FORECASTER Platform Tutorial

Virtual Screening from 2D molecules using FITTED

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Laval, Québec, Canada

21/02/2015

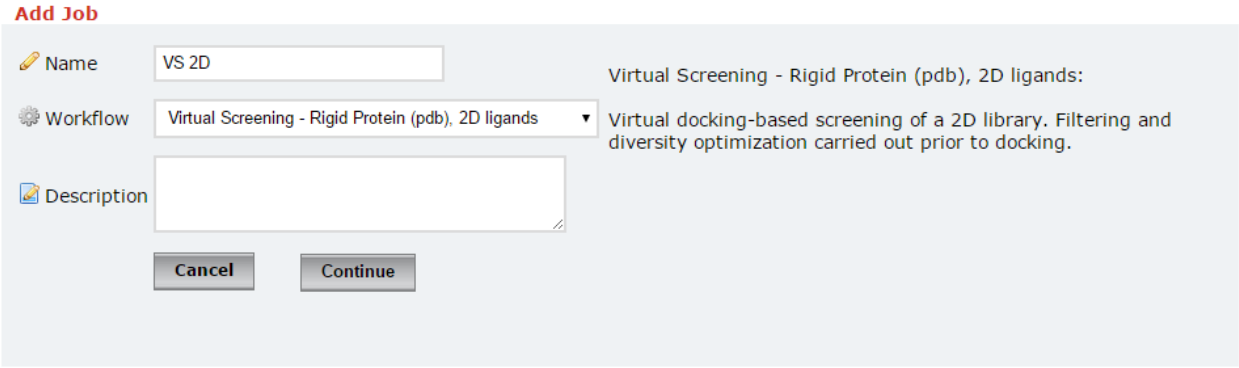
Virtual Screening Workflow, 2D ligands, Rigid Protein

In this example, we will be using the file tk_library2D.sdf that contains ~200 active and inactive TK ligands and 1e2k pdb file.

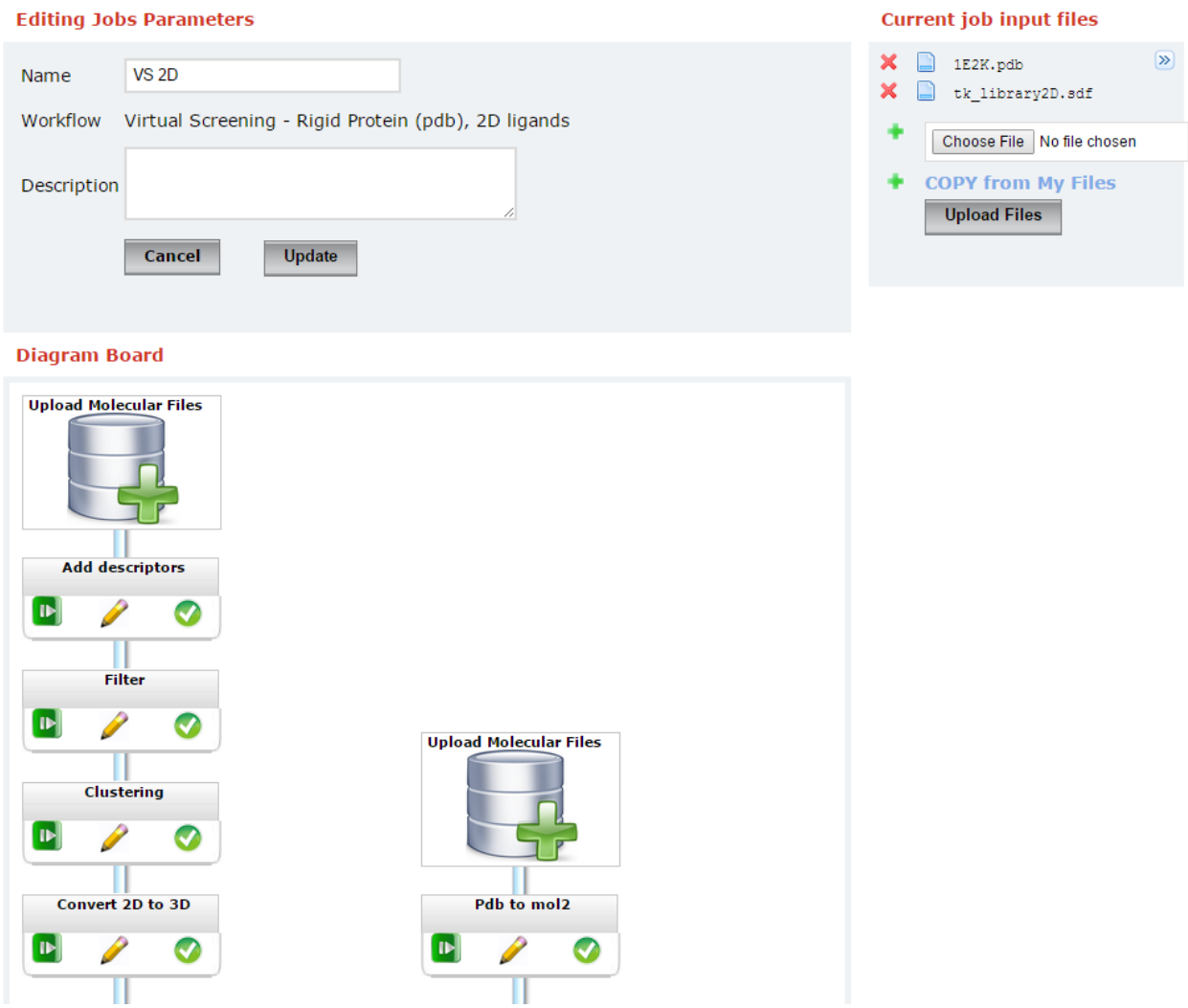
The files can be downloaded here: http://molecularforecaster.com/files/VS2D.zip

Add a new job from the job manager.

