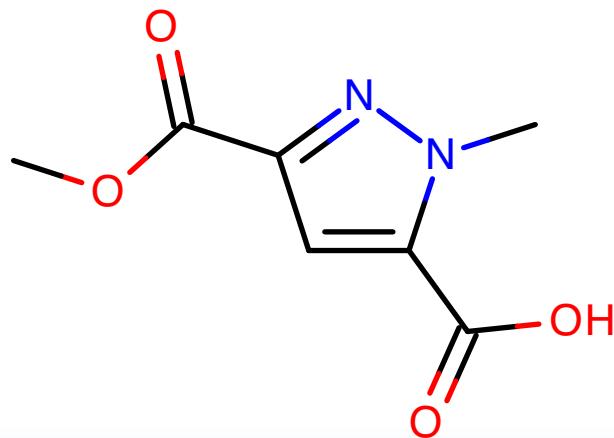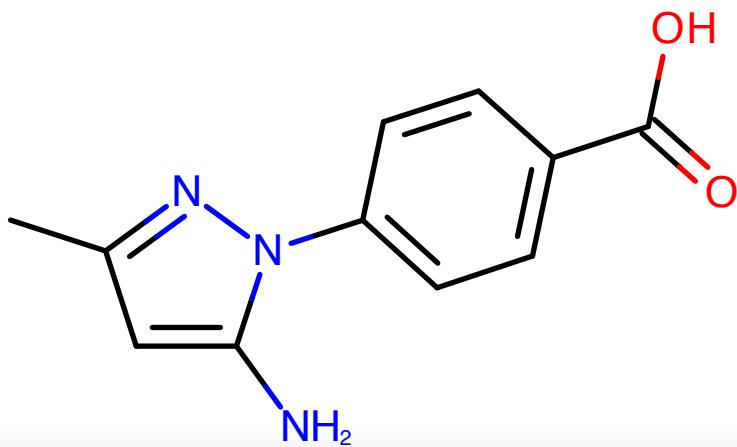
- Generate a set of 60 rotated waters

- Build a grid around each donor and acceptor

- 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
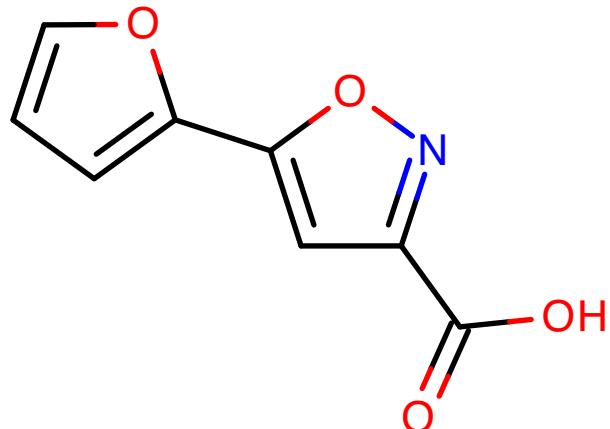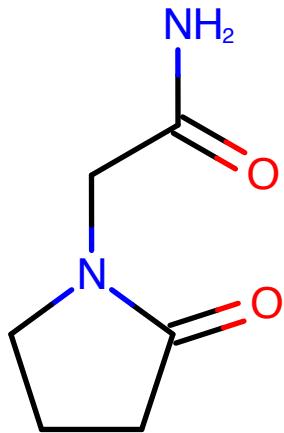
How many waters per site?

Check dimer and FF crystal opt.

How many waters per site?

Check dimer and FF crystal opt.

1. Experimental conformer: N=10?

How many waters per site?


Check dimer and FF crystal opt.

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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?

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?
   b. N=15?

How many waters per site?

Check dimer and FF crystal opt.

1. Experimental conformer: N=10?
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   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?

One monohydrate blind challenge so far
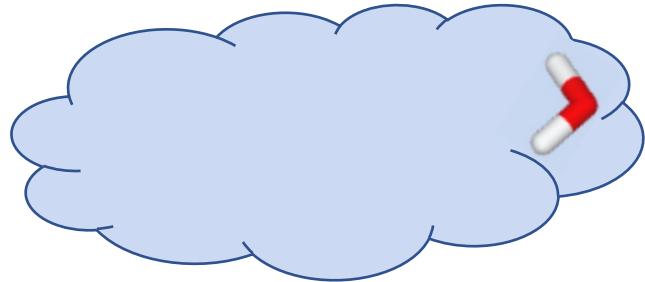
- 1H-bond donor, 5 acceptors

One monohydrate blind challenge so far
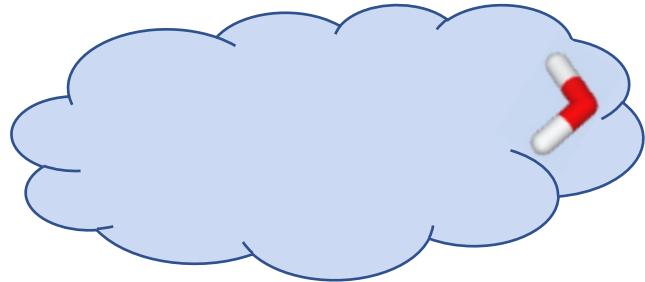
- 1H-bond donor, 5 acceptors
- 100 conformers at 0.5A

One monohydrate blind challenge so far
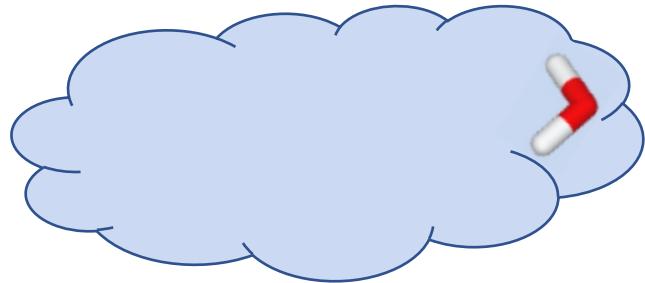
- 1H-bond donor, 5 acceptors

- 100 conformers at 0.5A

- 15 waters/site → 9,000 dimers

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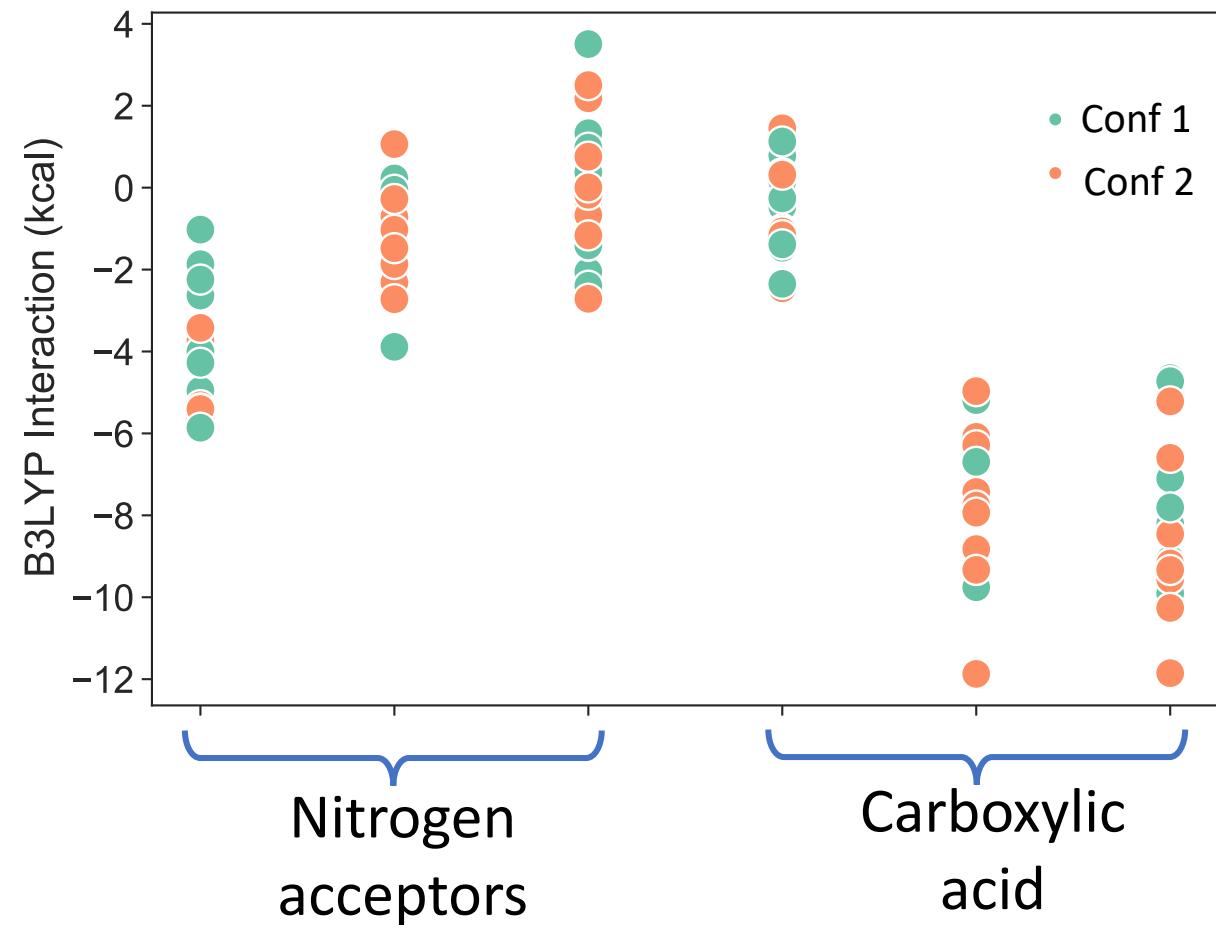
One monohydrate blind challenge so far

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

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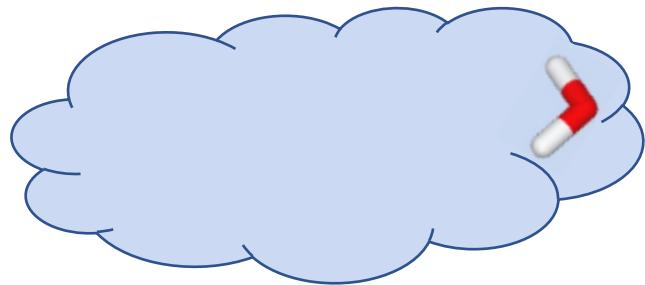
One monohydrate blind challenge so far

