

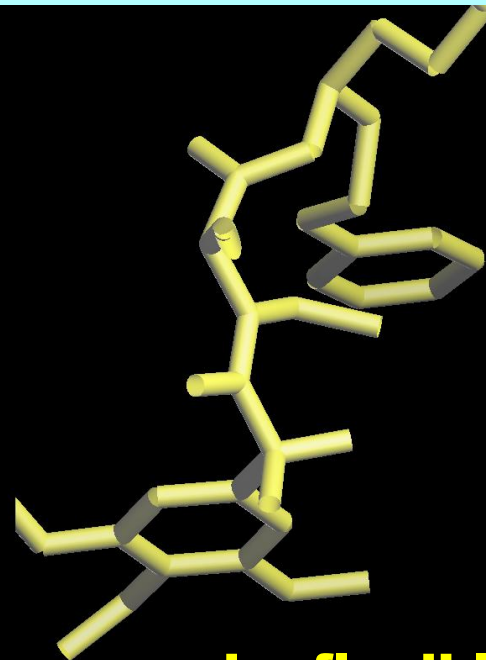
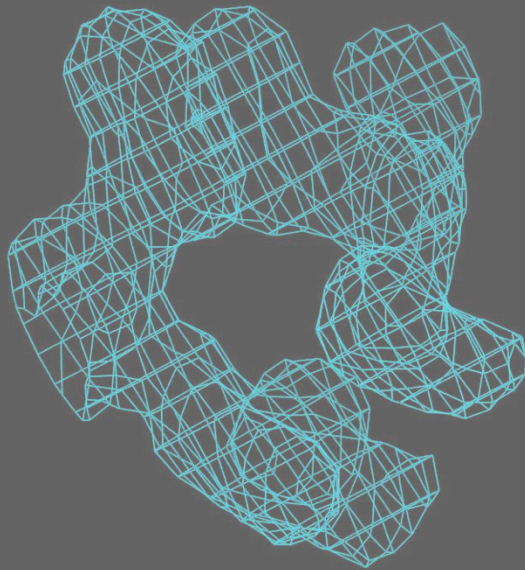
Finding ligands in electron-density maps

