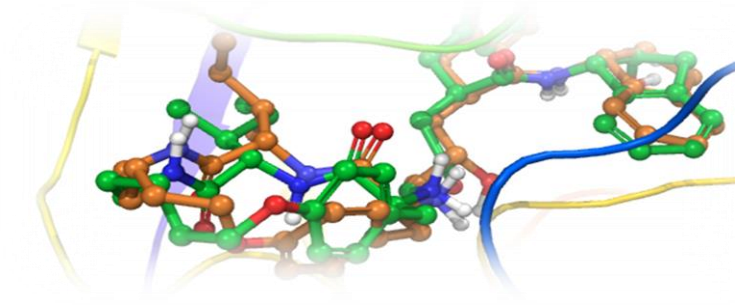
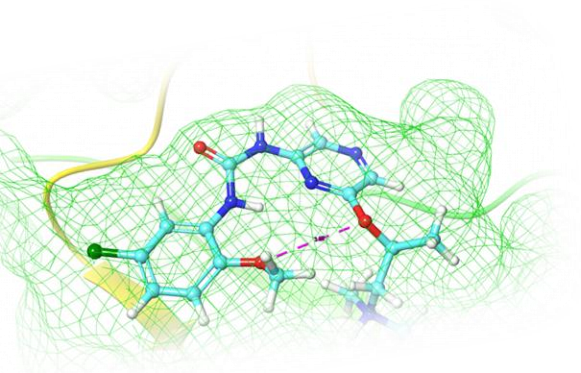


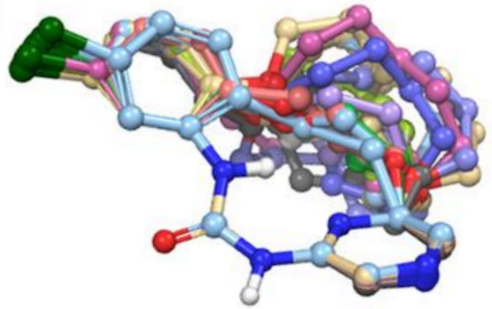
Conformational Sampling and Binding Affinity Prediction of Macrocycles

David Rinaldo, Dan Sindhikara

Strasbourg Summer School in Chemoinformatics

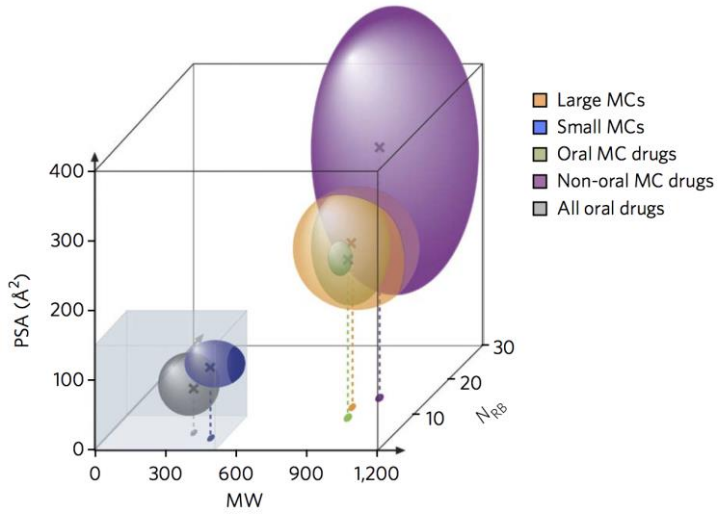
June 25th 2018





Macrocycles in Drug Design

- **Macrocycles are pervasive**
  (63 on market, 35 in development)[1]
- **Cyclization can impart conformational stability of known binder**
  (linear compound, PPIs)
- **Cyclization can expand Ro5 restrictions**[2]



status	class	route of administration	N
registered	small molecule	oral	1589
		oral, MW > 500	89
	macrocycle	oral	18
		parenteral	45
	cyclic peptide	oral	1
		parenteral	26
	macrolide	oral	14
		parenteral	9
clinical development	macrocycle	oral	15
		parenteral	20
	cyclic peptide	oral	3
		parenteral	8
	macrolide	oral	2
		parenteral	3
	"de novo designed"	oral	9
		parenteral	1

(1) Giordanetto, F., al & Kihlberg, J. (2014). J Med Chem 57(2), 278–295. (2) Villar, E. A. et (2014). Nat Chem Bio 10(9), 1–10.

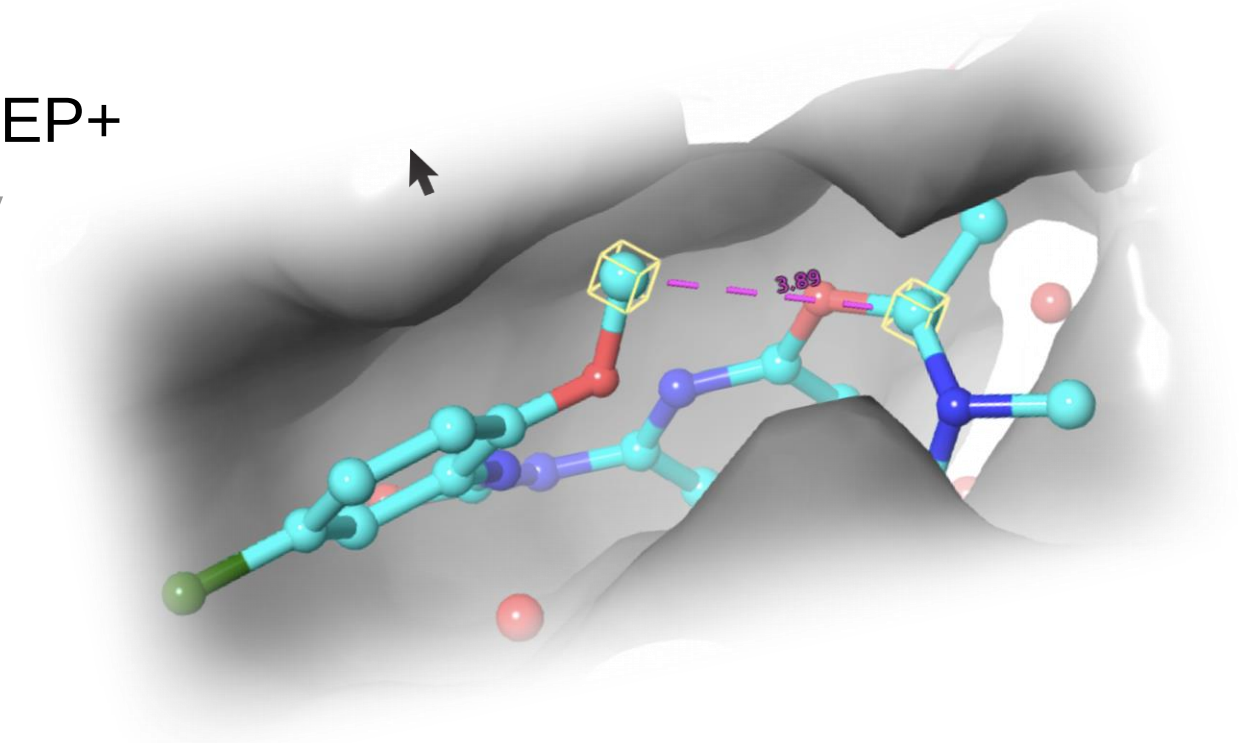
Challenges in Macrocycle Design

- Difficult synthetically
  - Cyclization reactions can be difficult, time-consuming
  - High MW can be burdensome
- Difficult computationally
  - Cyclization impedes sampling
  - Force field parameterization requires “unphysical” twisting of ring torsions
  - Chemical software not typically designed for large flexible rings
  - Design workflows must be adapted for macrocycle caveats

