LIGANDS Meetings

- Previously:
  - Developer ⟶ Users
- Now (also):
  - Users ⟶ Developers
  - There are issue/problems with CCP4 software
  - Should the developers be held to account?
  - If so, by whom?

Accountability Tracking, Bugs, Issues, Feature Requests

Accountability Tracking: Bugs, Problems and Issues Arising from the Ligand Fitting Trials

Program	Issue	Type	Date	Progress	Description	Dev Comment
Acedrg	SMILES annotation string terminates execution	Severe	26/09/2016	In repo EXP		
	COD vs CSD-based Acedrg for drug-like molecules	Severe	26/09/2016		Does the CSD provide enrichment?	
	SMILES annotation string for residue name	Moderate	26/09/2016	In repo EXP		
	It's slow	Moderate	26/09/2016			Fix will be in next CCP4 update
CCP4i2	Refinement Duplicate/truncated H atom names	Severe	26/09/2016			
	Remove Acedrg interface RDKit Conformers	Moderate	26/09/2016			
	Raise awareness of pyrogen	Low	26/09/2016			
	File for SMILES input	Low	26/09/2016			
	Refmac R-factor graph with no points is ugly	Low	26/09/2016		There's a graph. There are no points plotted	
	Acedrg output Picture too small	Low	26/09/2016			
	still too slow on a remote NFS to be usable	?	26/09/2016			
	Interface to Dimple?	Investigate	26/09/2016		For more automated ligand fitting	
Coot	All ligands are INH, handle dictionaries for each	Severe	26/09/2016	in master		Tricky
	Ligand Expert should be on by default	Moderate	26/09/2016	in master	Don't make me use configuration	In repo now, will be in next release
	Tidy up menu for Ligand tools	Moderate	26/09/2016			planned to be in 0.8.8
	Enable SRS searching in Lidia	Moderate	26/09/2016	in master		
	GUI availability of top-N solutions	Low	26/09/2016	in master		
	Ligand Fit Post-Refine checkbutton	NiceToHave	26/09/2016	in master		
	Better GUI on conformer generation	NiceToHave	26/09/2016	in master		Involves timeouts or threads
	Can we fit these ligands without intervention?	Investigate	26/09/2016			Research project - may need to redo ligand fitt
Lidia	Chirality failure on Acedrg dict → 2D	Severe	26/09/2016	in master		
	SMILES → 2D chirality failure	Severe	26/09/2016			
	What is happening when you press the apply button?	Moderate	26/09/2016		Tell me what's running and how it's going	Waiting for a fix in Acedrg output
	Lidia → Acedrg molecule should be *via* mmCIF	Moderate	26/09/2016			Currently is MOL file, move to mmCIF may hel

Important, not done
Moderate importance, not done
Done, available now/soon
Reseach Project
No Feedback

Minutes: Items to add to Tracker

- Atom name matching in AceDRG
- Ability to stop hydrogen shuffling in AceDRG

Minutes: Items to deleted from Tracker

- CCP4i2 Dimple interface

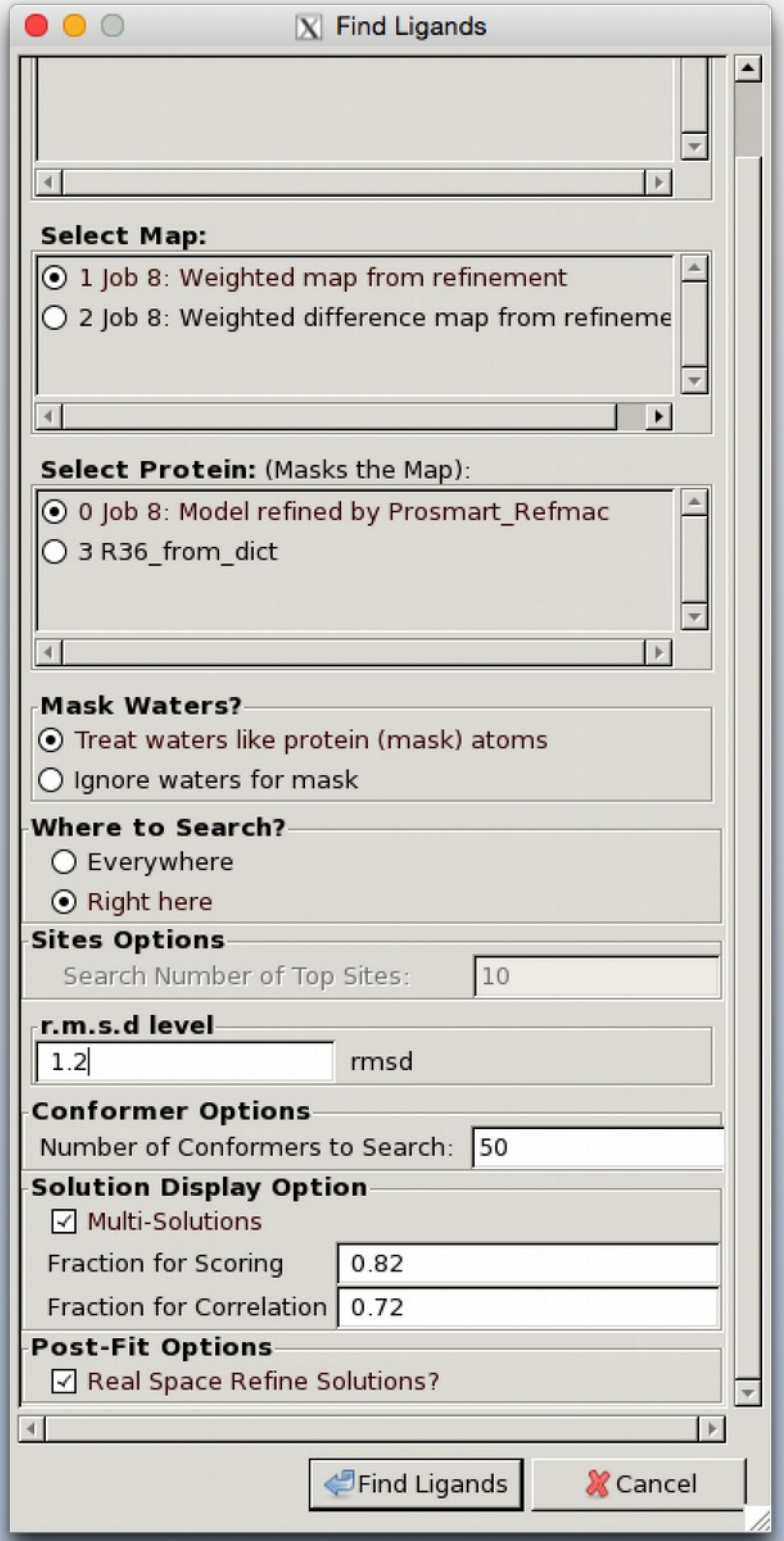
Coot Updates

Dec 2016

Coot Updates

- Coot 0.8.7 released
  - Lidia Canvas scaling
  - Lidia CH_3 Superatoms
  - Corrected bonds for WO4
  - File ⟶ SMILES removed
  - GUI/widget updates
    - as suggested by the previous meeting

