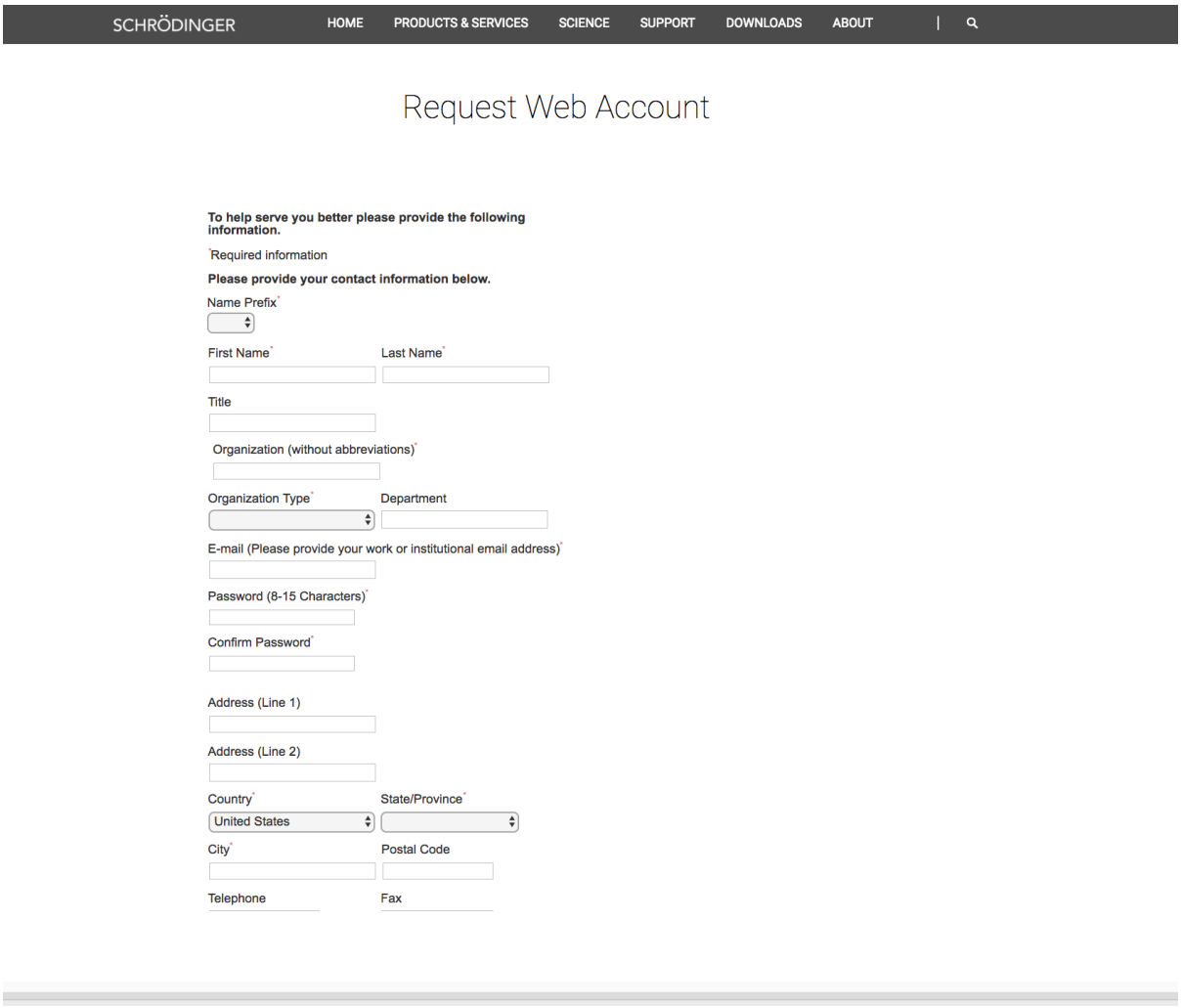
Molecular modeling exercise with MacroModel (Maestro)

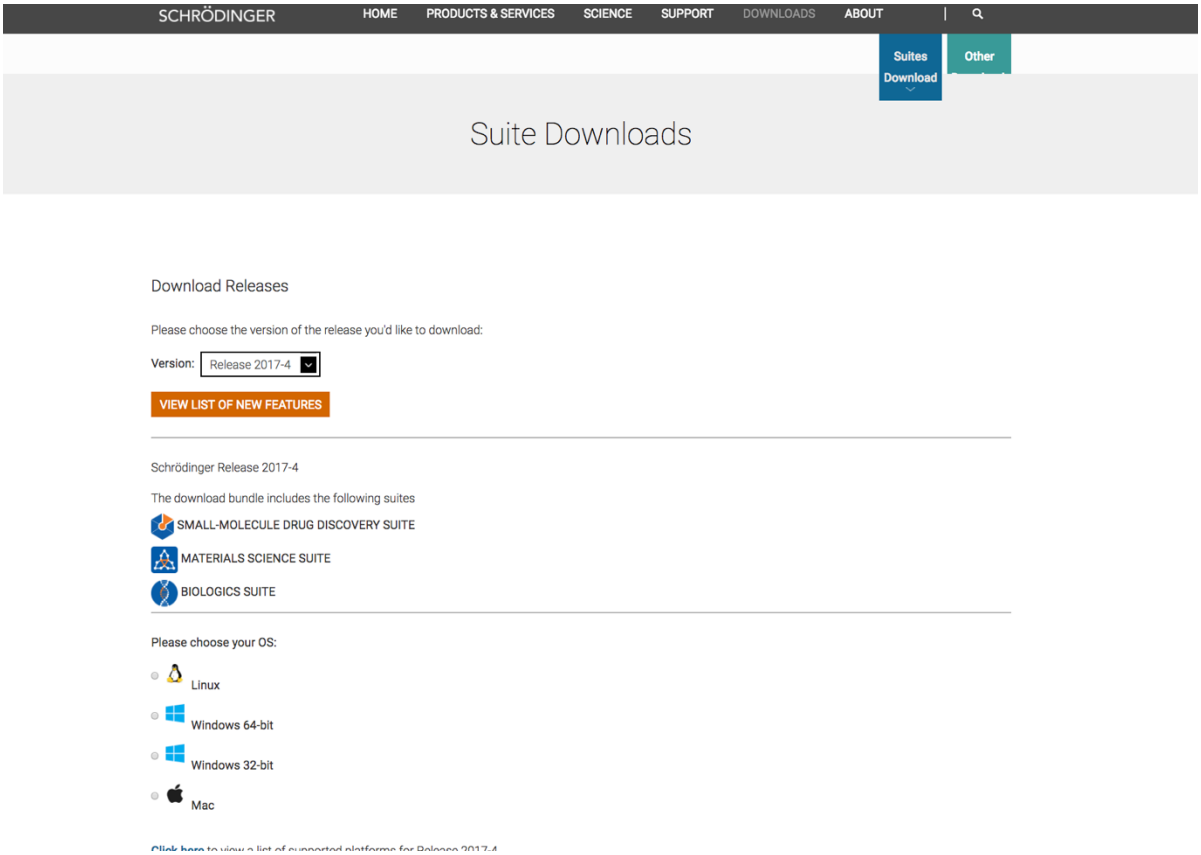
DOWNLOAD AND INSTALL

Schrodinger suite installation

Create a web account at https://www.schrodinger.com/request-account.