Schrodinger's Macrocycle Design Solutions

Schrödinger is expanding the limits of *in silico* macrocycle design

- Prime macrocycle conformational sampling
- Bioactive conformer stability
- Docking with Glide
- Free Energy Perturbation with FEP+
- Passive membrane permeability



Macrocycle Sampling

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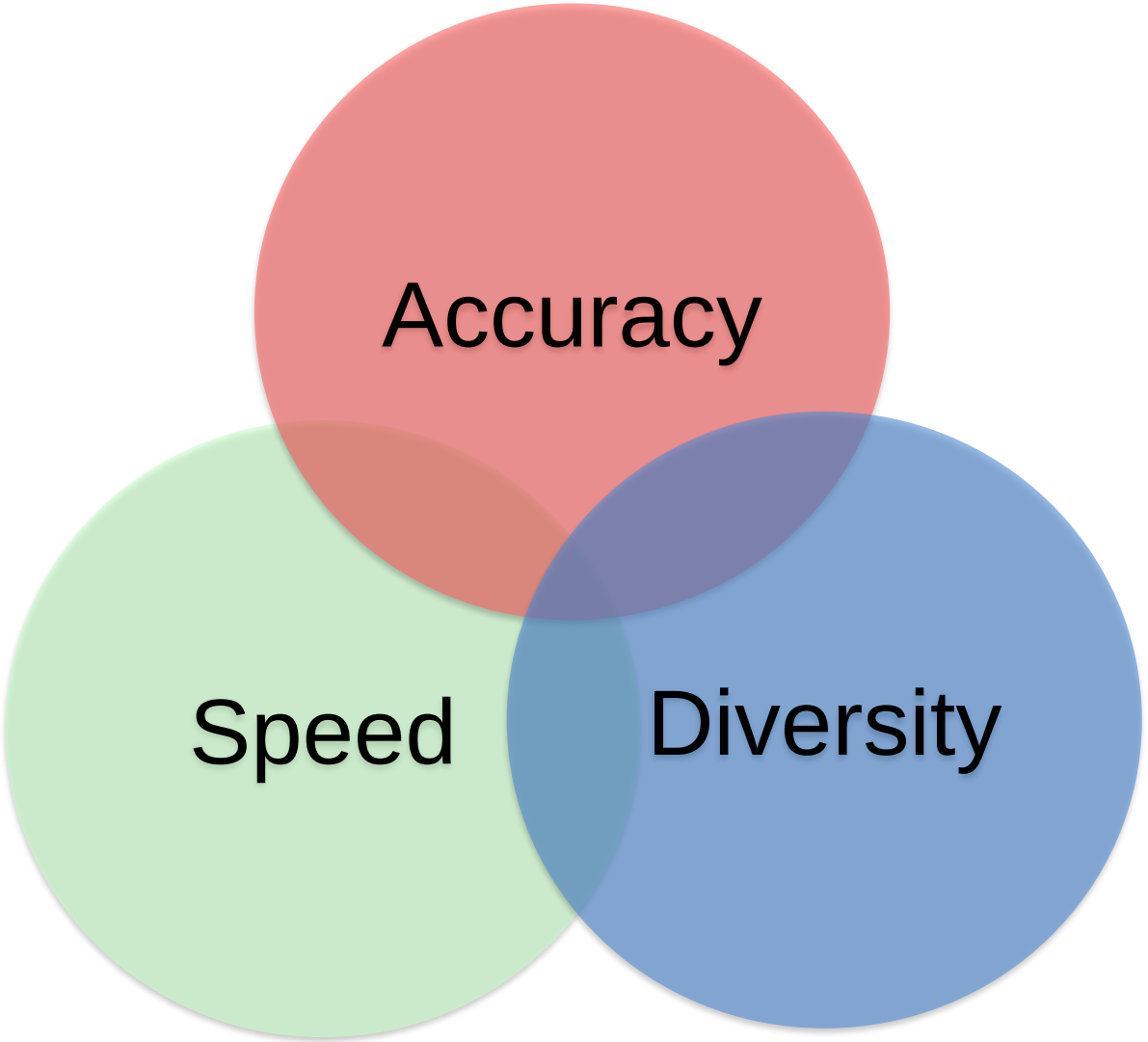
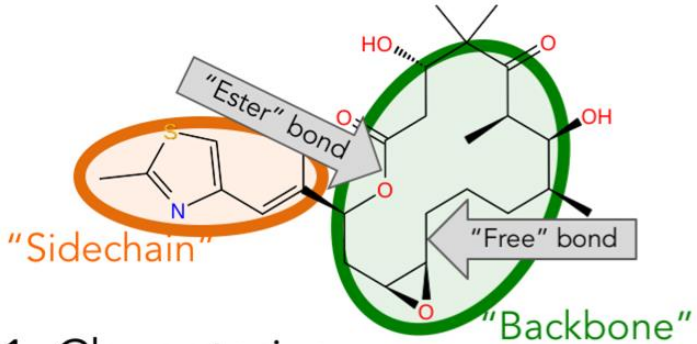
Sampling: Attributes of a functional sampler

Sampling algorithm designed to efficiently explore macrocycle conformational space, especially major ring conformations

- Accuracy
  - Match experimental conformations
- Speed
  - Fast enough to enable workflows
  - Quick turnaround during ideation
- Diversity
  - Sample not only crystal conformation, but also permeable, solvent, exploitable

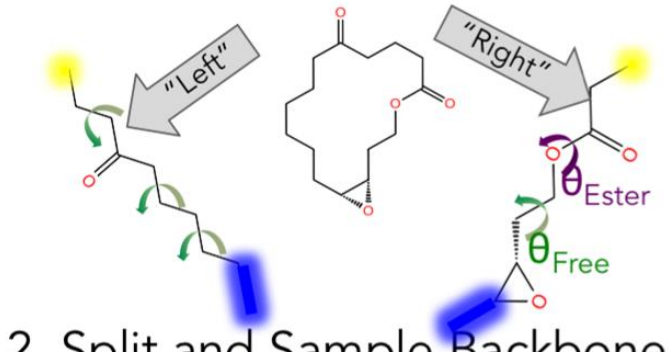


PrimeMCS Algorithm



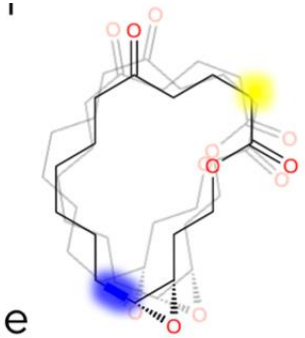
1. Characterize

Recognize macrocyclic topology, assign bond rotamers from library



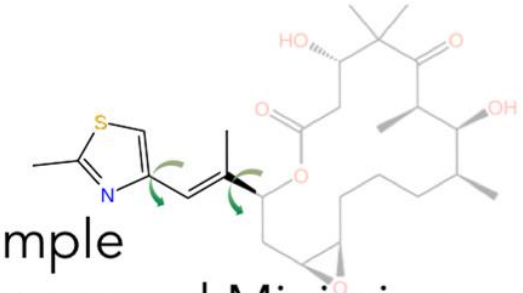
2. Split and Sample Backbone

Break* major ring, combinatorially sample "half-loops" using bond rotamers.