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

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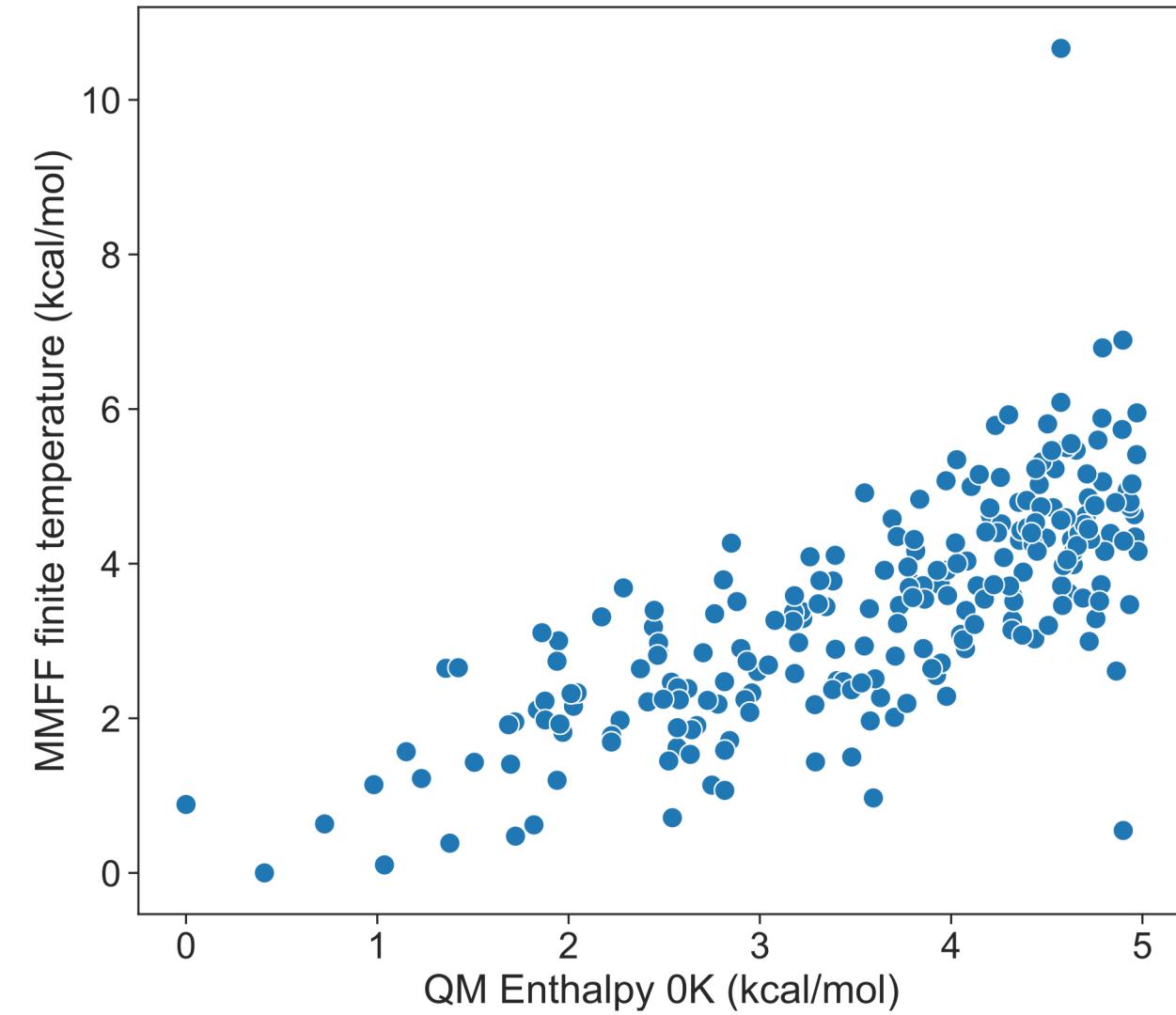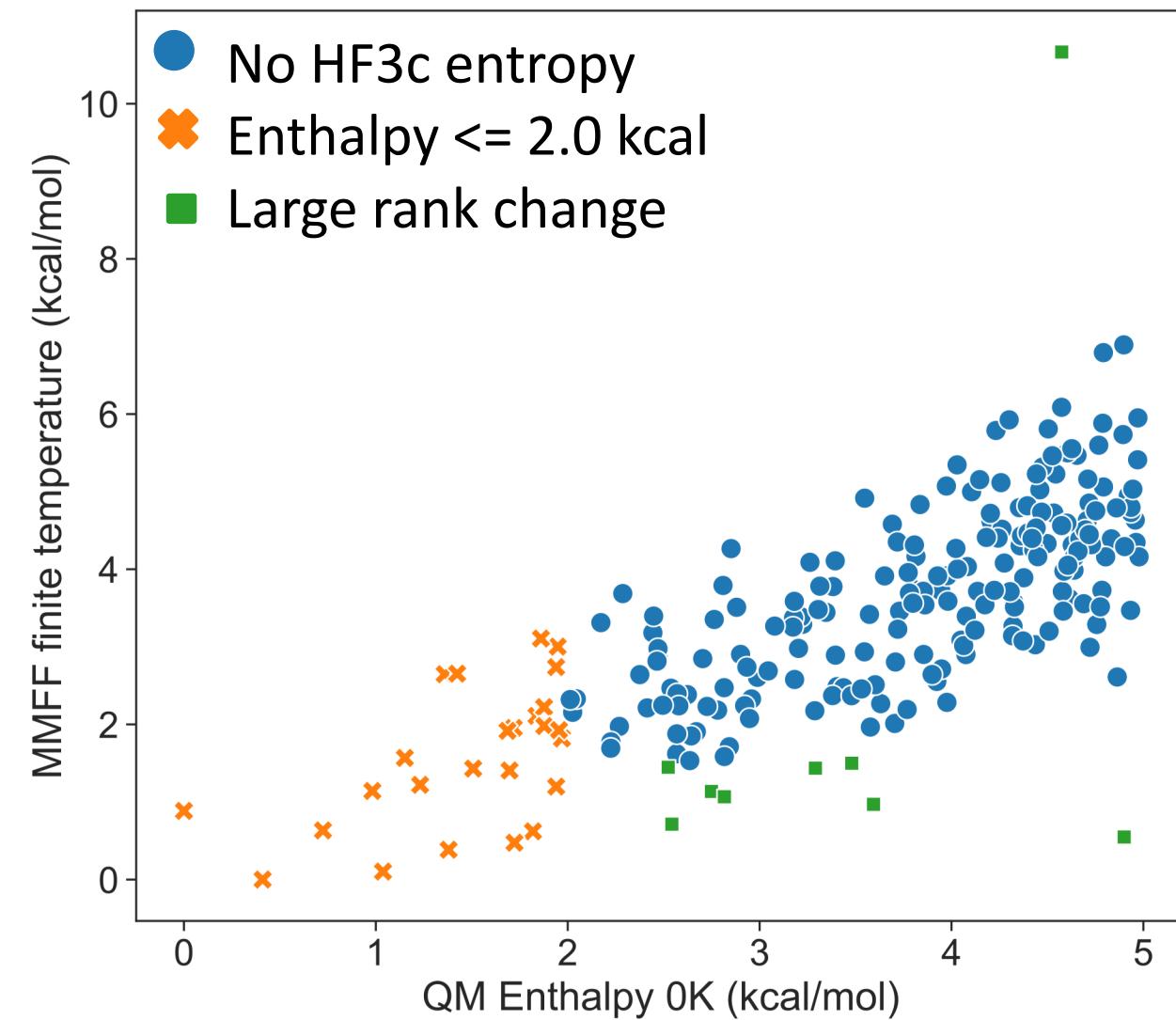
- 1H-bond donor, 5 acceptors
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- Submit MMFF and QM finite temperature predictions
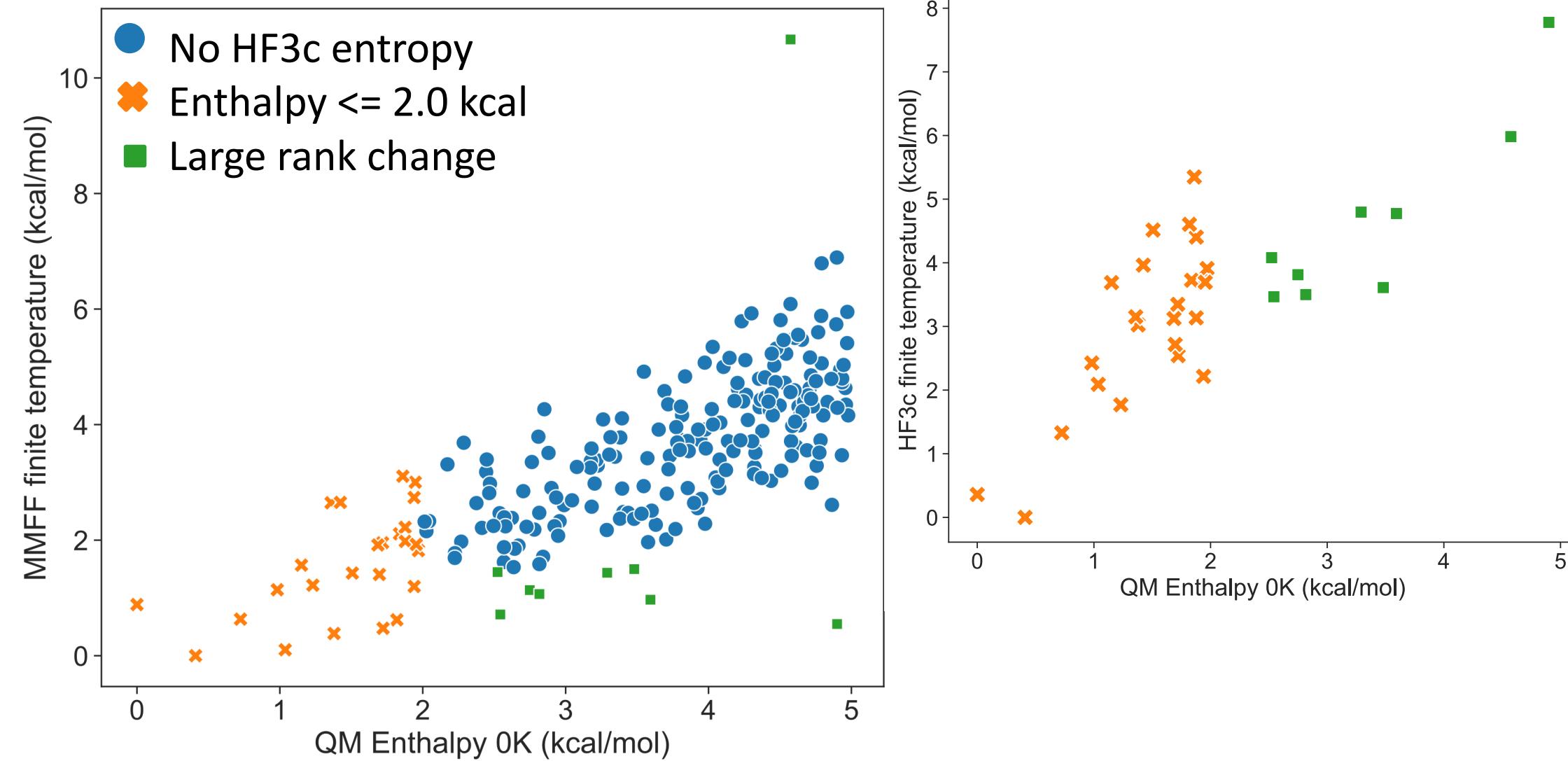
Final monohydrate predictions
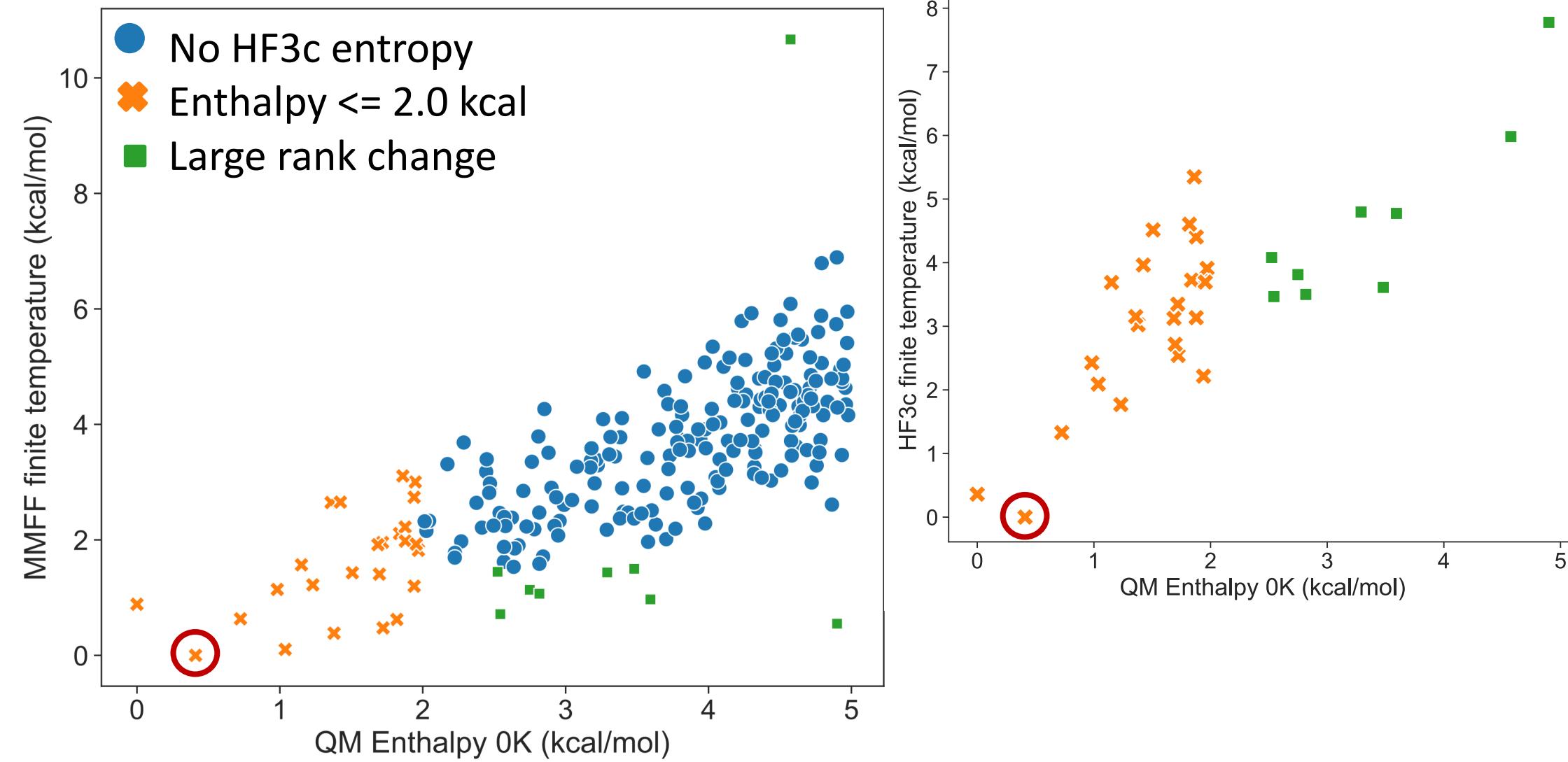
Final monohydrate predictions

Scatter plot. X-axis: QM Enthalpy 0K (kcal/mol), ranging 0 to 5. Y-axis: MMFF finite temperature (kcal/mol), ranging 0 to 10. Legend: blue circle = No HF3c entropy; orange X = Enthalpy <= 2.0 kcal; green square = Large rank change.