Choose the specified workflow and provide a new name for this job:



Upload the files either using the “Upload Molecular Files” icon or directly from the “Current job input files” section on the right side of the page.


Editing Jobs Parameters
Name
VS 2D
Workflow
Virtual Screening - Rigid Protein (pdb), 2D ligands
Description
Cancel
Update
Current job input files
1E2K.pdb
tk_library2D.sdf
Choose File
No file chosen
COPY from My Files
Upload Files
Diagram Board
Upload Molecular Files
Add descriptors
Filter
Clustering
Convert 2D to 3D
Upload Molecular Files
Pdb to mol2

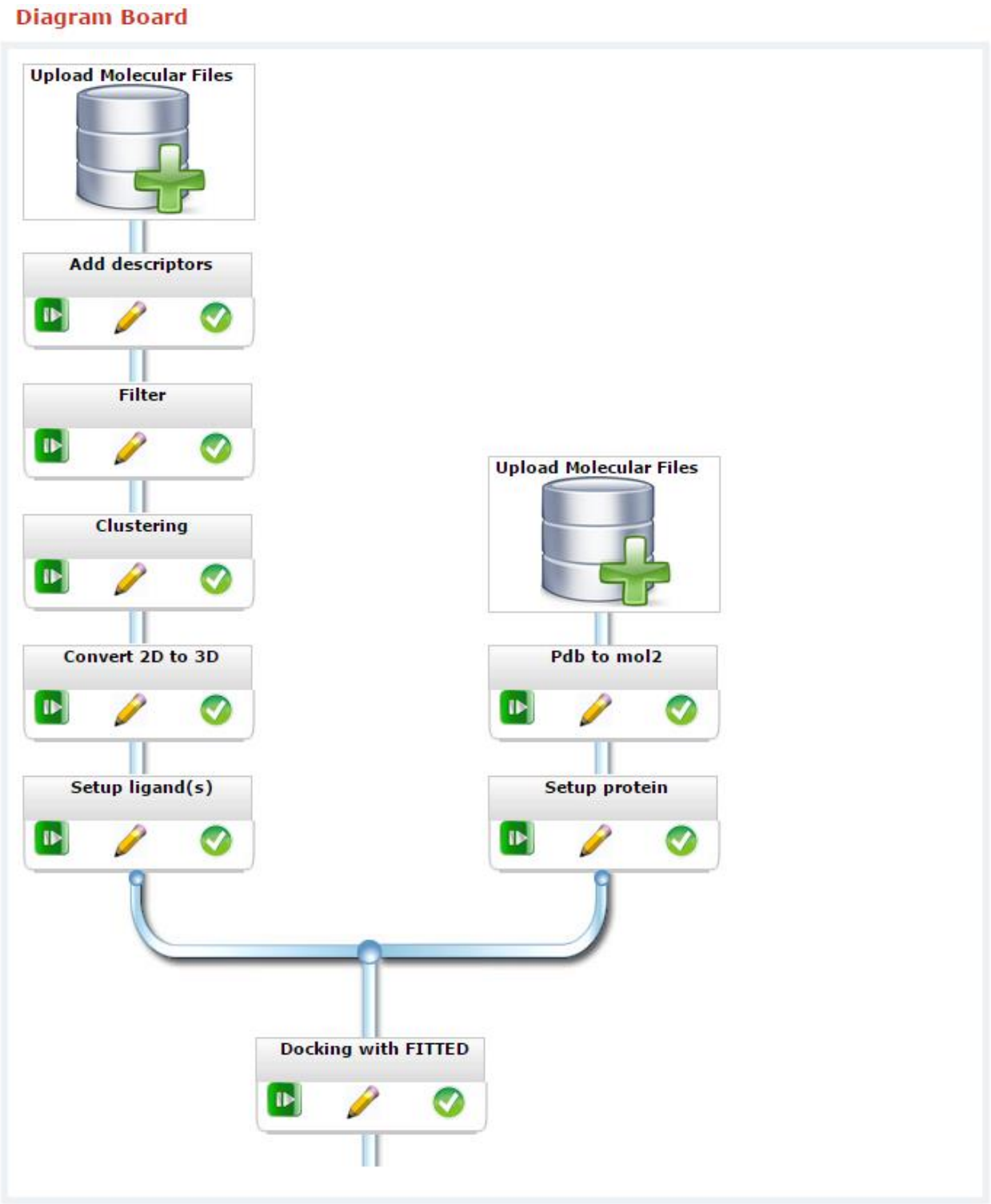
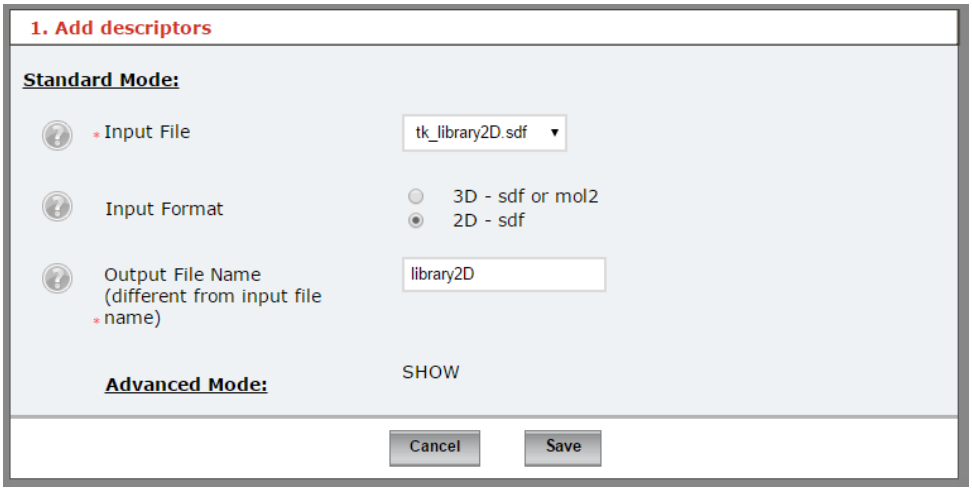
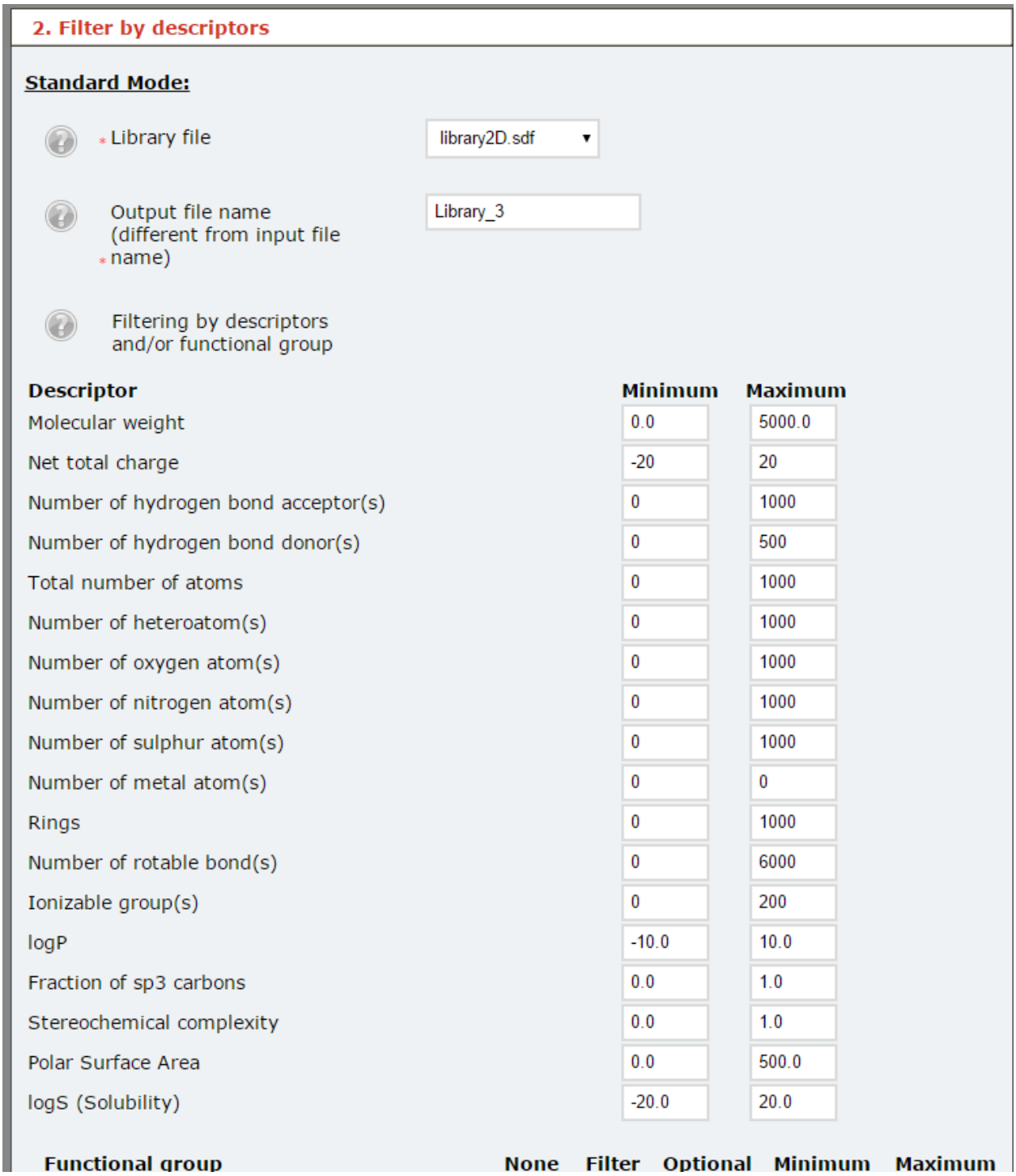