3. Re-form and cluster backbone

Find pairs of half-loops which form reasonable closed rings. If there's enough, cluster them, otherwise, go back to 2 with finer resolution



4. Sample R-groups and Minimize

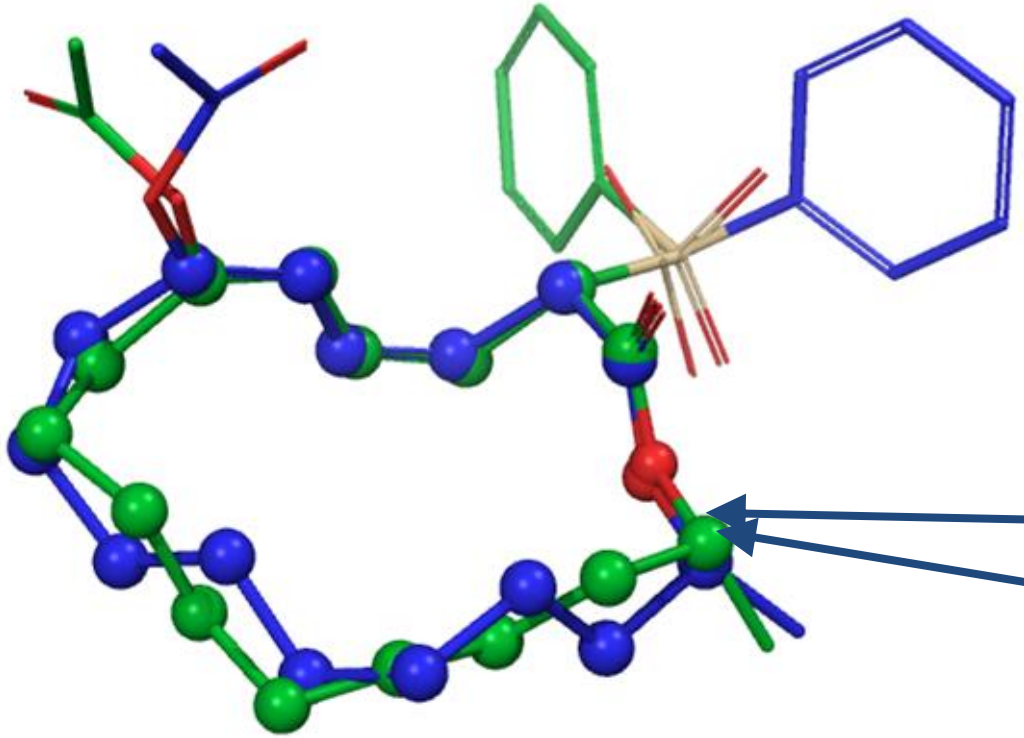
Build out r-groups from clustered ring backbones using bond rotamers. Minimize to relax backbone and repeat once.

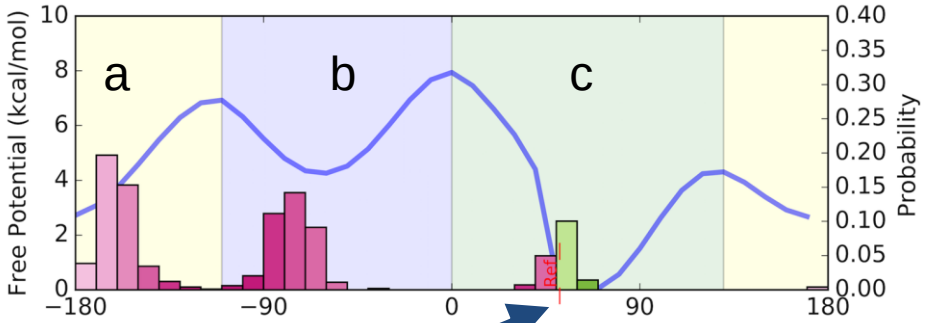
Algorithm details of note

- Originally developed @ Prof Matt P. Jacobsons Lab based on loop sampling algorithm
- In step 2, we cut the ring 10 different ways around the ring (spinroot 10), enabling 10x parallelism
- Cross-links are accounted for via inverse clash restraints
- Only one independent ring system is thoroughly sampled

Sindhikara D. et al., J Chem Inf Model, 57(8), 1881-1894, 2017.

Measuring Macrocycle Backbone Structure





cccbbbbccaacaa

cccbbbacaaccba

Backbone RMSD

Assuming that backbone sampling is the difficult part. Here we measure the best backbone RMSD of a structure in the ensemble to the crystal reference

Backbone Torsional Fingerprint

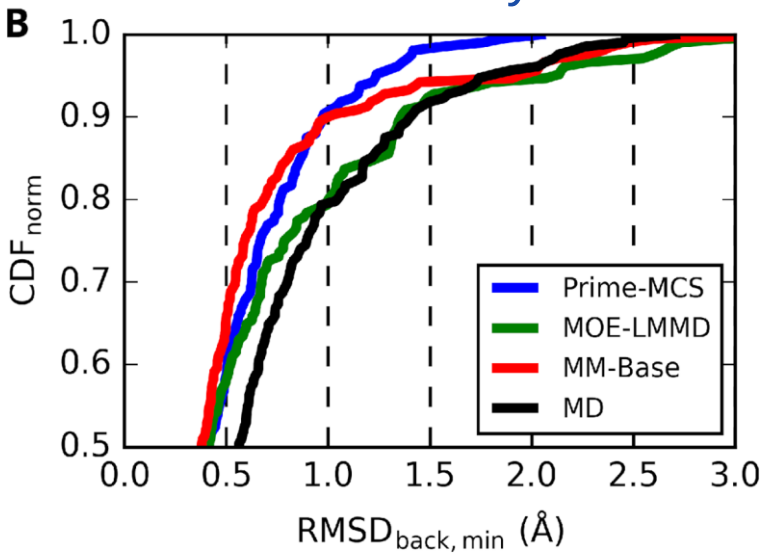
Using torsional scanning profiles, we can bin torsions into states. The superposition of all backbone states (torsional fingerprint) can be used to compare discretized conformations.

Sindhikara D. et al., J Chem Inf Model, 57(8), 1881-1894, 2017.

Measuring Accuracy, Diversity, and Speed

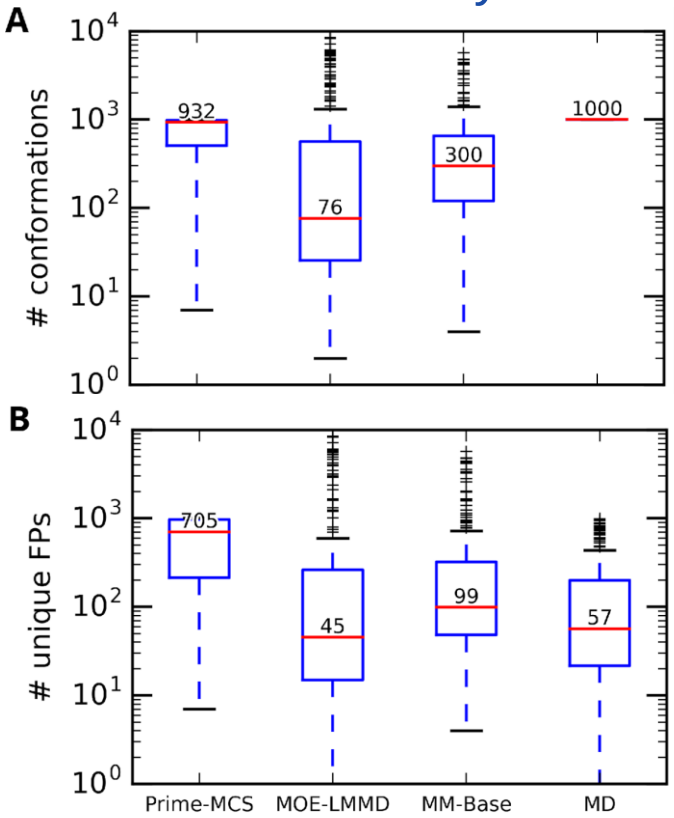
Test set consisting of 208 diverse crystal structures, Comparison of 4 different protocols [1]

