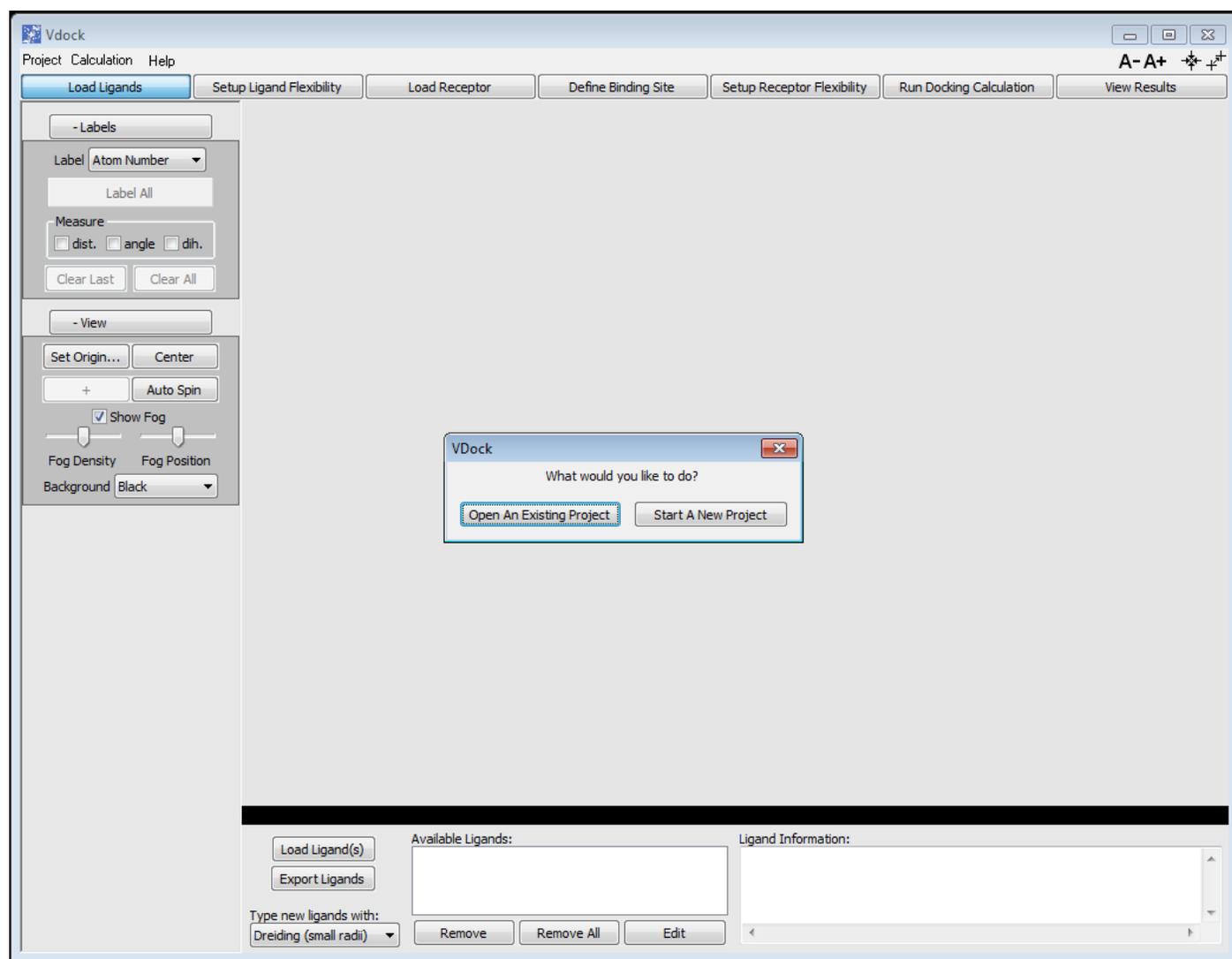


Vdock Examples and Tutorial



Introduction

Welcome! These short examples, which involve HIV-1 Protease and known inhibitors, will teach you the essentials of carrying out docking calculations using Vdock.

You will learn how to load ligands and a receptor, set up the parameters of a calculation, carry it out, and then how to visualize the results.

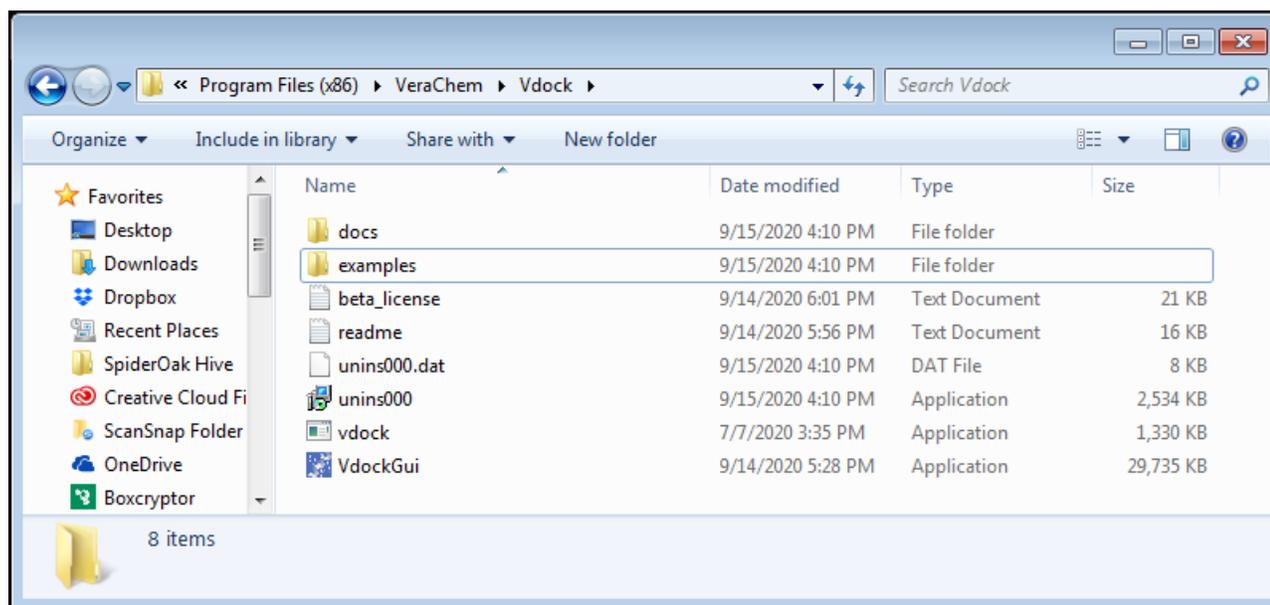
The Vdock graphical interface is designed to guide you through this process. The steps that need to be taken are laid out along the top as a row of buttons, starting with Load Ligands and ending with View Results. Each section has its own interface to aid you in the tasks specific to that stage.