Diagram Board
Upload Molecular Files
Add descriptors
Filter
Clustering
Convert 2D to 3D
Setup ligand(s)
Upload Molecular Files
Pdb to mol2
Setup protein
Docking with FITTED

Clicking on the pen in the middle on the boxes (sequentially, from top-left to bottom-right) will allow you to input the parameters for each actions of the workflow:



Make sure to select the correct Library file (from the previous step, library2D.sdf). The default settings will be kept for this example, but values can be defined as desired.



2. Filter by descriptors

Standard Mode:

* Library file: library2D.sdf

Output file name (different from input file name): Library_3

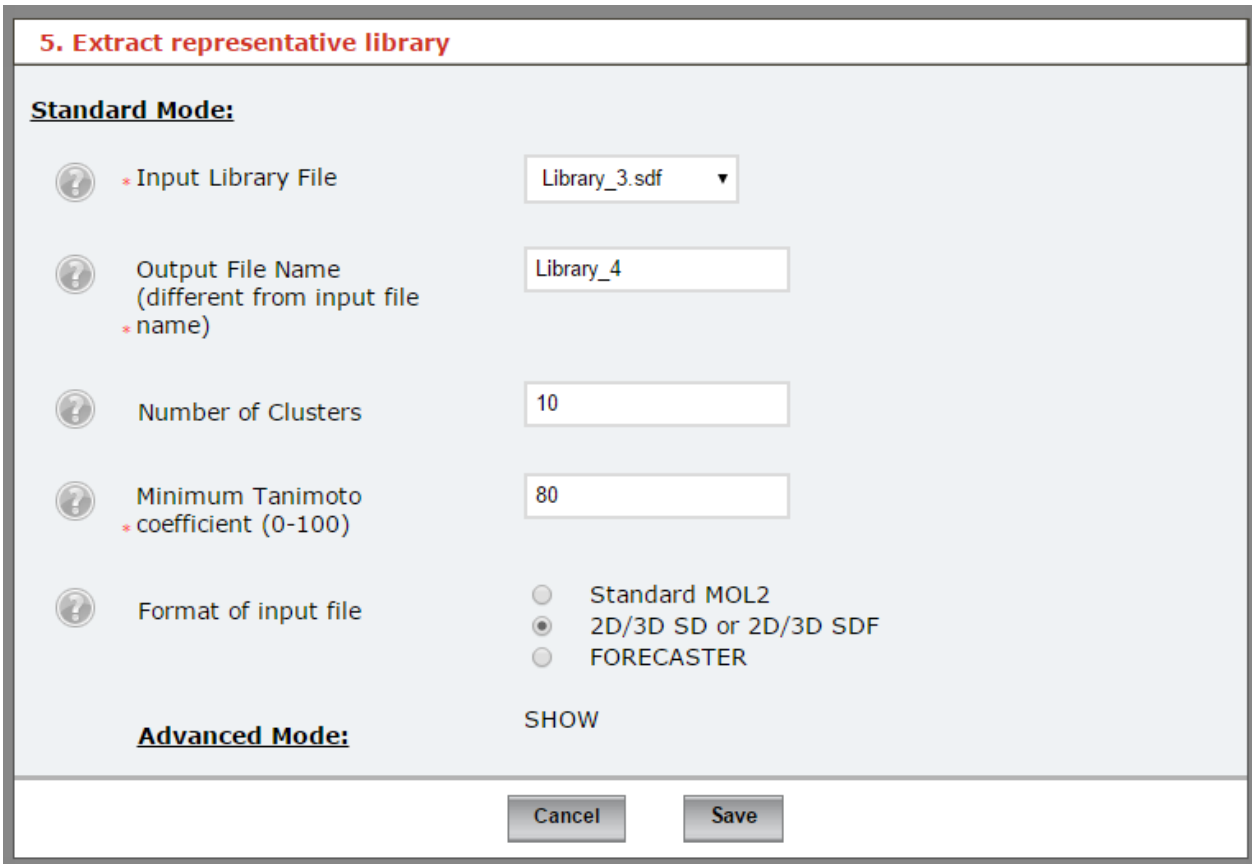
Filtering by descriptors and/or functional group

Descriptor	Minimum	Maximum
Molecular weight	0.0	5000.0
Net total charge	-20	20
Number of hydrogen bond acceptor(s)	0	1000
Number of hydrogen bond donor(s)	0	500
Total number of atoms	0	1000
Number of heteroatom(s)	0	1000
Number of oxygen atom(s)	0	1000
Number of nitrogen atom(s)	0	1000
Number of sulphur atom(s)	0	1000
Number of metal atom(s)	0	0
Rings	0	1000
Number of rotable bond(s)	0	6000
Ionizable group(s)	0	200
logP	-10.0	10.0
Fraction of sp3 carbons	0.0	1.0
Stereochemical complexity	0.0	1.0
Polar Surface Area	0.0	500.0
logS (Solubility)	-20.0	20.0

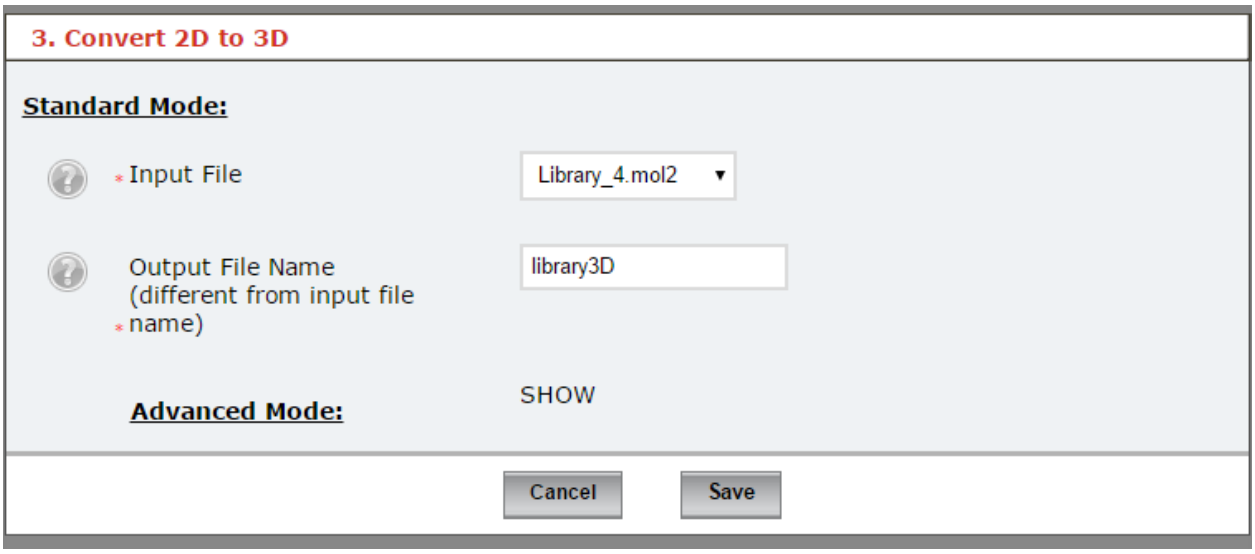
Functional group	None	Filter	Optional	Minimum	Maximum

Functional groups can be filtered out (Filter) or not filtered (None). When optional is selected, a minimum/maximum number of the specified functional group will be retained in the output library file.