Accuracy

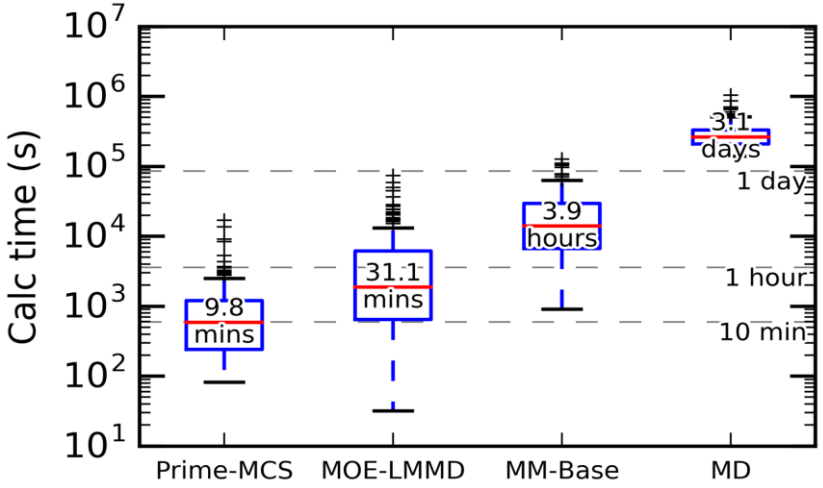


PrimeMCS finds < 1.0Å structure 90% of the time, worst outlier 2.1Å

Diversity



Speed



PrimeMCS jobs are 10x parallelizable, enabling extremely fast turnaround times.

Sindhikara D. et al., J Chem Inf Model, 57(8), 1881-1894, 2017.

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Predicting Stable Cyclizations of Linear Ligands

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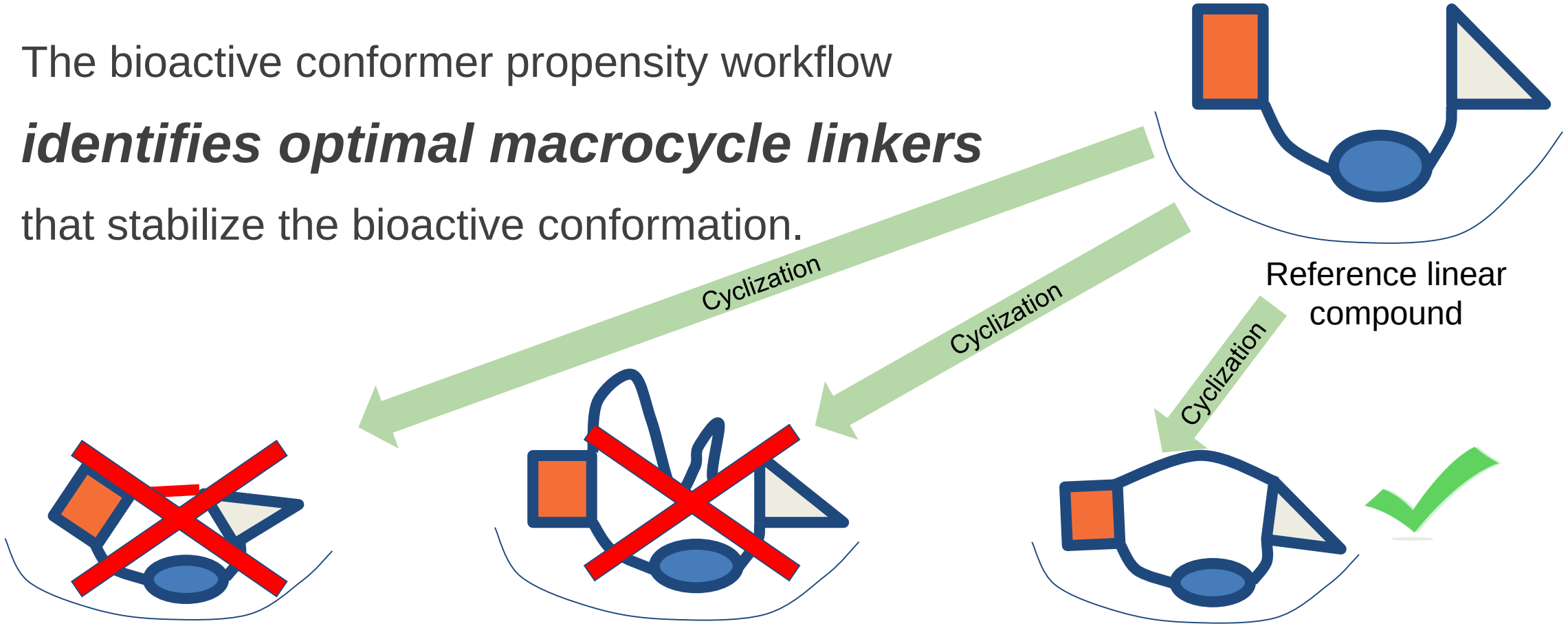
Cyclization tool: Macrocycle Bioactive Conformer Propensity

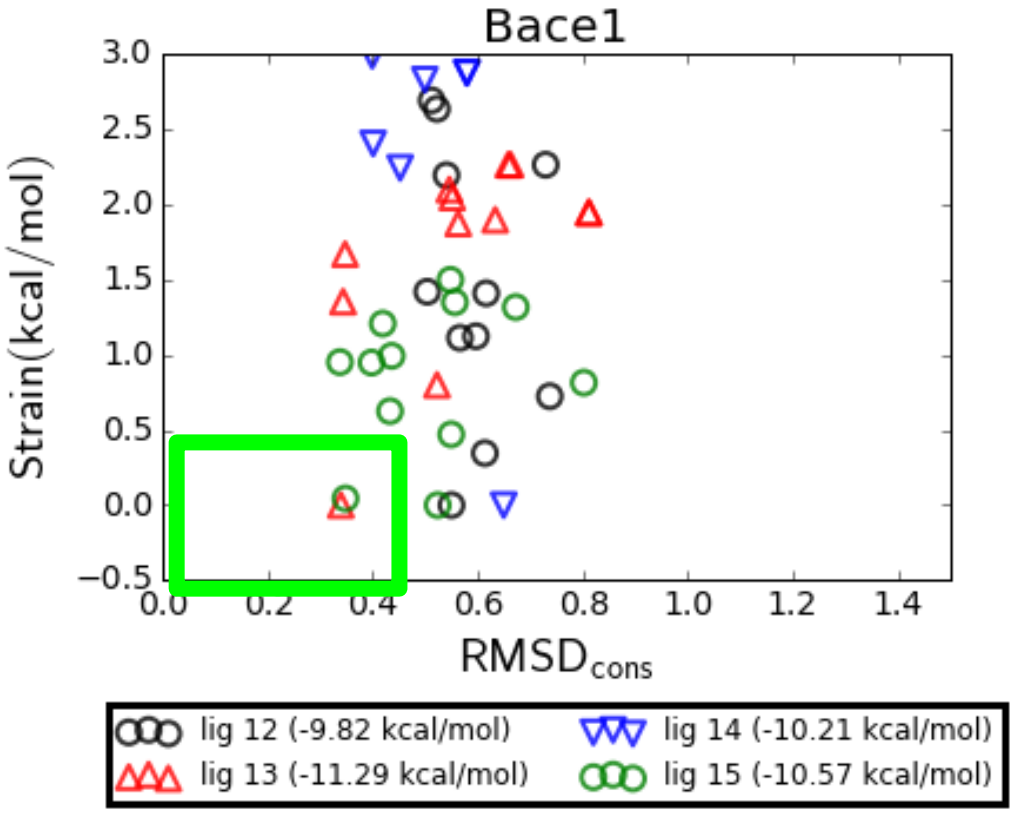
The bioactive conformer propensity workflow

identifies optimal macrocycle linkers

that stabilize the bioactive conformation.