Ligand Fitting Interface

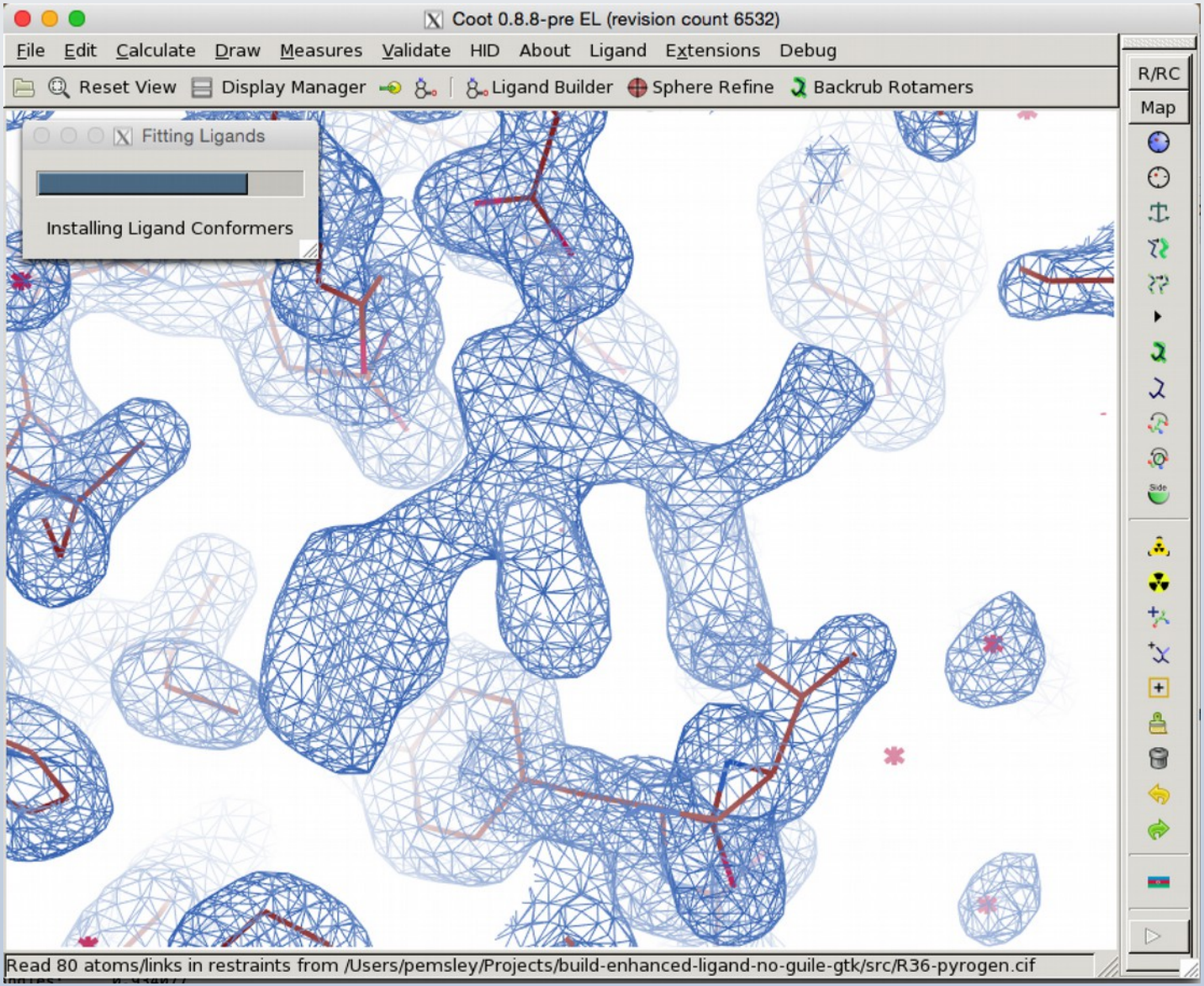


Conformer Enumeration Expert Mode

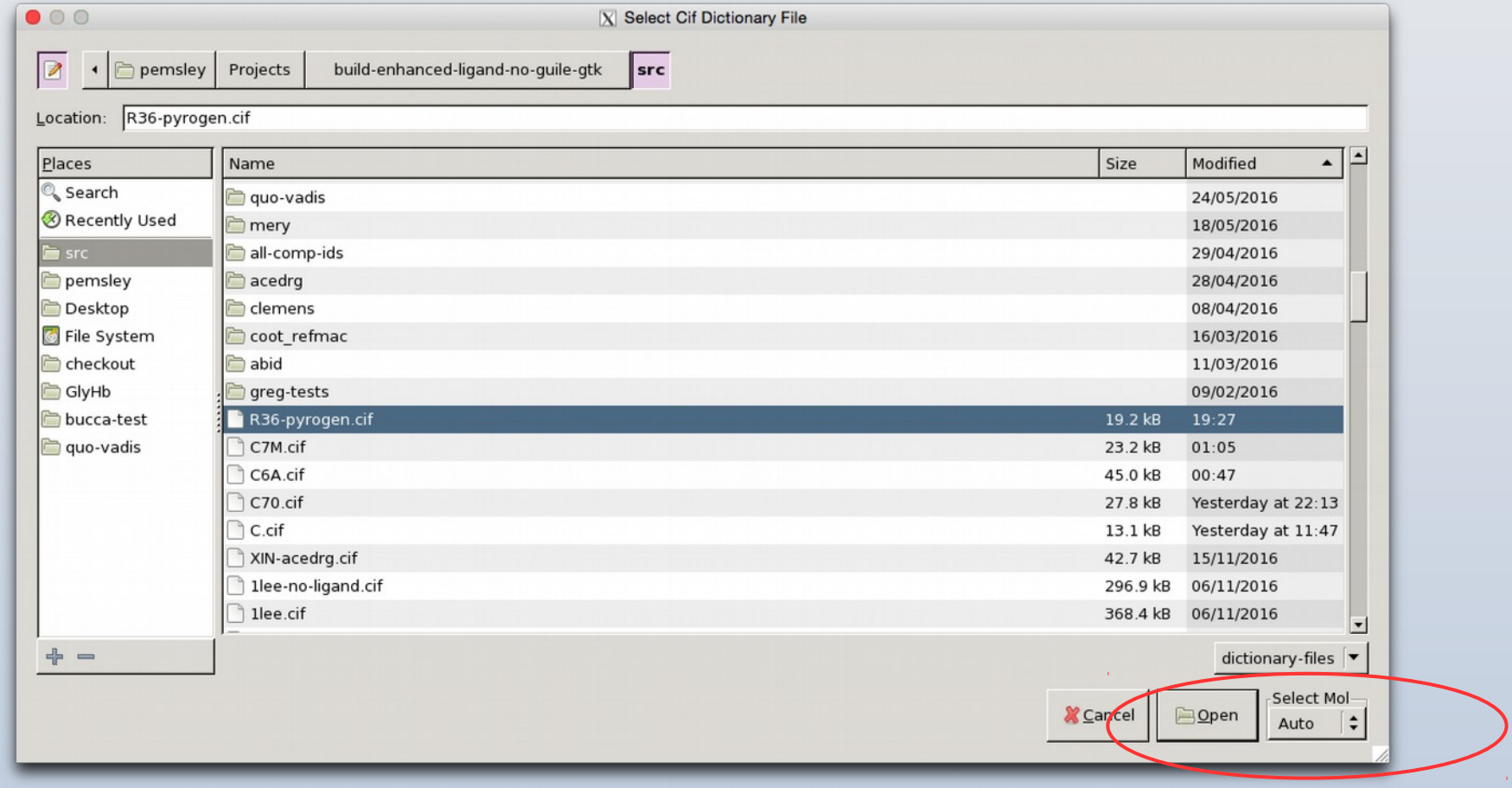
Multi-Solution

Post-Refinement

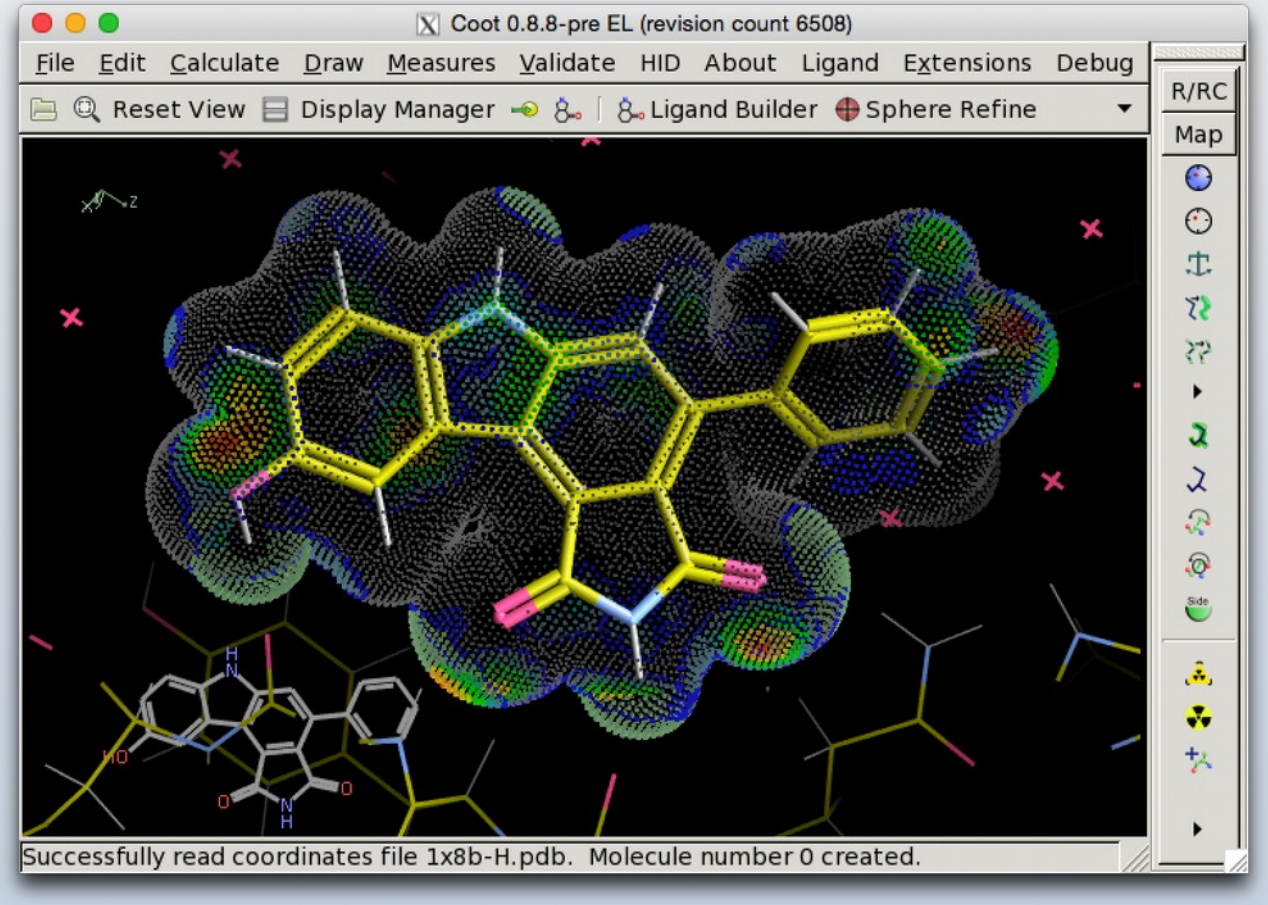
Ligand-Fitting Interface



Molecule-specific Dictionaries



New: *Coot* Ligand Interactions

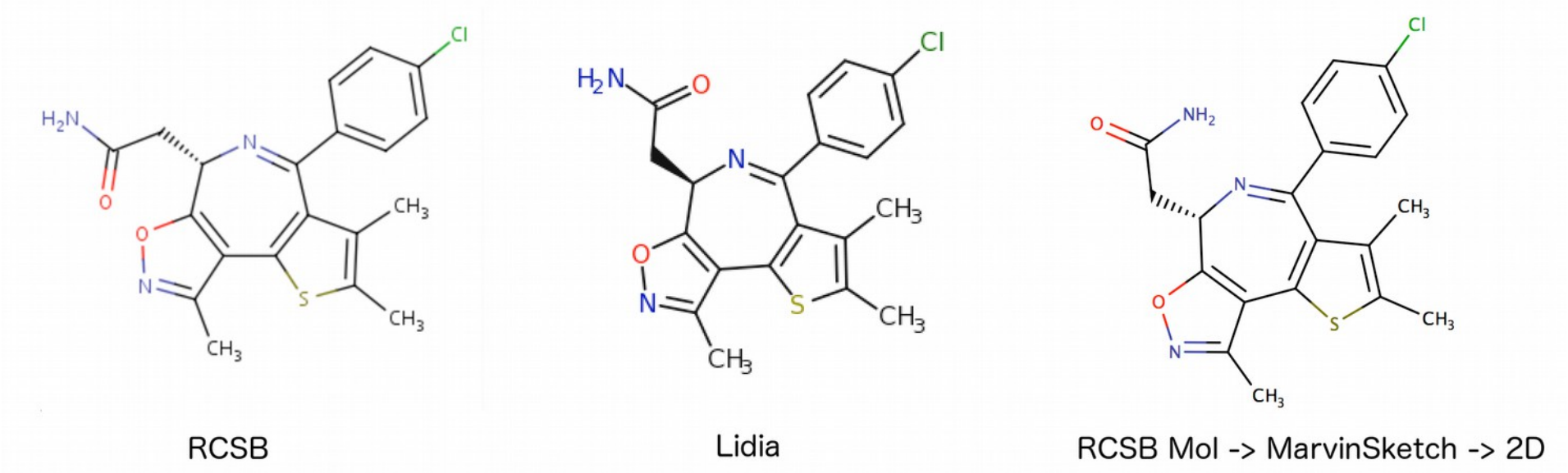


“Reduce” & “Probe”:

Protein (including HIS), RNA, DNA, Ligands

But not OH optimisation by clique analysis

1XB: an Example of the Chirality Problem

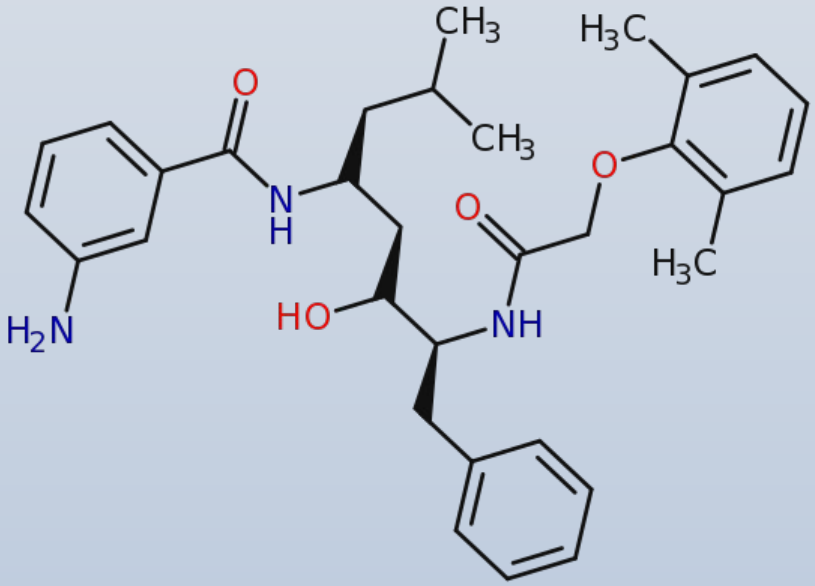


C14 has “S” pdbx stereo config

Ligand Fitting Trials 2

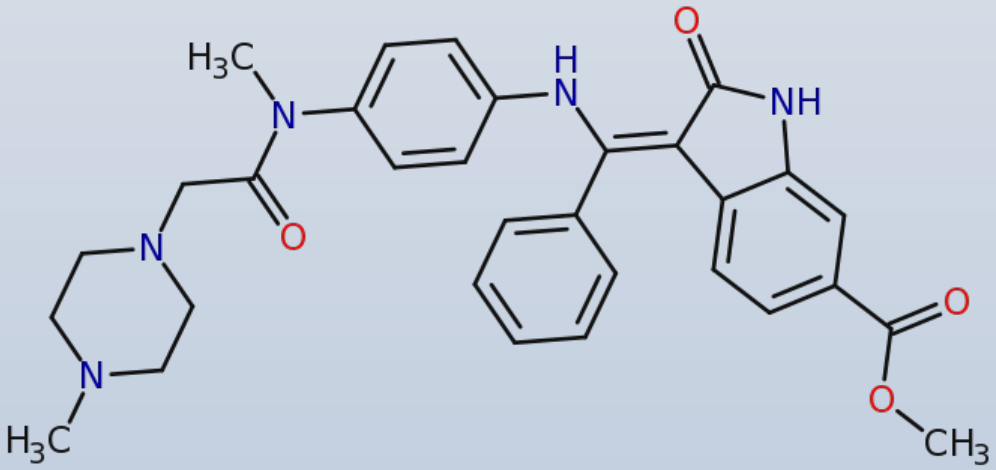
Ligand Fitting Trials 2: Dec 2016

- Problem 1:
  - Target: Plasmodium falciparum enzyme (an aspartic acid protease), important in malaria pathology
  - Resolution 1.9 Å
  - R-factor 23.6%



Ligand Fitting Trials 2: Dec 2016

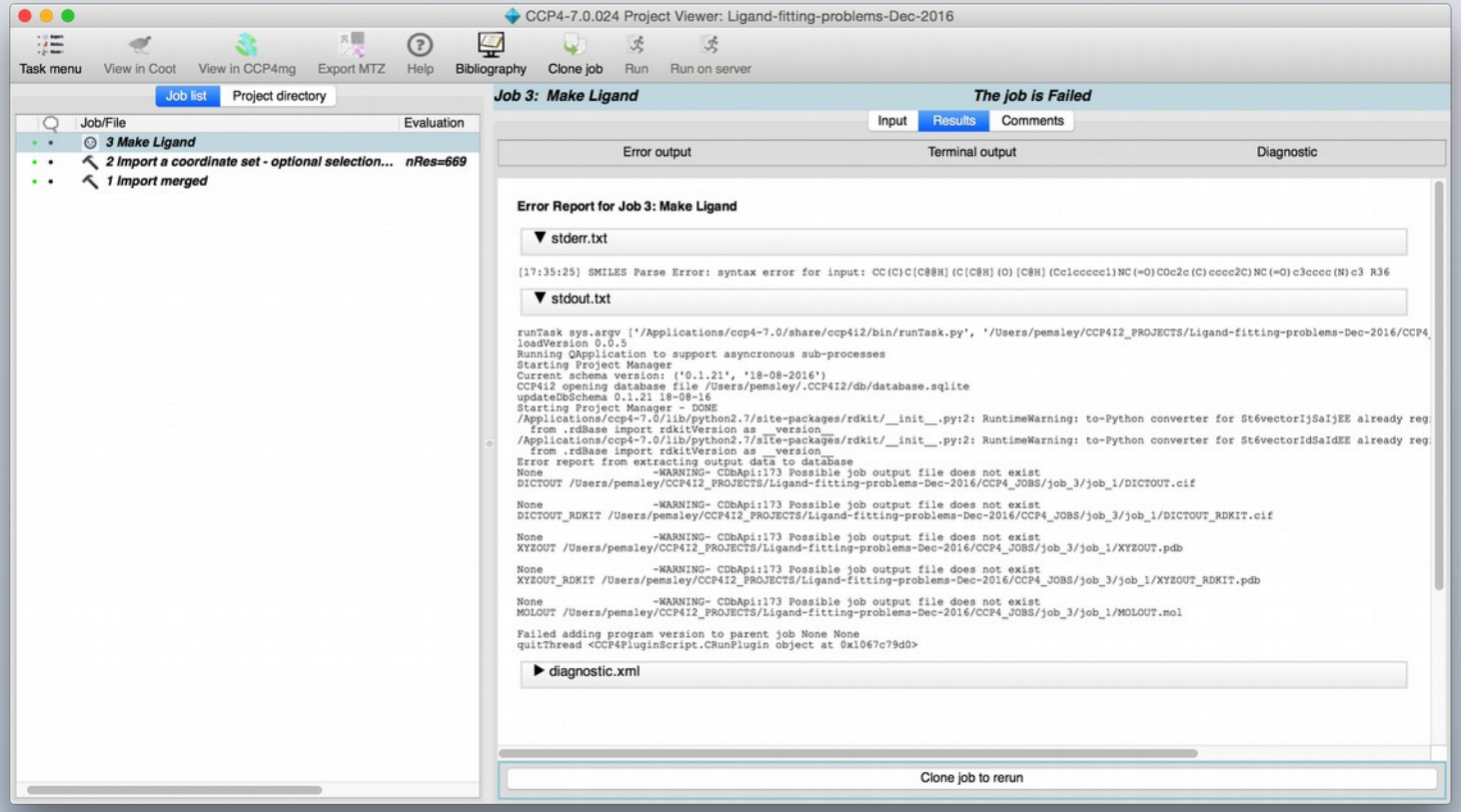
- Problem 2:
  - Adaptor Protein 2 Associated Kinase (AAK1)
  - Structural Genomic Consortium
  - Resolution 1.9 Å
  - R-factor 18.1%