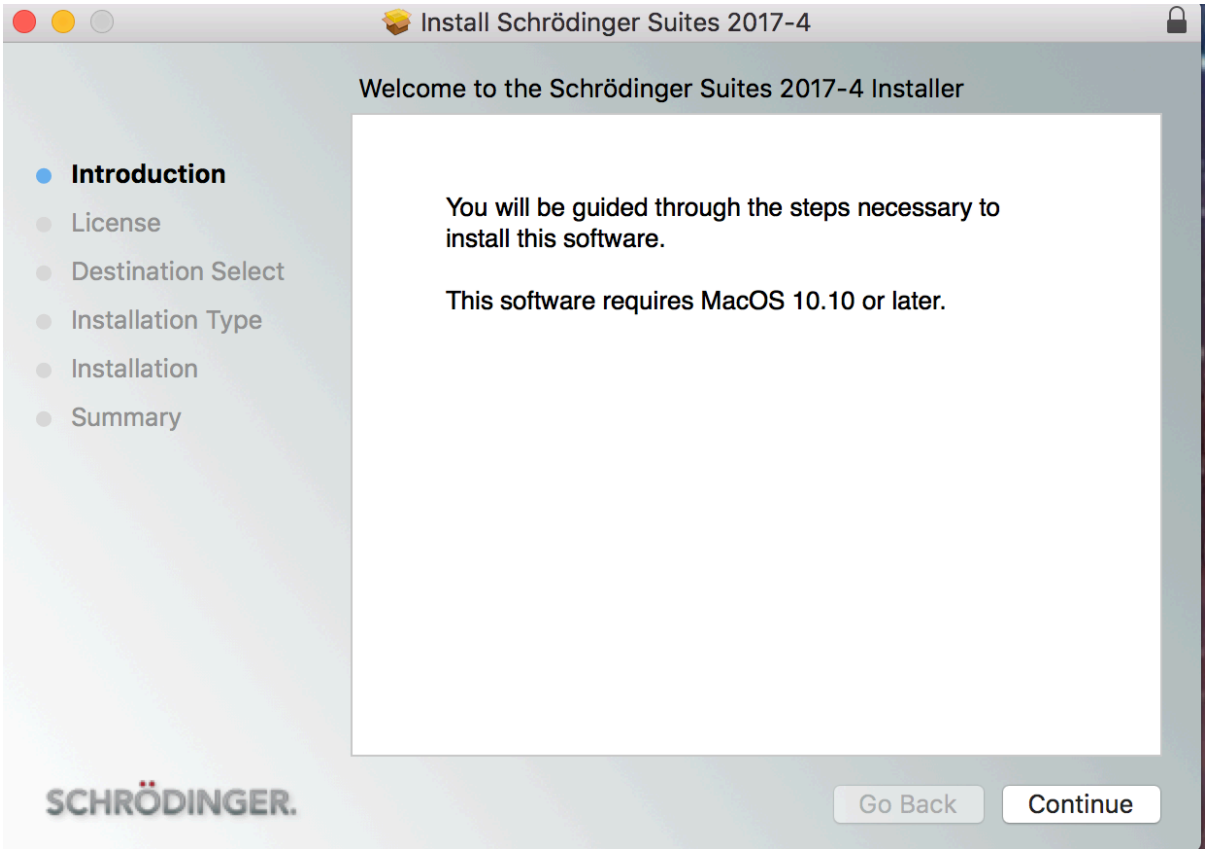
After you receive a confirmation email from schrodinger, click the link to validate your email. Then go to download and select the appropriate OS. Fill in with your credential when asked.



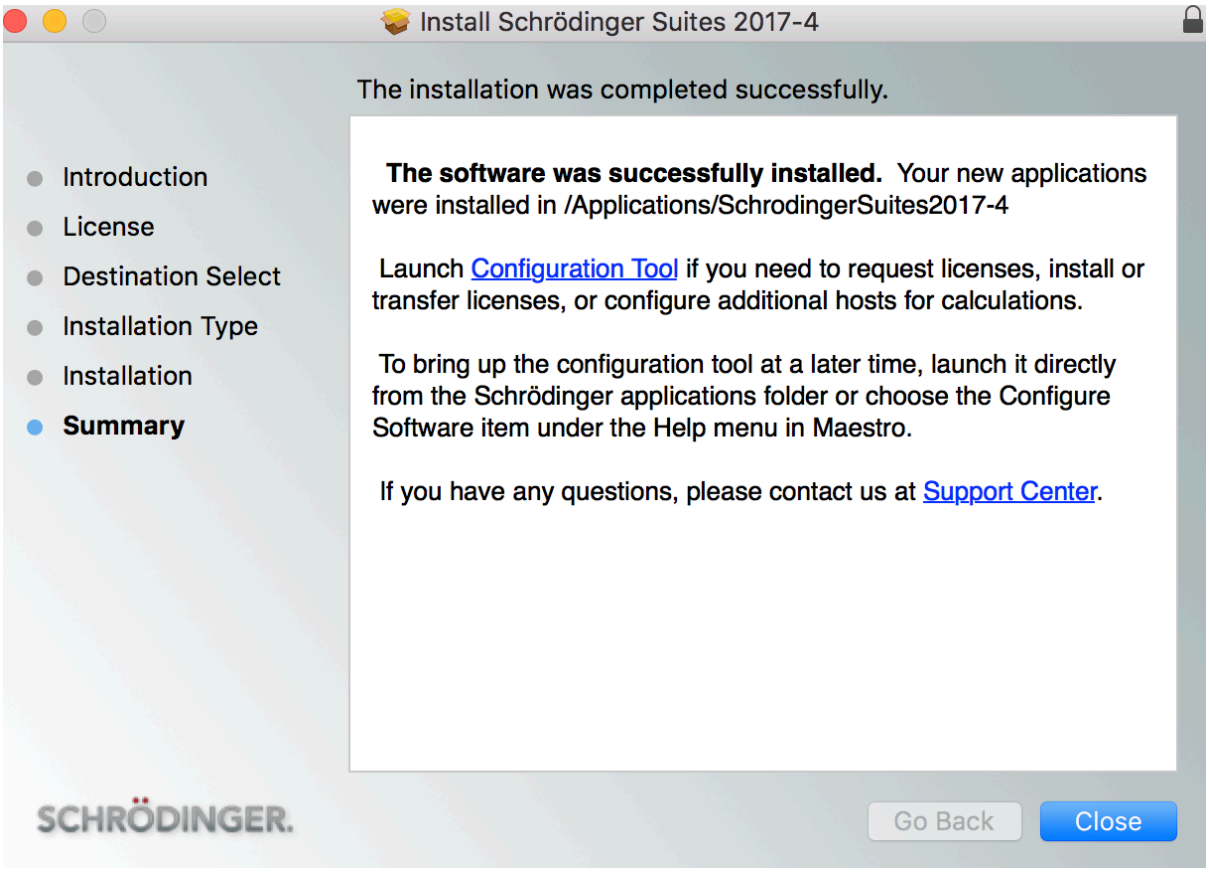
Run the installer and then to copy the license file into the schrodinger suite folder. Next, you need to run the configuration tool to set the license path.

N.B. the license file is the schrodinger.lic that you find in the same folder you found these instructions.

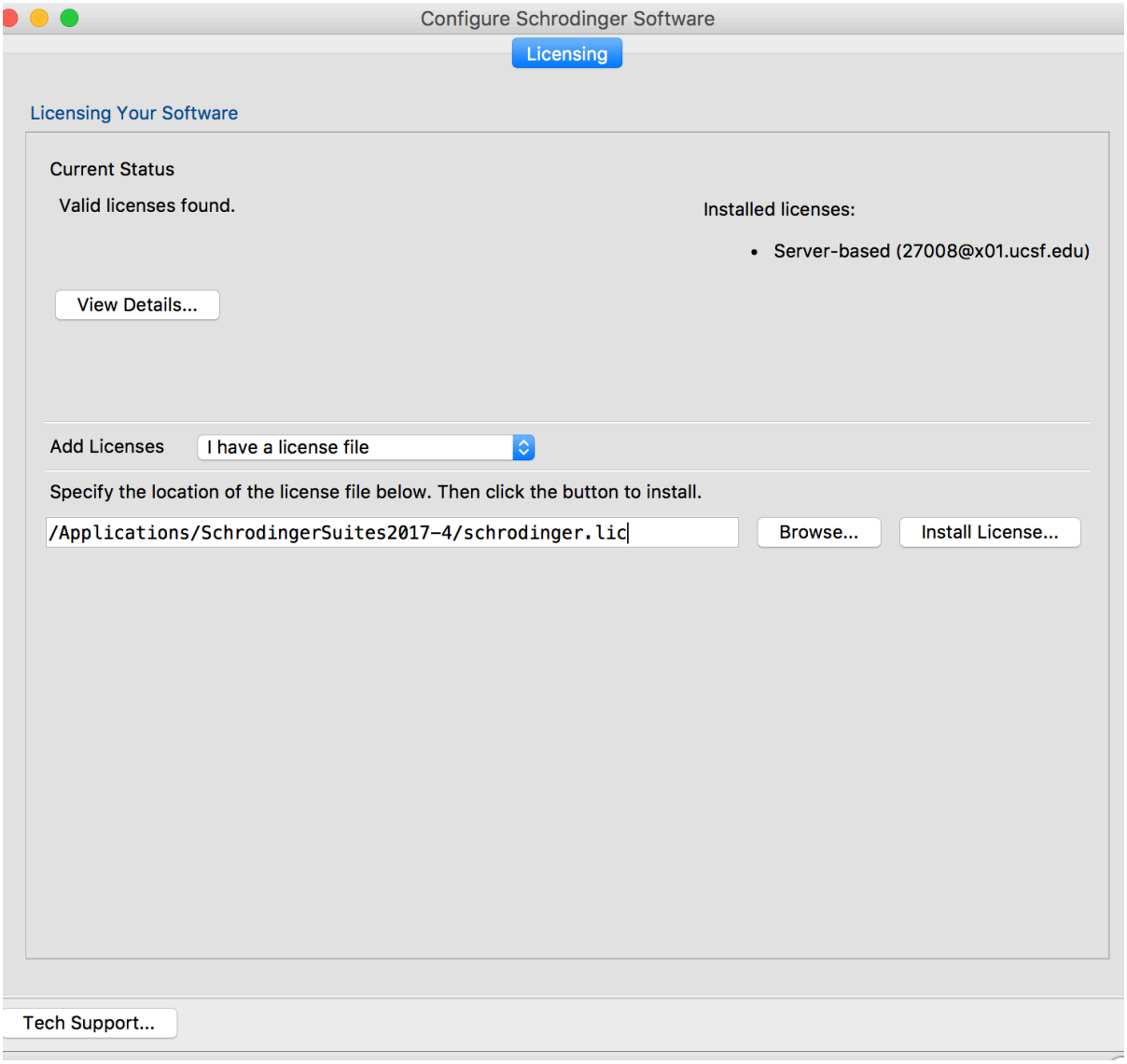
Example - Mac
If you download for mac, run the Schrodinger_Suites*.pkg installer and click continue in the Window below.