Tom Terwilliger
Los Alamos National Laboratory



Automated fitting of flexible ligands

A difference electron-density map

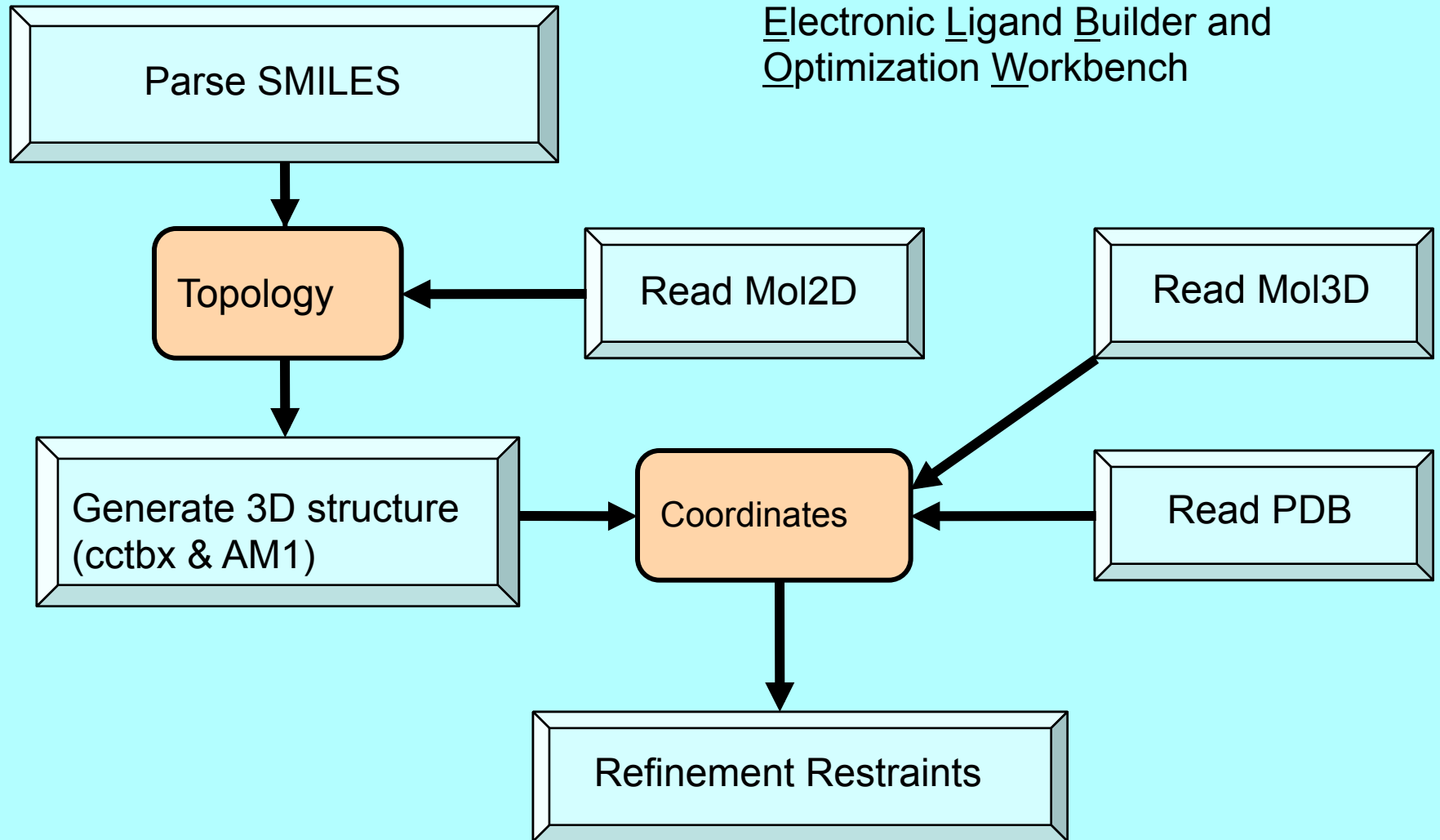


...and a flexible ligand to be fitted

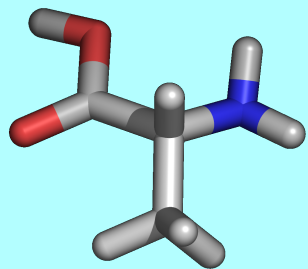
View 2

2-Aryl-2,2-Difluoroacetamide FKBP12

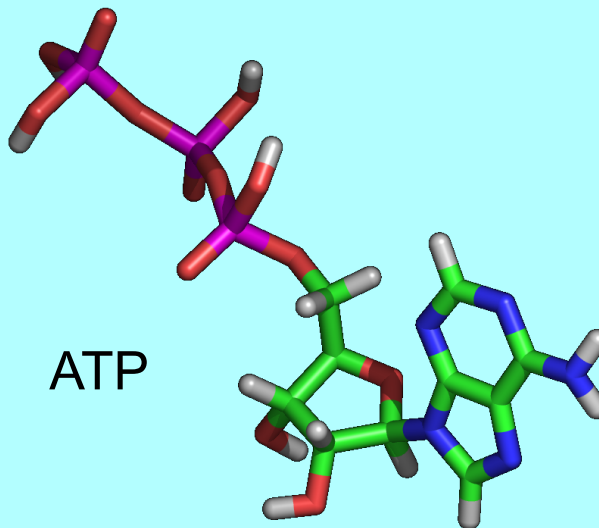