If you run into any trouble or would like to explore aspects of the software beyond what is described here, you can access the full documentation from the Help menu at the top of the window. This document can also be accessed from the same menu.

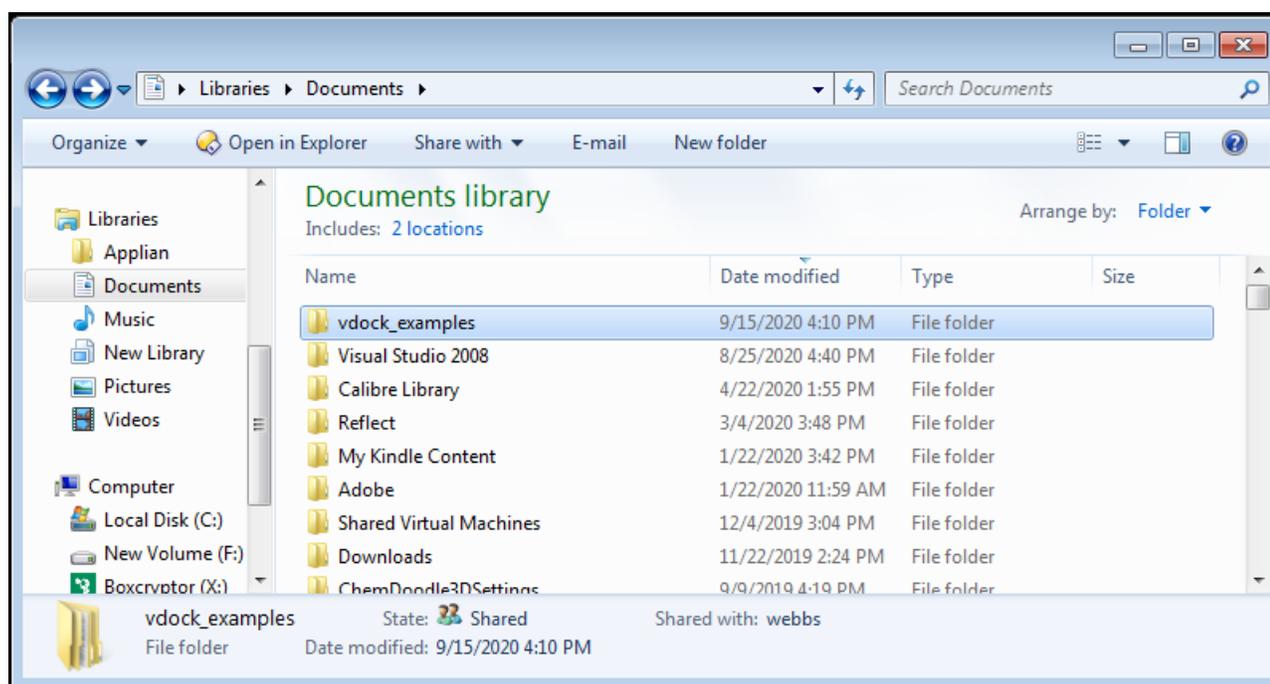
Preparing to run the examples

The first thing you should do is to make a copy of the example files for your own use. This preserves the original copy that was installed with the software and is necessary on some systems because file permissions can prevent writing to the installation directory.

Navigate to the install location of Vdock. If you picked the default location this will probably be `c:\Program Files (x86)\VeraChem\Vdock`



Copy the examples directory and paste it to a location of your choice (Documents works well) You might wish to rename the new directory from examples to `vdock_examples` to make it easier to find in the future.



HIV Protease and XK263

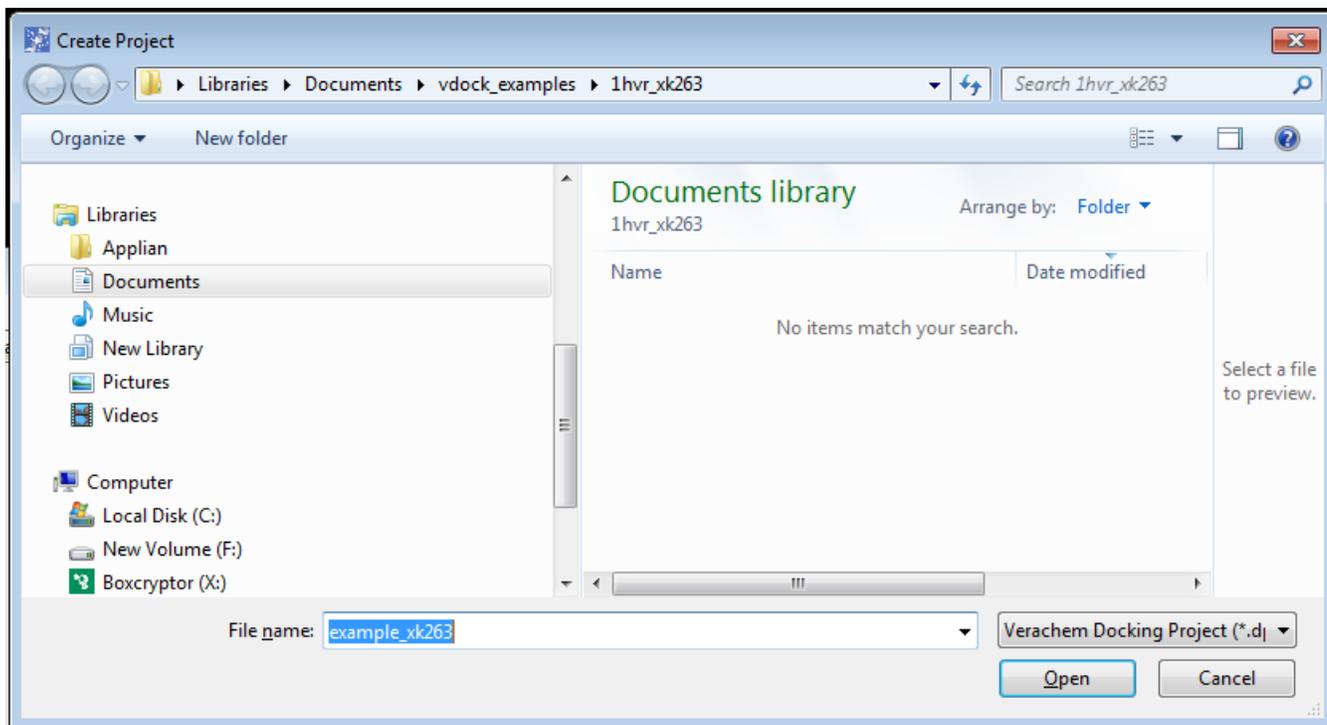
This example involves docking the cyclic urea inhibitor xk263 to HIV-1 protease using the 1hrv PDB structure.