Once the installation is done, click the **Configuration Tool** link in the window below to run the configuration tool to set the license path.



Scroll down the window to select “I have a license file” and specify the path of the license file by clicking Browse. Then click install License



If you are not within the UCSF network you will need to have the VPN on, because the license server is on x01.ucsf.edu.

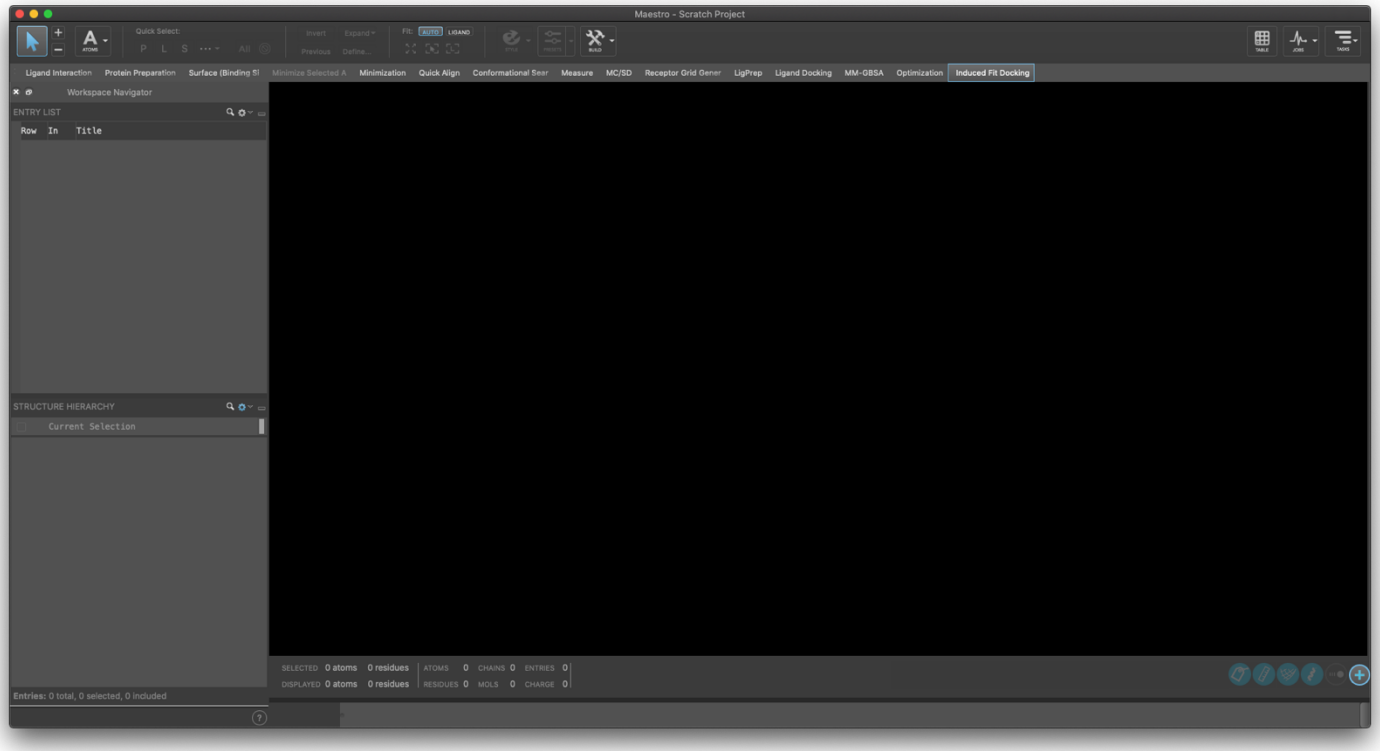
If MAC OS, you need to start Maestro with the following terminal command;

```
export SCHRODINGER=/opt/schrodinger/suites2019-1/
$SCHRODINGER/maestro -console &
```

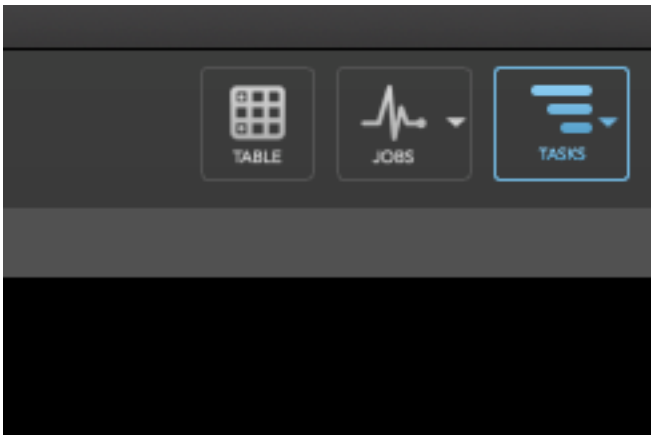
EXERCISE – Drawing and minimizing strychnine

From Yang "I am following Prof. James Nowick's chem203 spectroscopy class for the following MacroModel workshop."

Maestro start screen looks like this;



On the right top, click tasks then search for the following programs and make them your favorite by clicking stars (minimization MacroModel; Conformational Search MacroModel; Protein Preparation Wizard; Receptor Grid Generation; Ligand Docking Glide; LigPrep).



