Automatic Ligand Conformer Generation, Placement and Refinement Dictionary Generation Using AFITT

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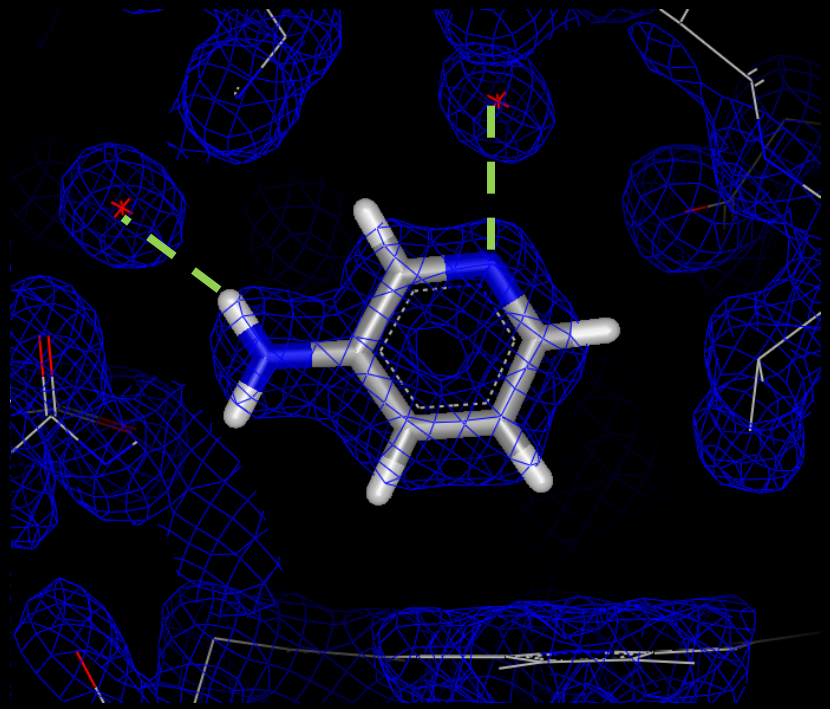
AFITT Outline