Start up Vdock by double-clicking on the blue desktop icon labeled VDock Interface. You can also open the Start menu and type vdock into the search field. That should display the Vdock Interface link as well.

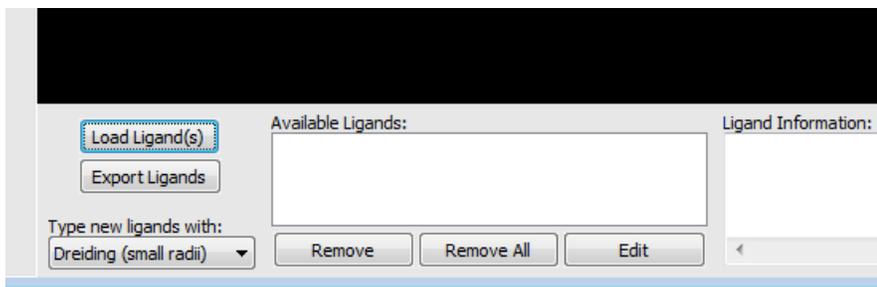


Select **New Project** from the dialog in the center of the screen

Navigate to **vdock_examples\1hrv_xk263** and pick a name for your project and select **Open**



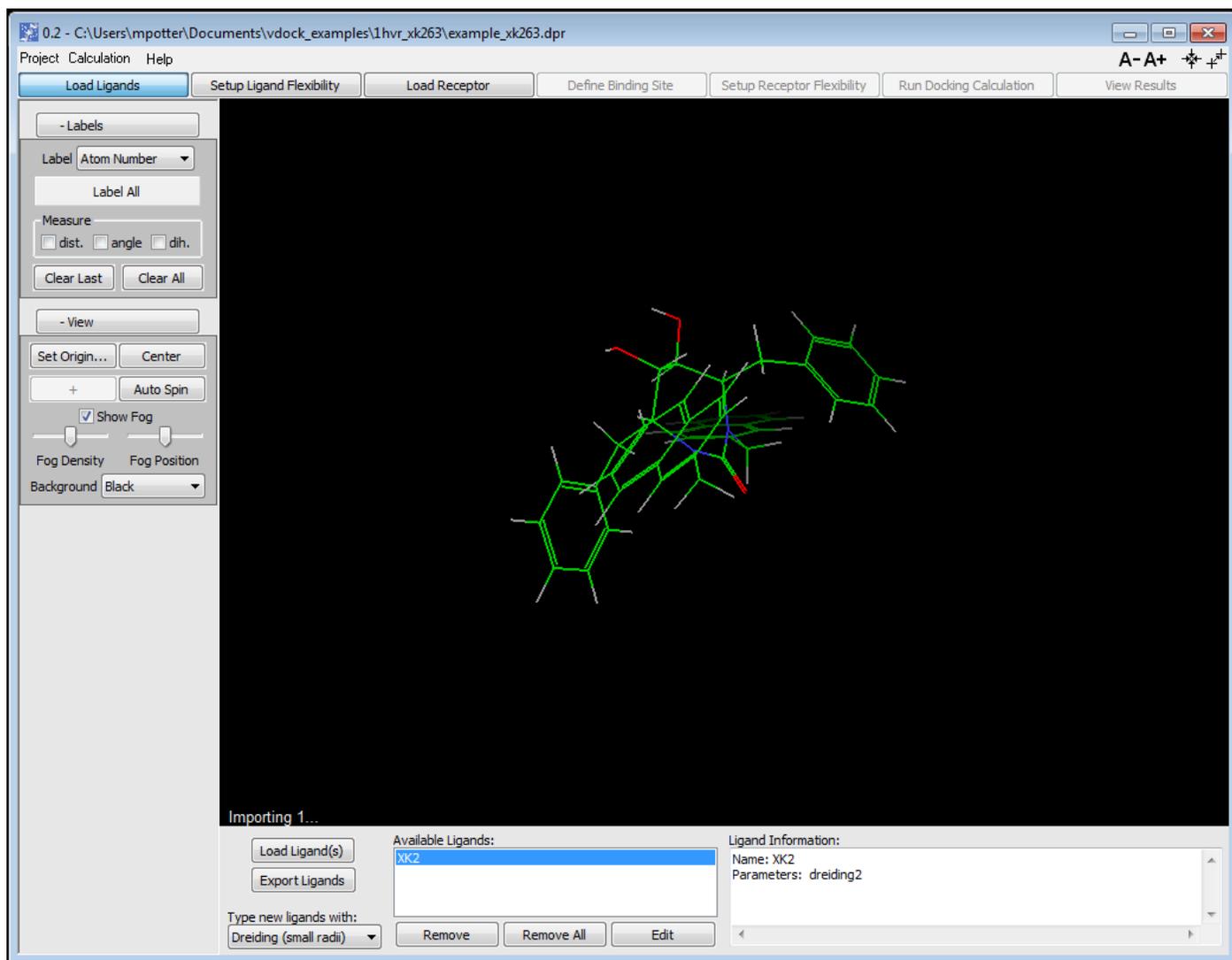
Select the **Load Ligands** button at the bottom left



Pick **XK2_model.sdf** and click **Open**

This file contains the xk263 inhibitor from the PDB file 1hrv. It is in the conformation found in that co-crystal structure.