“User” Hat

Problem 1: Acedrg Still Fails

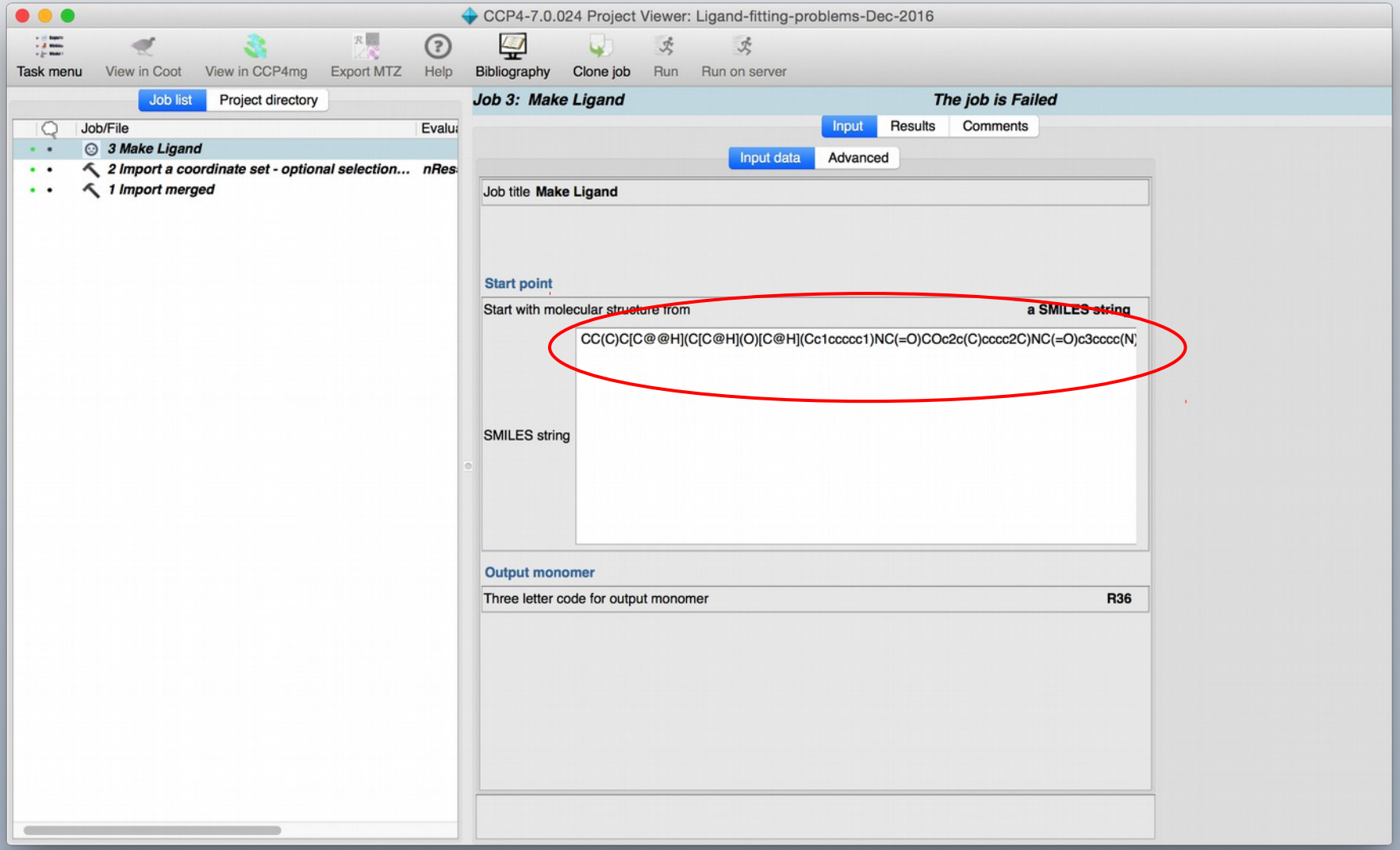
Cut and paste annotated SMILES string



CCP4 version 7.0.024
CCP4i2 version: 0.05
Acedrg version: ???

Problem 1: Acedrg Still Fails

- Vast space, uneditable SMILES string



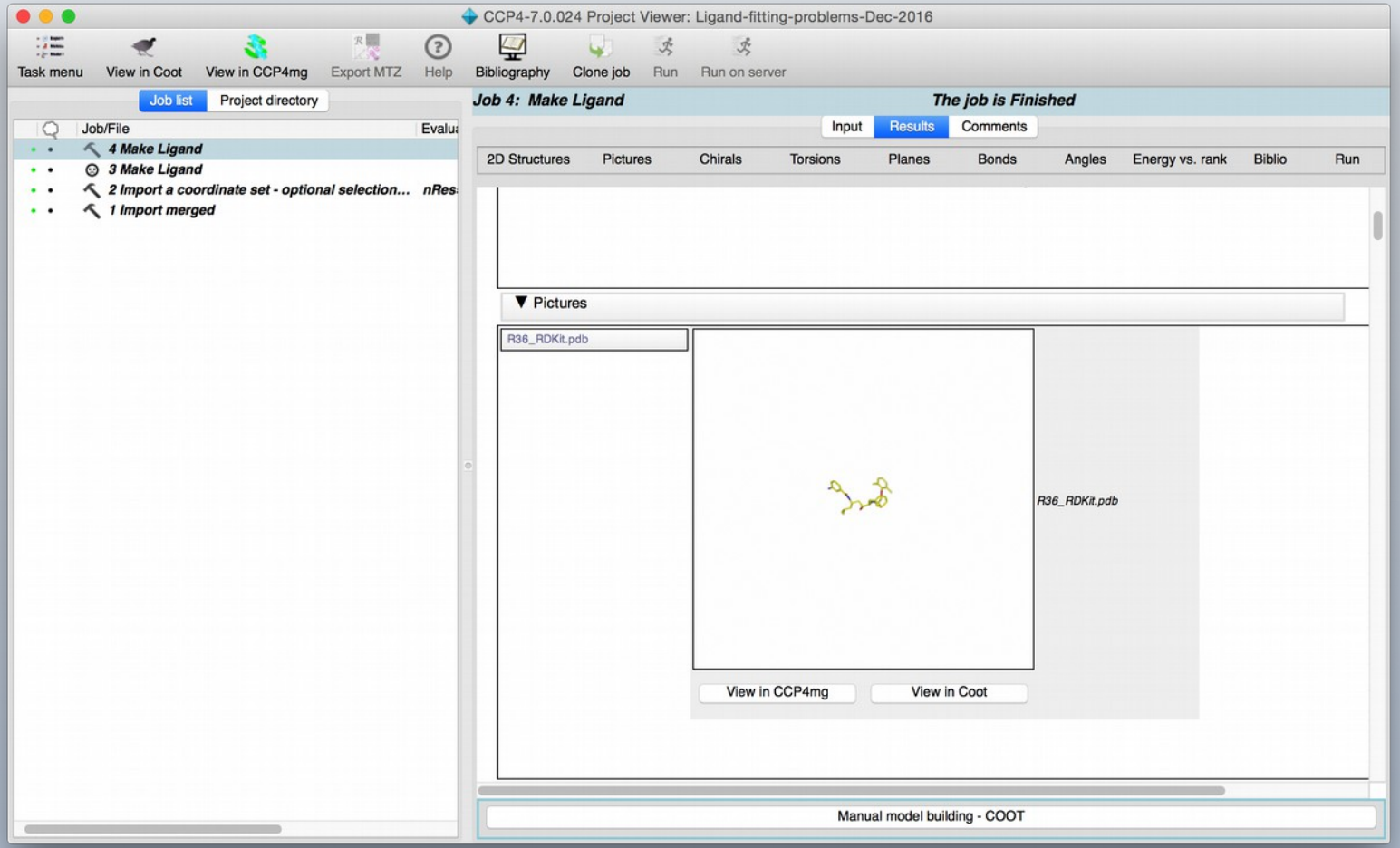
Problem 1: Acedrg Interface Fail

- (Still) no mechanism to provide a dictionary, a list of dictionaries, a list of three letter codes for reference atom name matching

- EJD: We need a program that will take a molecule description (e.g. SMILES, mol) and provide a list of molecules in the CCD that are similar
  - And CCP4i2 interface to this

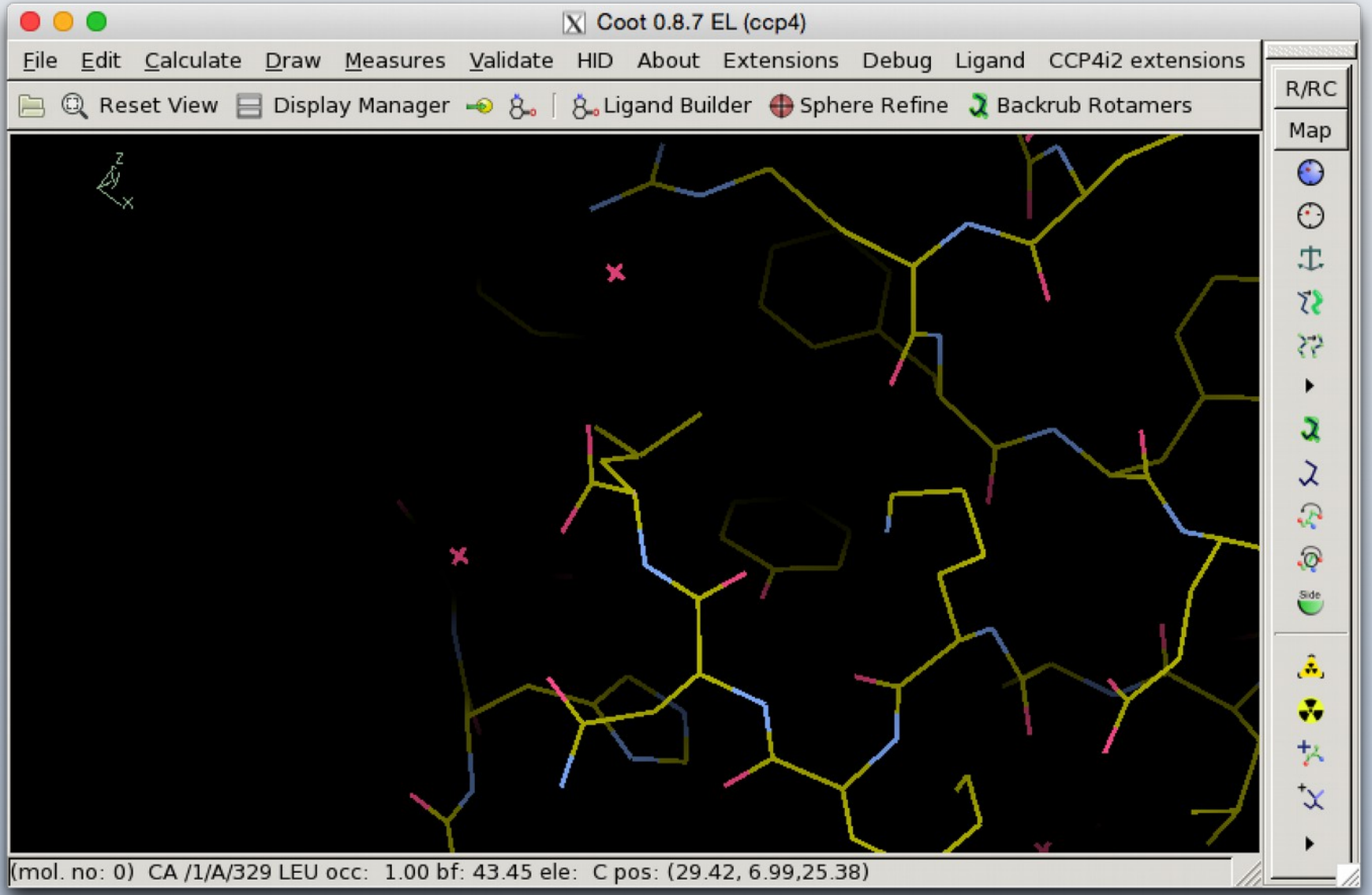
Problem 1: CCP4i2 Pictures Fail

- Still too small to be useful



Problem 1: Ugly *Coot*

- CCP4 Build of *Coot* for Mac is not antialiased:



Problem 1: Refmac Fails to Run

- OXT in residue LEU at C-terminus

```
 PDB_code:1LEE
 PDB_name:plasmepsin, aspartic protease, plasmodium falciparum, HYDROLASE
 PDB_date:XX-XXX-XX
 ------------------------------
 ERROR : atom :OXT  LEU               329  A    is absent in the library
 ATTENTION: atom:OXT  HOH              1341  A    is missing in the structure
 WARNING : HOH      1341 A     : back_atom for OXT  is absent
 Number of chains                  :       1
 Total number of monomers          :     669
 Number of atoms                   :    6185
 Number of missing atoms           :       1
 Number of rebuilt atoms           :    2539
 Number of unknown atoms           :       1
 Number of deleted atoms           :       0
 IERR =            1

There is an error. See above
===> Error: Fatal error. Cannot continue
```

Problem 1: *Coot* Flexible failed using Acedrg Dictionary

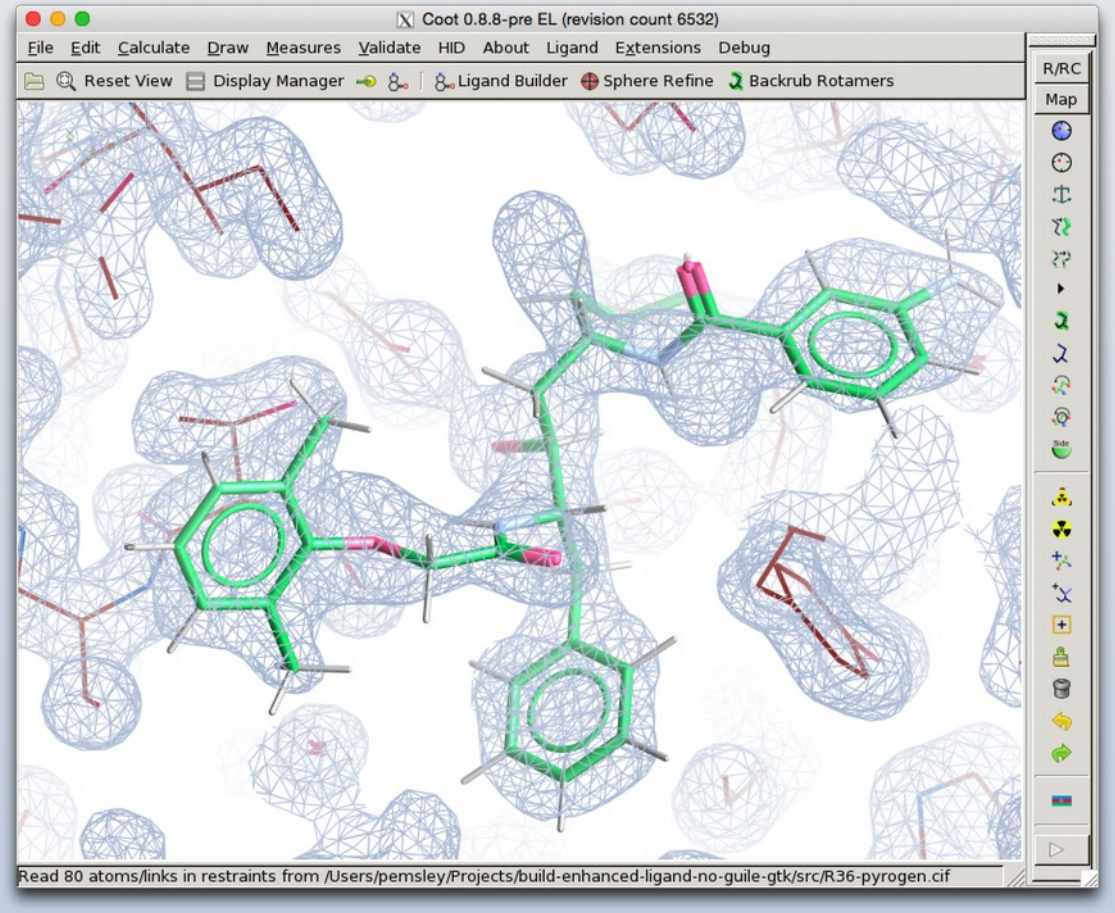
- Exited immediately with error message

```
ERROR: in install_simple_wiggly_ligands() Atom
name(s) not found in residue. Unassigned atoms:
" H1 "
```

- Non-conformer fit search Failed also
  - Acedrg conformer very unlike the density

Problem 1: Ligand Fitting with Pyrogen Dictionary

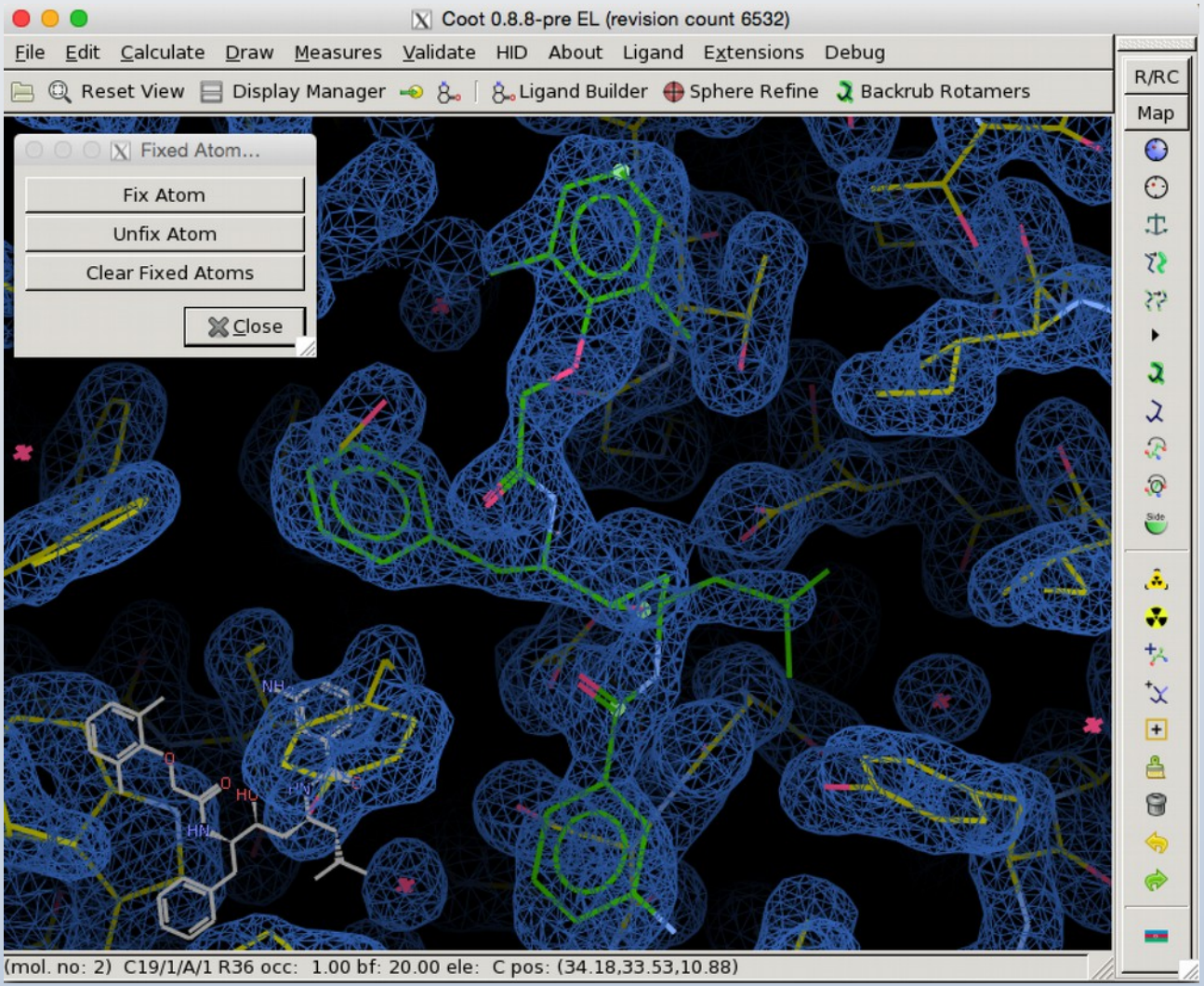
Increased to
200 Conformers



The amino group of the amino-benzamide is flipped out

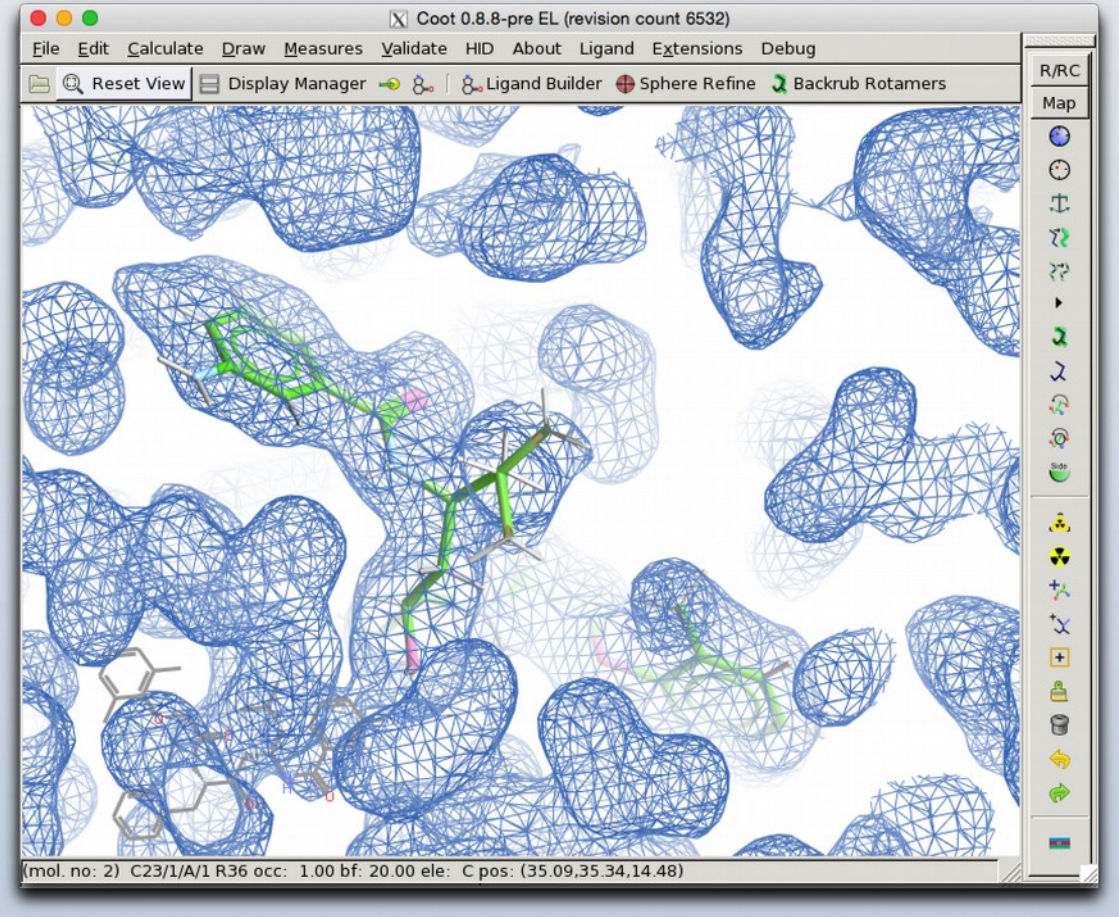
Why? Hint, hint!