Ligand generation in PHENIX



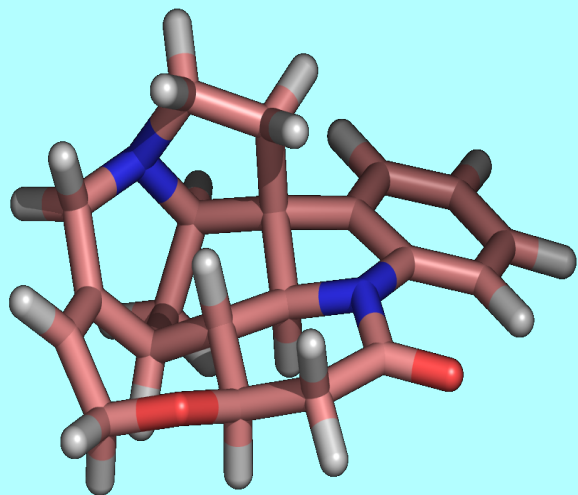
Auto-generated ligands



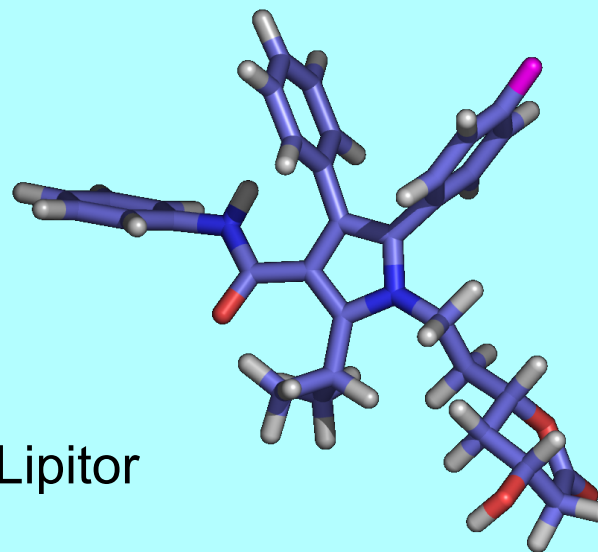
Alanine



ATP

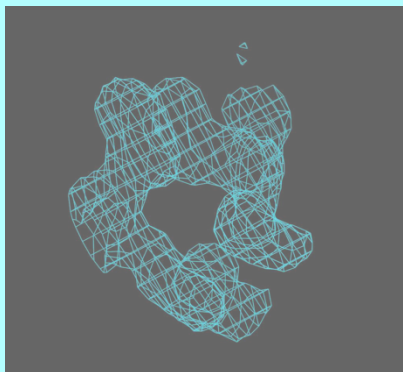


Strychnine



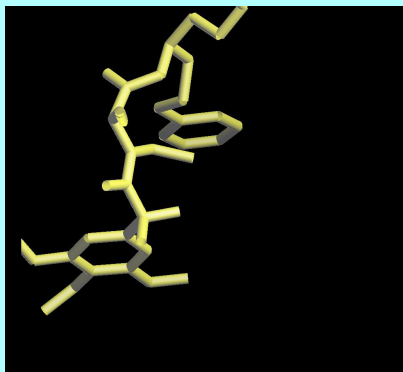
Lipitor

Fitting a flexible ligand (following ideas of Klei)