Final monohydrate predictions

Final monohydrate predictions

# Is sampling around donors and acceptors enough?

- 81 drug molecules from CSD with monohydrate structures

- 165 crystal structures

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Is sampling around donors and acceptors enough?

- 81 drug molecules from CSD with monohydrate structures

- 165 crystal structures → 164 have water near a donor or acceptor

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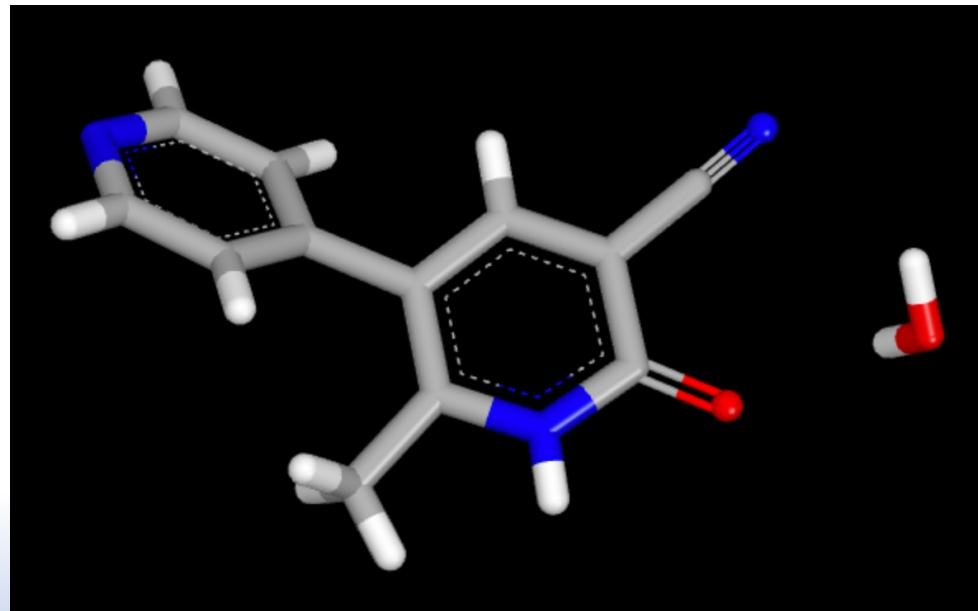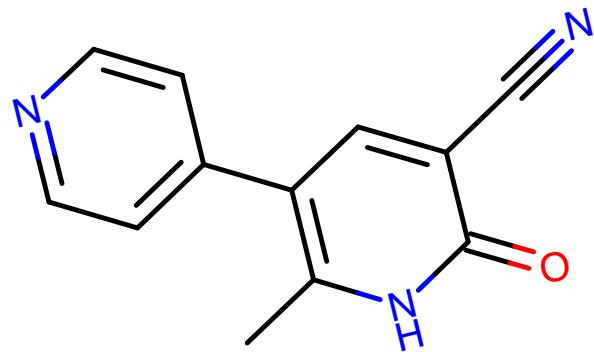
Is sampling around donors and acceptors enough?

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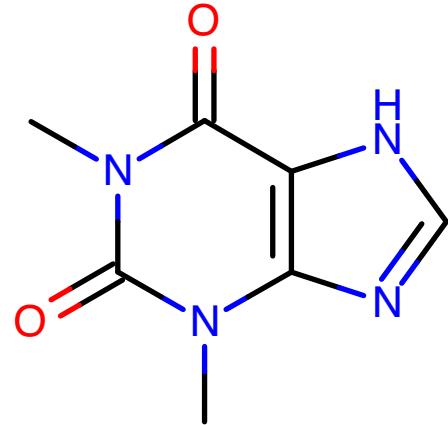
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- 5 monohydrate polymorphs
 - 1 has no H-bonds

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# Is sampling around donors and acceptors enough?