Problem 1: (Back to Acedrg dictionary): Use Fixed Atoms



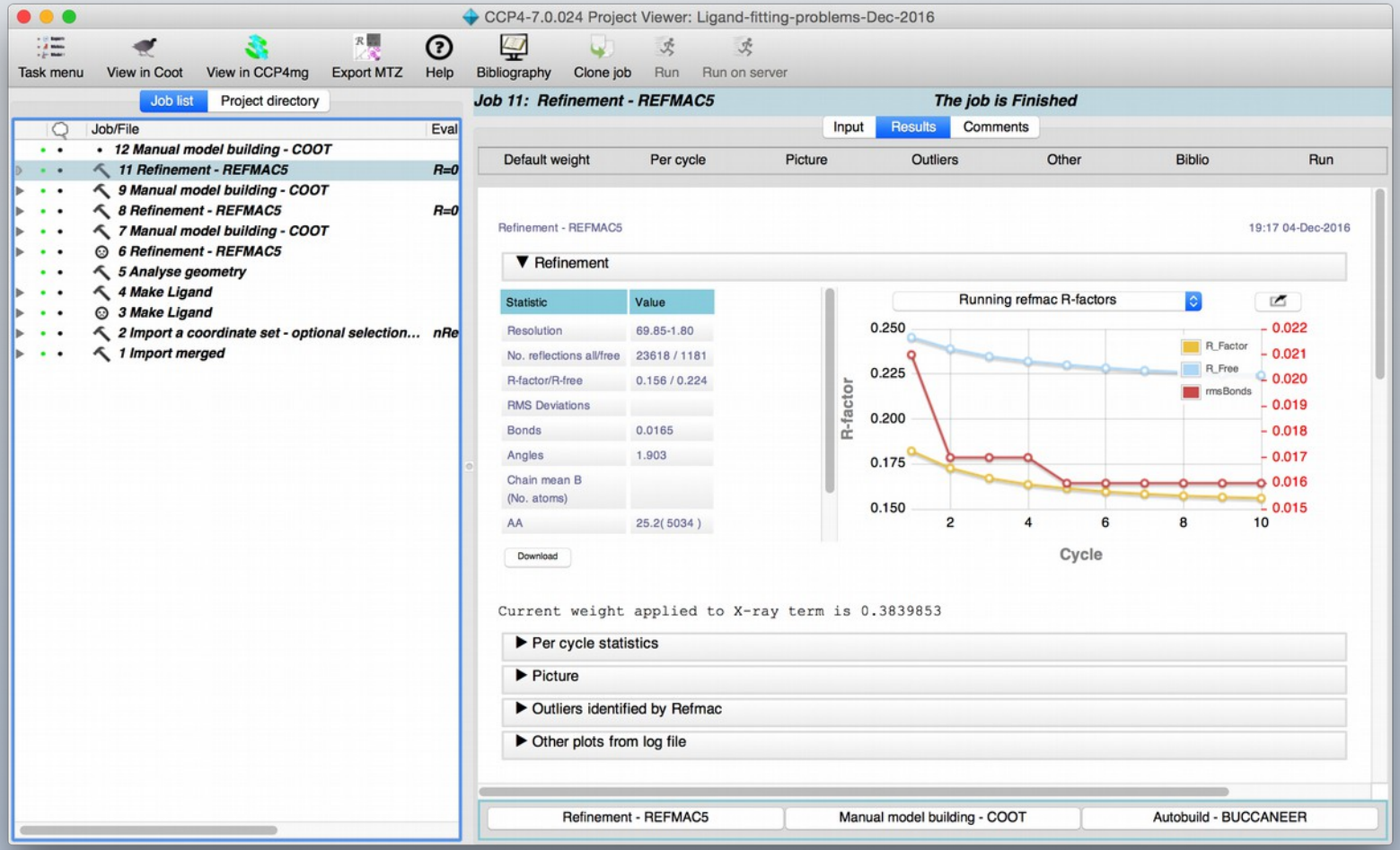
Fix Atoms (Green Spots) and drag them into place (very manual)

Problem 1: JED-Flip the “Valine” sidechain

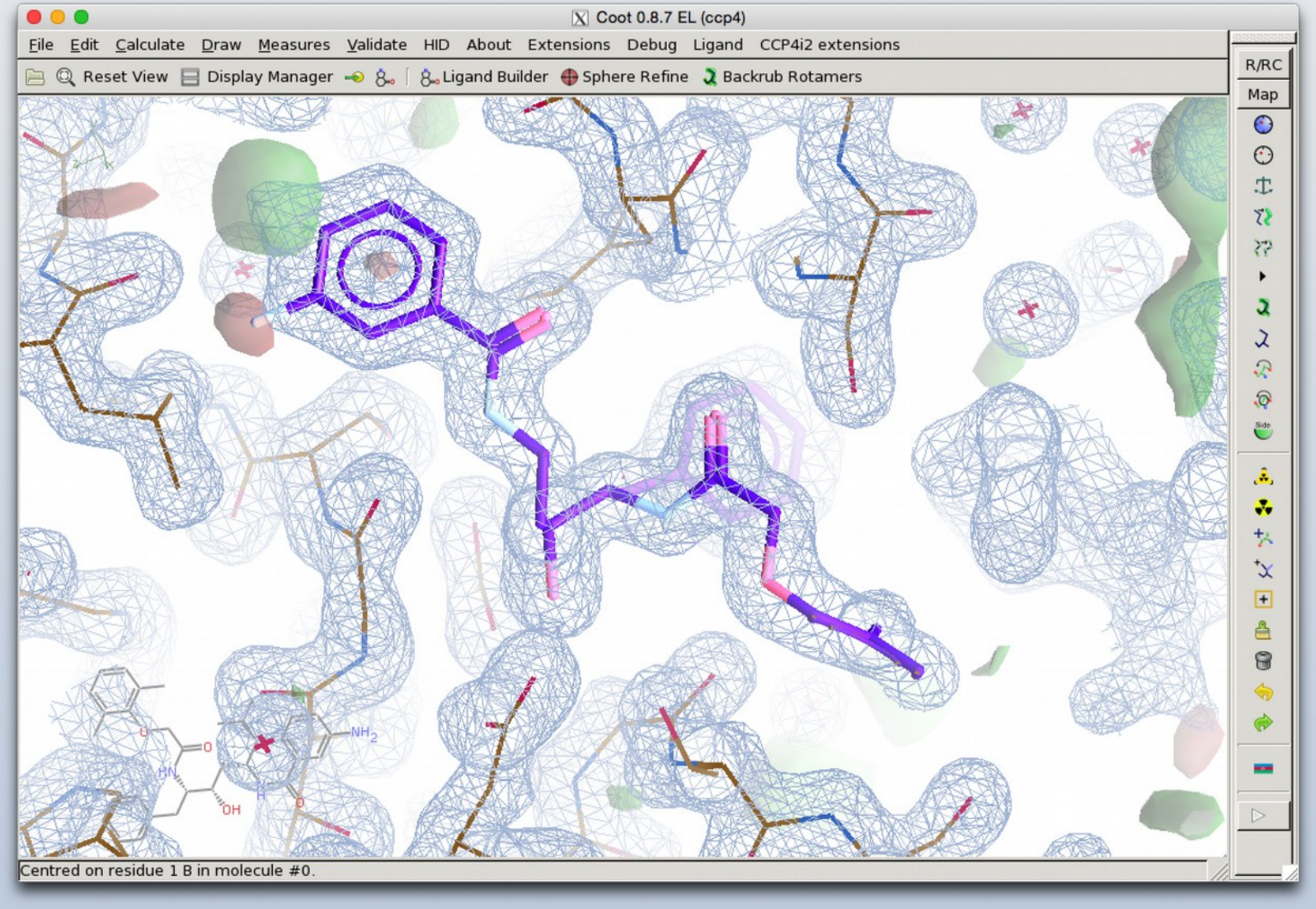


Refmac in CCP4i2

- Works OK

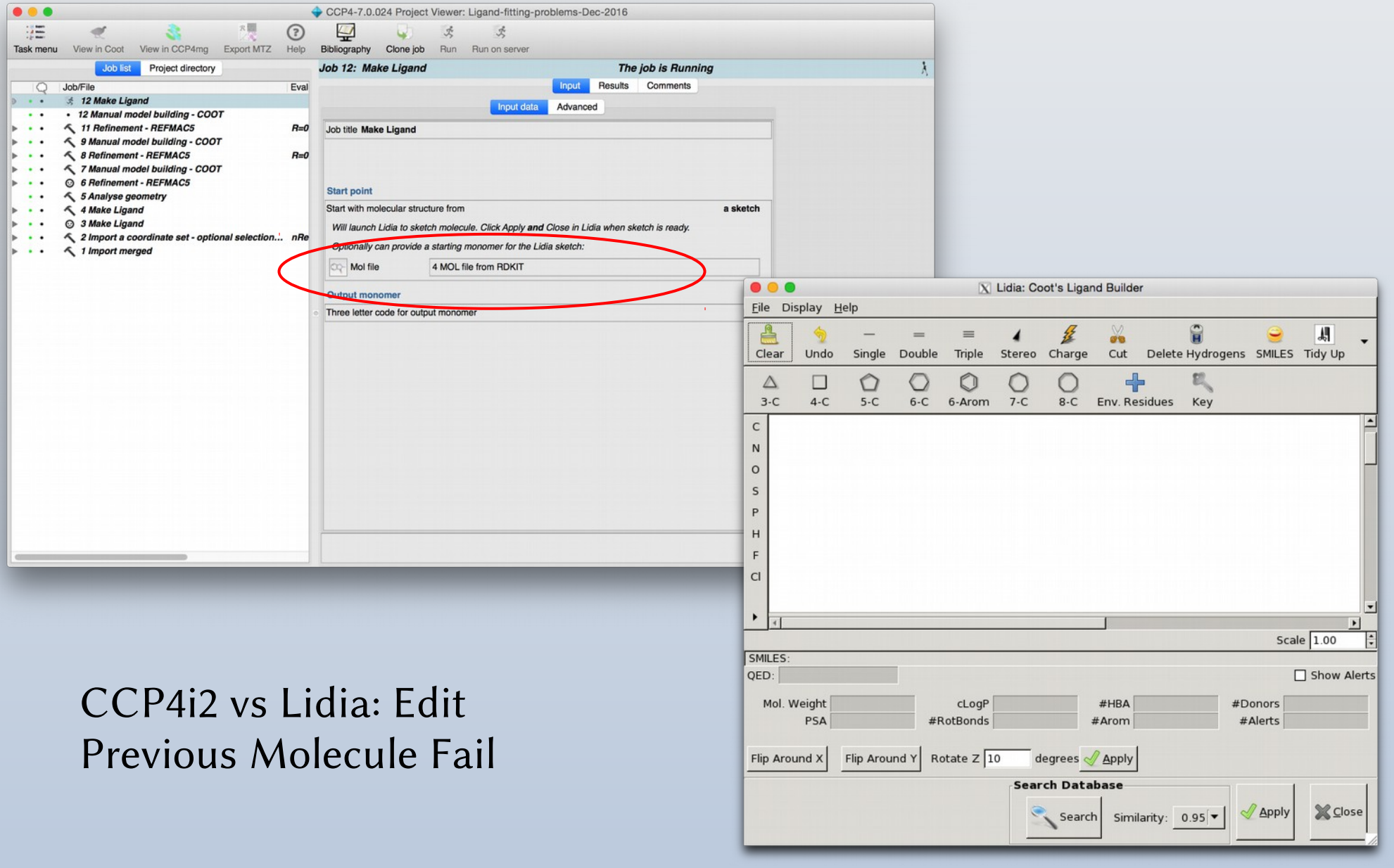


Problem 1: Is it the right ligand?



No, it isn't

Edit the Molecule: How?