Where is the ligand?
Choose the largest region of contiguous density

What are rotatable bonds? Analyze ligand for allowed rotations

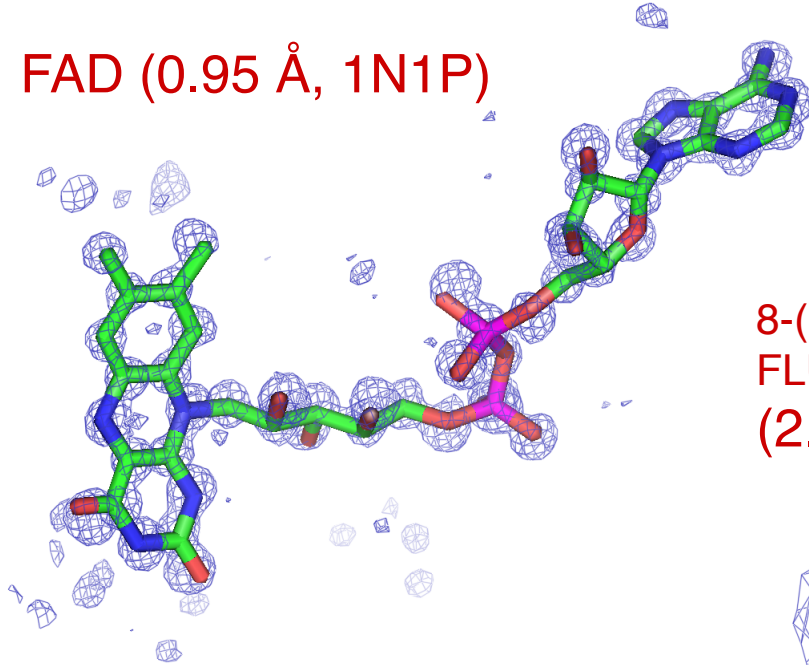


What is the orientation of the ligand? Fit core of ligand

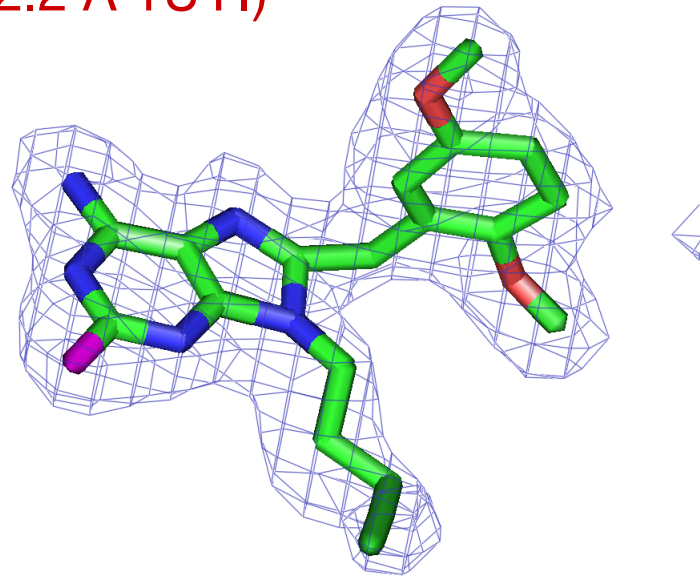
What is the conformation of the ligand? Trace the ligand from core

Fitting Fo-Fc density at resolutions from 0.95 Å to 4.5 Å

FAD (0.95 Å, 1N1P)

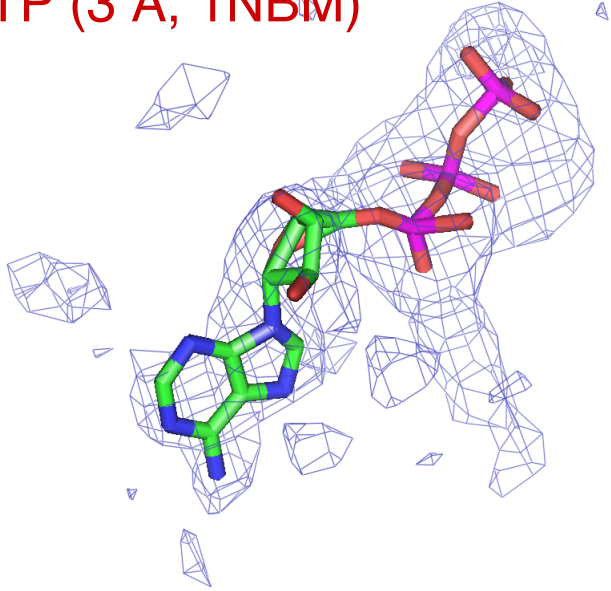


8-(2,5-DIMETHOXY-BENZYL)-2-
FLUORO-9-PENT-9H-PURIN-6-YLAMINE
(2.2 Å 1UYI)