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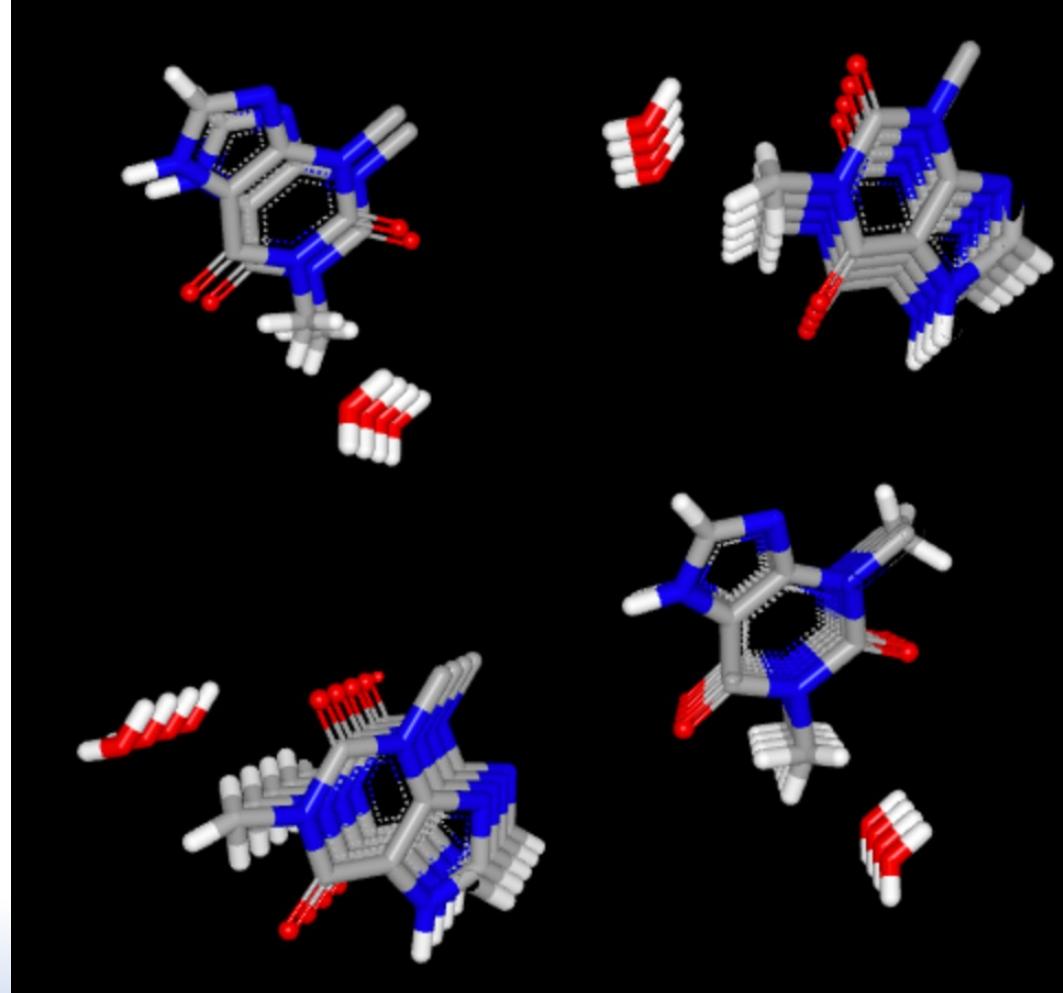
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# Is sampling around donors and acceptors enough?
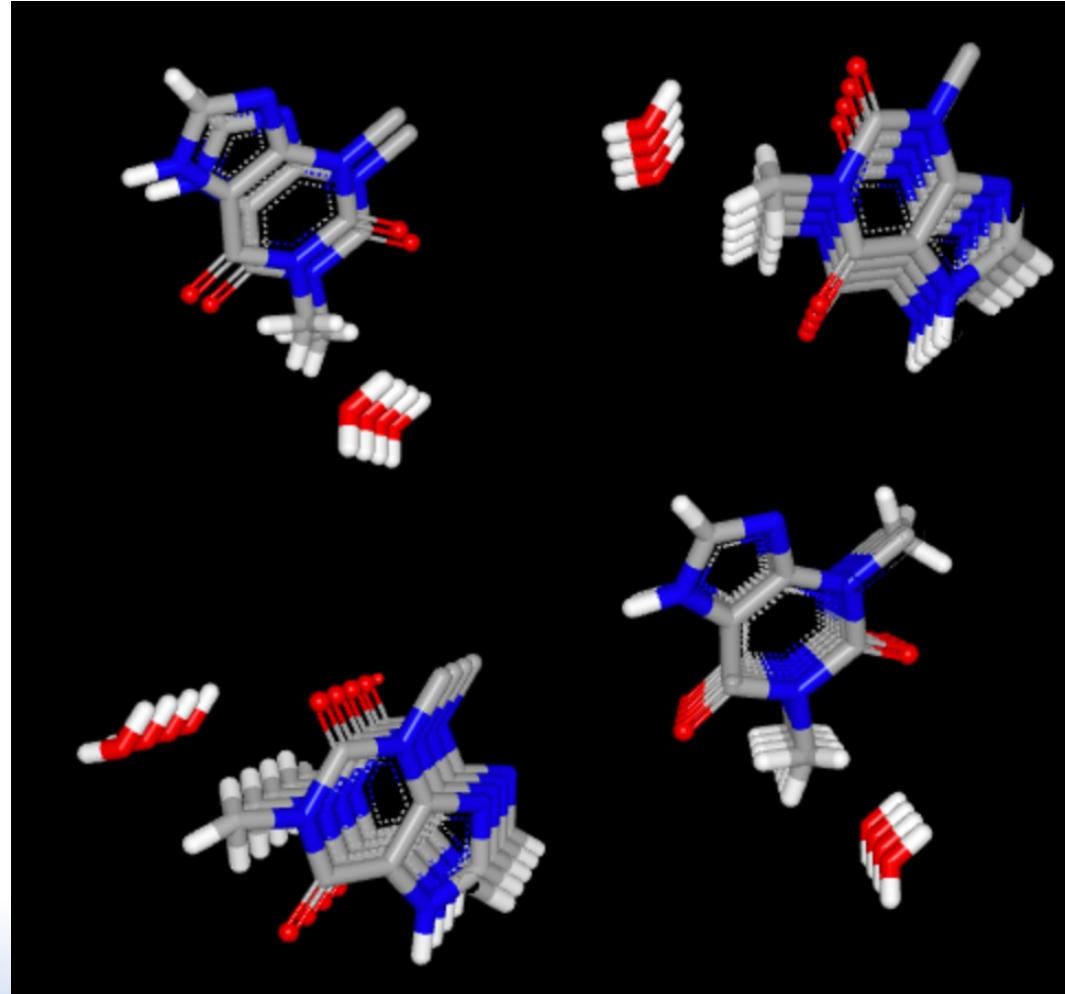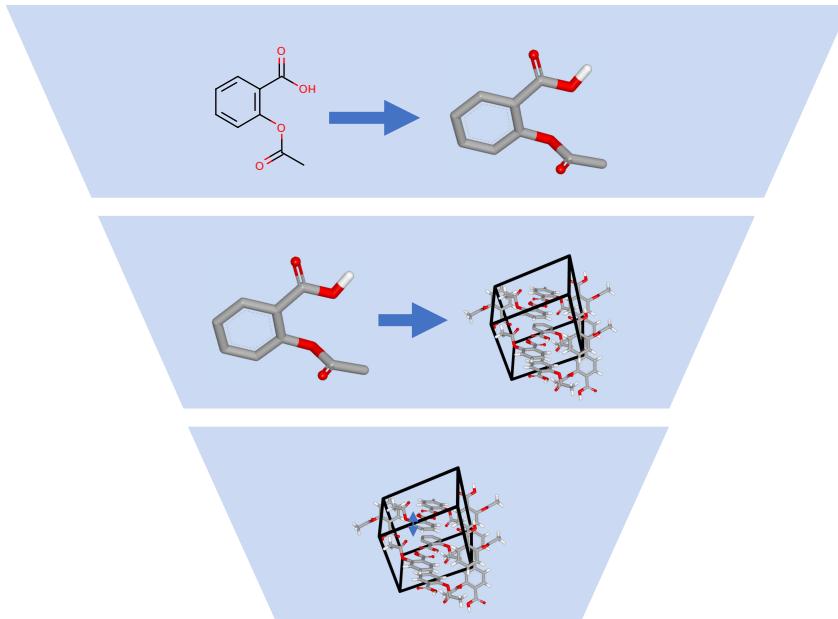
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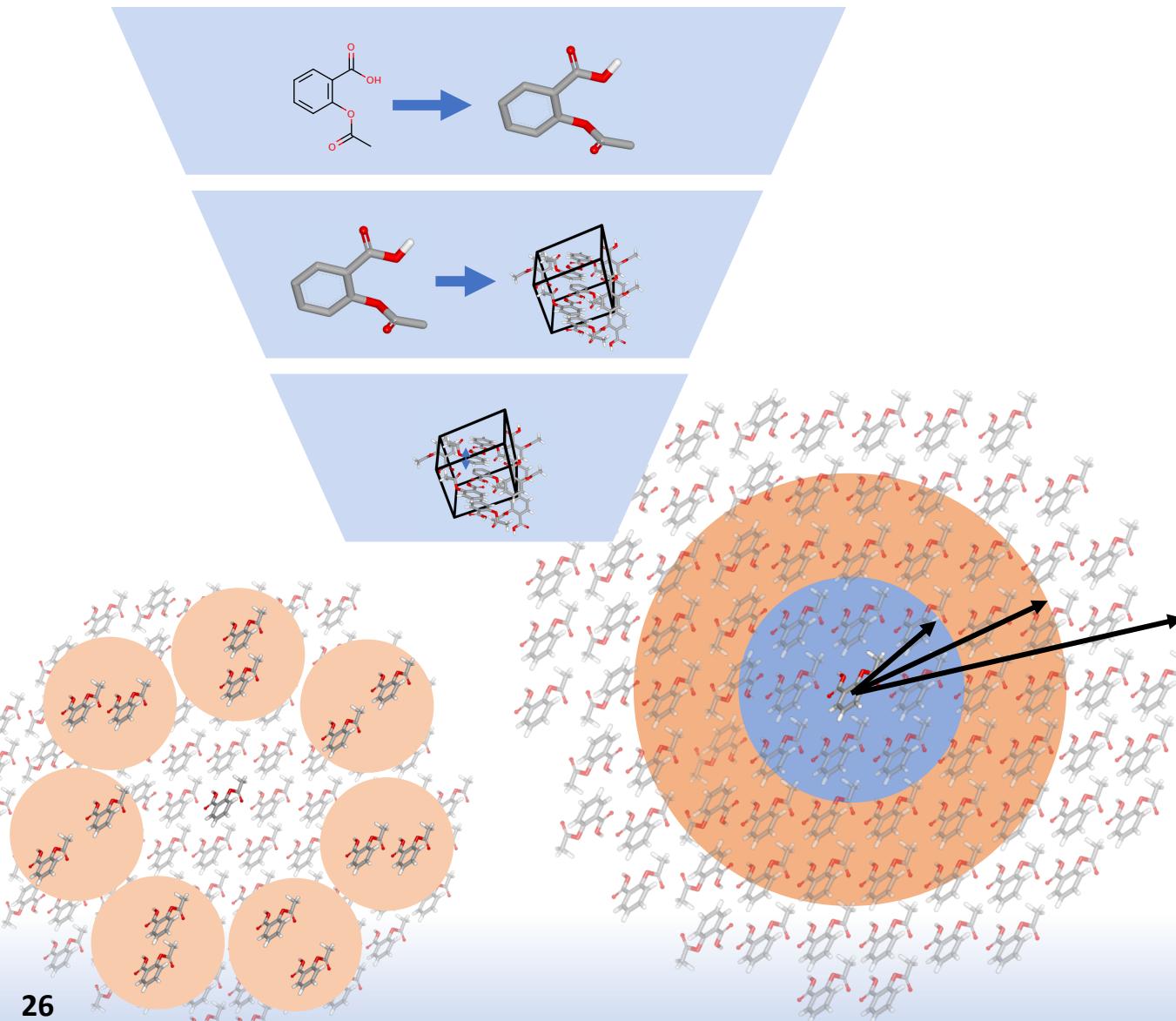