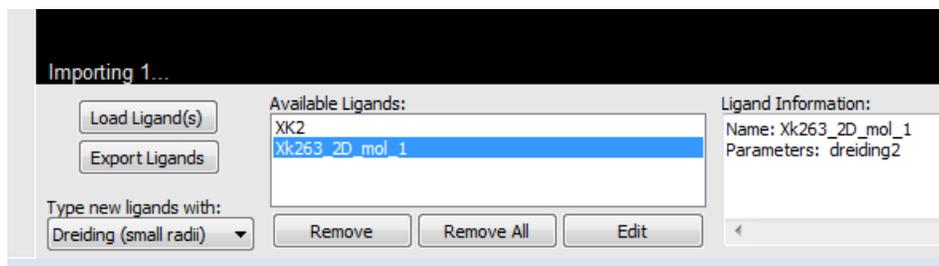
xk263 will appear in the 3D graphics window



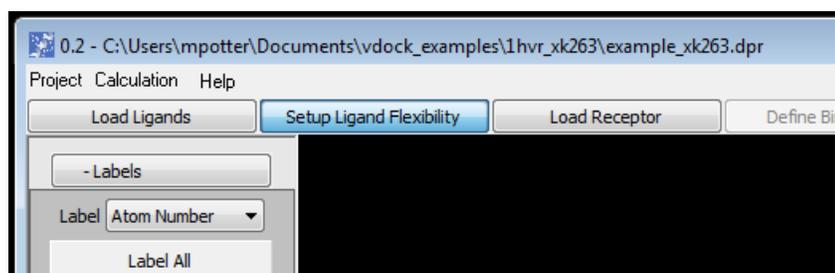
Select the **Load Ligands** button again and this time pick **xk263_from_2D_vconf.sdf** and click **Open**.

This file contains a different conformation of xk263. This time the molecule was drawn in 2D using VeraChem's **Vdraw** software and then **Vconf** used to convert this to 3D and carry out a conformational search to find low energy conformations. This conformation is the lowest energy one that was found. We are including it to demonstrate a realistic scenario in which one might want to dock a molecule for which you have no docked conformation already and one must start from scratch with a 2D structure. This is considerably more challenging than simply redocking a ligand that was extracted from a complex pdb structure.

After the load it complete you will see two entries in the **Available Ligands** box at the bottom of the window.

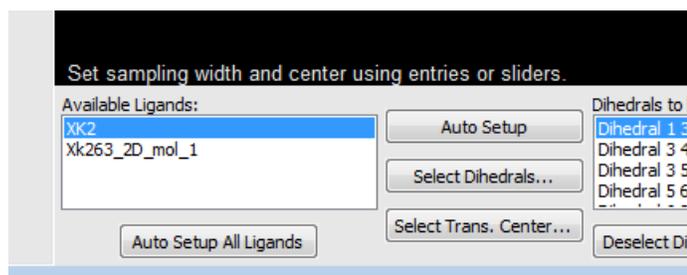


Next select the **Setup Ligand Flexibility** button at the top of the window.



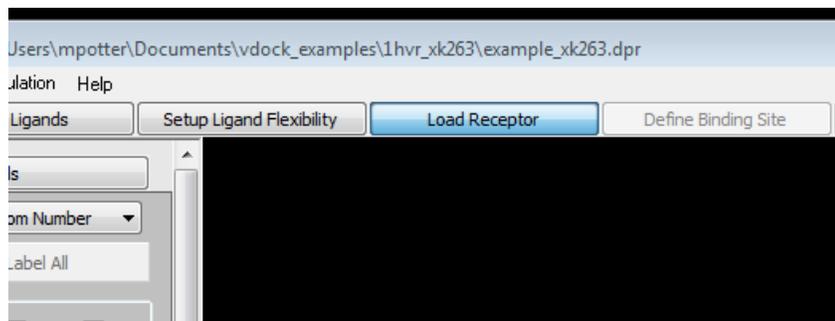
The **Setup Ligand Flexibility** window is used to control how much flexibility in the ligand will be sampled during the docking calculation. Vdocking only searches around rotatable bonds (it does not change bond angles or lengths). It is here where you can decide which rotatable bonds to sample and what range to sample over.

Next, select the **Auto Setup All Ligands** at the bottom



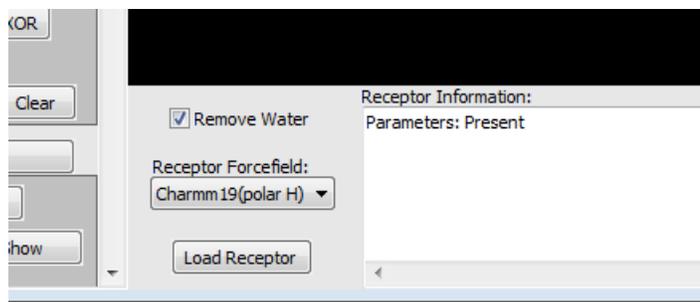
The **Auto Setup All Ligands** button can be used to implement the most common sampling scheme, that is to sample all rotatable bonds in all ligands over their entire range. This is the most common option to select. If, in the future, you wish to limit sampling then you can use the other tools on this page to do so.

Now select the **Load Receptor** button at the top to switch to the window for loading your receptor.