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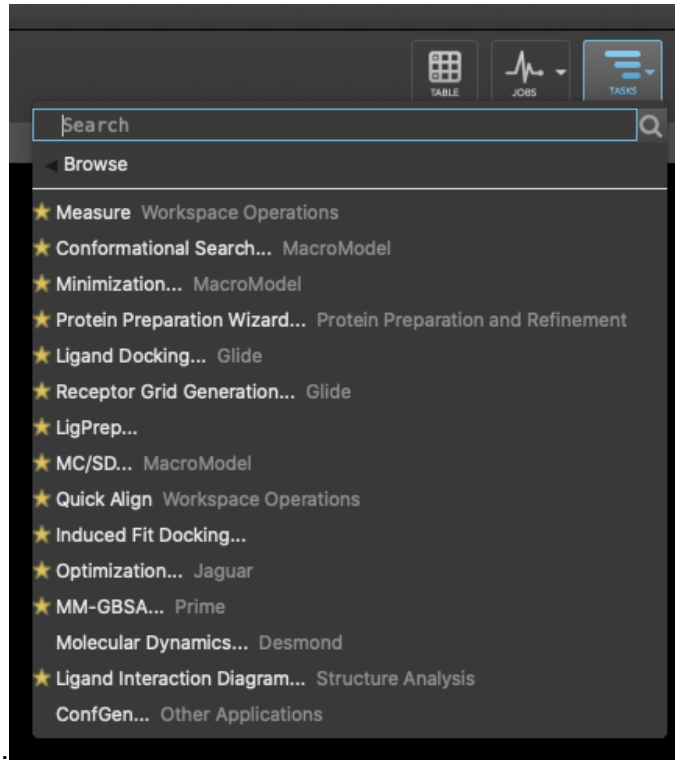
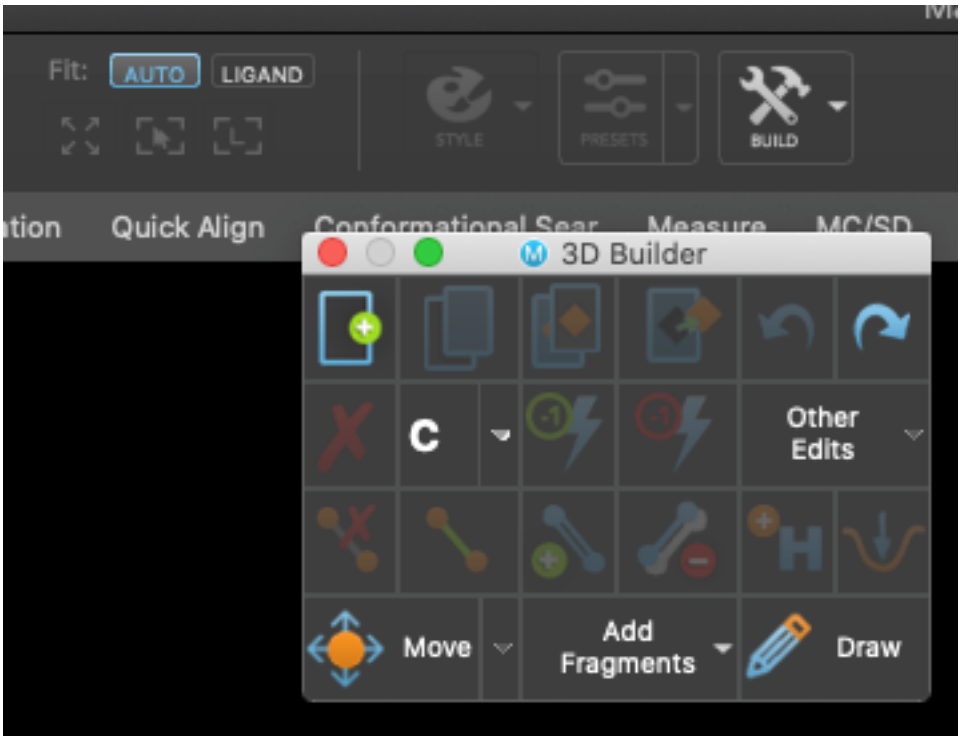


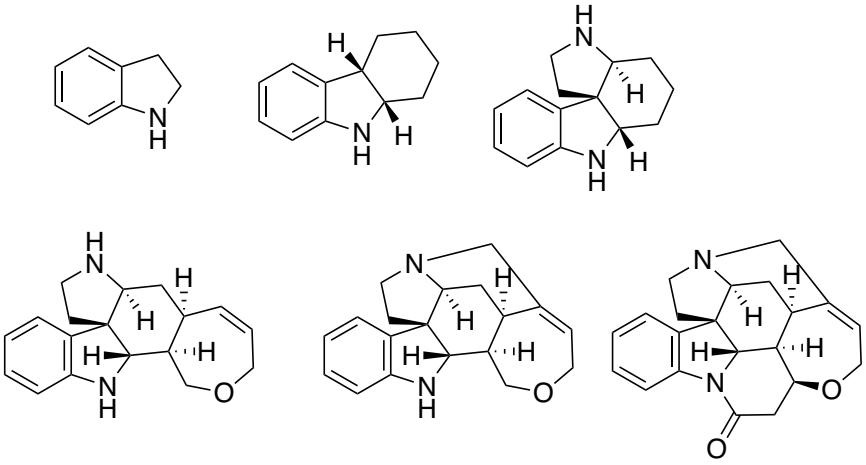
The favorite programs will now show up on the top tab as shown below;

We are now start going to build strychnine for this exercise.

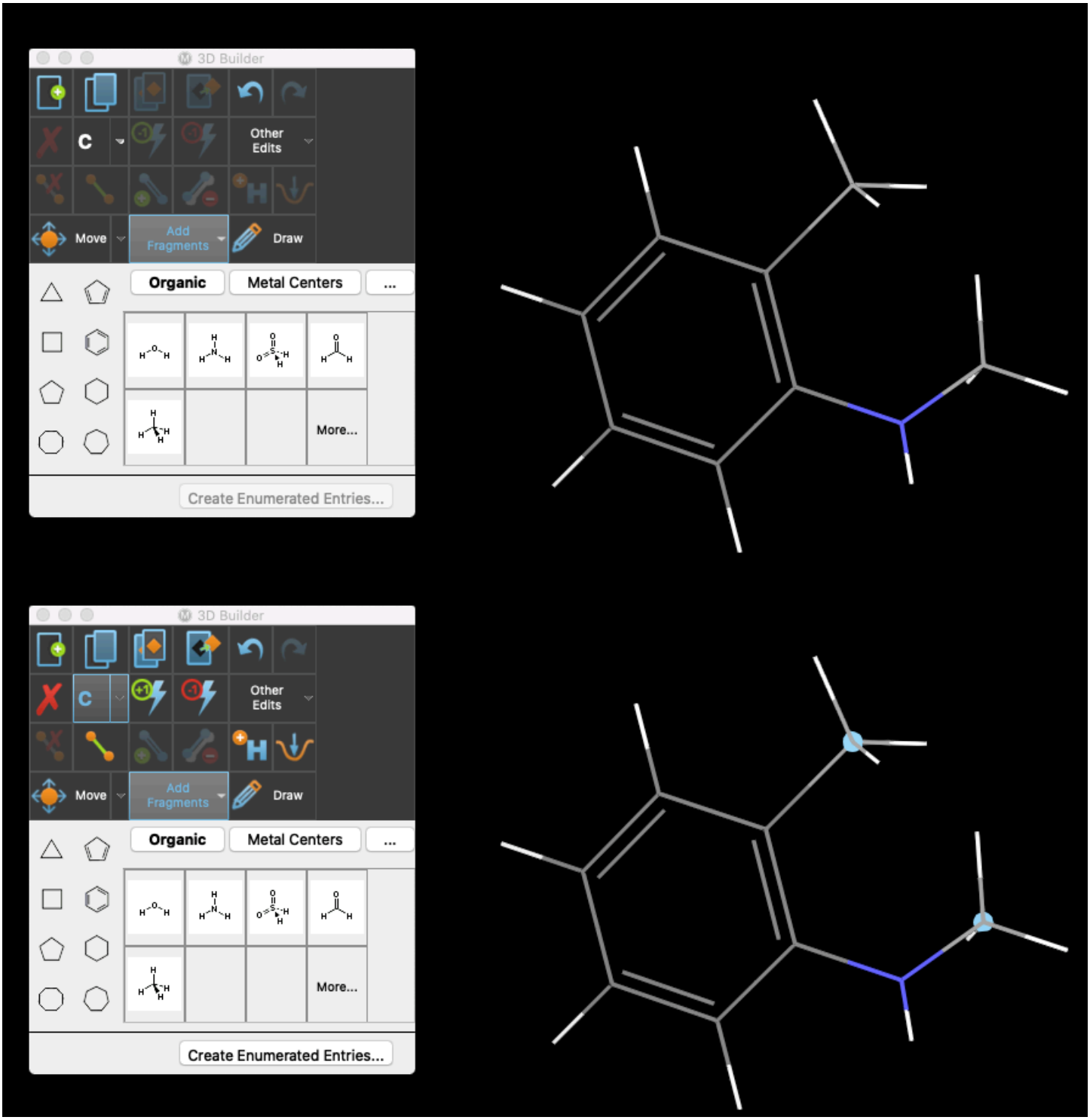
Click Build from the top tab and the 3D Builder tab should appear. Just like one would be drawing on PyMOL, draw the small molecule.