- 5 monohydrate polymorphs
 - 1 has no H-bonds
- Density = 0.717 g/mL
- Deposited in 1971
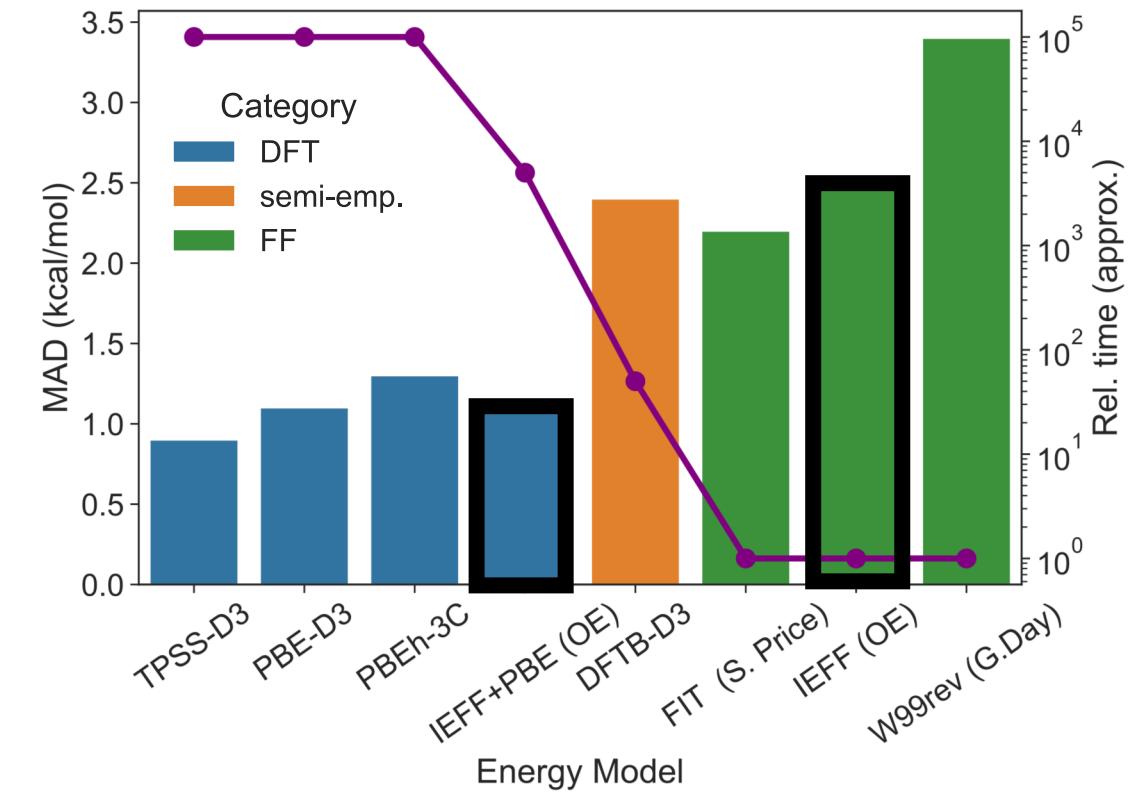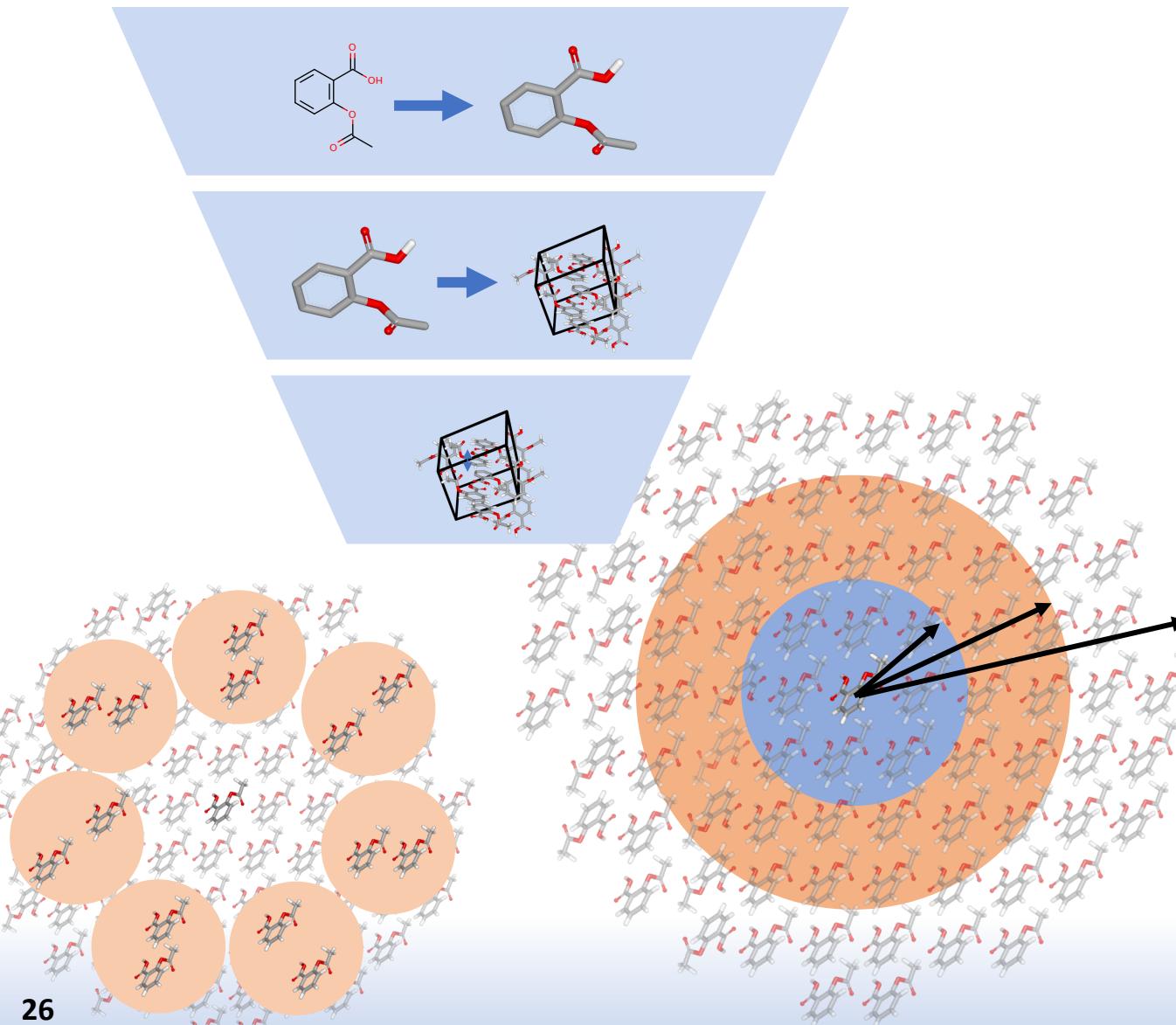
Summary and next steps
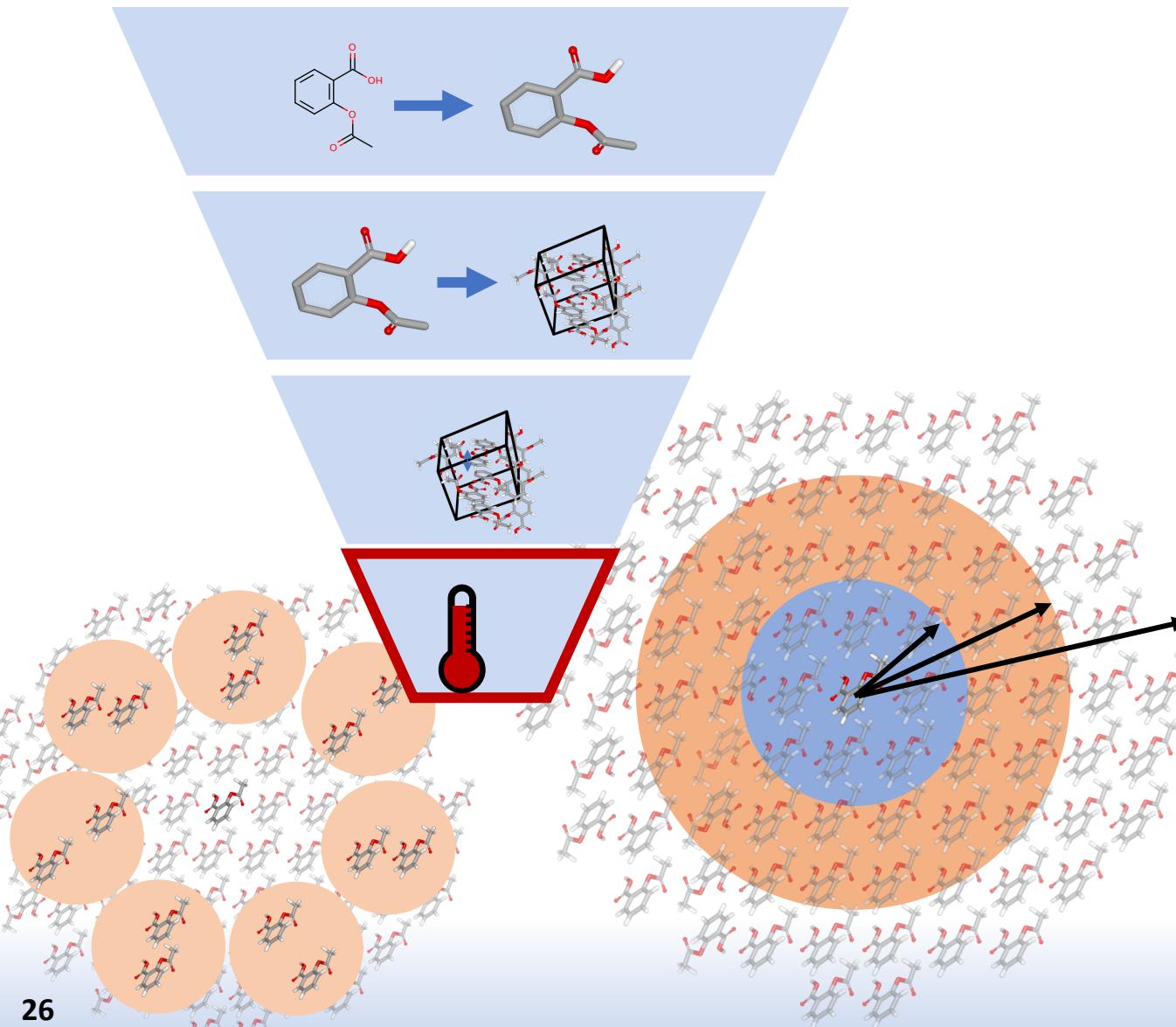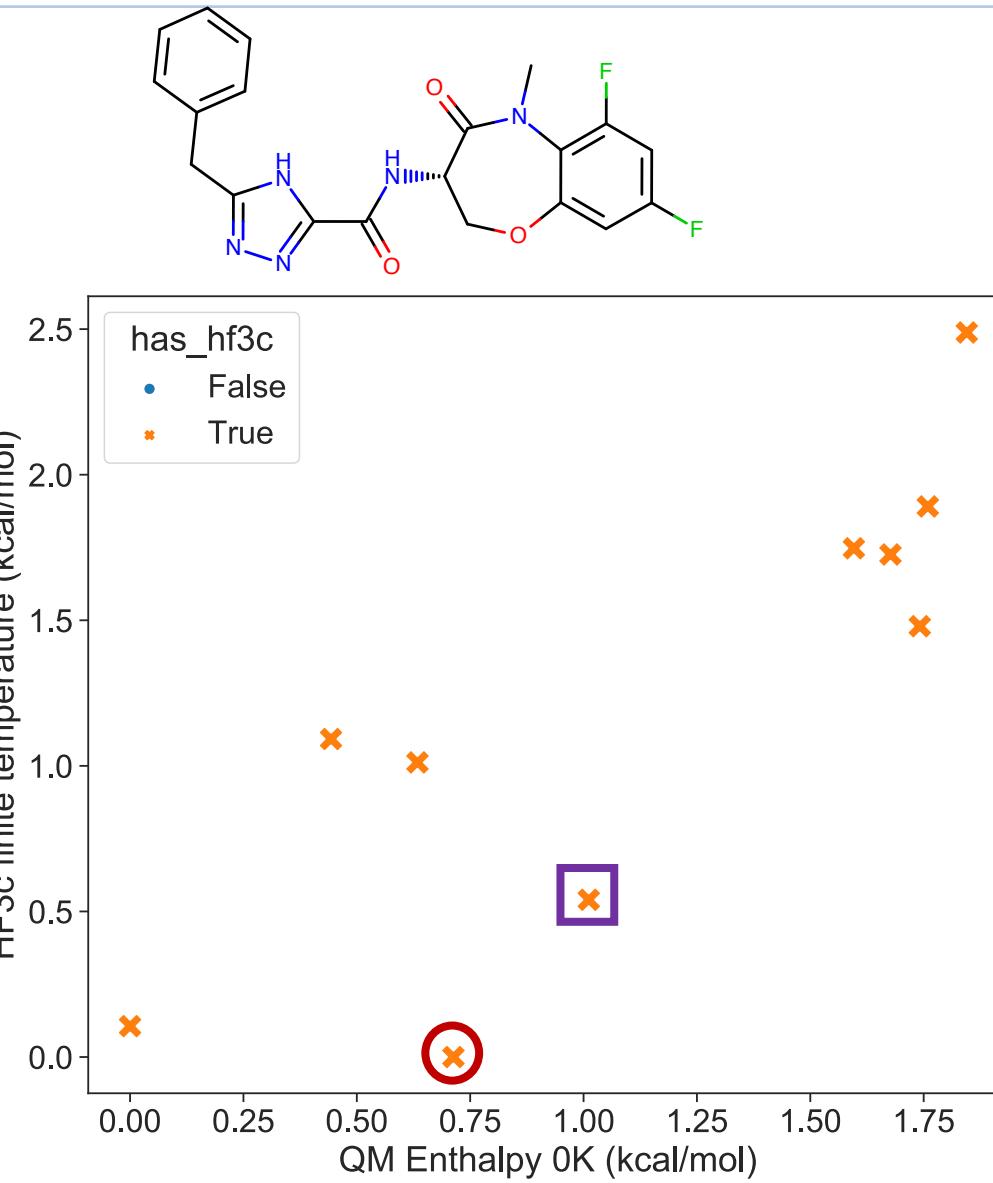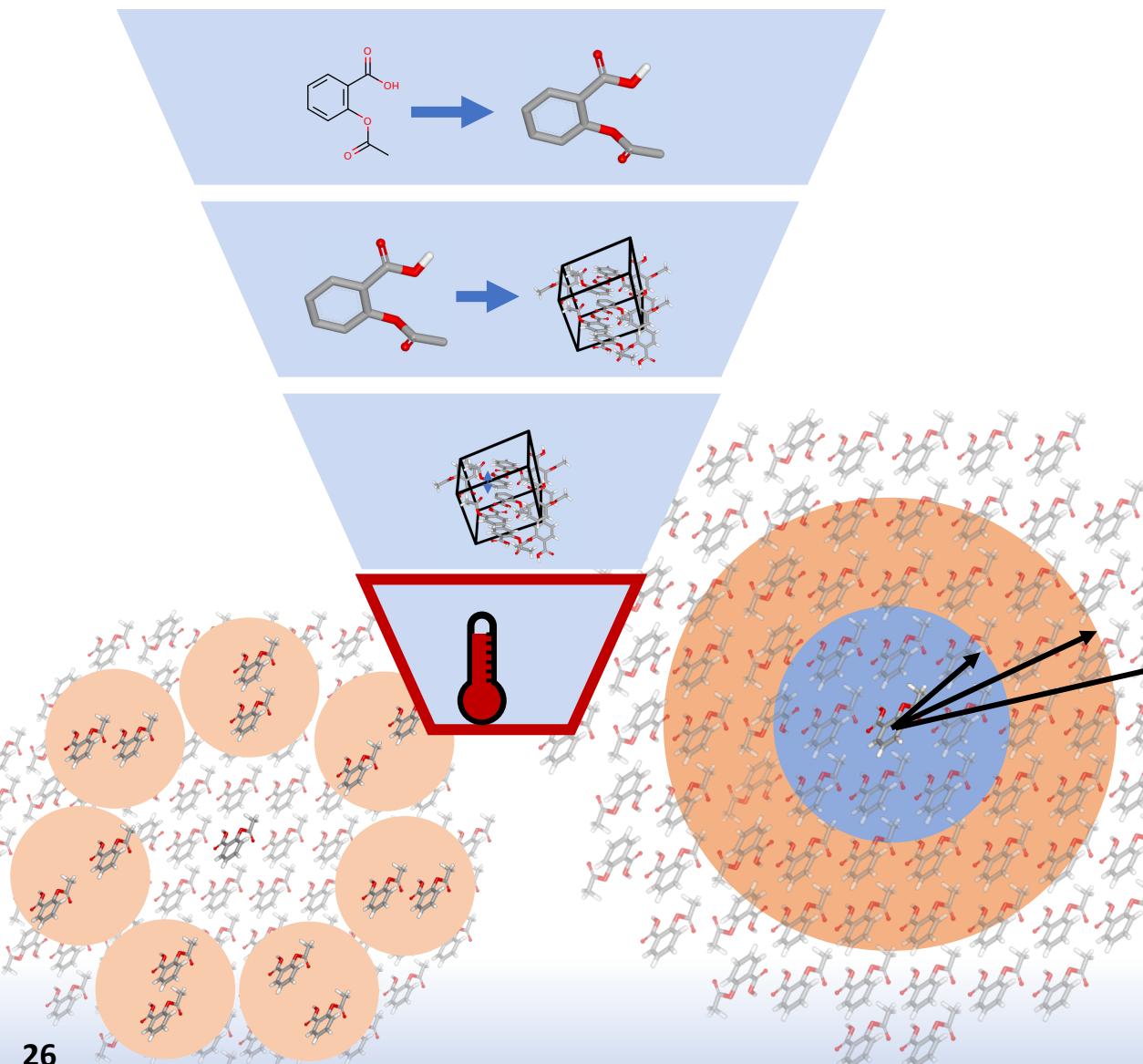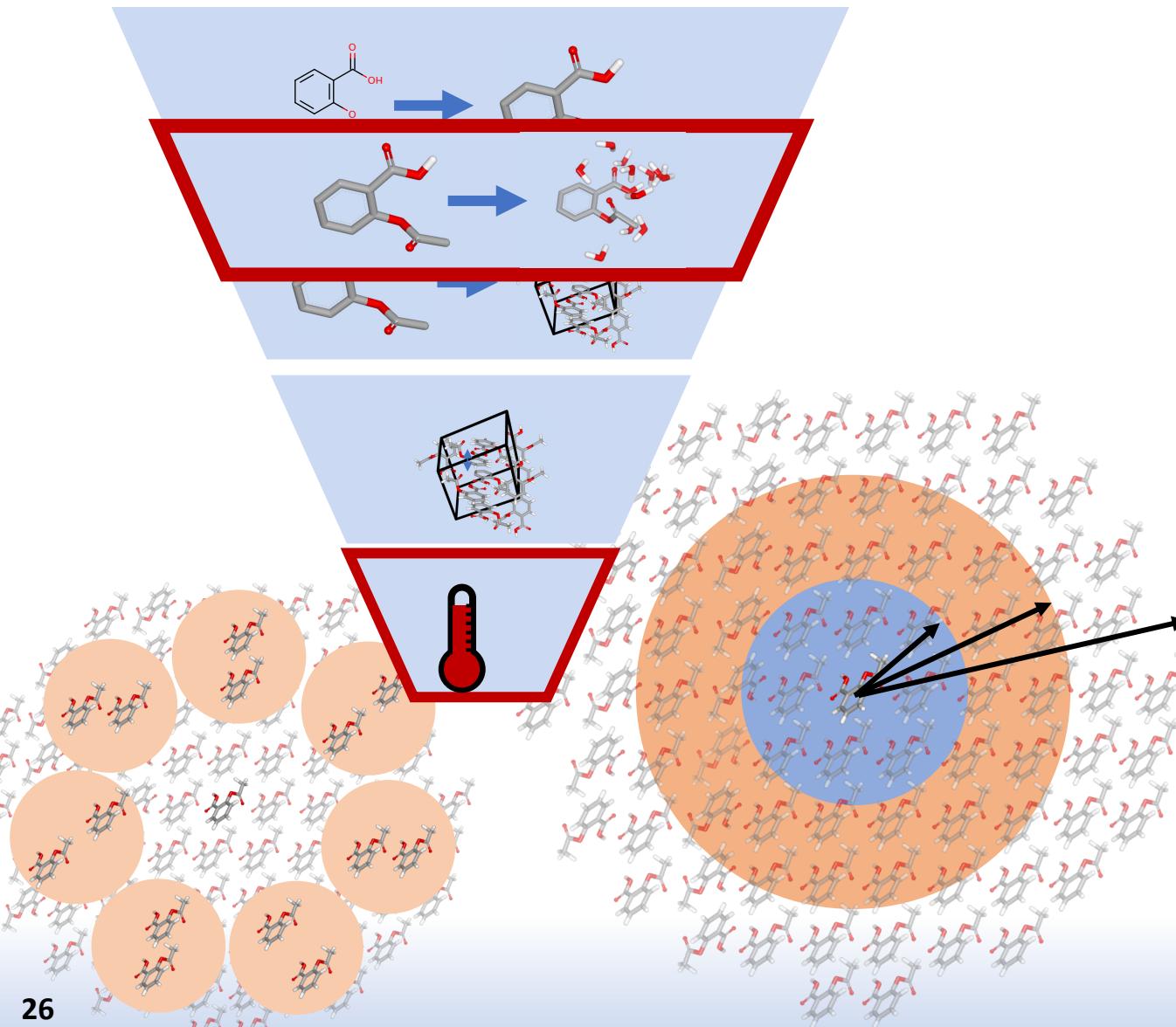