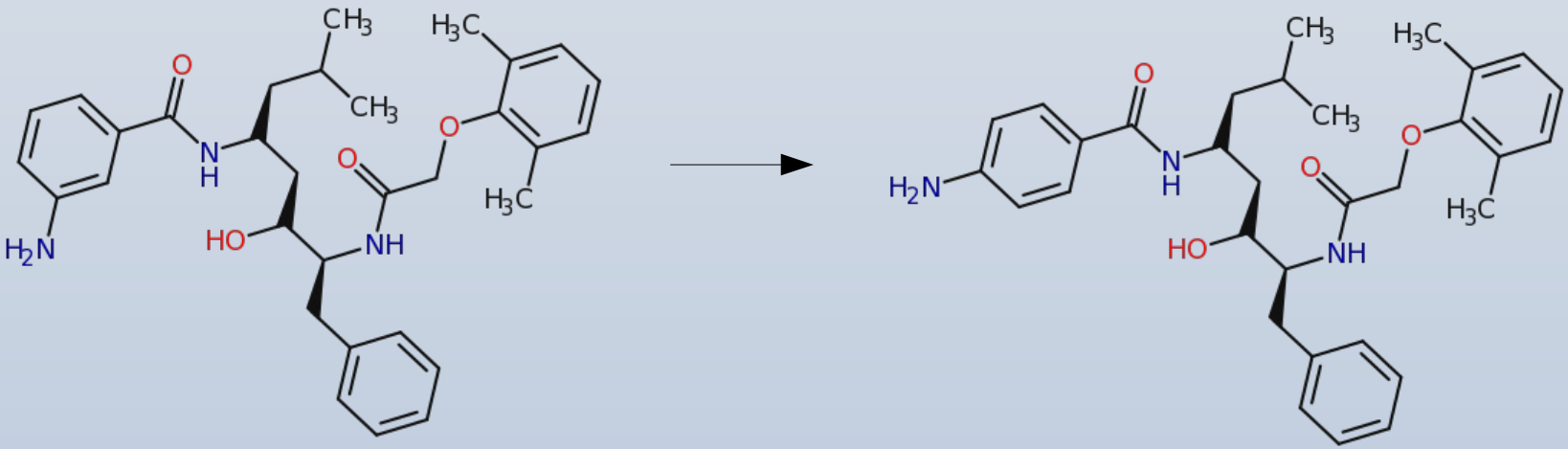


CCP4i2 vs Lidia: Edit Previous Molecule Fail

meta ⟶ para

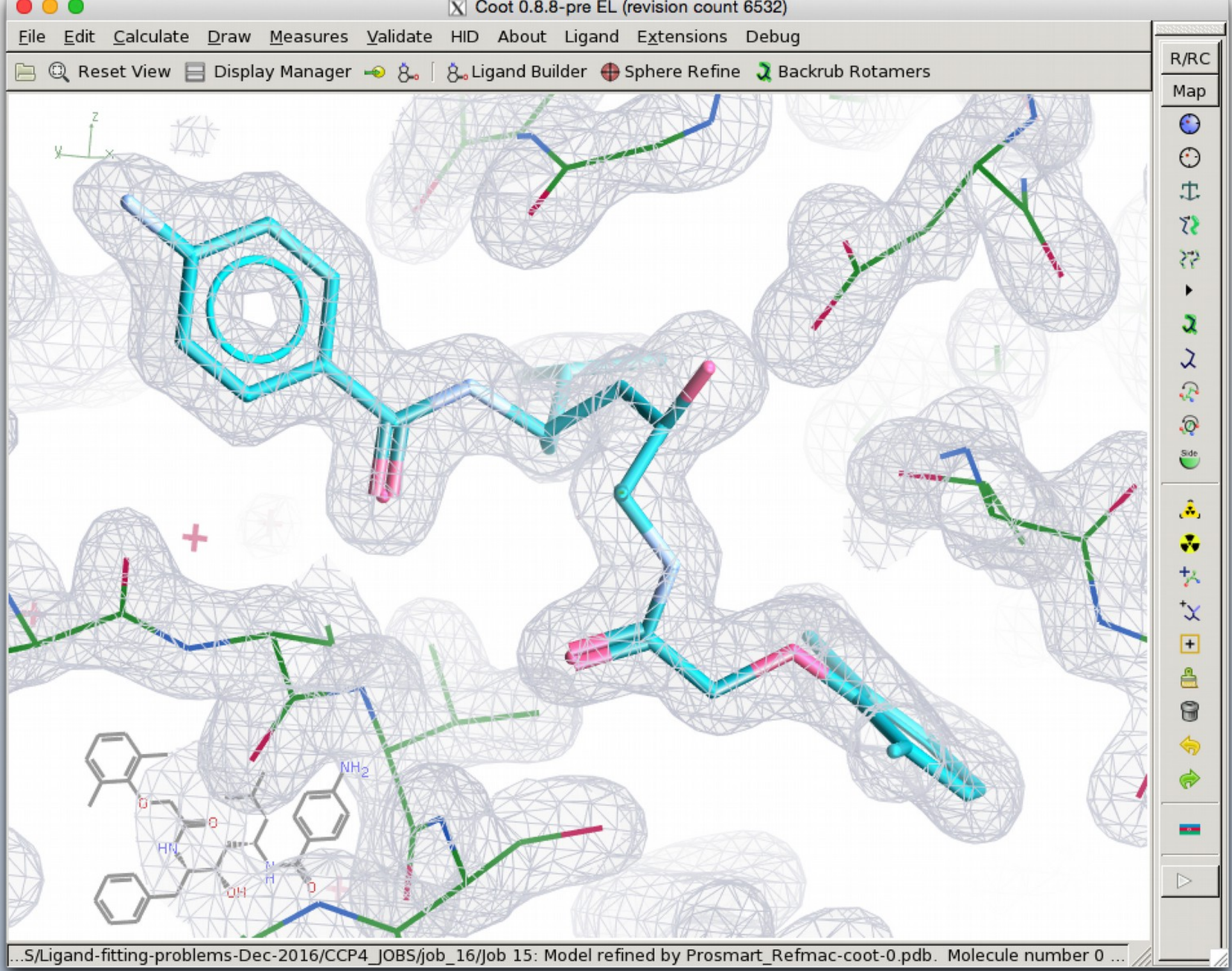
So, back to Lidia…

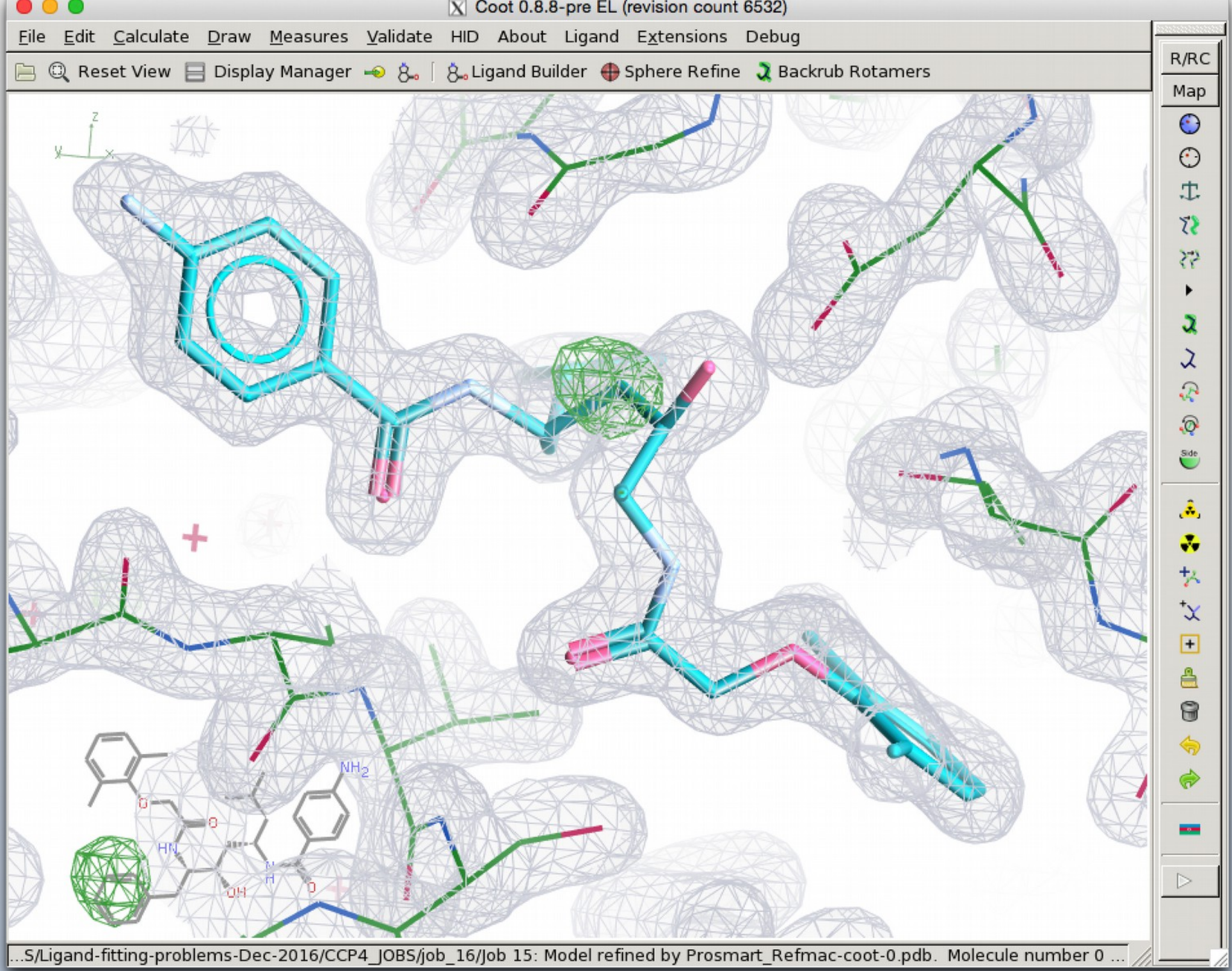
Read in SMILES string
Edit molecule
Apply