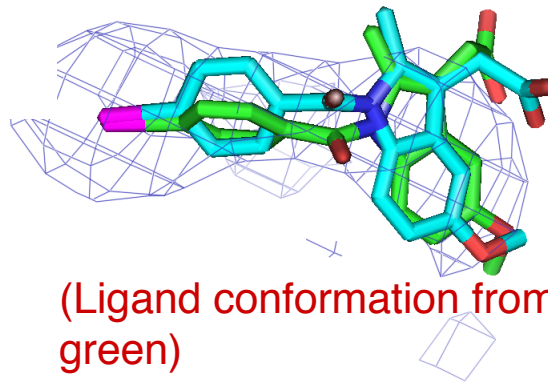


Fitting Fo-Fc density at resolutions from 0.95 Å to 4.5 Å

ATP (3 Å, 1NBM)



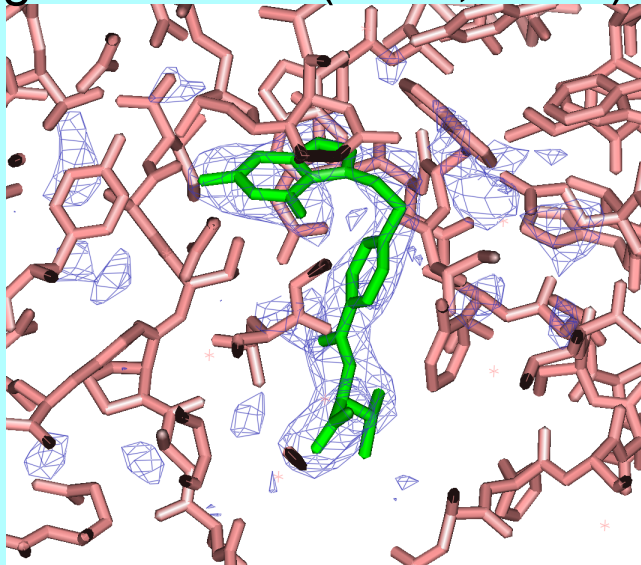
(1-(4-iodobenzoYL)-5-Methoxy-2-Methyl-Indole-3-acetic acid (4.5 Å, 1PGF)



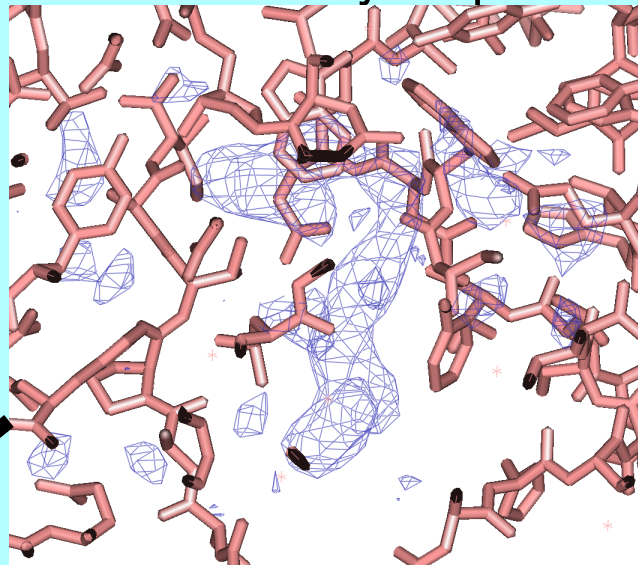
(Ligand conformation from 1PGF in green)

Fitting ligand density in the PDB

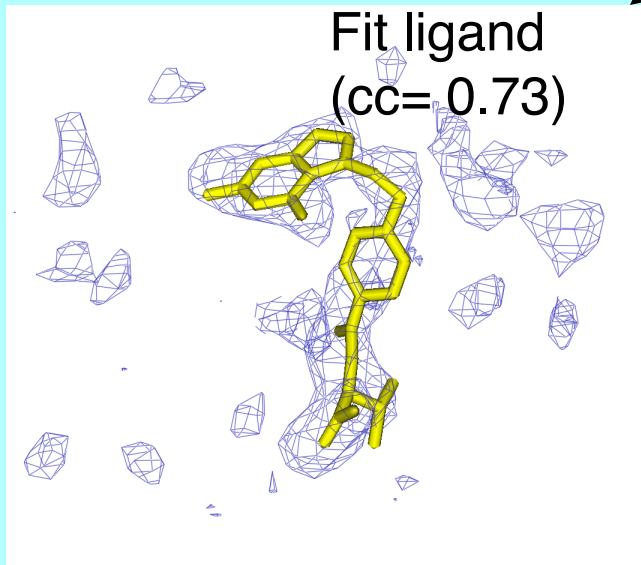
Ligand in PDB (1JUT, 2.8 Å)