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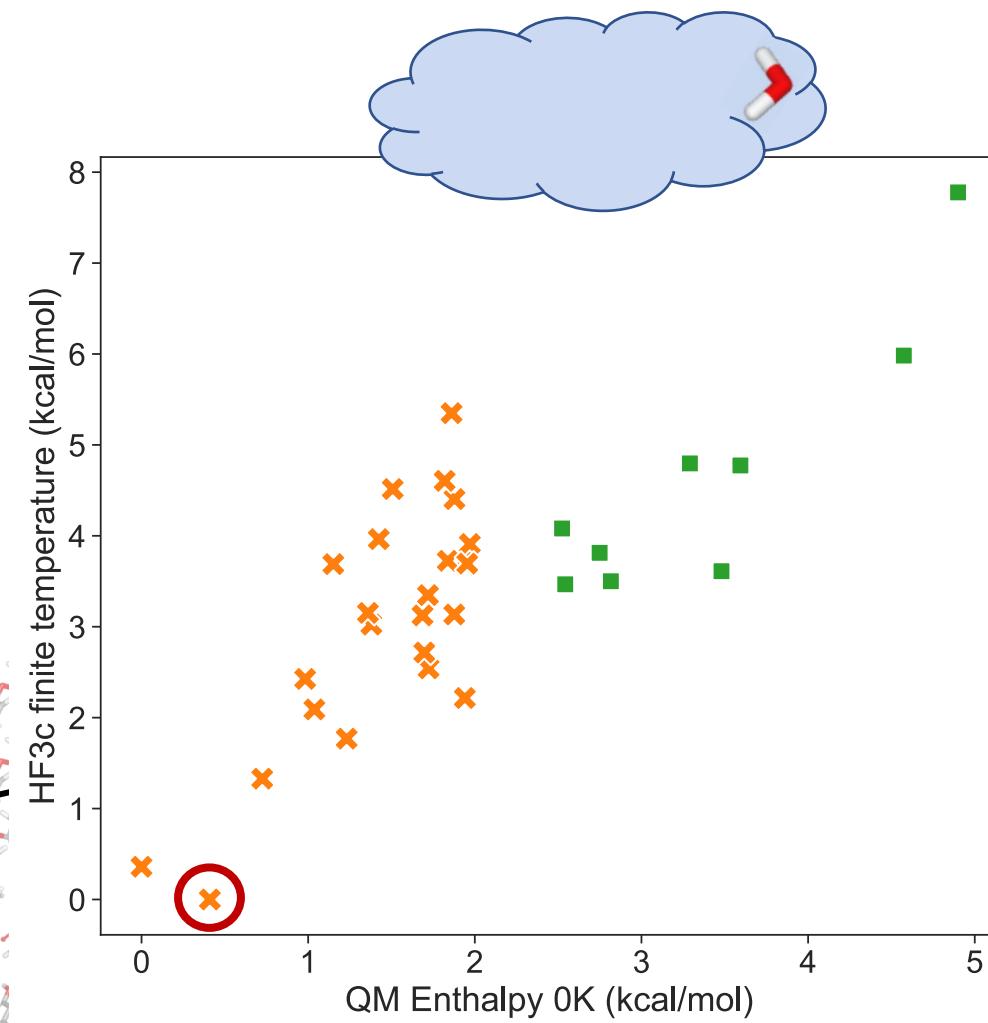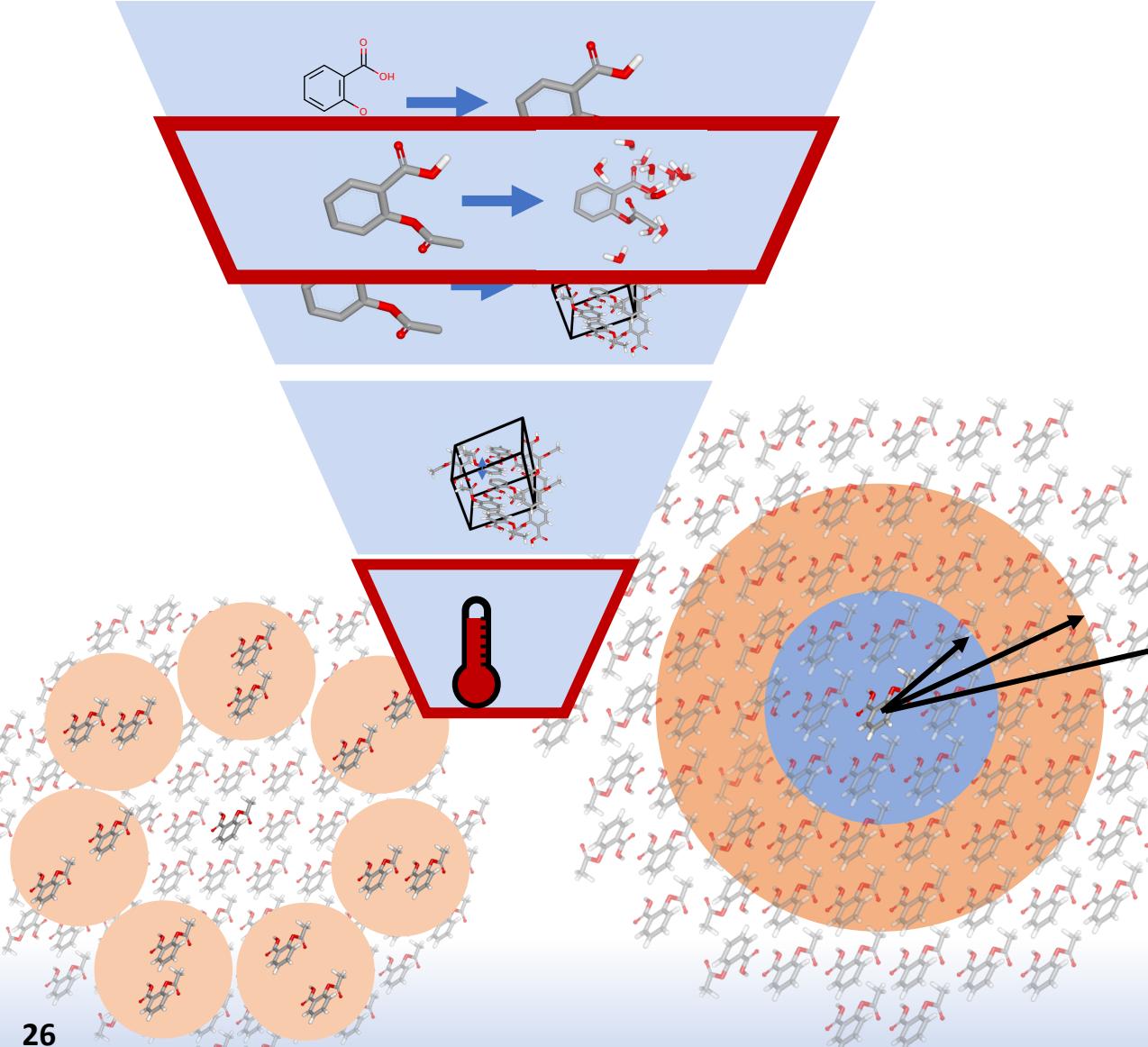
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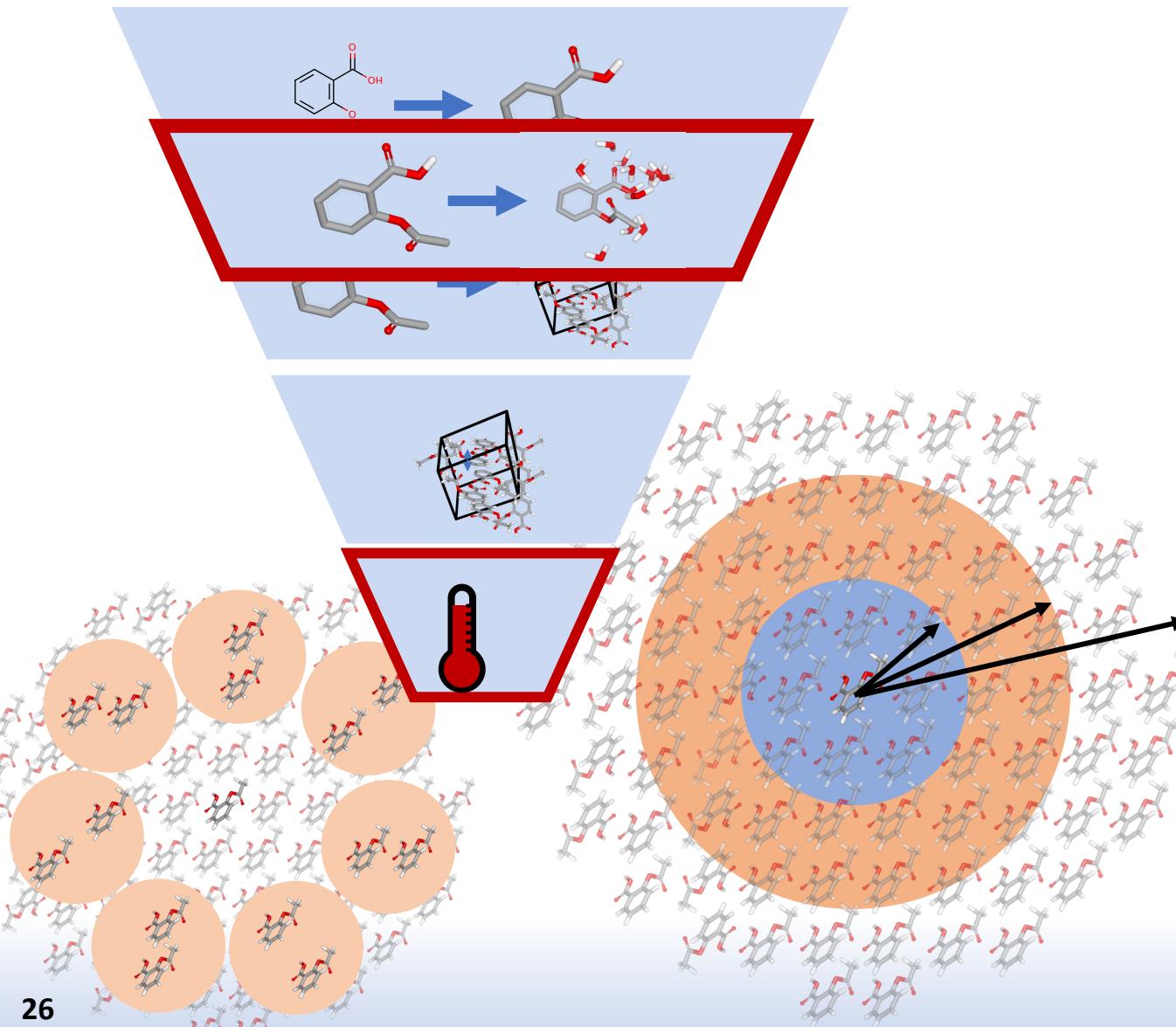
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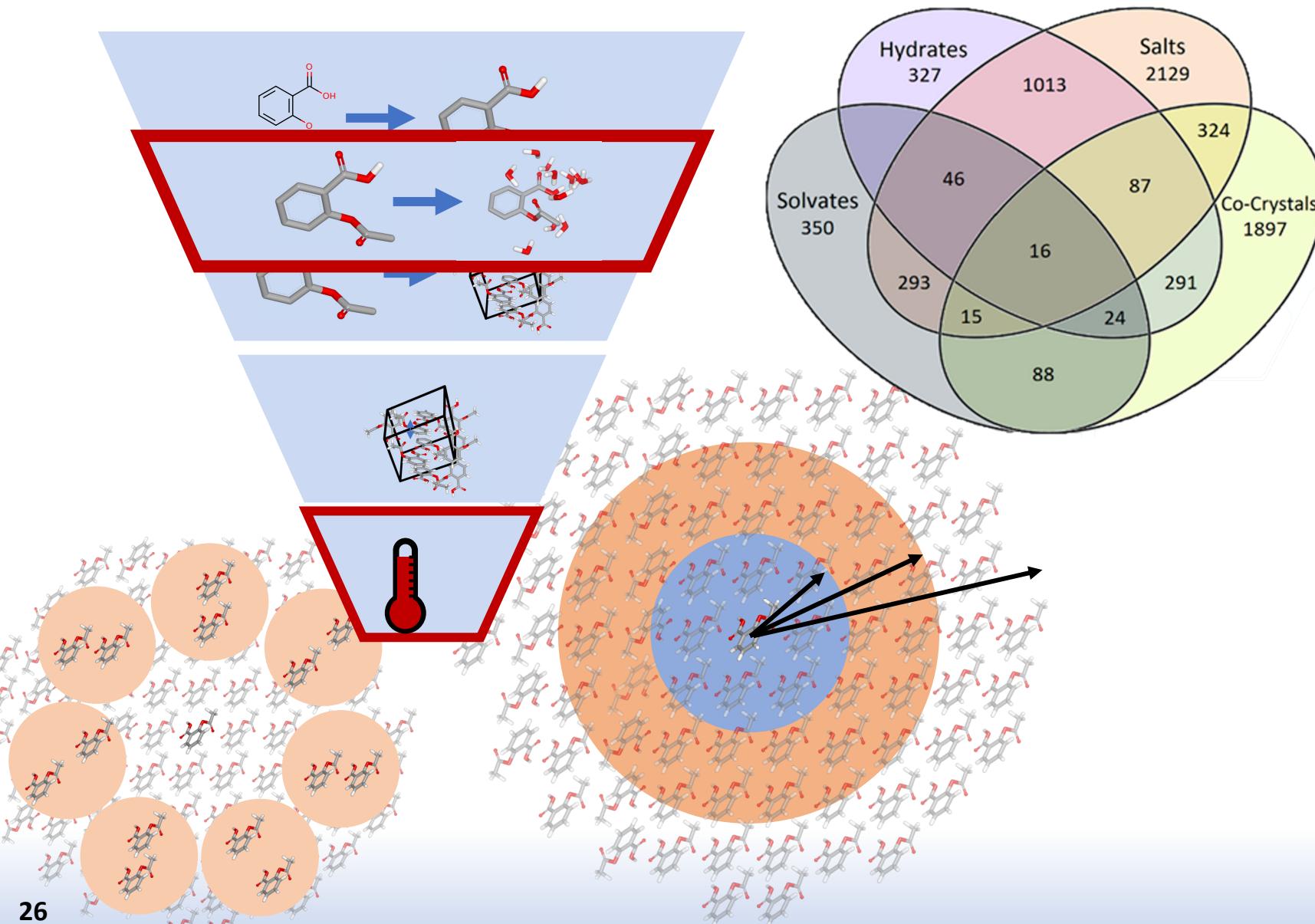
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