Strain vs RMSD of “Conserved” Region for Sampled Conformers



Prime energy vs RMSD of Bioactive SMARTS

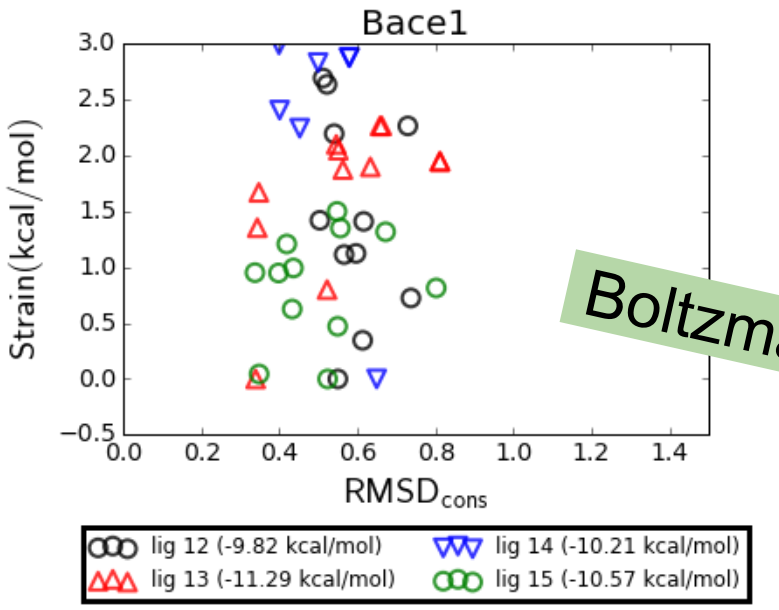
Examined Case: Huang Y, Strobel ED, Ho CY et al. Bioorg. Med. Chem. Lett. 20(10), 3158–3160 (2010).

1. **Sample each ligand using PrimeMCS**

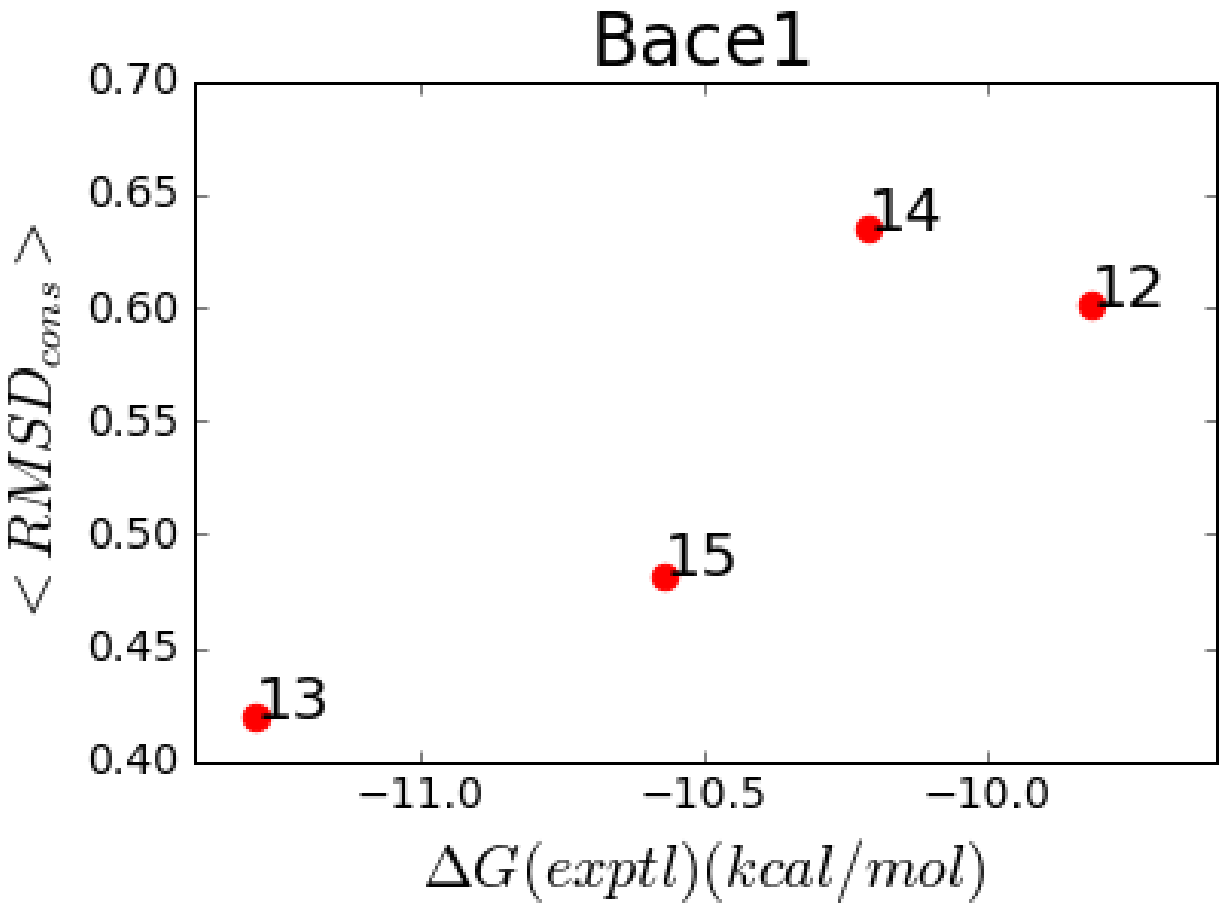
2. **Calculate the RMSDs** of the substructure important for activity for each member of the ensemble to the interacting portion of the known active ligand. (RMSD and relative energy are plotted.

3. **Calculate the expected RMSD** by Boltzmann weighting over the ensemble (next slide) to quantify ***propensity for the bioactive conformer***