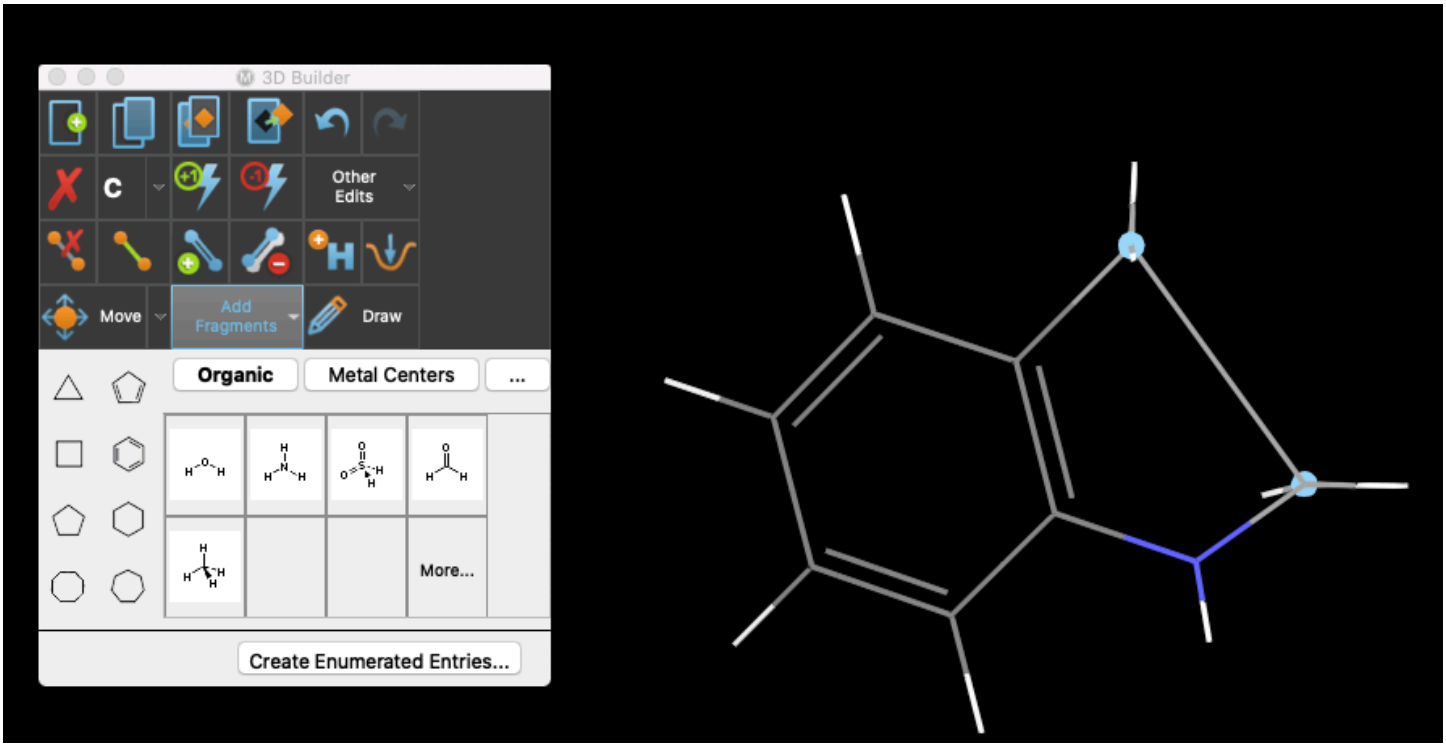


I suggest you take these steps to draw strychinine.

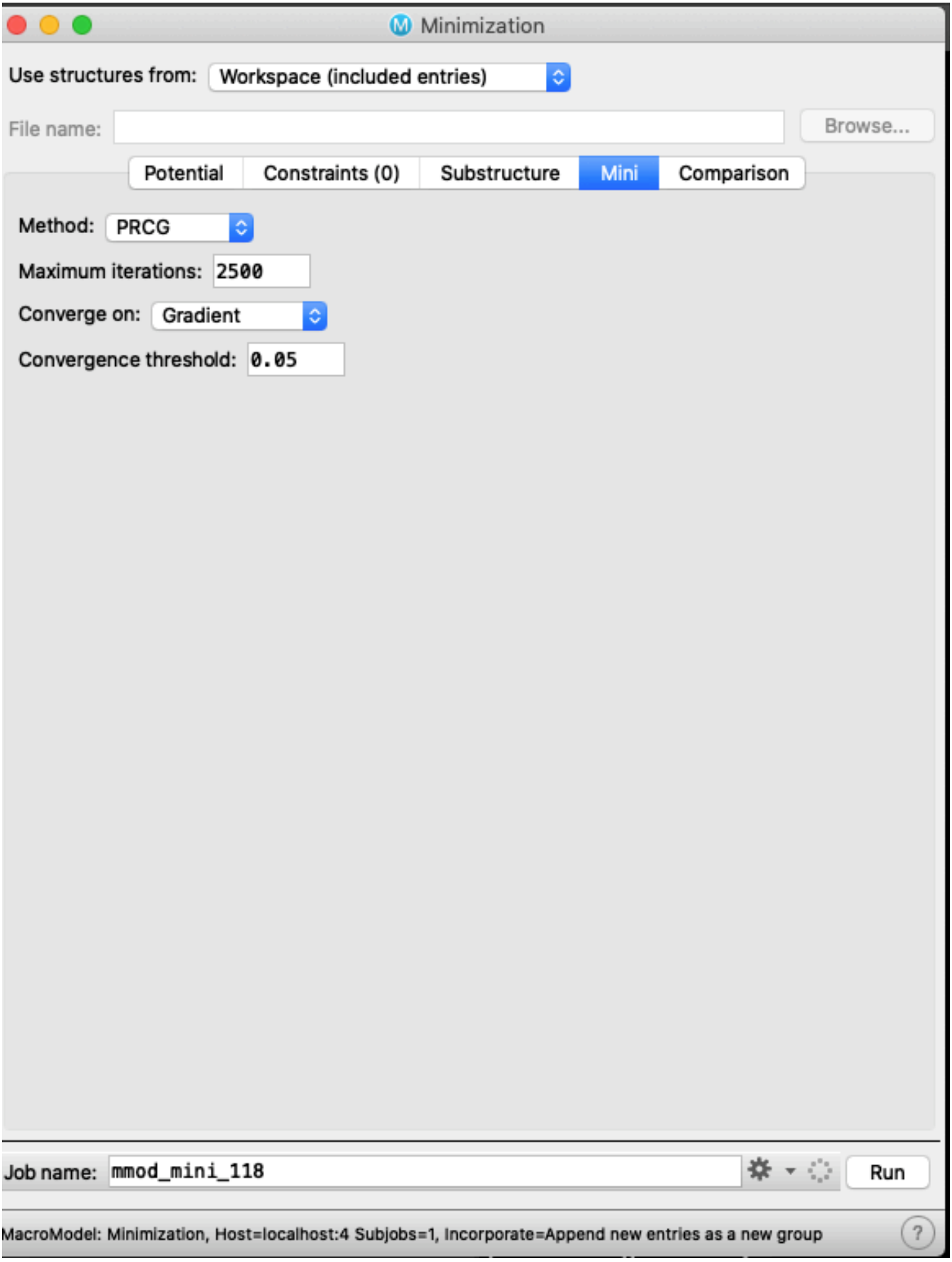


For each step, we are going to minimize the structure. To link the two atoms, one can select the two atoms with shift+left mouse click, then click the button with two orange circles with a green line.


3D Builder
Other Edits
Move
Add Fragments
Draw
Organic
Metal Centers
...
More...
Create Enumerated Entries...
3D Builder
Other Edits
Move
Add Fragments
Draw
Organic
Metal Centers
...
More...
Create Enumerated Entries...