- Review of ligand fitting and scoring

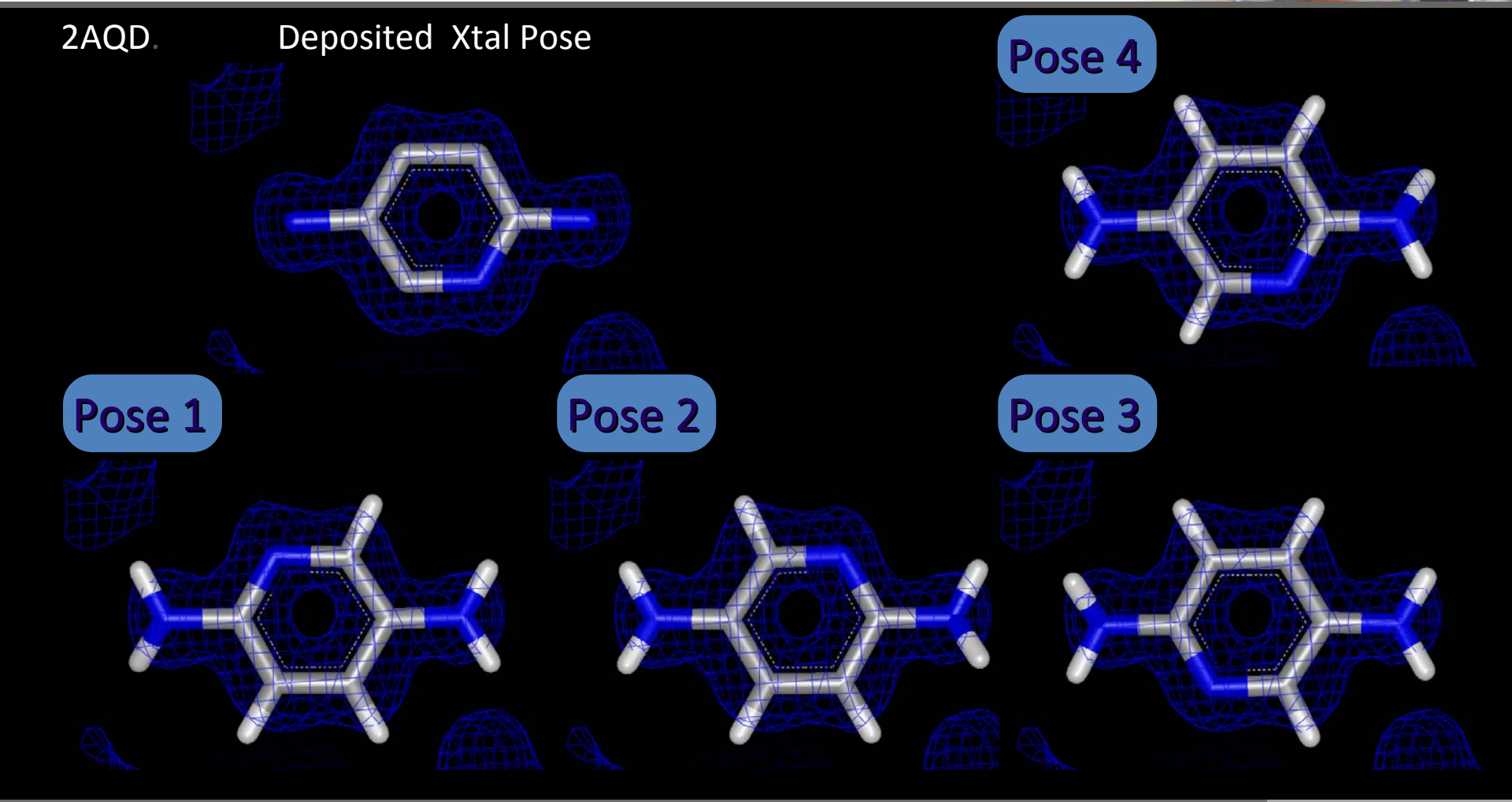
- New features
  - Improved poor density fitting
  - Automated protein preparation
  - Global Phasing helper files

AFITT - Ligand fitting

- 4 metrics for scoring ligand after fitting
  - Real-space Correlation Coefficient (rscc)
  - Protein environment (docking scores)
    - Piecewise Linear Potential (PLP)
    - Chemscore
  - Strain

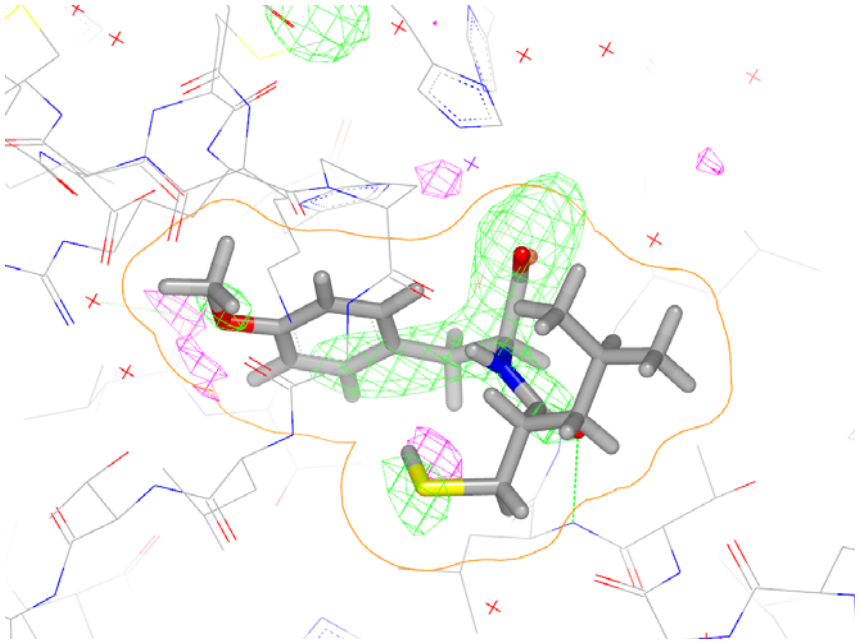


Exhaustive search



AFITT 2.3 – poor density fitting

- Better searching and optimization
  - Better fitting for low occupancy and poor density