<$RMSD_{cons}$> Simplifies Conformational Propensity

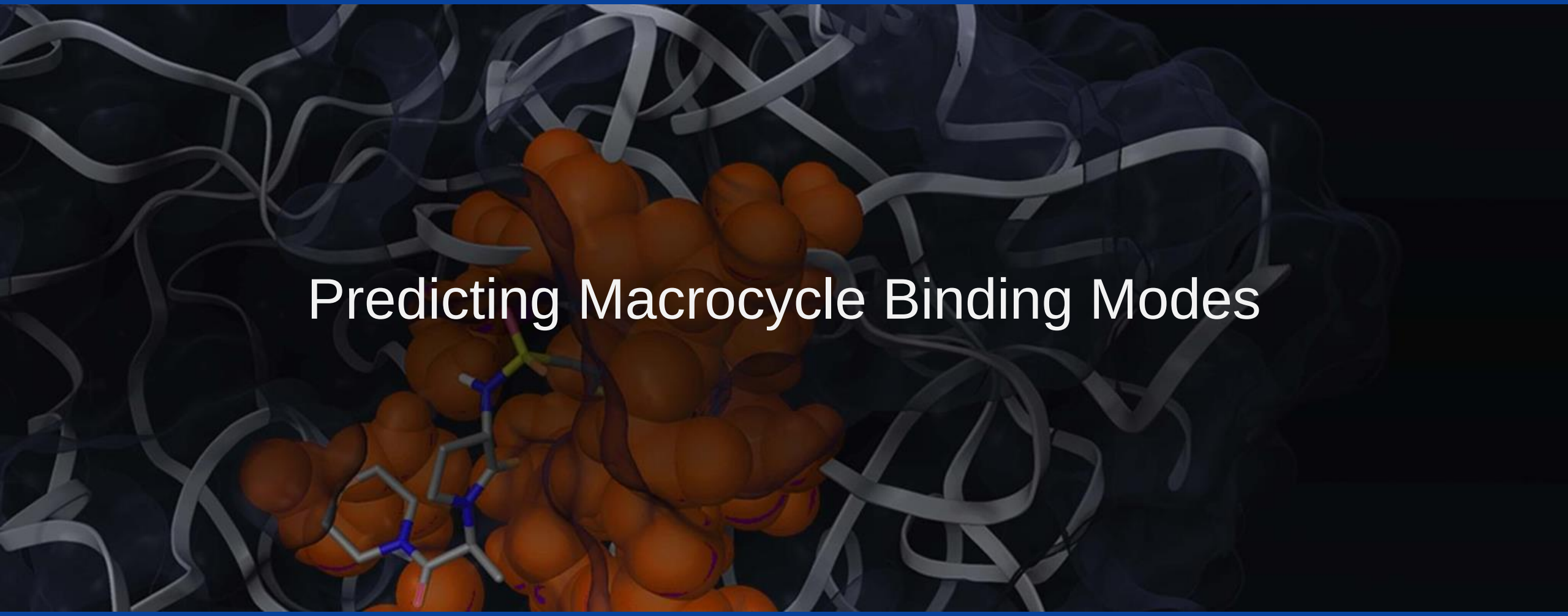


Boltzmann weighting



Expected RMSD (right) of bioactive region selects* more active macrocycles due to their more stable bioactive conformations.

*Similar performance for additional systems in



Predicting Macrocycle Binding Modes

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Integrating Prime Macrocycle Sampling with Glide

PrimeMCS

Efficiently samples macrocycle ring conformations

Doesn't directly account for environmental effects

Glide docking

Efficiently accounts for receptor environment

Relies on templates for ring conformations

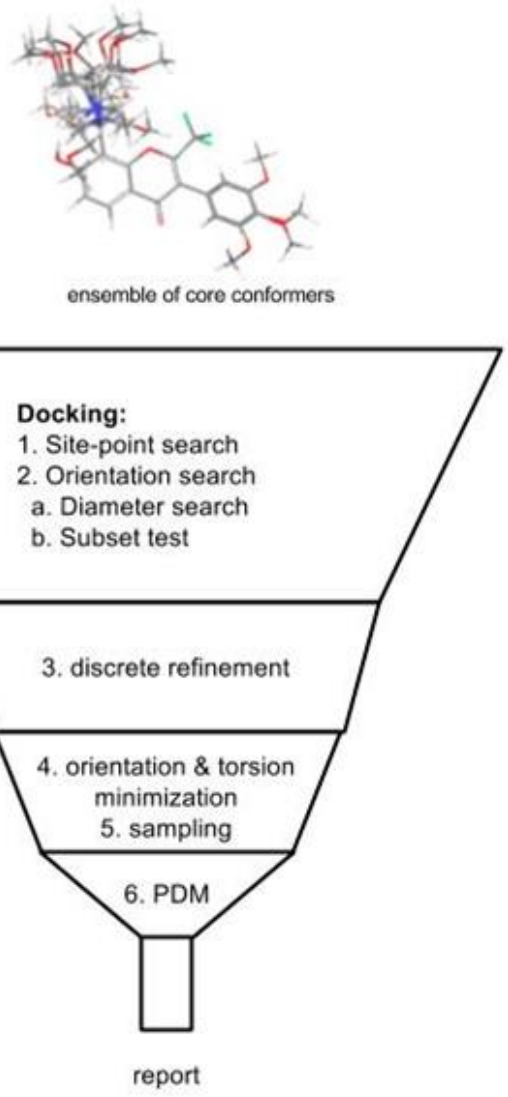
Glide "macrocycle mode"

Generates ring templates using PrimeMCS "on-the-fly" for contextual sampling

Sampling and docking parameters optimized for macrocycle docking

Integrating PrimeMCS into Glide

- Glide uses a filtering-based workflow to go from conformers to poses
- For macrocycle **PrimeMCS** is used to generate on the fly ring templates to be utilized in the initial core conformer ensemble generation (confgen)
- We use an **“expanded funnel”** to reflect the additional conformational and pose complexity added by macrocycles

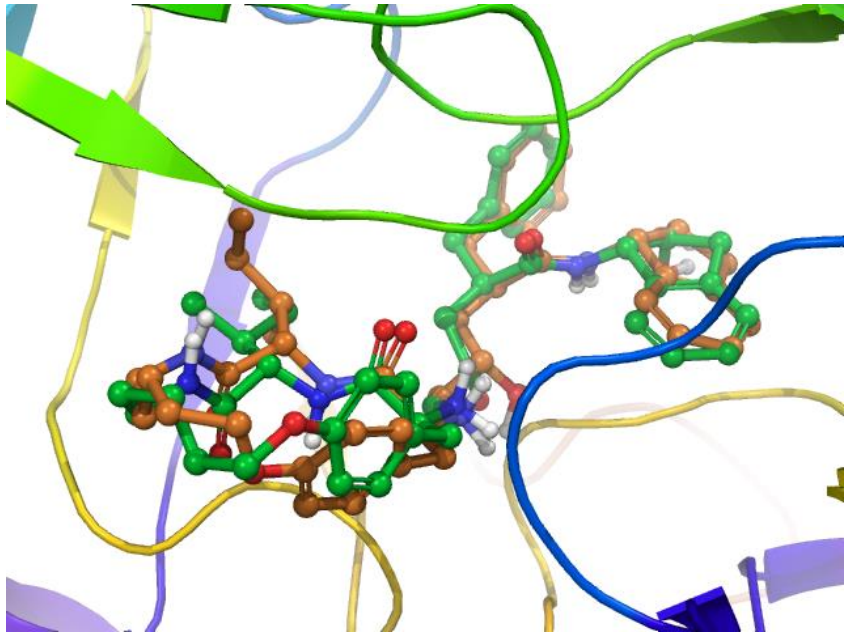


PrimeMCS-integrated Glide Docking Results

Dataset of 67 cocrystallized macrocycles, median 16 backbone atoms

PrimeMCS-based Glide self-docking with no restraints **found top poses under 2.0 Å 70% of the time**, significantly better than with rigid rings, but not as good as docking the native conformation.