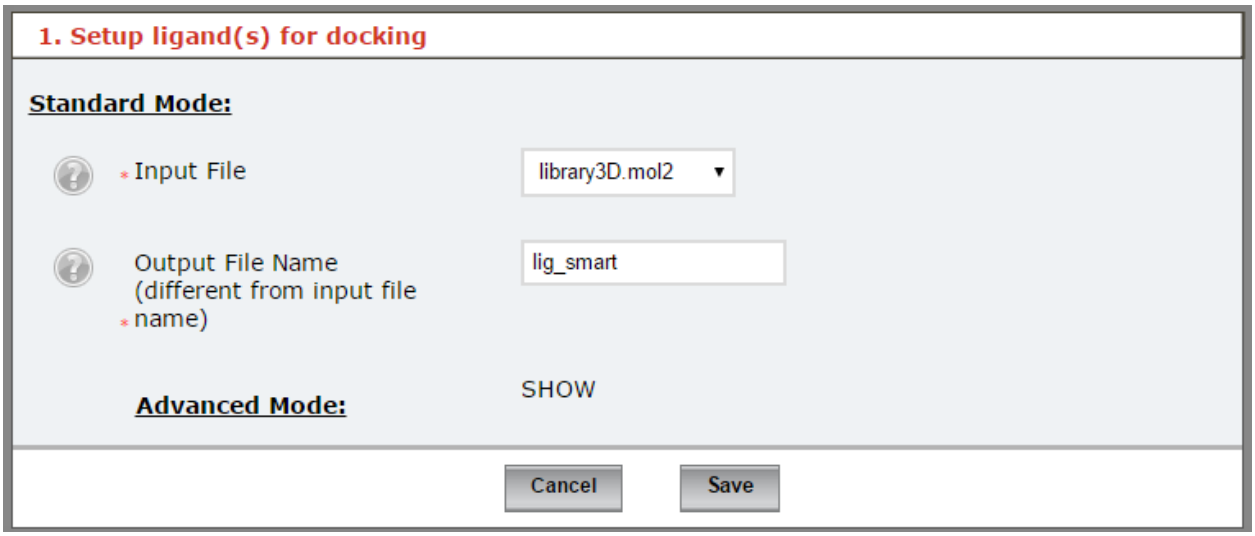
Make sure to select the correct input Library File from the previous step (Library_3.mol2). The Number of clusters is the number of ligands to be kept in the output library. The Tanimoto coefficient is used for similarity threshold. The format of input file needs to be set to 2D/3D SDF.



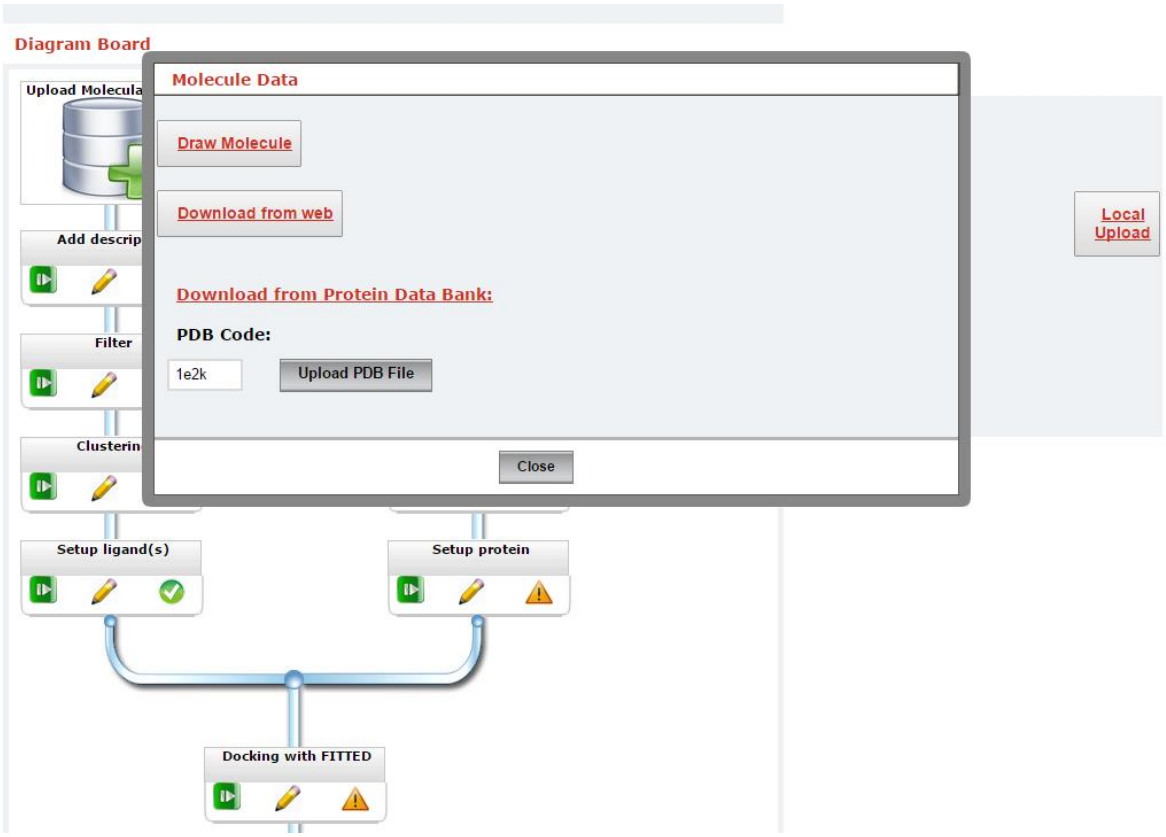
The library will then be converted from 2D to 3D.