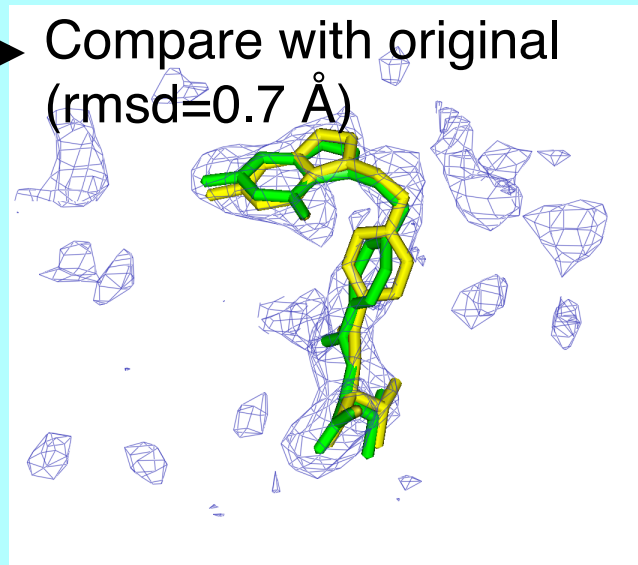
Fo-Fc density map



Fit ligand
(cc= 0.73)



Compare with original
(rmsd=0.7 Å)