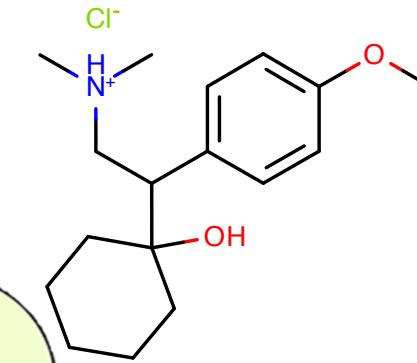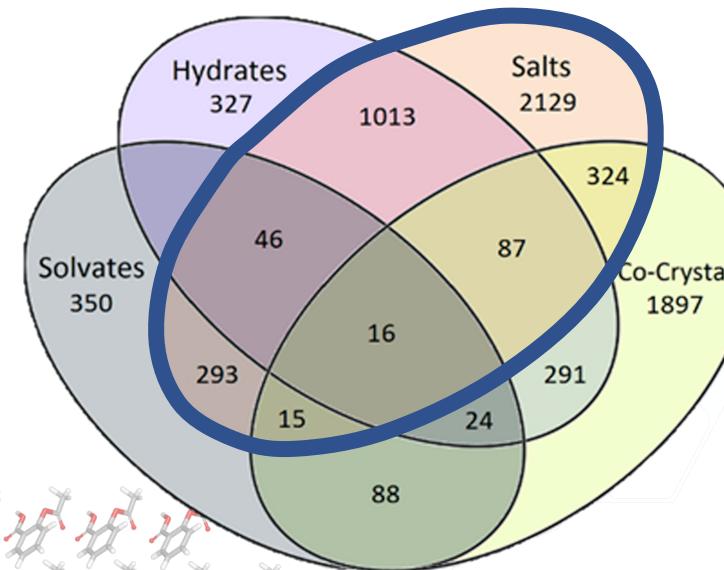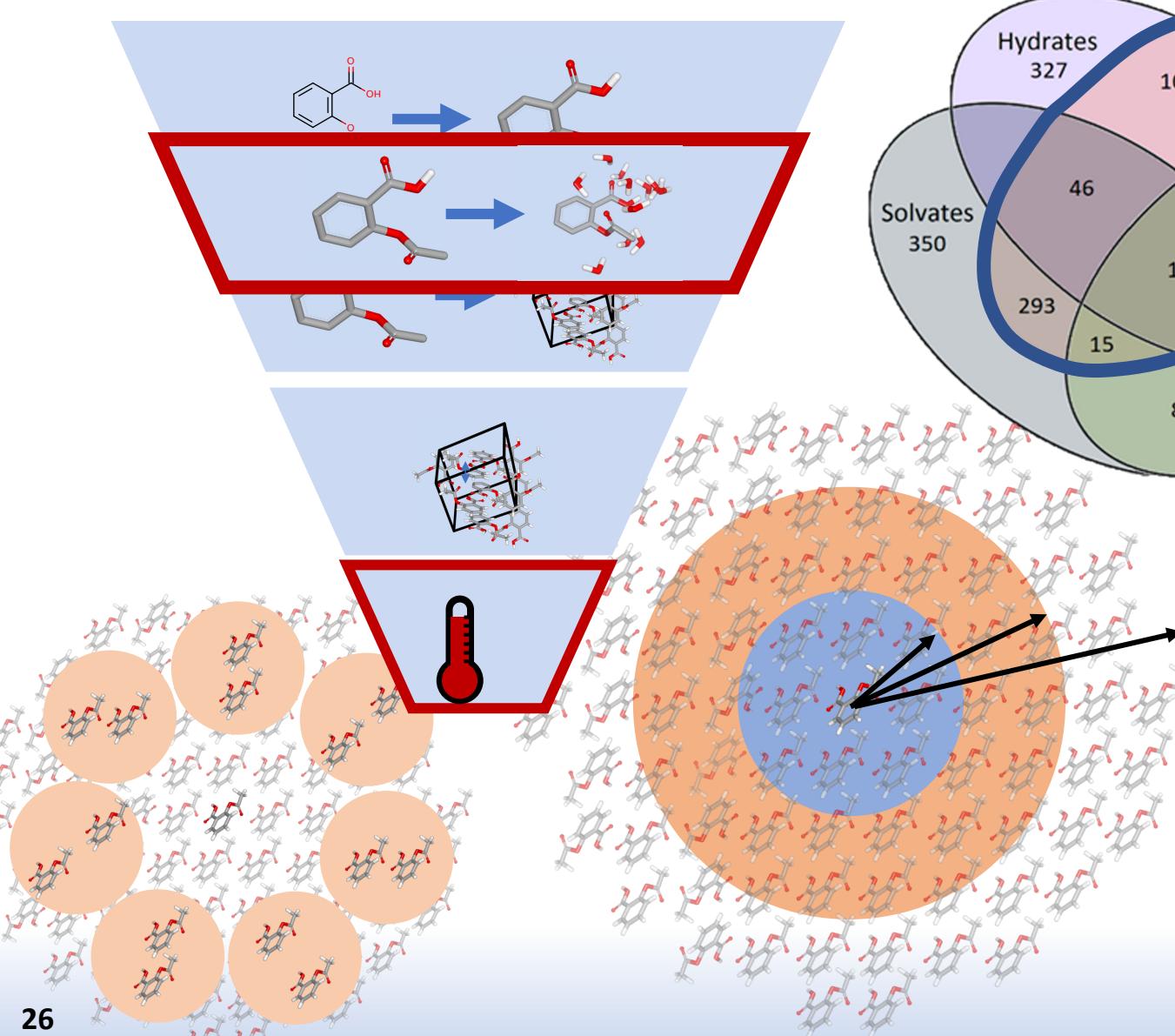
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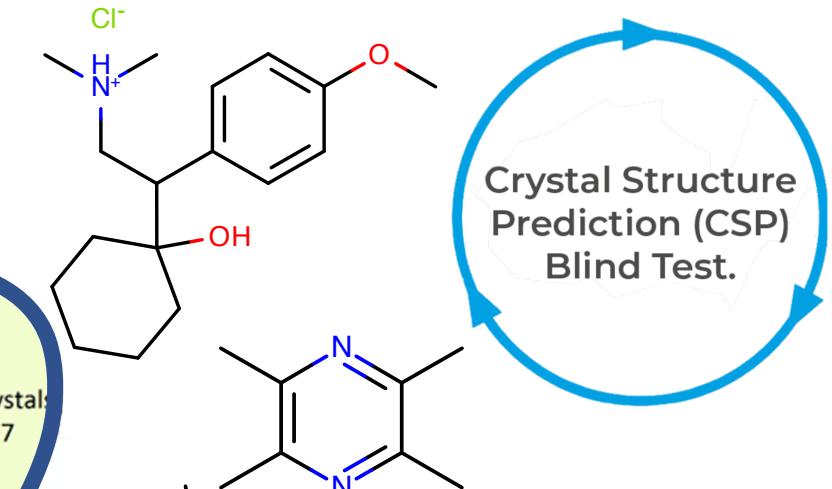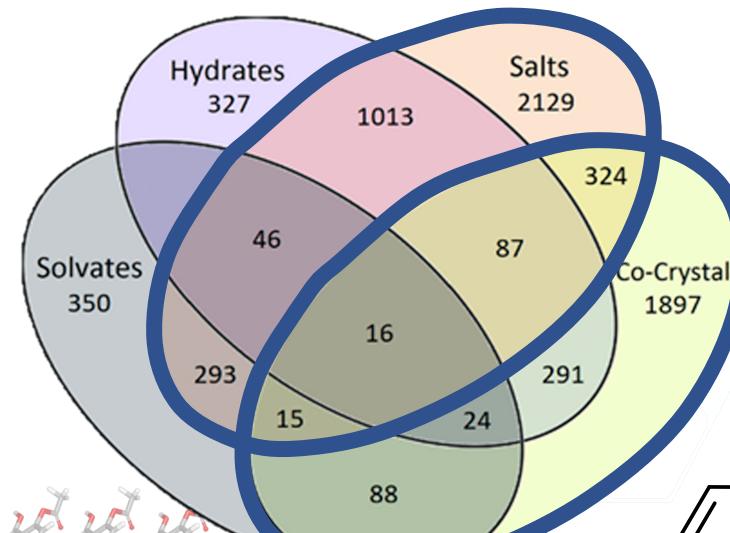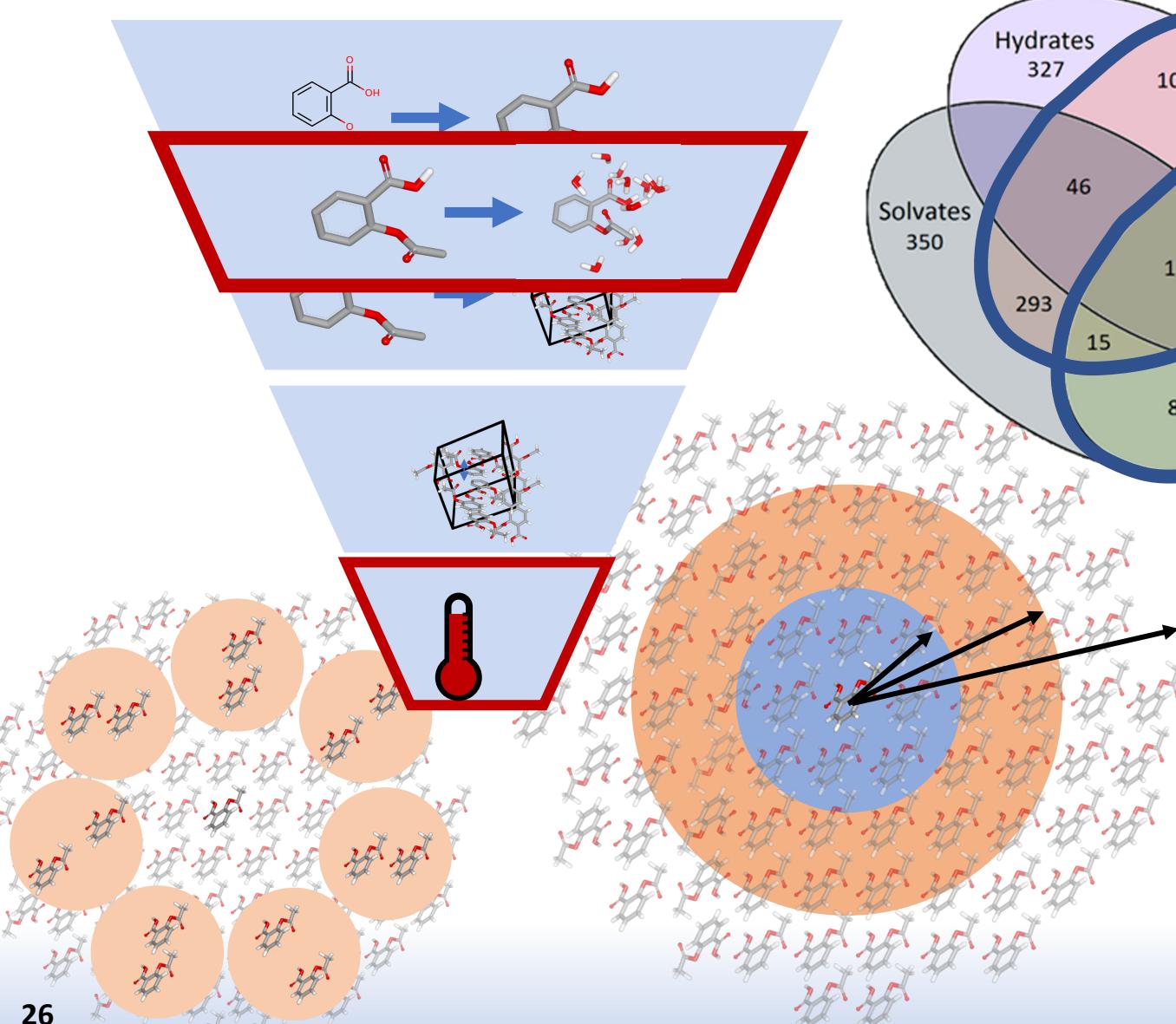
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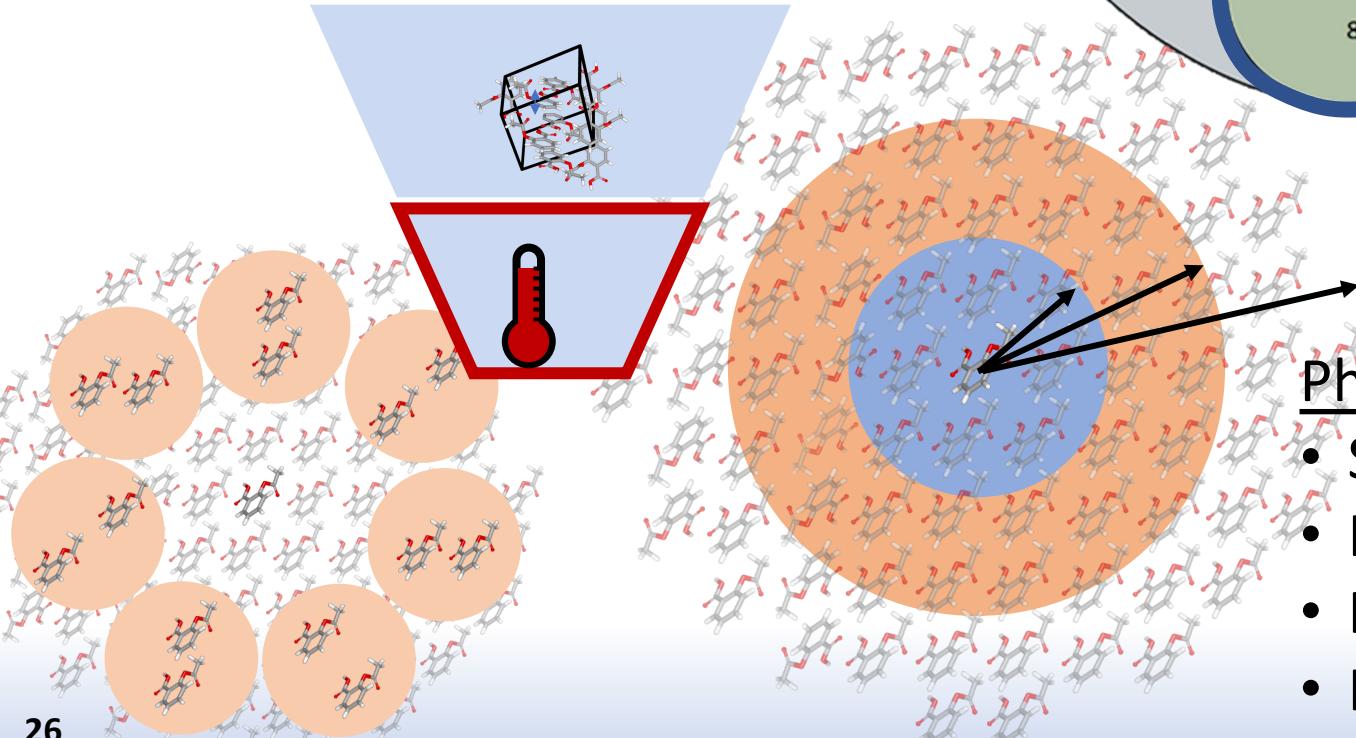