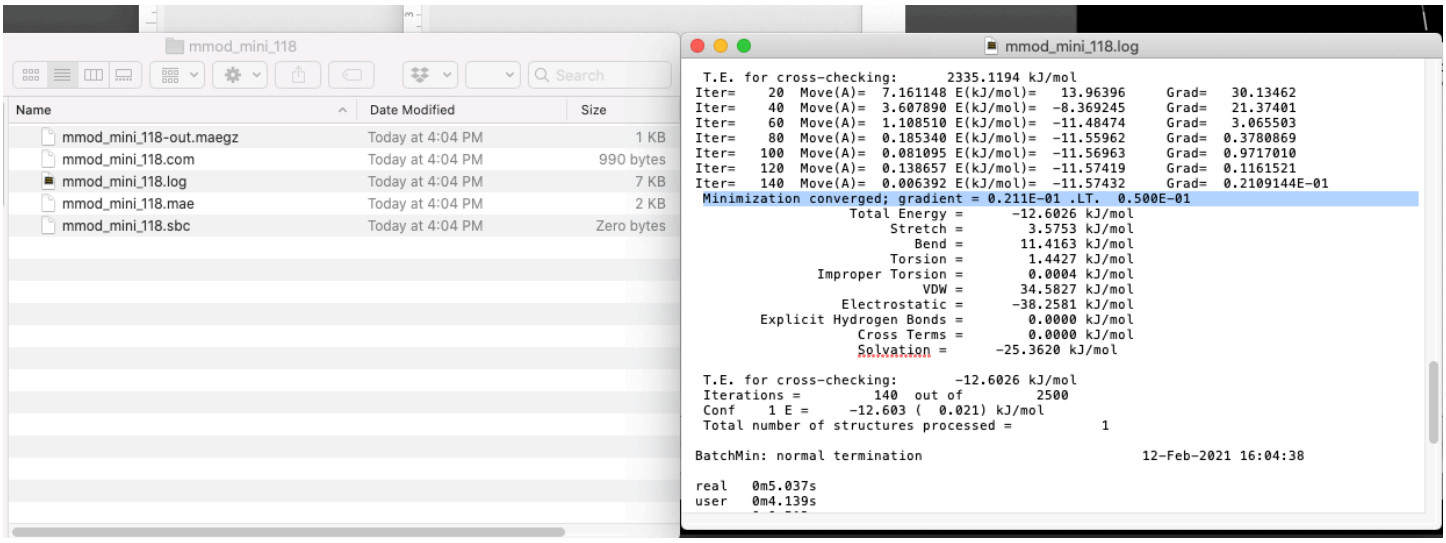
Once we have this ugly looking dihydro indole, we are going to minimize the structure. From the tabs, click miminization, then click run.


Minimization
Use structures from:
Workspace (included entries)
File name:
Browse...
Potential
Constraints (0)
Substructure
Mini
Comparison
Method:
PRCG
Maximum iterations:
2500
Converge on:
Gradient
Convergence threshold:
0.05
Job name:
mmod_mini_118
Run
MacroModel: Minimization, Host=localhost:4 Subjobs=1, Incorporate=Append new entries as a new group

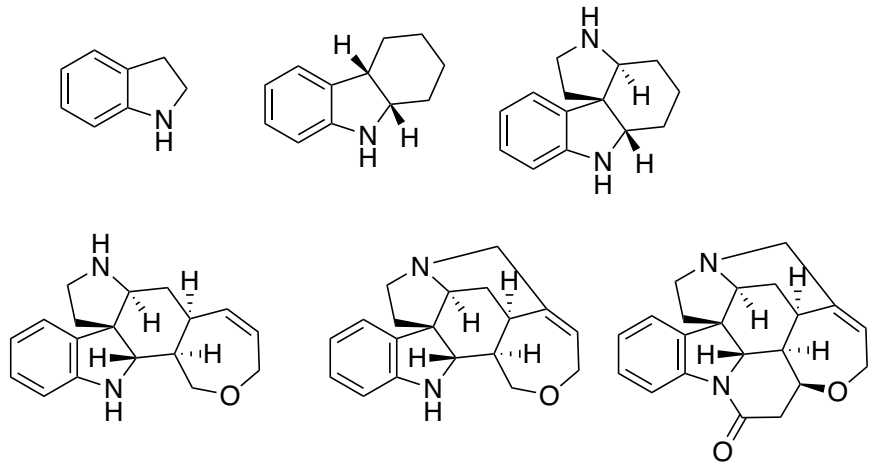
After the run is complete, a new row is created with minimized beautiful looking dihydro indole.

After each minimization run, you want to check that the minimization converged by going to the folder. For MAC OS, it is in the maestro folder. (Users\YOUR COMPUTER NAME\mmod_mini_xxx{or your choice of Job name}) In the folder, you will see five files. If you open the log file in text editor, you will see that the minimization converged (highlighted in the picture below).

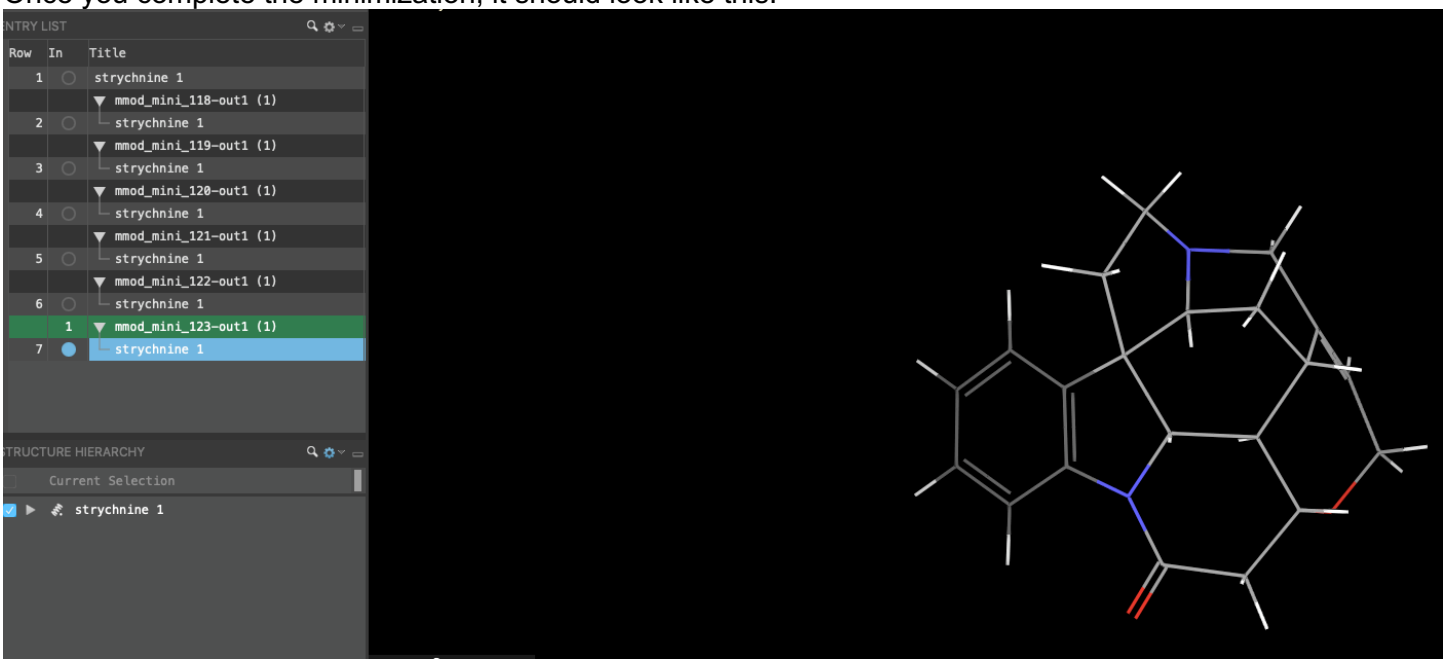
If your structure is big and did not converge, you want to increase the maximum iterations from 2500 to higher number.



With these, please complete drawing the strychnine minimizing each structure below;