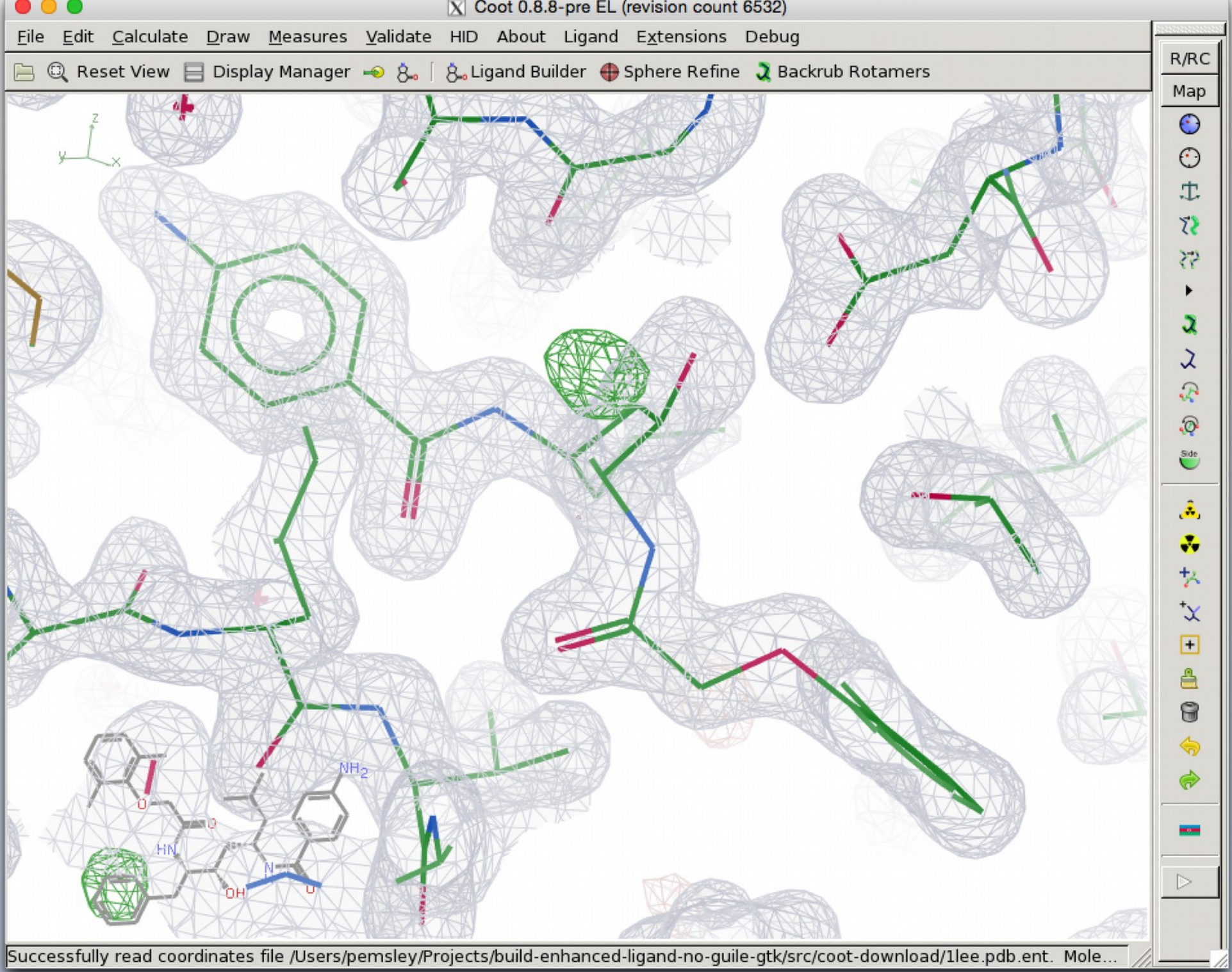


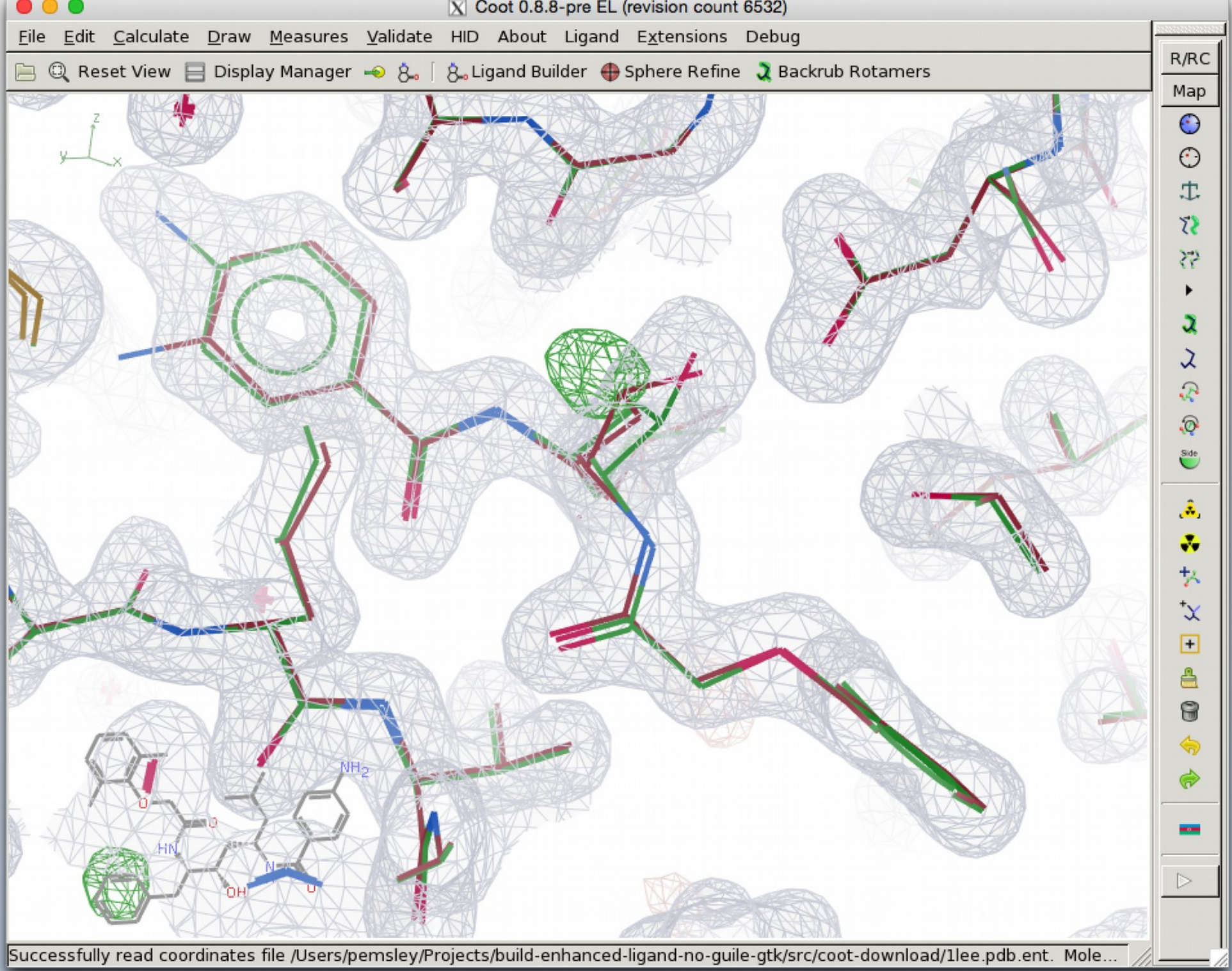
Re-refine

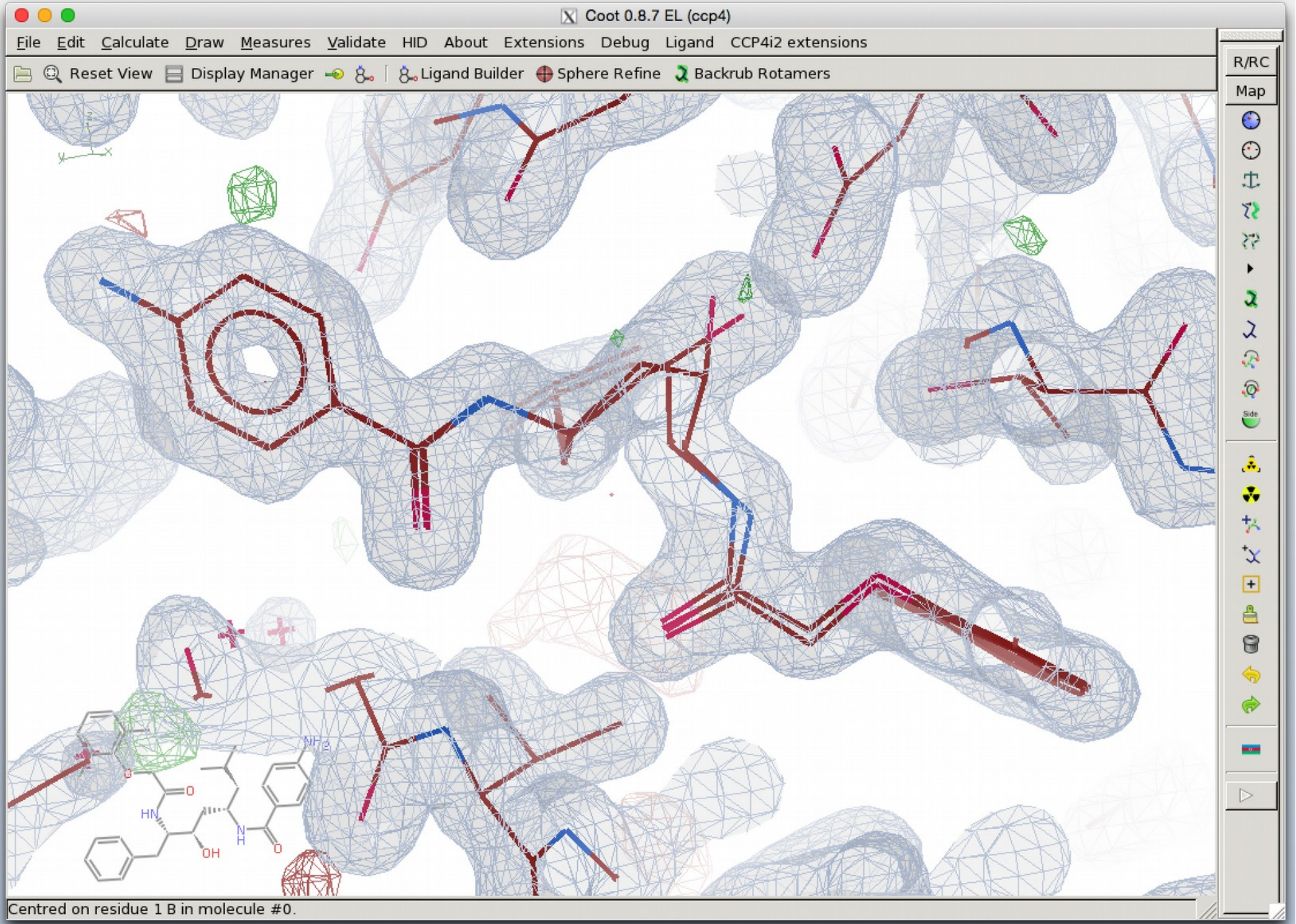
- In the updated, Acedrg dictionary, the atom names are the same, one bond is different
  - Read old model and use new dictionary
  - RSR Refine
    - Not needed of course, once the above is recognised
  - Refmac
  - Works fine now, inconsistent chirality of C19
  - R and R-free 15.6% 22.4%


Coot 0.8.8-pre EL (revision count 6532)
File Edit Calculate Draw Measures Validate HID About Ligand Extensions Debug
Reset View
Display Manager
Ligand Builder
Sphere Refine
Backrub Rotamers
R/RC
Map
Side
NH2
HN
OH
...S/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_16/Job 15: Model refined by Prosmart_Refmac-coot-0.pdb. Molecule number 0 ...

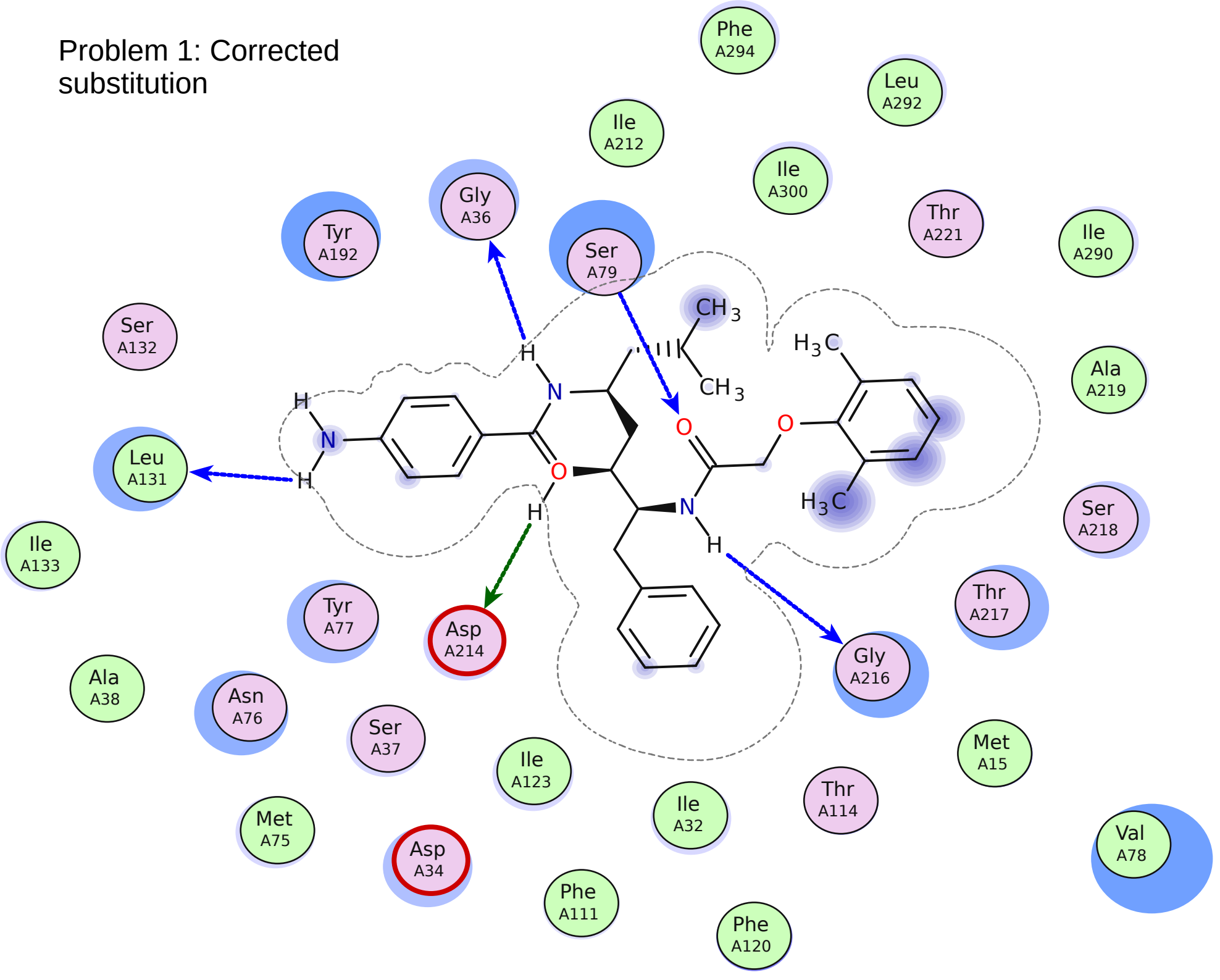

Coot 0.8.8-pre EL (revision count 6532)
File Edit Calculate Draw Measures Validate HID About Ligand Extensions Debug
Reset View
Display Manager
Ligand Builder
Sphere Refine
Backrub Rotamers
R/RC
Map
Side
NH2
HN
OH
...S/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_16/Job 15: Model refined by Prosmart_Refmac-coot-0.pdb. Molecule number 0 ...


Coot 0.8.8-pre EL (revision count 6532)
File Edit Calculate Draw Measures Validate HID About Ligand Extensions Debug
Reset View
Display Manager
Ligand Builder
Sphere Refine
Backrub Rotamers
R/RC
Map
Side
NH2
HN
OH
N
O
Successfully read coordinates file /Users/pemsley/Projects/build-enhanced-ligand-no-guile-gtk/src/coot-download/1lee.pdb.ent. Mole...


Coot 0.8.8-pre EL (revision count 6532)
File Edit Calculate Draw Measures Validate HID About Ligand Extensions Debug
Reset View
Display Manager
Ligand Builder
Sphere Refine
Backrub Rotamers
R/RC
Map
Side
NH2
HN
OH
N
O
Successfully read coordinates file /Users/pemsley/Projects/build-enhanced-ligand-no-guile-gtk/src/coot-download/1lee.pdb.ent. Mole...


Coot 0.8.7 EL (ccp4)
File Edit Calculate Draw Measures Validate HID About Extensions Debug Ligand CCP4i2 extensions
Reset View
Display Manager
Ligand Builder
Sphere Refine
Backrub Rotamers
R/RC
Map
Centred on residue 1 B in molecule #0.