Make sure to select the correct Input File (library3D.mol2).

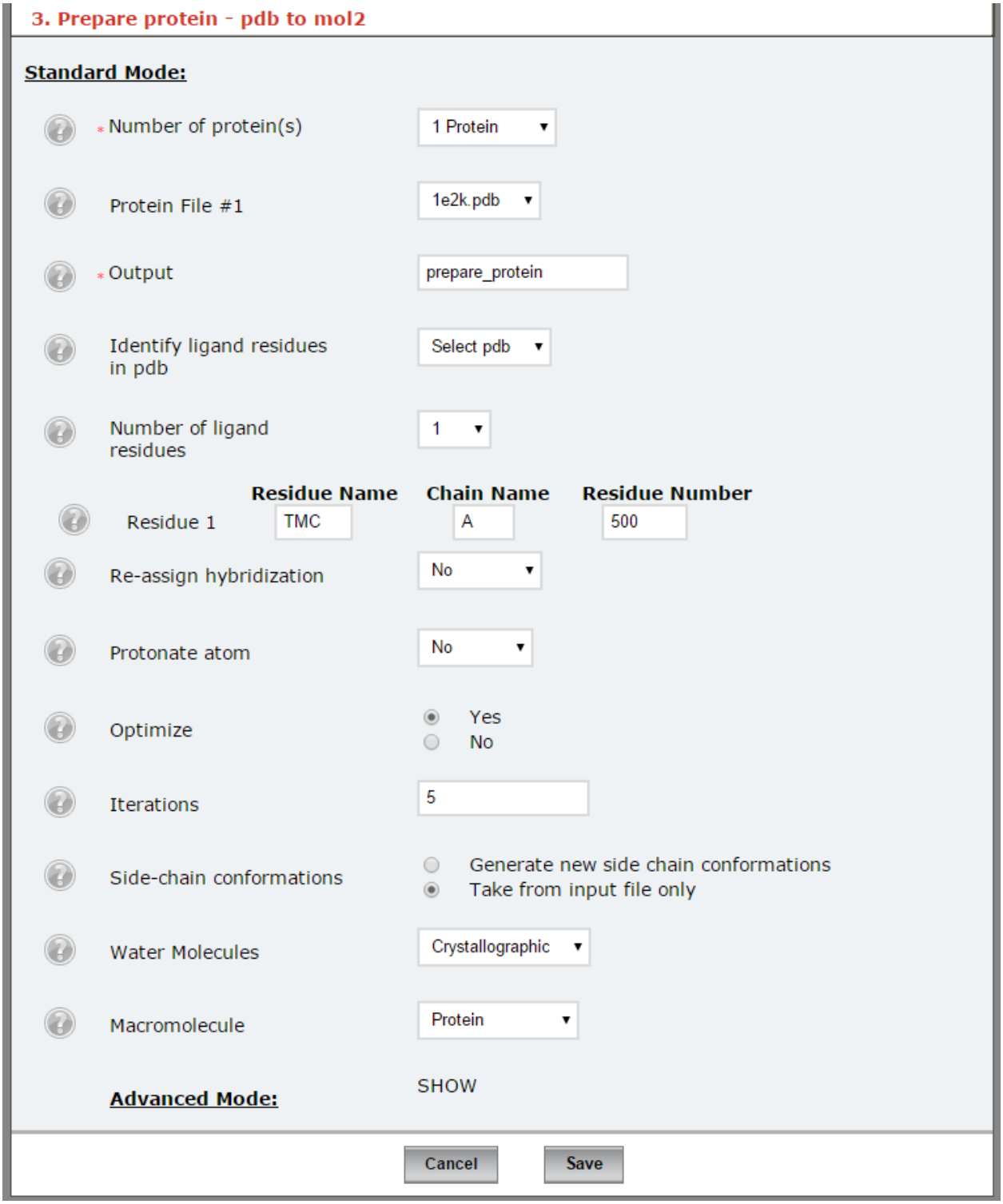


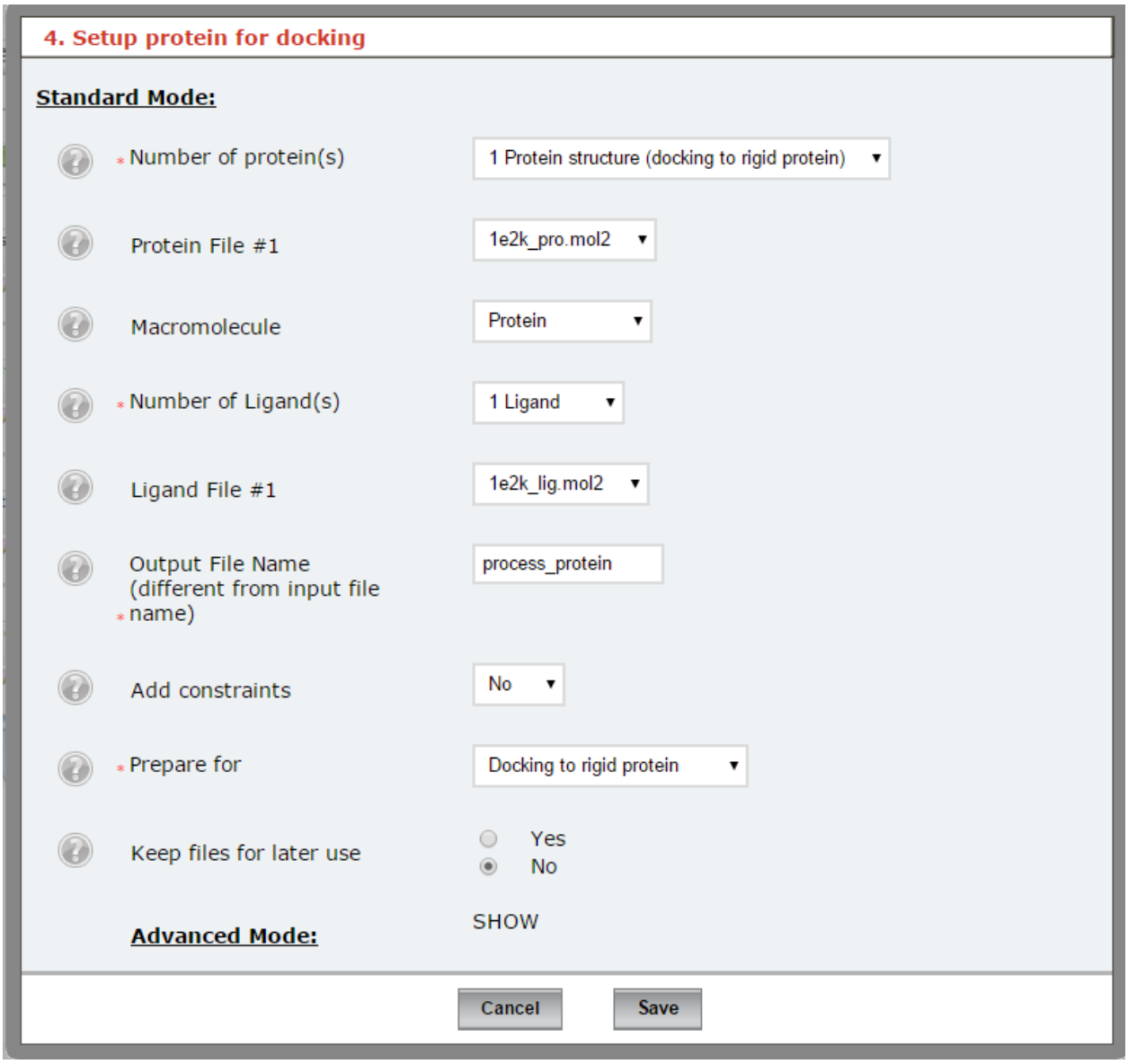
We are using the 1e2k protein which can be uploaded, transferred from “My Files” or downloaded directly from the PDB website.