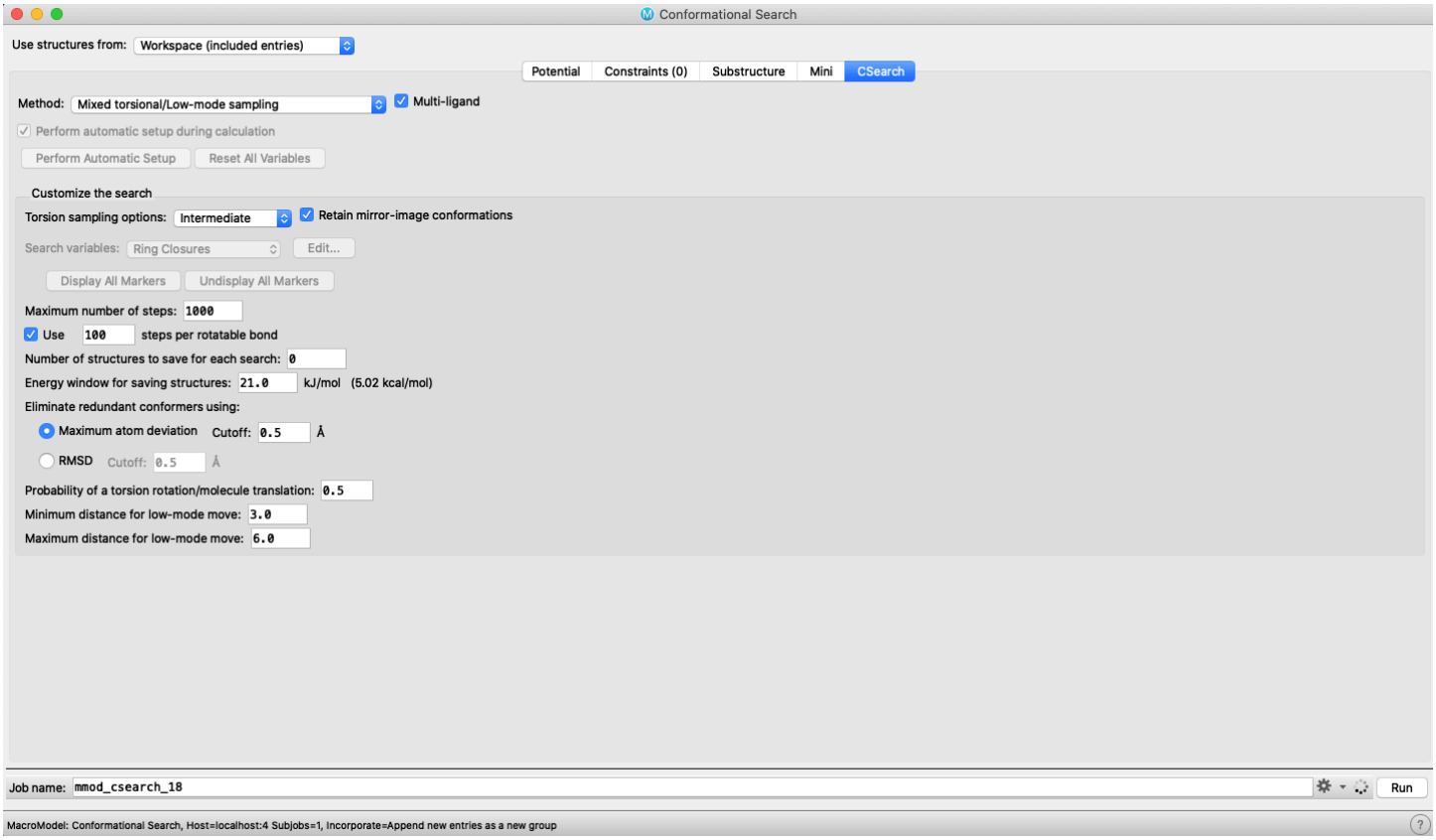


Once you complete the minimization, it should look like this.

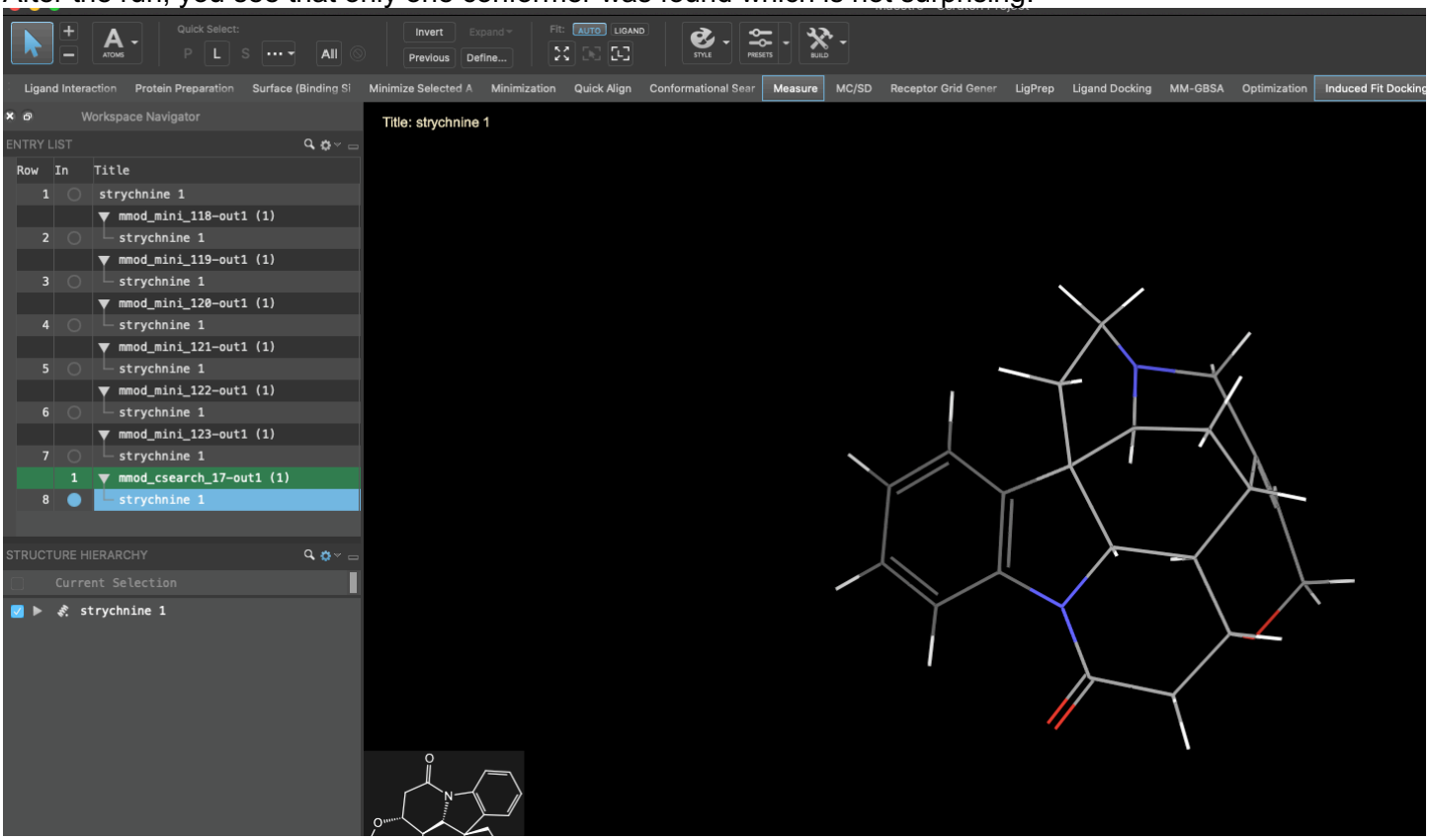


If you want to look at the structure in PyMOL, you go to Workspace→Send to PyMOL→Selected Entries and PyMOL session will open up with your structure.

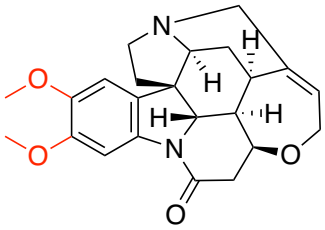
With the strychnine molecule, let's run conformational search. Click conformational search in one of your favorite tabs and click run. (This may take a long time)