Statistical Test

- McNemar (Discordant pairs)
  - Set a cutoff
    - ≤ 2 Å
  - Count the number of successes and failures

	2.3-T	2.3-F
2.1-T	✓	x_B
2.1-F	x_A	✗

$$Z = \frac{x_A - x_B}{\sqrt{x_A + x_B}}$$

AFITT 2.3 versus 2.1

- 2.3 outperforms 2.1
  - Moderate to poor density

≤ 2 Å	Afitt 2.3>2.1 p value
Moderate to poor (n=62)	
McNemar (59%)	**0.041**
Poor (n=38)	
McNemar (37%)	0.159

AFITT 2.3 outperforms 2.1

- Different methods of fitting poor density
  - Default
  - Box (define active site)
  - Blobs/box
    - Can't find density?
    - Use active site definition

Paired t-test	$\bar{x}$	Afitt 2.3>2.1 p value
Moderate to poor (n=62)		
Default	6.7	**0.040**
Box	3.1	**0.005**
Blobs/box	2.4	**0.015**
Poor (n=38)		
Default	10.7	0.058
Box	4.4	**0.010**
Blobs/box	3.6	**0.018**

Blobs/Box outperforms Default

- Which methods is better?
  - Default
  - Box (define active site)
  - Blobs/Box
    - Can't find density?
    - Use active site definition

Paired t-test	p value
Moderate to poor (n=62)	
Box > Default	**0.010**
Blobs/Box > Default	**0.003**
Blobs/Box > Box	**0.037**
Poor (n=38)	
Box > Default	**0.006**
Blobs/Box > Default	**0.003**
Blobs/Box > Box	0.088

Substantial difference?

- Which methods is better?
  - Default
  - Box (define active site)
  - Blobs/box
    - Can't find density?
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Paired t-test	p value
Moderate to poor (n=62)	
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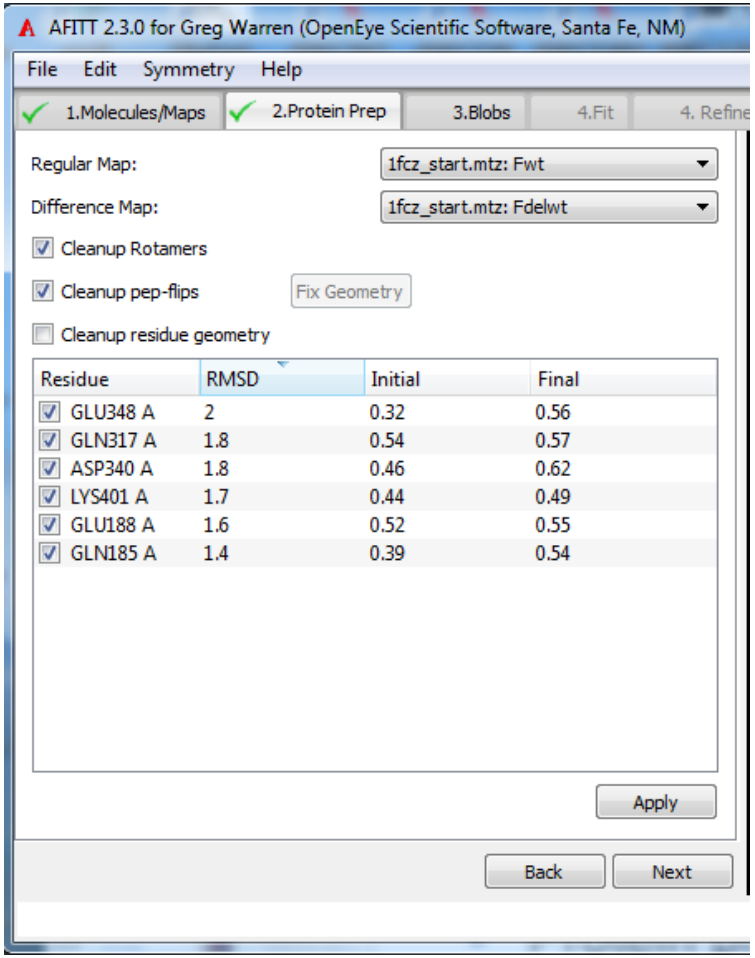
Blobs/Box > Box	0.088