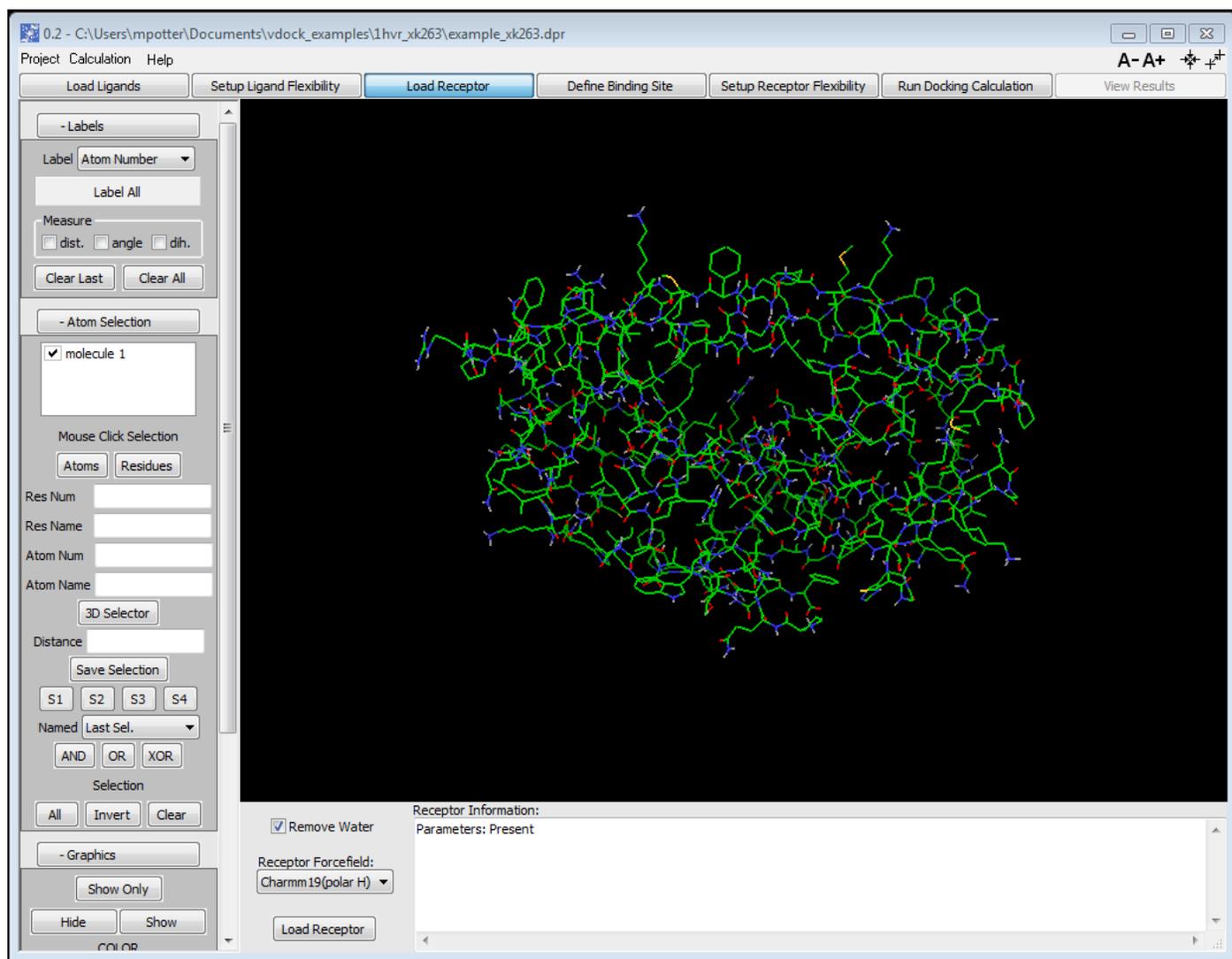
This window is used to load the receptor structure you will use in the docking calculation. This is also where you can choose the molecular mechanics force field to use and carry out the assignment of parameters.

Click the **Load Receptor** button at the bottom and select **1hvr.pdb** in the file selection dialog that appears. Then click open.



The **Charmm19(polar H)** forcefield is selected by default. **Charmm22(all atom)** is also a supported option.

The receptor structure will be displayed in the 3D graphics window.



Information regarding loading of the receptor structure and its parameterization is displayed in the console window, separate from the main graphical interface.

```
Vdock Interface
Extract ligand(s) from molecule object master ...
Extracted ligand(s) contains:
Non-standard residue Frag(XK2,263,A)
Ligand pdb filename: tmp160203350710423901_coxtal_ligand_vc.pdb
Automagically type the protein only ...
Number of atoms in master molecule object is 1890
Number of atoms in molecule object for typing is 3120
Force field is charmm19
Load parameter library file: C:\Users\mpotter\AppData\Local\Temp\MEI25~1\verachem\parameters\verachem_libraries\charmm19.lib
Will write mol file to tmp160203350710423901_vc.mol
Will write crd file to tmp160203350710423901_vc.crd
Will write top file to tmp160203350710423901_vc.top
Use molecule object dihedrals False
Total charge is 4.0
```

Any ligands that are detected during the loading process will be saved in pdb format in the same directory as the project file. The filename(s) will be reported in the console window. You can see that one such ligand was found. If any errors occur during this process they will also be displayed in the console window.