	Native conformation	Rigid ring	PrimeMCS-based
% Top pose under 2.0Å	91%	43%	70%
Median Serial CPU time	~1m	~1m	30m



1d4k 1.1Å docked structure

Macrocycle FEP+

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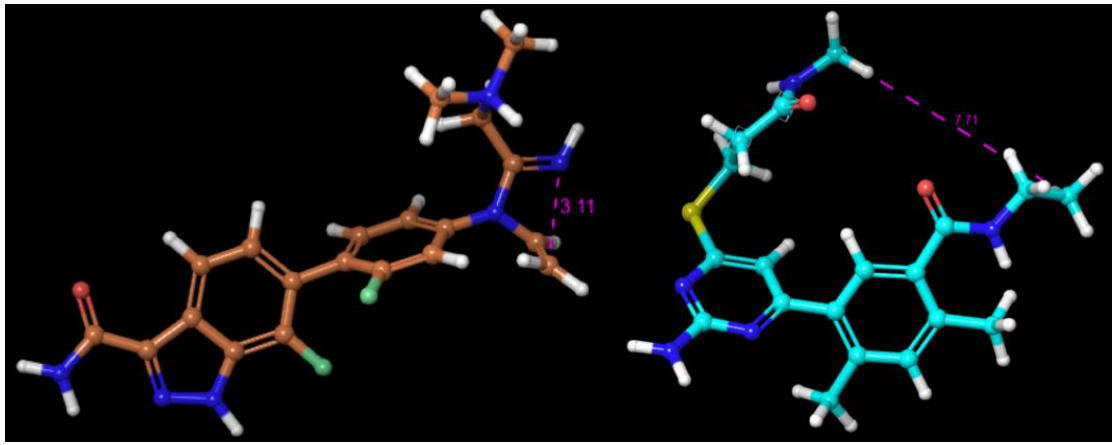
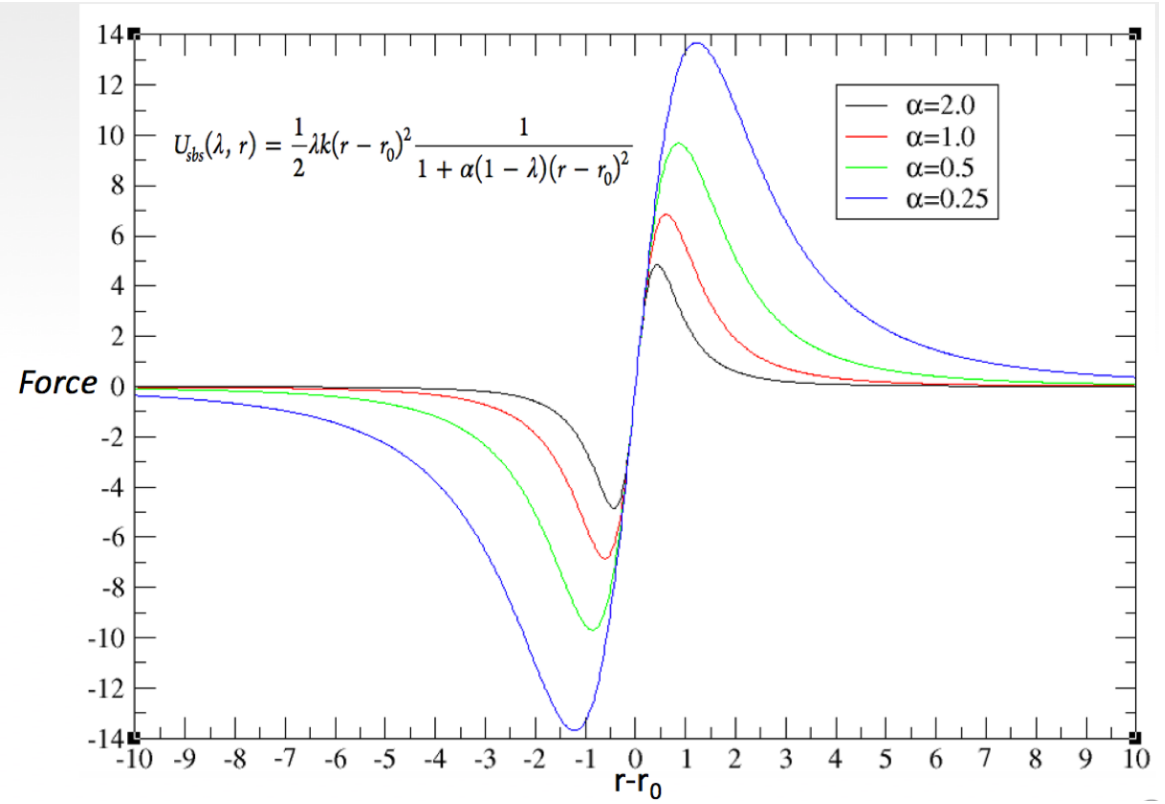
Macrocycle FEP+

- Core-hopping technology (soft bond scaling) has enabled macrocyclization reactions in FEP+
- Macrocycles are automatically detected and run with optimal scaling parameters



Bonds can be formed even across long distances



Corresponding force of scaled soft bond potential (above) enables smooth macrocycle bond formation across FEP+ lambda schedule

Yu H.. et al., J Chem. Theory Comput., 13, 6290-6300, 2017.

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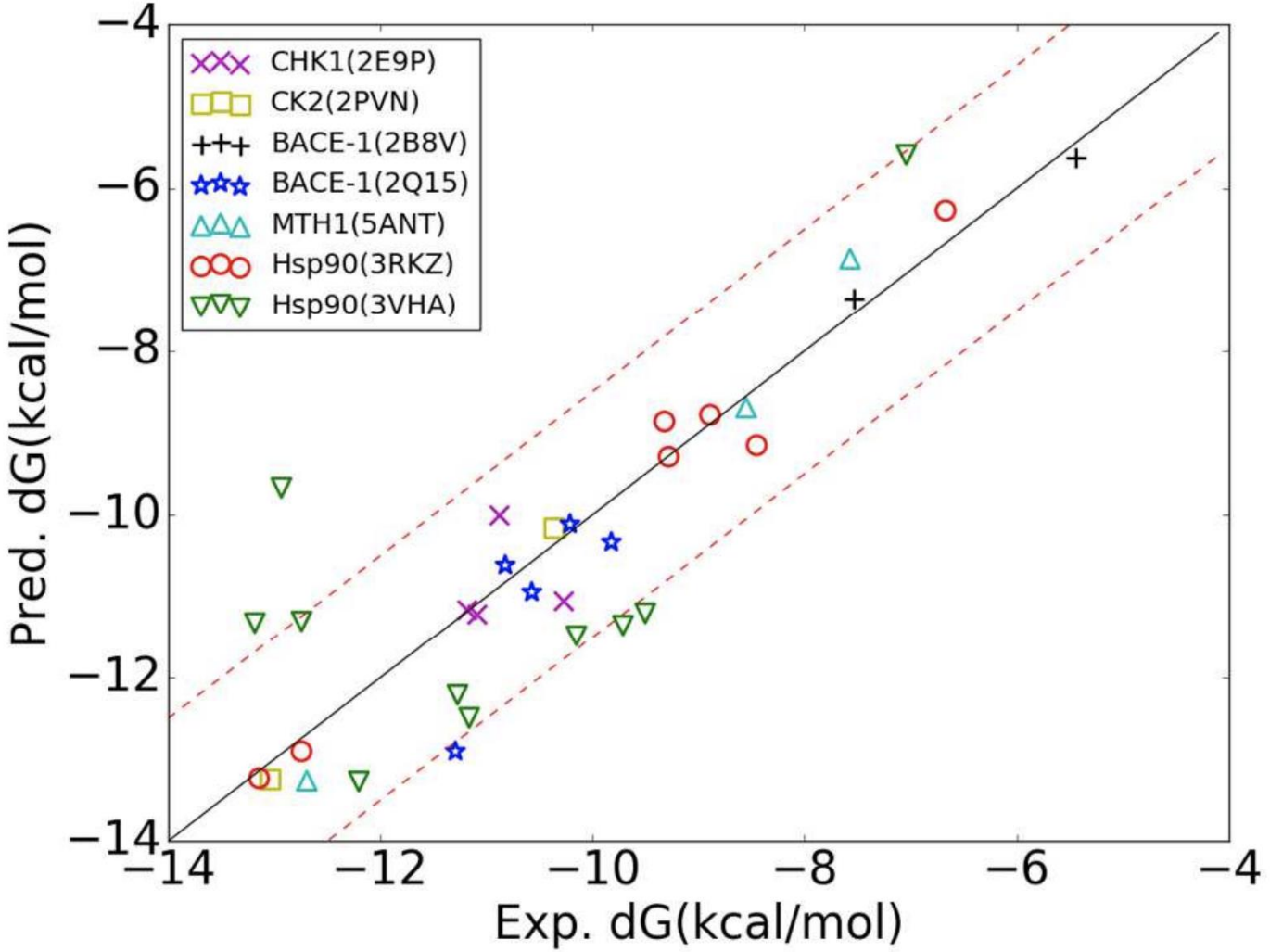
Macrocycle FEP+ Retrospective Study Results