AFITT 2.3 – poor density fitting

- Better searching and optimization
  - Better fitting for low occupancy and poor density
- Summary
  - v2.3 is better
  - For poor density
    - Box better than default
    - CL
      - -blobsThenBox best

AFITT 2.3 – Protein prep

- Protein prep
  - Refit side chains
  - peptide flips
  - both



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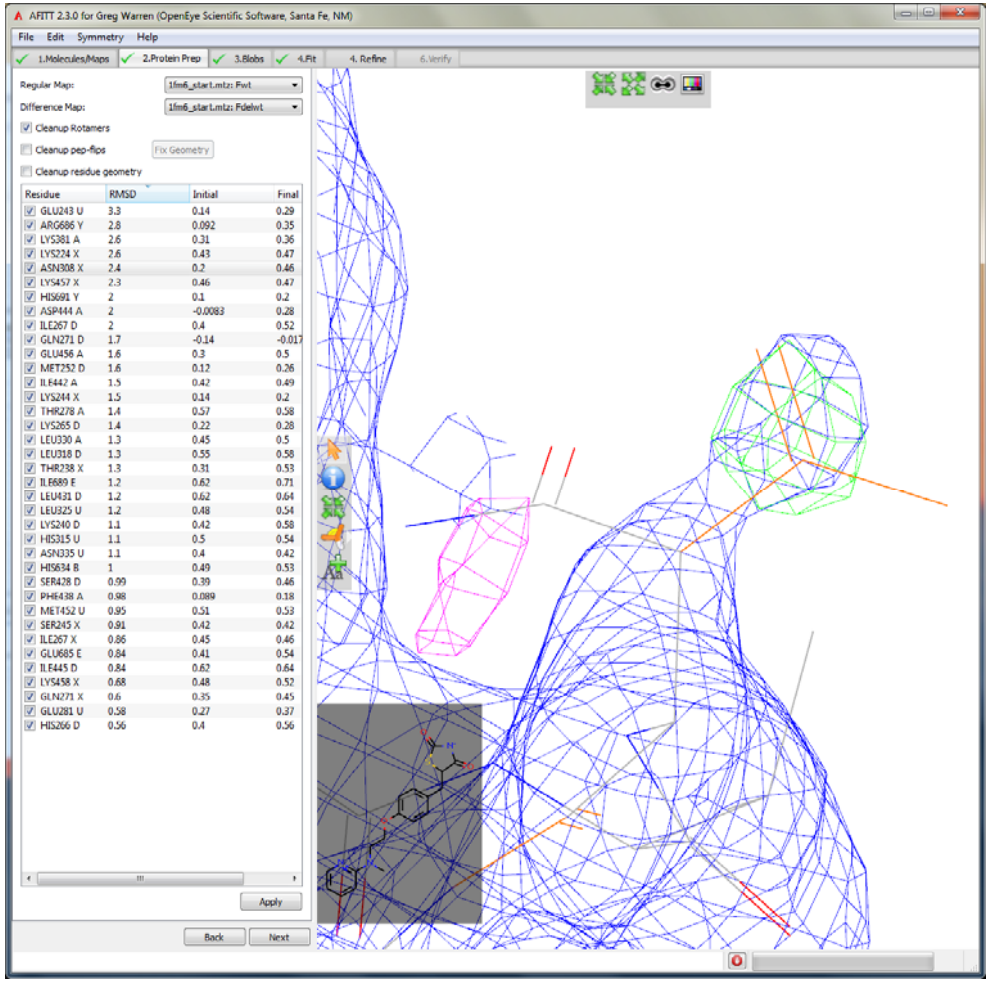
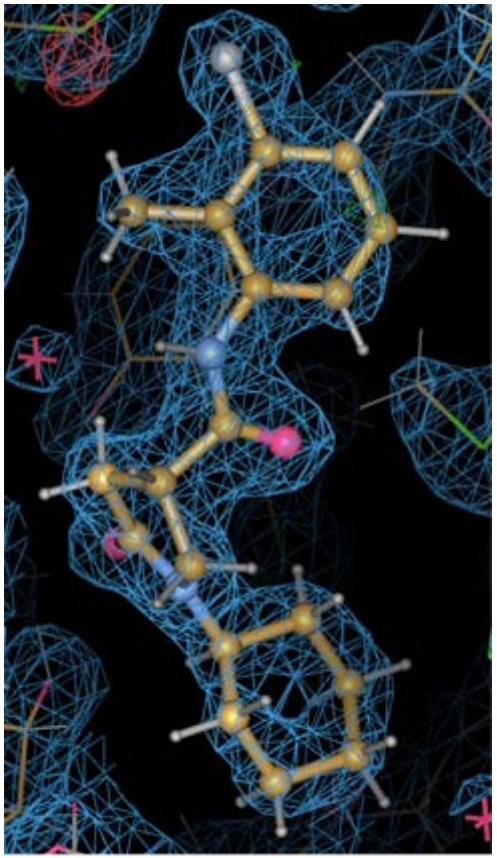