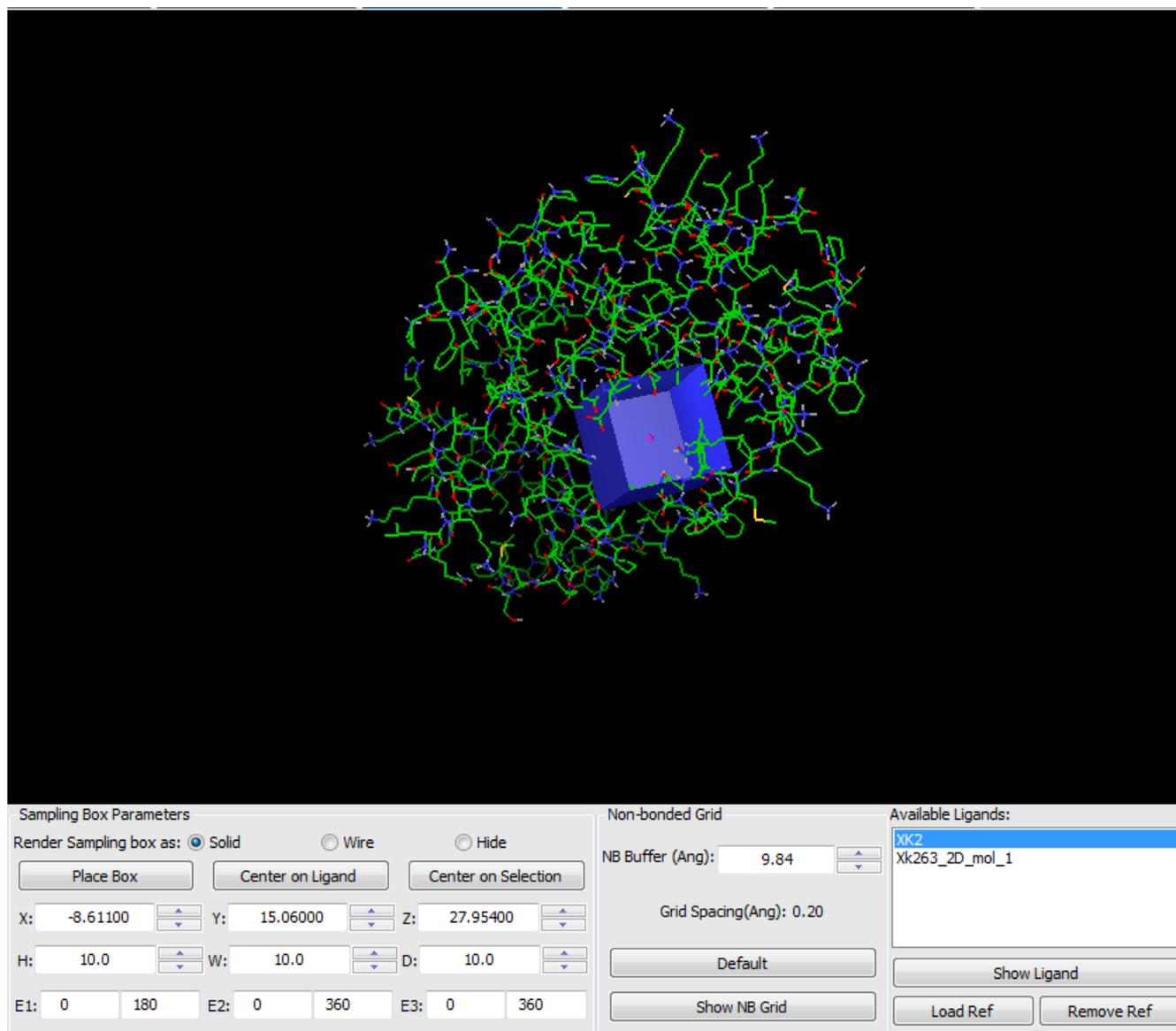
Next, select the **Define Binding Site** button at the top of the main window.

The screenshot shows the Vdock software interface. The top toolbar has several buttons: "Load Ligands", "Setup Ligand Flexibility", "Load Receptor", "Define Binding Site" (which is highlighted in blue), "Setup Receptor Flexibility", "Run Docking Calculation", and "View Results". The main window displays a 3D molecular model of a protein-ligand complex. The left sidebar contains various tool panels: "- Labels" (with a dropdown for "Atom Number", "Label All", and "Measure" options for distance, angle, and dihedral), "- Atom Selection" (with checkboxes for "Receptor" and "XK2", and "Mouse Click Selection" buttons for "Atoms" and "Residues"), and "- Graphics" (with "Show Only", "Hide", and "Show" buttons). The bottom panel shows "Sampling Box Parameters" (with "Render Sampling box as" options for Solid, Wire, and Hide, and "Place Box", "Center on Ligand", and "Center on Selection" buttons) and "Available Ligands" (with a list containing "XK2" and "Xk263_2D_mol_1", and "Show Ligand", "Load Ref", and "Remove Ref" buttons).

This window is used to specify the region of 3D space that will be searched by the ligands during the docking process. This is a user-defined cube which is usually centered on a known binding site of the receptor.

In this case, we know that the ligand XK2 is in the binding site of the receptor, because it was built from the ligand present in the 1hrv pdb structure. So, we can use it to place the sampling box.

Make sure that XK2 is selected and highlighted in blue in the **Available Ligands** box at the lower right, then click the **Center on Ligand** button in the bottom center.



The screenshot displays the Vdocking software interface. The main window shows a 3D molecular model of a protein (green and blue) with a blue sampling box centered on a ligand (XK2). The interface includes several control panels:

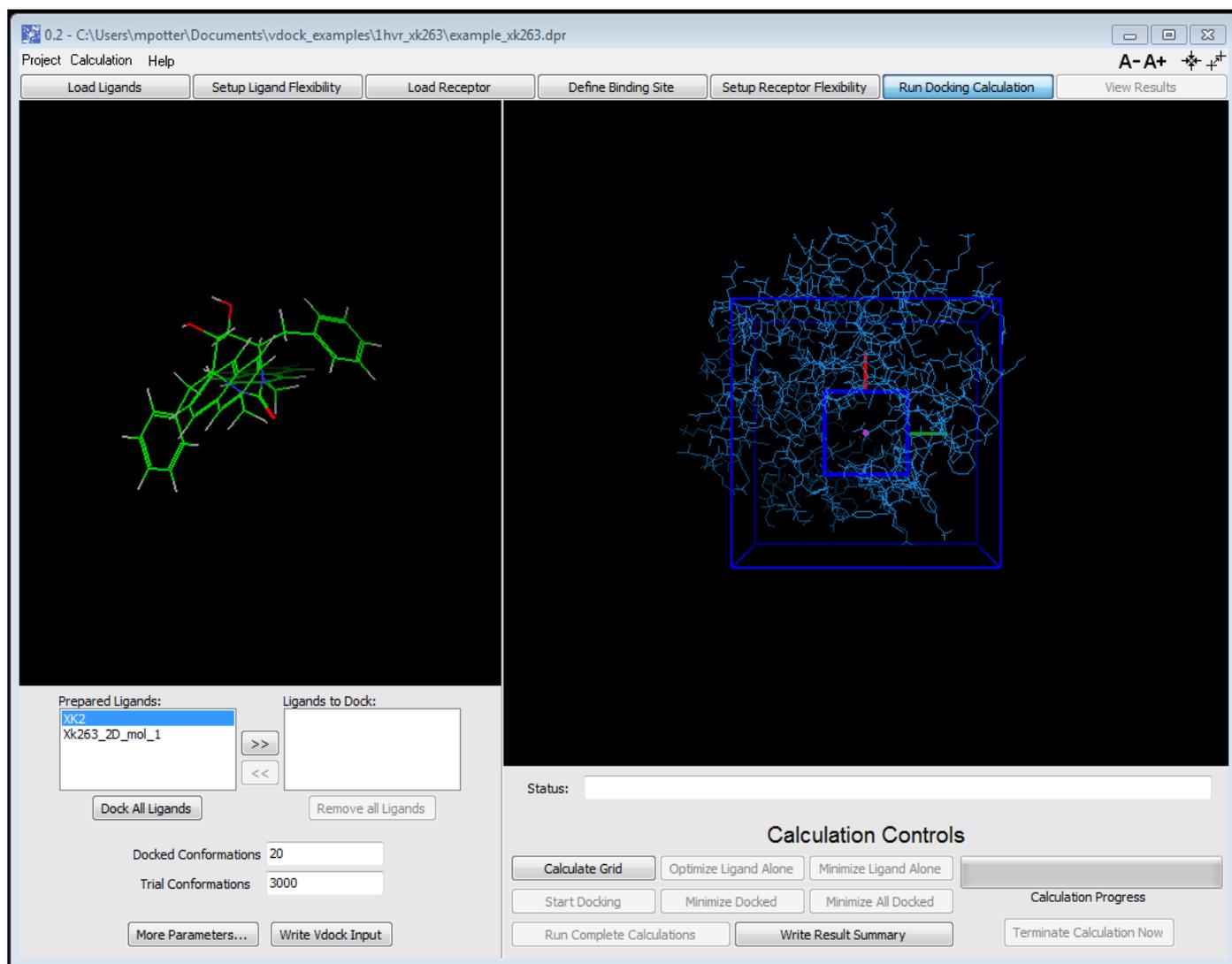
- Sampling Box Parameters:** Render Sampling box as: Solid, Wire, Hide. Buttons: Place Box, Center on Ligand, Center on Selection. Coordinates: X: -8.61100, Y: 15.06000, Z: 27.95400. Dimensions: H: 10.0, W: 10.0, D: 10.0. Euler angles: E1: 0, 180; E2: 0, 360; E3: 0, 360.
- Non-bonded Grid:** NB Buffer (Ang): 9.84. Grid Spacing(Ang): 0.20. Buttons: Default, Show NB Grid.
- Available Ligands:** List: XK2 (highlighted), Xk263_2D_mol_1. Buttons: Show Ligand, Load Ref, Remove Ref.