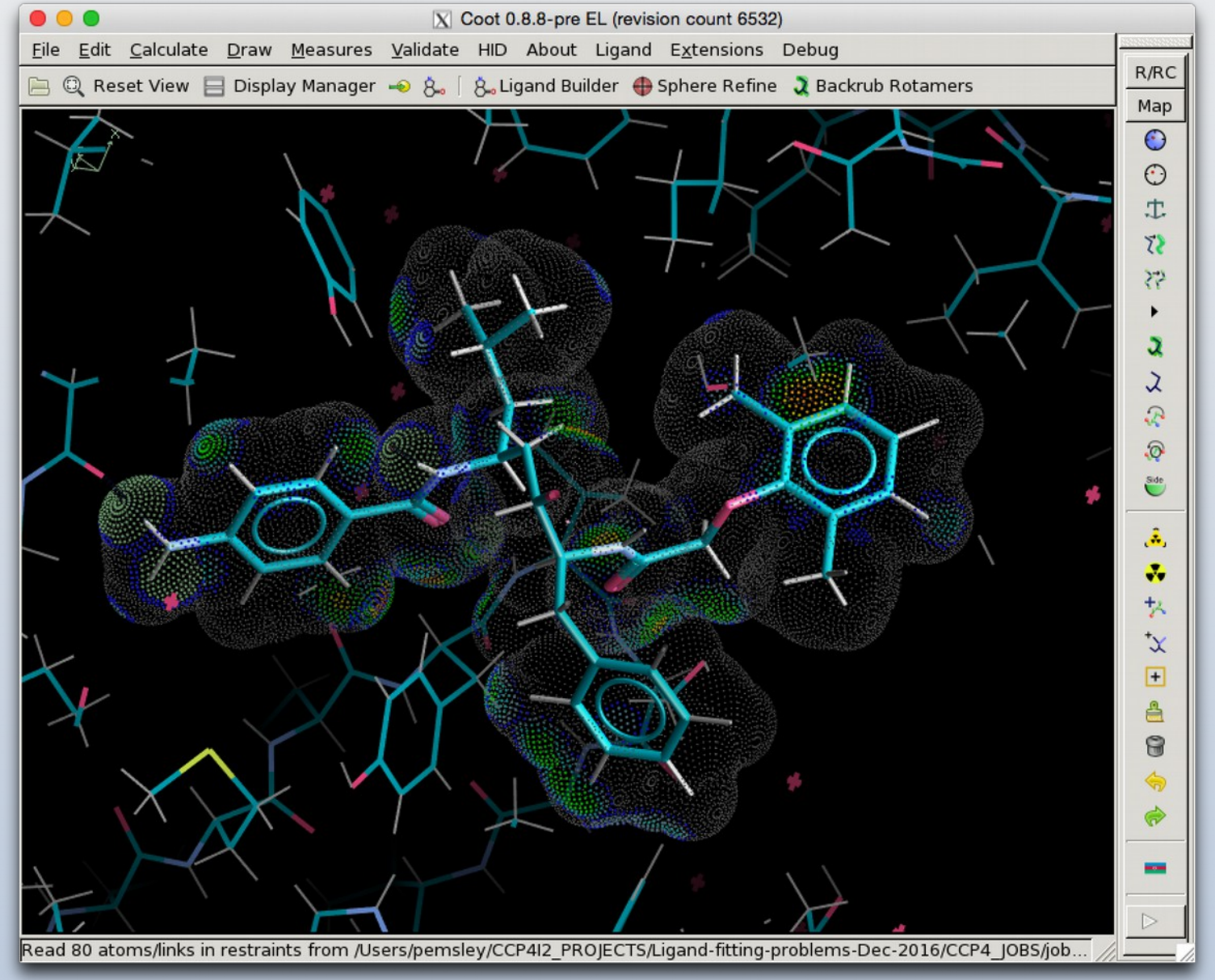
Problem 1: Corrected substitution



Coot Flatland Ligand Environment View

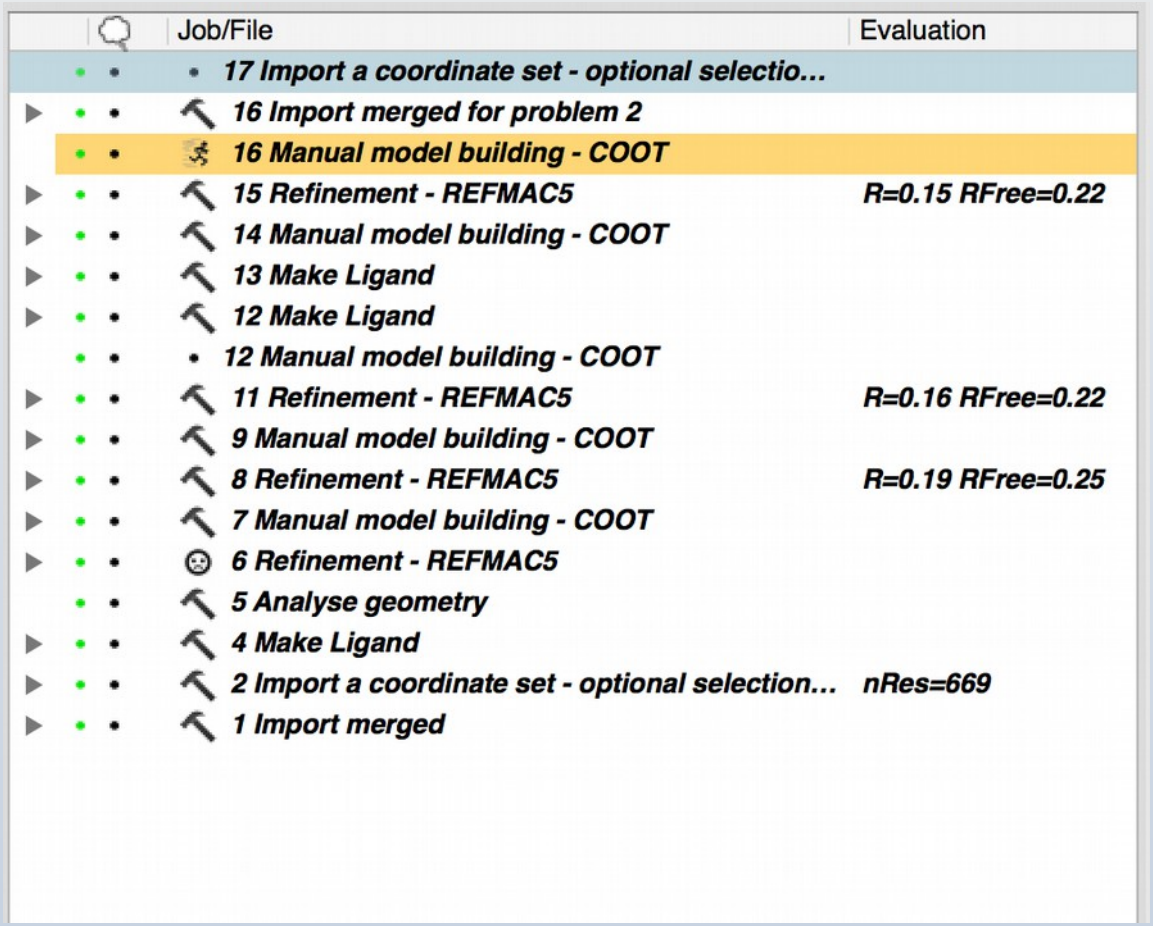
- congestion problems
- SVG, pdf output looks fine
- png output is boxed/truncated

Coot's Probe & Reduce



Pre-release (not release)

Problem 2: Importing



- Two Job 12s, two job 16s. Surely that a mistake?
- All text is ***bold italic*** - ugly

Problem 2: Issues

- Similar issue to Problem 1
  - Acedrg output files fail with multiple conformations in Coot
- Ligand search without conformation search works in this case
- The positions of the hydrogen atoms is important
  - stripping hydrogen atoms when producing the output is a reasonable default… but
  - how do I tell CCP4i2 to leave them on?
    - not obvious to me
- I edited the SMILES string to add H to the piperazine
- RDKit is still being used at the back-end of the Acedrg job

Problem 2: Issues

- I edited the SMILES string to add H to the piperazine
- Stop coot start again
  - XIN dictionary read at start-up
  - Get Monomer
  - No hydrogens!
  - Why...?
  - Because they are not in the dictionary

XIN dictionary from Acedrg

XIN	C24	C	CR16	0.000	0.844	-0.96	-0.644
XIN	C25	C	CR16	0.000	-0.347	-0.356	-0.719
XIN	C26	C	CR6	0.000	-3.137	-0.152	0.738
XIN	C27	C	CR16	0.000	-2.673	-0.057	1.997
XIN	C28	C	CR16	0.000	-2.688	-1.237	2.887
XIN	C29	C	CR16	0.000	-3.156	-2.408	2.443
XIN	C30	C	CR16	0.000	-3.645	-2.528	1.054
XIN	C31	C	CR16	0.000	-3.627	-1.465	0.241
XIN	H1	H	H	0.000	.	.	.
XIN	H2	H	H	0.000	.	.	.
XIN	H3	H	H	0.000	.	.	.
XIN	H4	H	H	0.000	.	.	.
XIN	H5	H	H	0.000	.	.	.
XIN	H6	H	H	0.000	.	.	.

- Acedrg need to output correct Hydrogen atom names with coordinates

CCP4i2 & *Coot*

- Running Refmac
  - Makes CCP4i2 sluggish, beachball and the computer turns on its fans to full power – processes refmac5, ccp4i2, kernel_tasks. Then unresponsive
- There was a lot of opening and closing coot
- I don't like that
  - I'd rather work in coot and submit refinement jobs, and import and export new models and ligands
  - i.e. CCP4i2 should be a browser and database interface
  - not the only "front-end" by which jobs can be executed
  - I want a database/job browser in Coot
  - Compared to the Phenix interface, it's primitive and static
- `.dict` is not a good extension for a restraints dictionary cif file
  - use `.cif` or `.pdbxr`
  - The file selector uses `*.cif`

CCP4-7.0.024 Project Viewer: Ligand-fitting-problems-Dec-2016

Task menu | View in Coot | View in CCP4mg | Export MTZ | Help | Bibliography | Clone job | Run | Run on server

Job list | Project directory

Job/File	Evaluation
31 Refinement - REFMAC5	
30 Import a coordinate set - optional selectio...	nRes=1
29 Make Ligand	
25 Refinement - REFMAC5	R=0.19 RFree=0.22
24 Manual model building - COOT	
23 Make Ligand	
22 Manual model building - COOT	
21 Make Ligand	
20 Refinement - REFMAC5	R=0.20 RFree=0.22
19 Import merged	
17 Import a coordinate set - optional selectio...	nRes=619
16 Import merged for problem 2	
15 Refinement - REFMAC5	R=0.15 RFree=0.22
14 Manual model building - COOT	
13 Make Ligand	
12 Make Ligand	
11 Refinement - REFMAC5	R=0.16 RFree=0.22
9 Manual model building - COOT	
8 Refinement - REFMAC5	R=0.19 RFree=0.25
7 Manual model building - COOT	
6 Refinement - REFMAC5	
5 Analyse geometry	
4 Make Ligand	
2 Import a coordinate set - optional selection...	nRes=669
1 Import merged	

Job 31: Refinement - REFMAC5 — **The job is Running**

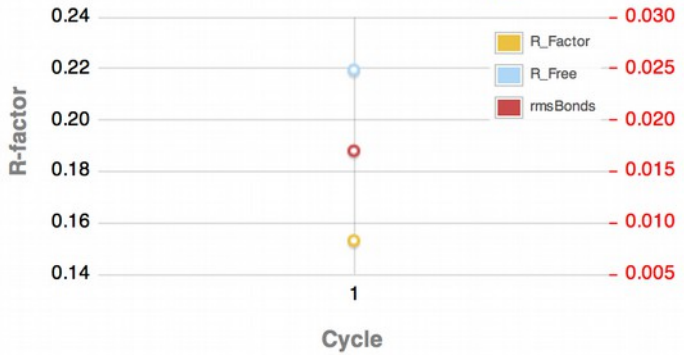
Input | Results | Comments

Default weight

▼ Refinement

Cycle	R-factor	R-free	RMS Deviation
1	0.1531	0.2195	0.017

Running refmac R-factors




```
Current weight applied to X-ray term is 0.4014201
```

Terminal output

```
opentask times total 0.0682530403137
opentask times drawing 1.00135803223e-05
ERROR loading params file /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_31/input_params.xml
 SYMINFO file set to /Applications/ccp4-7.0/lib/data/syminfo.lib
extractMtzData spaceGroup I 2 2 2
 SYMINFO file set to /Applications/ccp4-7.0/lib/data/syminfo.lib
extractMtzData spaceGroup I 2 2 2
Can convert ? 4 no 2
CTextViewer.open /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_31/log.txt application/refmac-external-restraints True
opentask times total 0.342795133591
opentask times drawing 0.218330144882
Done resetting side bar
Icon not found arcimboldo
2016-12-06 18:15:29.288 ccp4i2[66583:3330033] modalSession has been exited prematurely - check for a reentrant call to endModalSession:
blockLocal prosmart_refmac False
Copying file /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_13/R36_RDKIT.dict-C19-both.cif to
/Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_IMPORTED_FILES/R36_RDKIT.dict-C19-both_1.cif
CDbApi.createImportFile calculated checksum /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_13/R36_RDKIT.dict-C19-both.cif
f57f6d6396a53b78ccd705e175f8b51c
Database recording file /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_IMPORTED_FILES/R36_RDKIT.dict-C19-both_1.cif imported from
/Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_13/R36_RDKIT.dict-C19-both.cif file id: fd5c9dd4bbdf11e681bd60f81dd2910c
PROJECTSMANAGER.importFiles resetting path DICT /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_IMPORTED_FILES/R36_RDKIT.dict-
C19-both_1.cif
Recording file in database matches existing XYZIN /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_30/XYZOUT.pdb
8986a90abbd911e6ae7560f81dd2910c 498c75e6bbd911e6b5af60f81dd2910c
Recording file in database XYZIN /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_30/XYZOUT.pdb
8986a90abbd911e6ae7560f81dd2910c
Recording file in database matches existing F_SIGF /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_1/OBSOUT.mtz
966383e6ba4711e6a4b260f81dd2910c 6d876ea8ba4711e68eec60f81dd2910c
Recording file in database F_SIGF /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_1/OBSOUT.mtz
966383e6ba4711e6a4b260f81dd2910c
Recording file in database matches existing FREERFLAG /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_1/FREEOUT.mtz
9663abcaba4711e6ae1460f81dd2910c 6d876ea8ba4711e68eec60f81dd2910c
Recording file in database FREERFLAG /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_JOBS/job_1/FREEOUT.mtz
9663abcaba4711e6ae1460f81dd2910c
Recording file in database matches existing DICT /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_IMPORTED_FILES/R36_RDKIT.dict-C19-
both_1.cif fd5c9dd4bbdf11e681bd60f81dd2910c 93fb4d6ebbd911e6b0df60f81dd2910c
Recording file in database DICT /Users/pemsley/CCP4I2_PROJECTS/Ligand-fitting-problems-Dec-2016/CCP4_IMPORTED_FILES/R36_RDKIT.dict-C19-both_1.cif
fd5c9dd4bbdf11e681bd60f81dd2910c
```