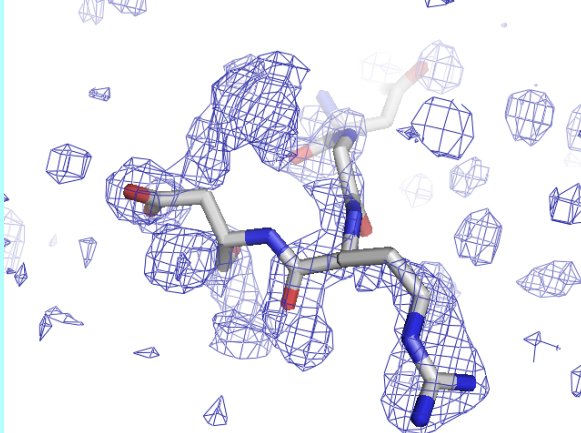
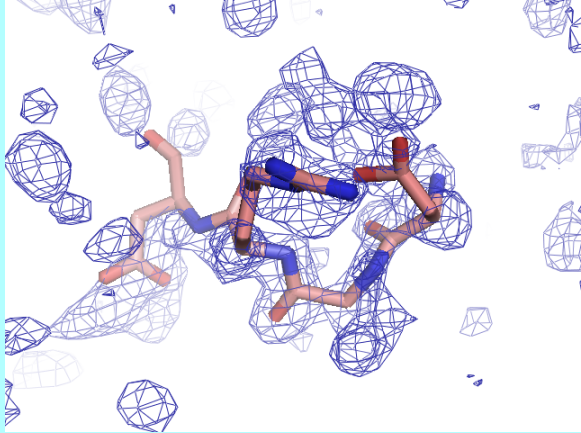
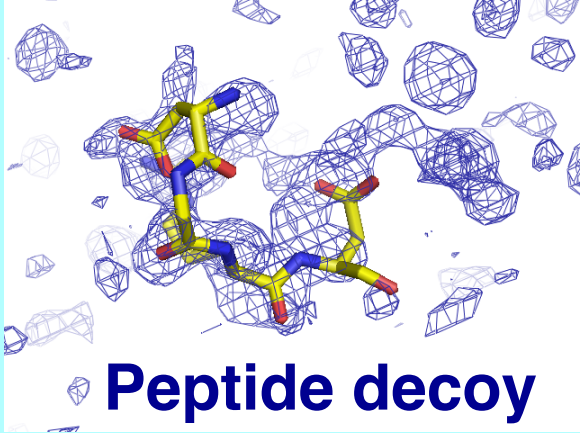
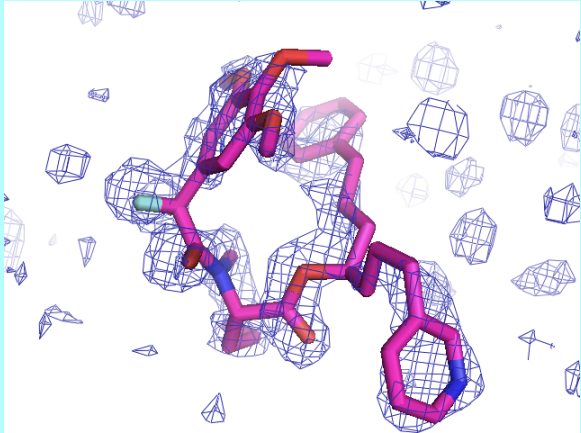
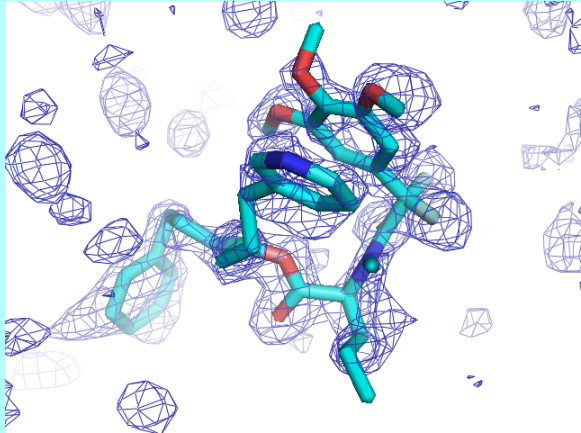
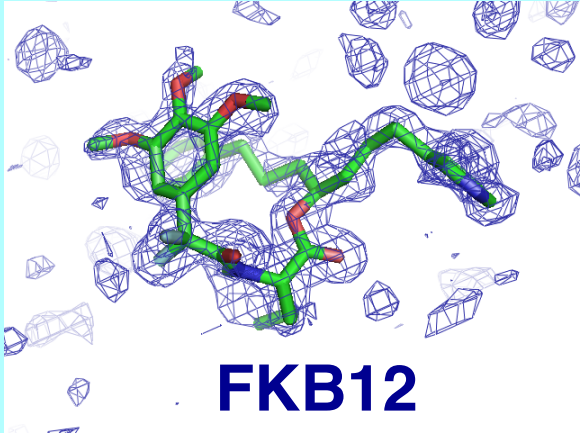


Fitting ligand density in the PDB

Based on 6209 PDB entries with 9319 ligands

	Ligands in PDB fitting Fo-Fc map with CC ≥ 0.75	All Ligands
Number of ligands	6590	9319
Mean CC of ligand in PDB	0.85	0.78
Mean CC of fitted ligand (unrefined)	0.76	0.72
Rmsd ≤ 1.0 Å	2715 (41%)	3004 (32%)
Rmsd ≤ 2.0 Å	4666 (71%)	5421 (58%)
Rmsd > 10 Å	310 (5%)	1417 (15%)

phenix.find_all_ligands – 1J4R (3 molecules of FKB12)



Site 1

Site 2

Site 3

The PHENIX Project



Lawrence Berkeley Laboratory

Paul Adams, Ralf Grosse-Kunstleve, Pavel Afonine, Nat Echols, Nigel Moriarty, Jeff Headd, Nicholas Sauter, Peter Zwart



Los Alamos National Laboratory

Tom Terwilliger, Li-Wei Hung



Randy Read, Airlie McCoy, Gabor Bunkoczi, Rob Oeffner

Cambridge University



Duke University

Jane & David Richardson, Vincent Chen, Chris Williams, Bryan Arendall, Laura Murray



An NIH/NIGMS funded
Program Project