The sampling box will move to the binding site.

This cube may also be placed either manually, using the **Place Box** button and the mouse, or it can be placed on a reference structure, loaded specifically for the task, or on any set of selected atoms, using the **Center on Selection** button. Please see the full Vdocking documentation, which can be found in the Help menu for details.

For purposes of this example we will skip the **Setup Receptor Flexibility** window. It is used to select rotatable bonds in side chains of residues in the receptor to sampling simultaneously with the ligand.

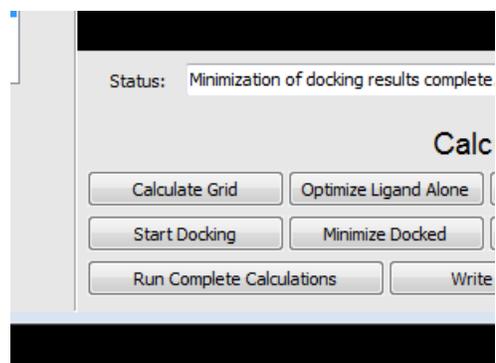
So, now select the **Run Docking Calculation** button at the top of the window.



This window is used to select which ligands to dock from those you have loaded and prepared. You can also set the search parameters which govern the length and thoroughness of the docking. On the right are controls for actually executing the calculation and monitoring its progress. There are many adjustable parameters that can be accessed using the **More Parameters...** button, but the main ones are available from the main window. **Docked Conformations** sets the number of conformations of the ligand, docked to the protein that you would like to generate. **Trial Conformations** is roughly the number of different conformations that will be generated for each of the docked conformations produced. Out of the total number of trial conformations, the one with the lowest potential energy will be selected. That is, if **Docked Conformations** is set to 20 and **Trial Conformations** to 3000, then 20 searches of 3000 trial conformations each will be run. The lowest energy from each search will be saved as one of the 20 docked conformations produced. See the full documentation, accessible from the **Help** menu for details.

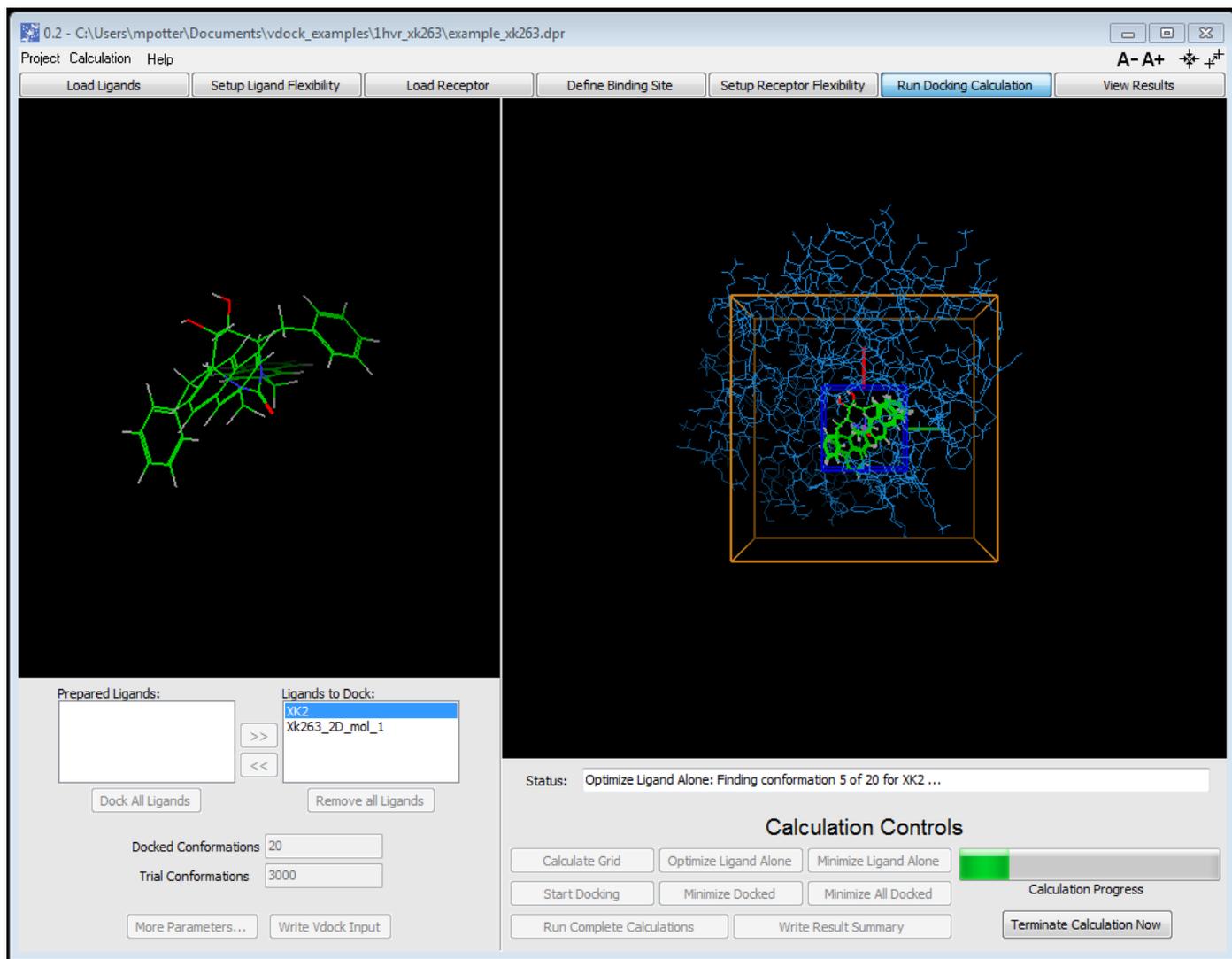
Click the **Dock All Ligands** button on the left panel to select both ligands you have prepared for docking.