- Seven retrospective cases of macrocyclization
- ΔΔG
  - MUE: 0.71
  - RMSE 0.92

Macrocycle FEP+ currently achieves accuracy on par with small molecule FEP+



Yu H.. et al., J Chem. Theory Comput., 13, 6290-6300, 2017.

Macrocycle FEP+ at Bayer

CHEM MED CHEM

Computational Macrocyclization: From de novo Macrocycle Generation to Binding Affinity Estimation

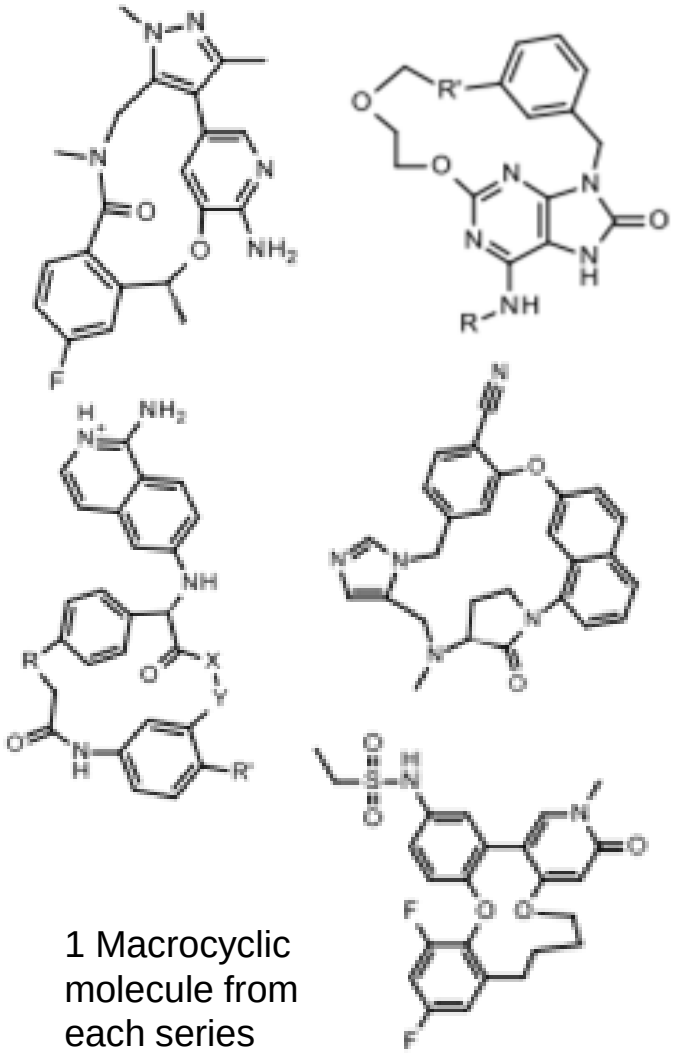
Vincent Wagner[a], Linda Jantz[b], Dr. Hans Briem[a], Kai Sommer[b], Prof. Matthias Rarey[b], Dr. Clara D. Christ[a]*

[a] Bayer AG, Drug Discovery, Medicinal Chemistry, 13353 Berlin (Germany)
[b] Universität Hamburg, ZBH - Center for Bioinformatics, 20146 Hamburg, (Germany)

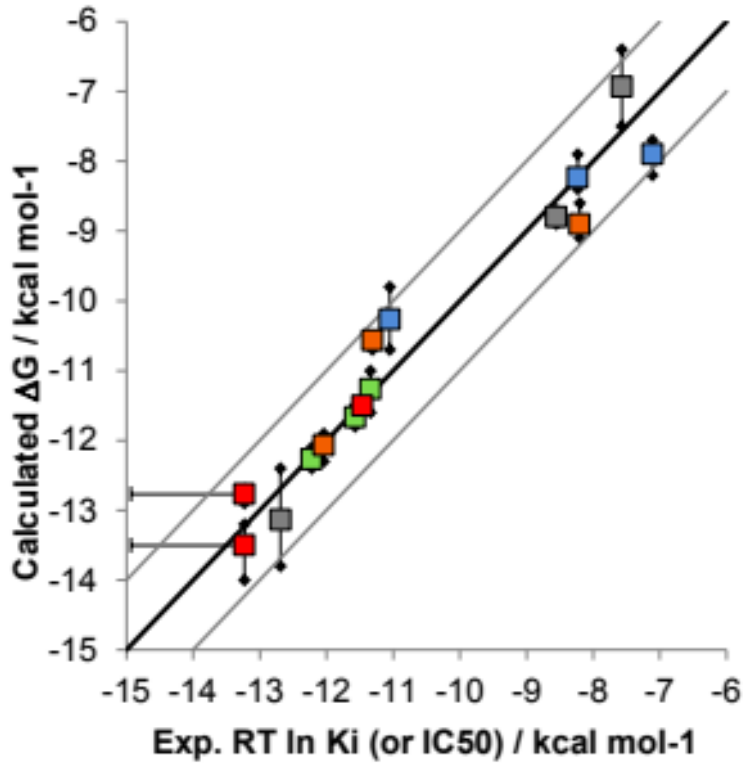
The effect of macrocyclization on binding affinity was predicted for 5 diverse pharmaceutically-relevant targets.

FEP+ was able to predict all binding affinities to within 1kcal/mol

Many series involved a mix of marocyclic and linear molecules



1 Macrocyclic molecule from each series



Calculated versus experimental binding affinities for all targets. Mean (squares), minimum and maximum values. Colored by molecules in the same series.

Macrocycle Tools Summary

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Summary of Schrödinger's Macrocycle Design Tools

- Schrodinger tools offer comprehensive capabilities for macrocycles
- Prime-MCSs sampling enables many workflows
  - Macrocycle bioactive conformer stability calculations
  - Docking within Glide
  - Membrane permeability predictions
- FEP+ for macrocycles
- We are actively developing macrocycle tools and workflows!

Acknowledgements

- Sampling
  - BMS
    - Shana Posy
    - Steve Spronk
    - Dan Cheney
  - UCSF
    - Matthew P Jacobson
    - Siegfried Leung
  - Schrödinger
    - Ken Borrelli
    - Tyler Day
- FEP+
  - Haoyu Yu
  - Lingle Wang
  - Robert Abel
  - Yuqing Deng
- Docking
  - Ivan Tubert-Brohman
- Prime
  - Ed Miller
- Infrastructure
  - Tor Colvin
  - Dan Nealschneider

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Scientific leader in life sciences and materials research