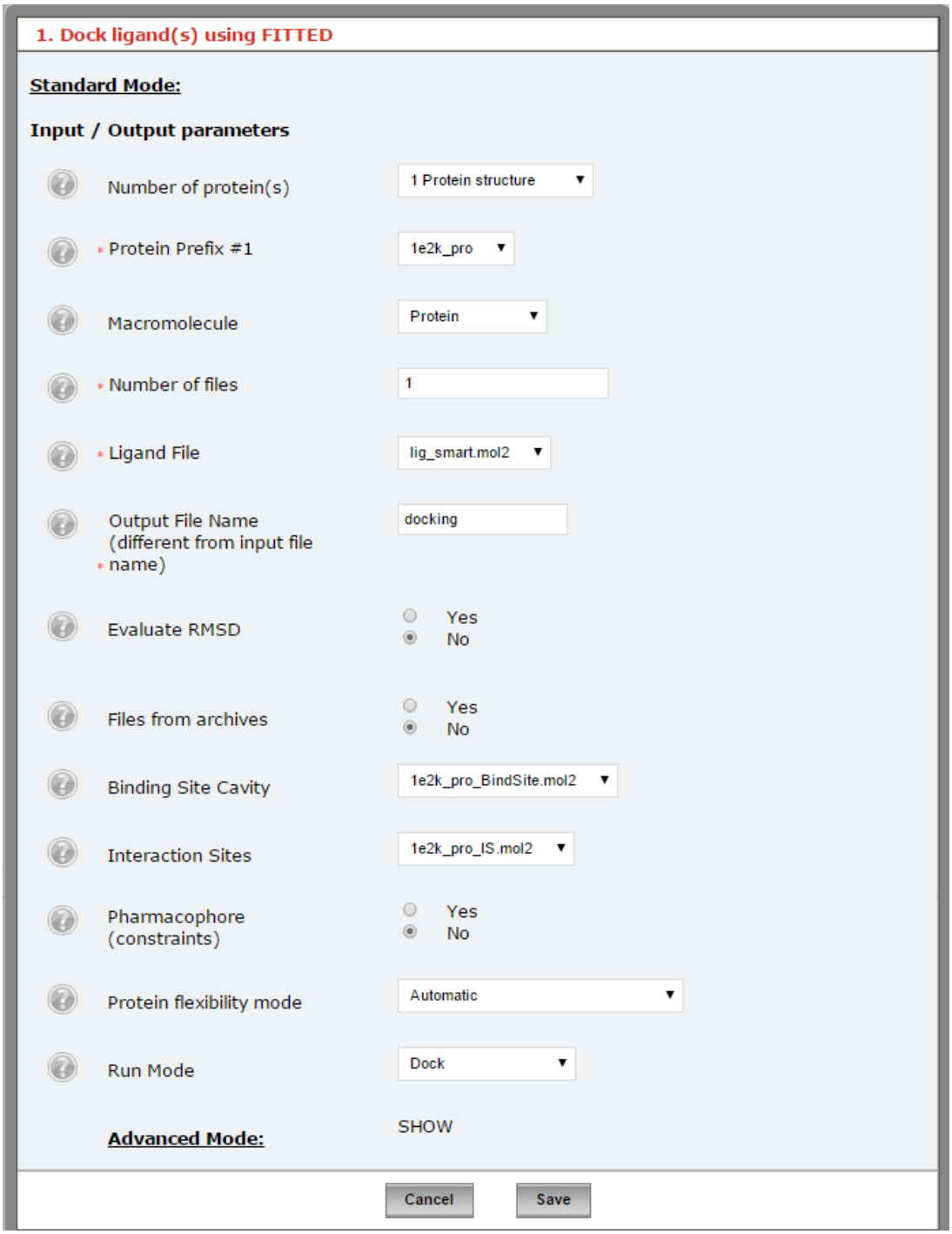


To identify correctly the ligand residue, please refer to the file:

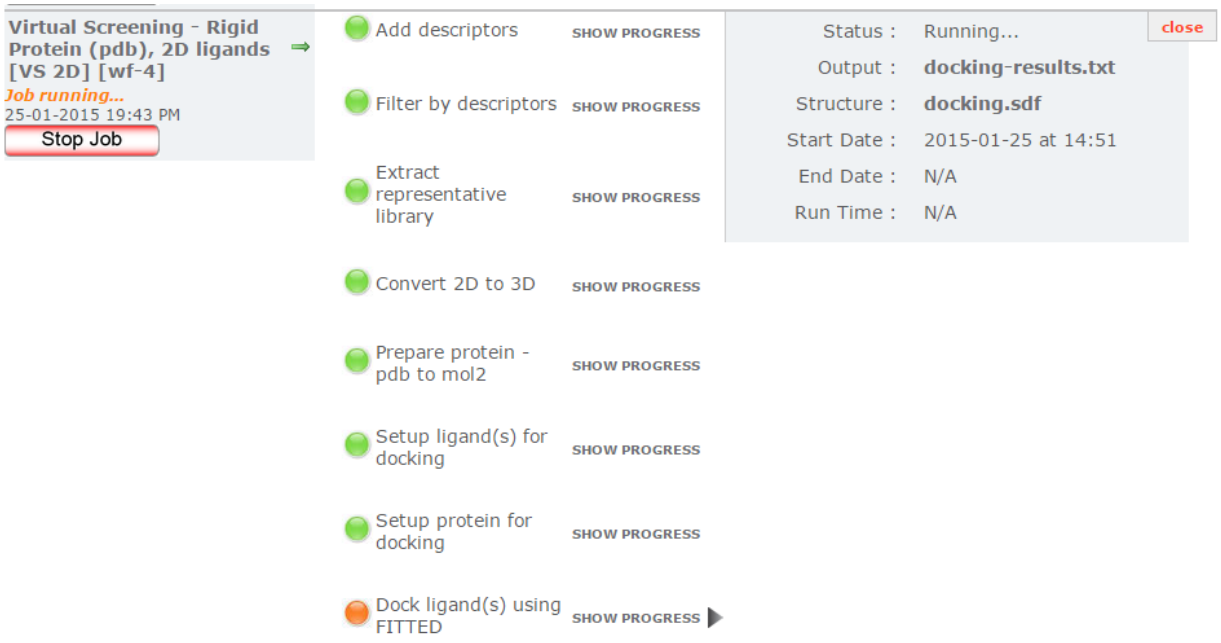
http://molecularforecaster.com/docs/Forecaster_Platform.pdf




4. Setup protein for docking
Standard Mode:
* Number of protein(s)
1 Protein structure (docking to rigid protein)
Protein File #1
1e2k_pro.mol2
Macromolecule
Protein
* Number of Ligand(s)
1 Ligand
Ligand File #1
1e2k_lig.mol2
Output File Name (different from input file name) *
process_protein
Add constraints
No
* Prepare for
Docking to rigid protein
Keep files for later use
Yes
No
Advanced Mode:
SHOW
Cancel
Save



In this workflow, as we have defined, the 10 most diverse ligand from the library will be docked against the protein 1e2k. We have kept the number of ligand small enough for the purpose of the example, but in a real scenario, one can start from a library of over a million molecule and after filtering and clustering, reduce this number to few thousands (depending of the cpu capabilities based on calculations time concerns).


Virtual Screening - Rigid Protein (pdb), 2D ligands [VS 2D] [wf-4]
Job running...
25-01-2015 19:43 PM
Stop Job
Add descriptors
SHOW PROGRESS
Filter by descriptors
SHOW PROGRESS
Extract representative library
SHOW PROGRESS
Convert 2D to 3D
SHOW PROGRESS
Prepare protein - pdb to mol2
SHOW PROGRESS
Setup ligand(s) for docking
SHOW PROGRESS
Setup protein for docking
SHOW PROGRESS
Dock ligand(s) using FITTED
SHOW PROGRESS
close
Status : Running...
Output : docking-results.txt
Structure : docking.sdf
Start Date : 2015-01-25 at 14:51
End Date : N/A
Run Time : N/A