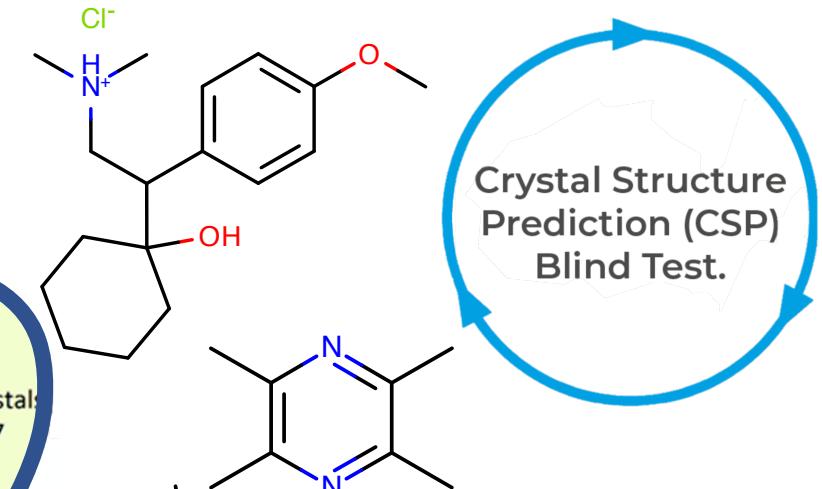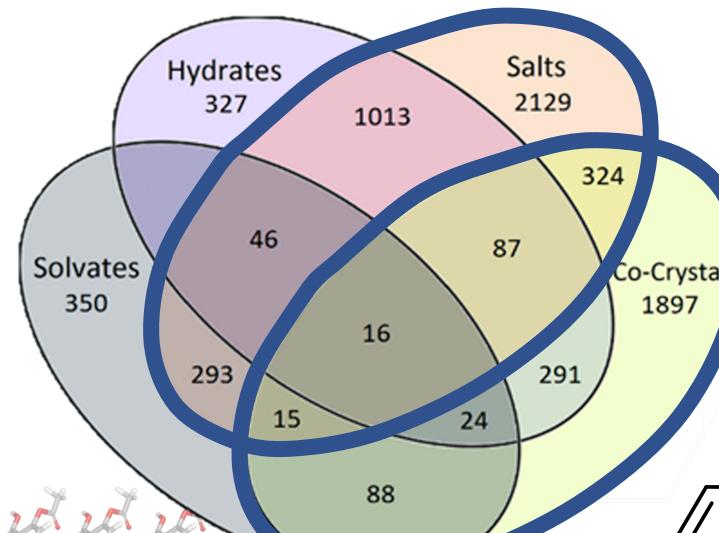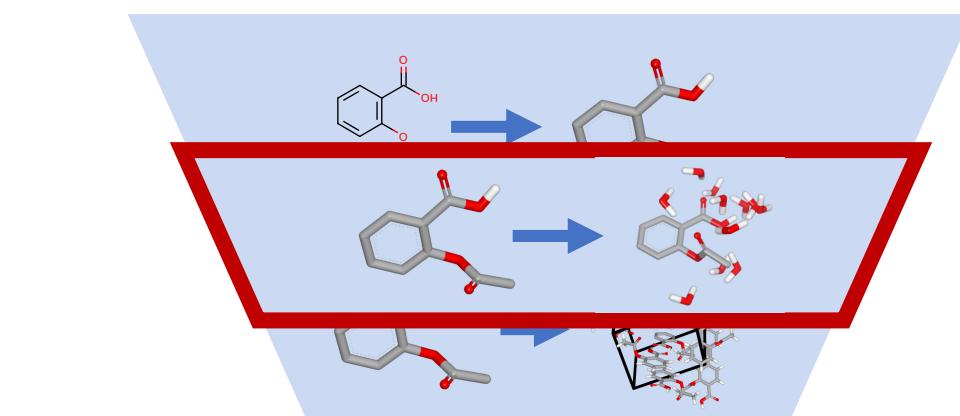
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Physical properties:
- Solubility and dissolution
- Hardness and elasticity
- Habit and morphology
- Hygroscopicity

Acknowledgements

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