Global Phasing and OpenEye collaboration

- OE helper files for BUSTER
  - MMFF94s
  - AM1
  - PM3

Ligand geometry refinement with MMFF94 in Buster

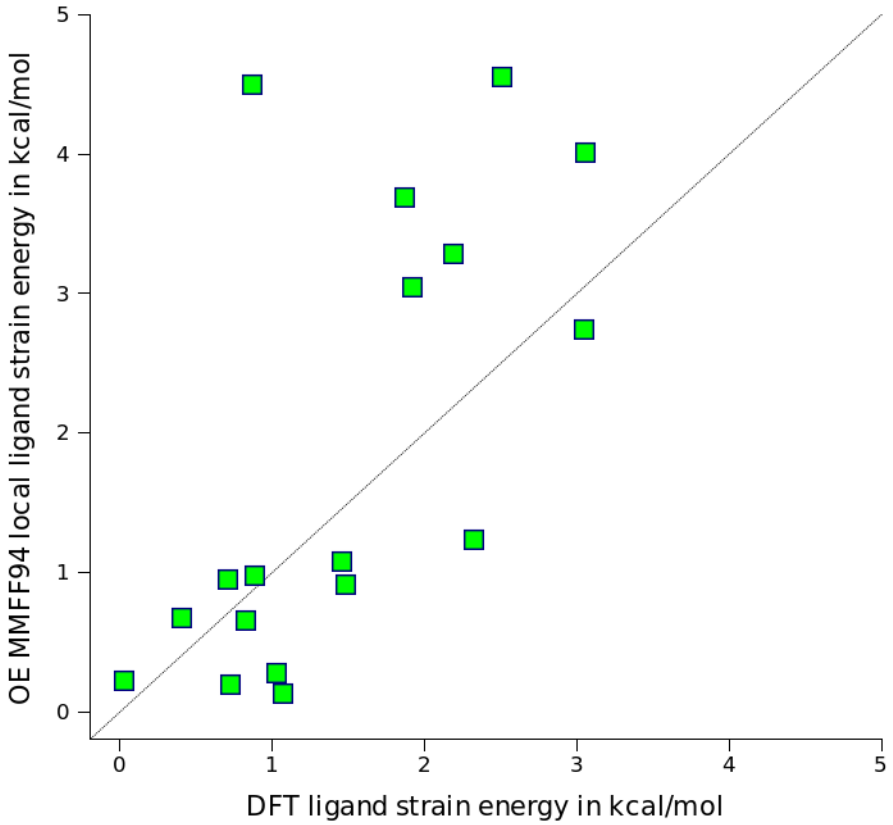
- OpenEye helper file
  - BUSTER gets MMFF94 energy for ligand
  - Force field applied instead of conventional restraints
- Consistent treatment
  - AFITT ligand fit
  - BUSTER refinement
  - Strain energy assessment post refinement