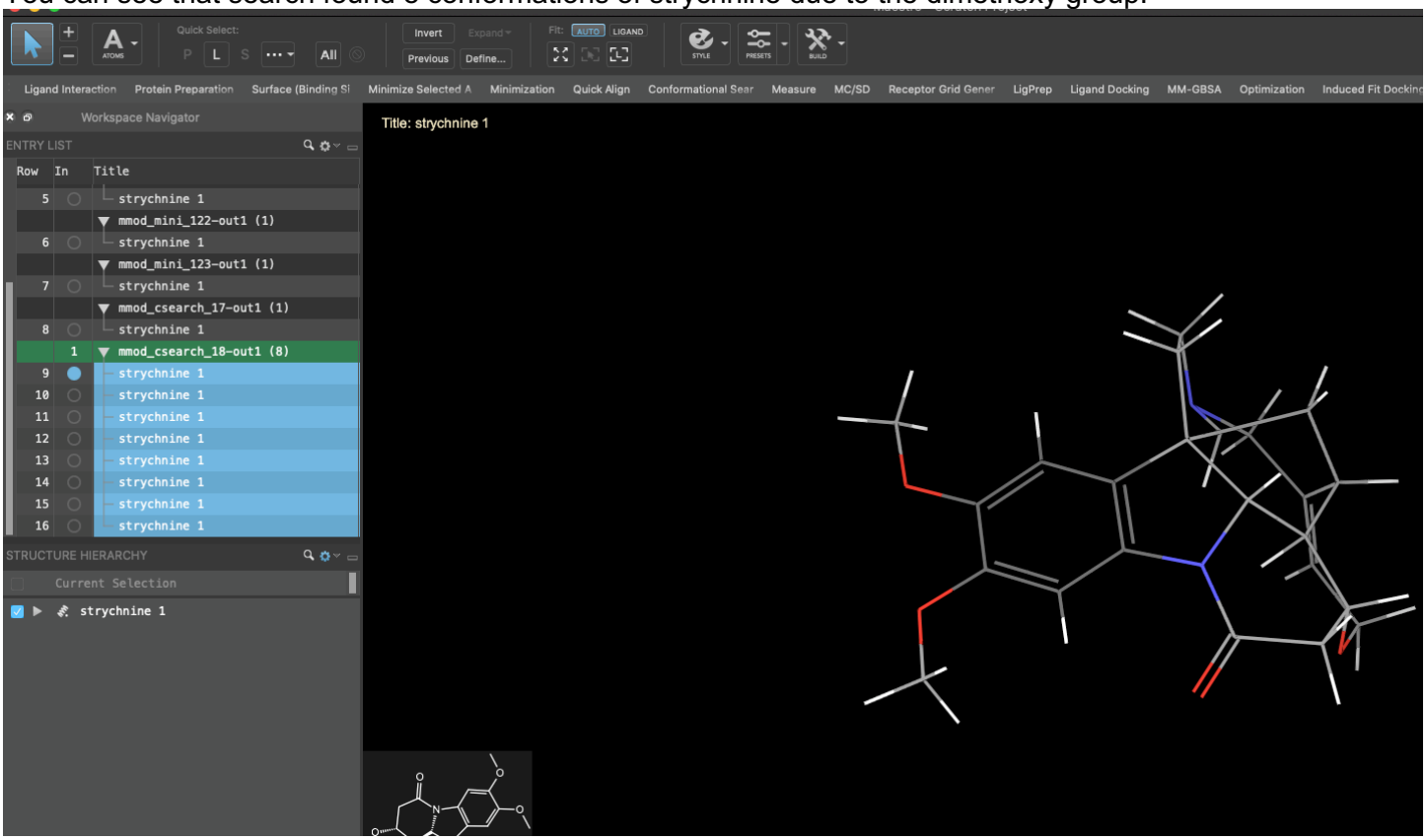
After the run, you see that only one conformer was found which is not surprising.



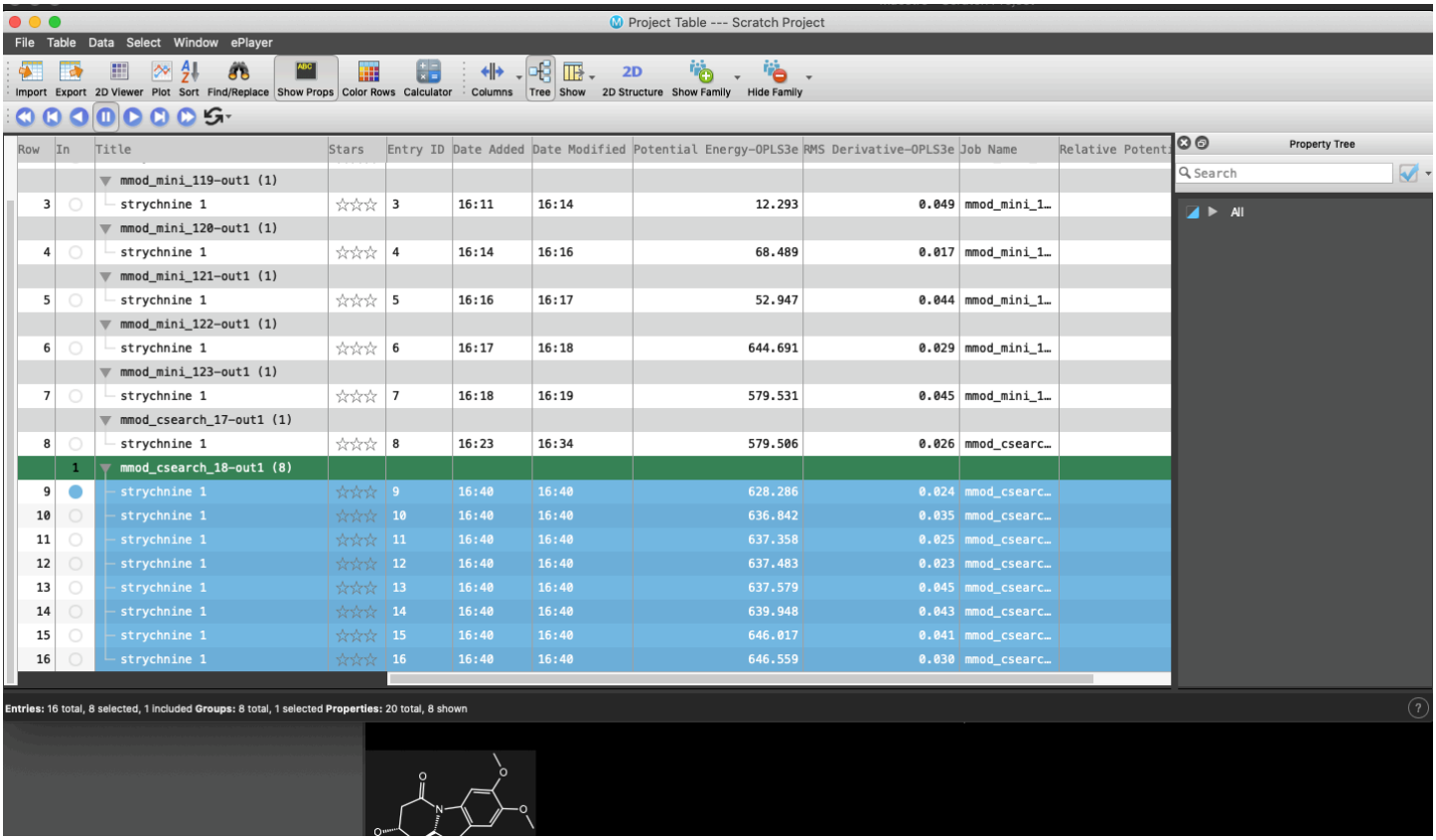
Now let's try the derivative of strychnine, Brucine 3 and run conformational search.



You can see that search found 8 conformations of strychnine due to the dimethoxy group.



Further, you can click the “table” button located on the right top and look at the relative potential energy to determine the energy levels of various conformations.



Row	In	Title	Stars	Entry ID	Date Added	Date Modified	Potential Energy-OPLS3e	RMS Derivative-OPLS3e	Job Name	Relative Potenti
		mmod_mini_119-out1 (1)								
3		strychnine 1	☆☆☆	3	16:11	16:14	12.293	0.049	mmod_mini_1…	
		mmod_mini_120-out1 (1)								
4		strychnine 1	☆☆☆	4	16:14	16:16	68.489	0.017	mmod_mini_1…	
		mmod_mini_121-out1 (1)								
5		strychnine 1	☆☆☆	5	16:16	16:17	52.947	0.044	mmod_mini_1…	
		mmod_mini_122-out1 (1)								
6		strychnine 1	☆☆☆	6	16:17	16:18	644.691	0.029	mmod_mini_1…	
		mmod_mini_123-out1 (1)								
7		strychnine 1	☆☆☆	7	16:18	16:19	579.531	0.045	mmod_mini_1…	
		mmod_csearch_17-out1 (1)								
8		strychnine 1	☆☆☆	8	16:23	16:34	579.506	0.026	mmod_csearc…	
	1	mmod_csearch_18-out1 (8)								
9		strychnine 1	☆☆☆	9	16:40	16:40	628.286	0.024	mmod_csearc…	
10		strychnine 1	☆☆☆	10	16:40	16:40	636.842	0.035	mmod_csearc…	
11		strychnine 1	☆☆☆	11	16:40	16:40	637.358	0.025	mmod_csearc…	
12		strychnine 1	☆☆☆	12	16:40	16:40	637.483	0.023	mmod_csearc…	
13		strychnine 1	☆☆☆	13	16:40	16:40	637.579	0.045	mmod_csearc…	
14		strychnine 1	☆☆☆	14	16:40	16:40	639.948	0.043	mmod_csearc…	
15		strychnine 1	☆☆☆	15	16:40	16:40	646.017	0.041	mmod_csearc…	
16		strychnine 1	☆☆☆	16	16:40	16:40	646.559	0.030	mmod_csearc…	

********** few other notes;

(A) For running peptides, I suggest you use the MMFFs force field as it accounts for the planarity of the amides.
(B) one can add the constraints in the minimization and the conformation search to keep certain atoms frozen or keep next to certain atoms.