2h7p BUSTER re-refinement with MMFF94s for ligand local strain energy < 1.0 kcal/mol

Validation by Dr. Oliver Smart

- PDB ligand structures reported by Sitzmann *et al*. to have hig local strain energy using DFT
- Select 19 examples
  - Refine in BUSTER with DFT o MMFF94s
  - Determine local strain energy
- BUSTER DFT results
  - Low strain energy (<5 kcal/mol
- BUSTER MMFF results
  - strain compares well to DFT
- CPU time
  - DFT days
  - MMFF94 negligible



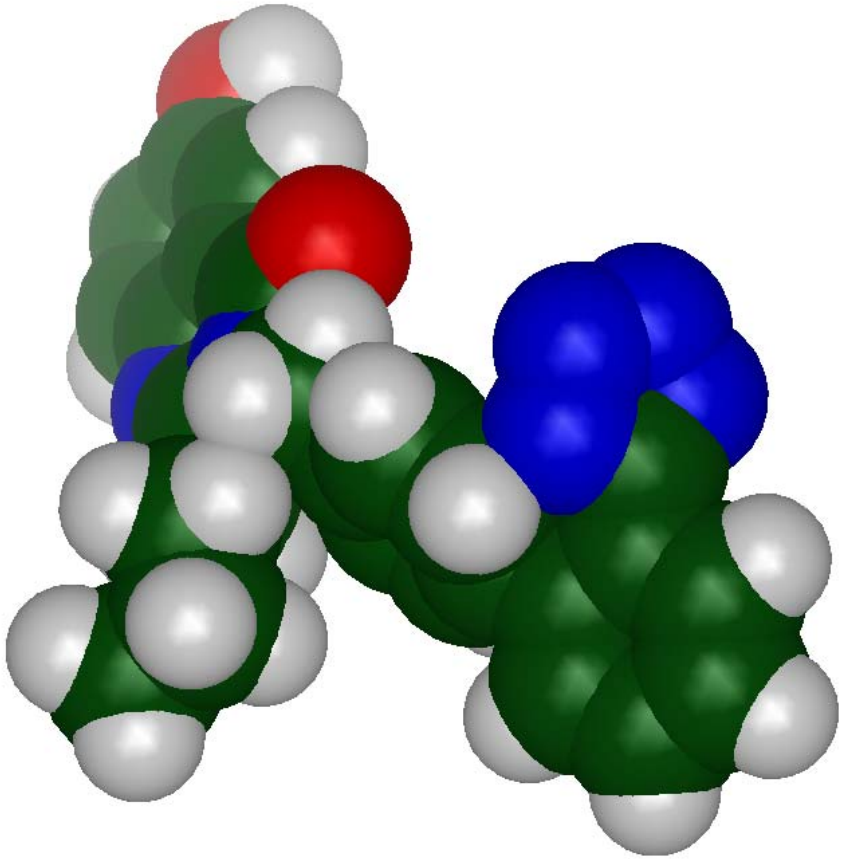
GΦL
Global Phasing Limited

M. Sitzmann *et al., JCIM,* **52,** 739 (2012).

OpenEye Scientific Software

Summary

- AFITT
  - Automatically
    - Find density
    - Fit ligand
    - Generate a dictionary file
  - Low strain
  - 3 ligand scoring methods
    - RSCC
    - Docking scores
      - PLP
      - Chemscore
  - Strain



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- Oliver Smart
- Gerard Bricogne

OpenEye Scientific Software

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