Now click the **Run Complete Calculations** button on the bottom left of the right panel.

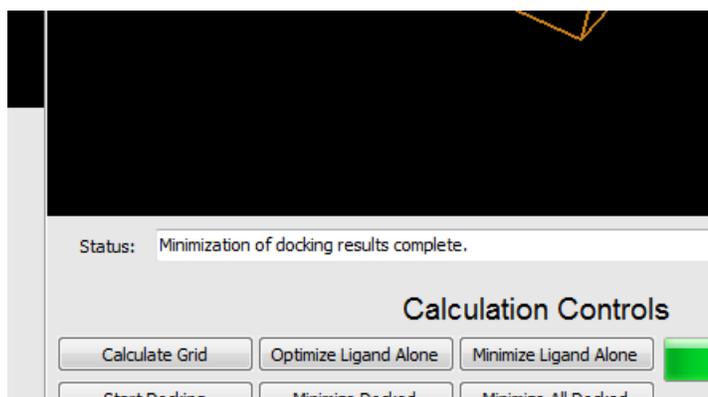


This will start the docking calculations for the selected ligands and will following those calculations with a number of other calculations which can help in interpretation of the results. These include a conformational optimization of the ligands by themselves, without the protein present, as well as minimization of both the conformations found for the ligands by themselves and the docked conformations. This is helpful as the docking algorithm itself only optimizes the energy with respect to position, orientation, and rotatable bonds. A full minimization extends that optimization to the remaining degrees of freedom (bond lengths and bond angles for example).

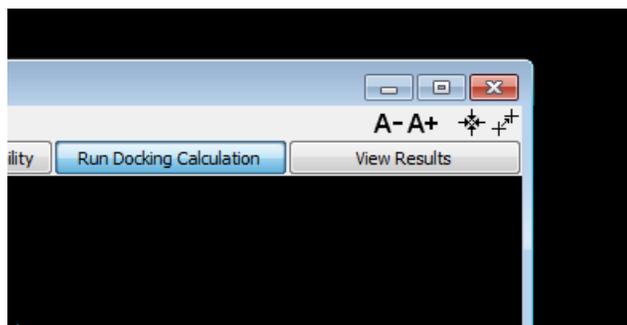
While the calculations are executing in the background, a process that should take only a few minutes, the docking GUI will display information about which ligand is being docked and the progress of the individual calculation that is running at that point (might be docking, ligand alone optimization, or minimization). Docked conformations are displayed as they are found.



Once the calculations are complete, as indicated by a **Minimization of docking results complete** message in the status bar of the right panel,



click the **View Results** tab at the top right.



which will take you to the **View Results** interface.

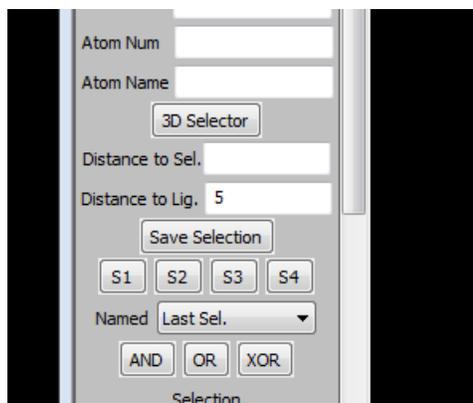
The screenshot shows the 'View Results' window of a docking software. The main area displays a 3D molecular model of a protein (blue) with a docked ligand (green). The right panel shows a 'Potential Energy' graph and a list of energy values: Potential Energy: -91.9126, Binding Energy: -83.4568, Interaction E.: -89.2894, Interaction: VdW: -79.6272, Interaction: Coulomb: -9.6621, Interaction: VdW Rep.: 56.4085, Interaction: VdW Attr.: -136.0357, Internal E.: -2.6232, Internal: VdW. The left panel contains controls for labeling and atom selection. The bottom panel shows 'Available Ligands' with 'Xk2' and 'Xk263_2D_mol_1' listed, and buttons for 'Show All', 'Keep', 'Back', 'Forward', 'Invert', 'Accumulate', and 'Clear Strs'.

Category	Value
Potential Energy	-91.9126
Binding Energy	-83.4568
Interaction E.	-89.2894
Interaction: VdW	-79.6272
Interaction: Coulomb	-9.6621
Interaction: VdW Rep.	56.4085
Interaction: VdW Attr.	-136.0357
Internal E.	-2.6232
Internal: VdW	-

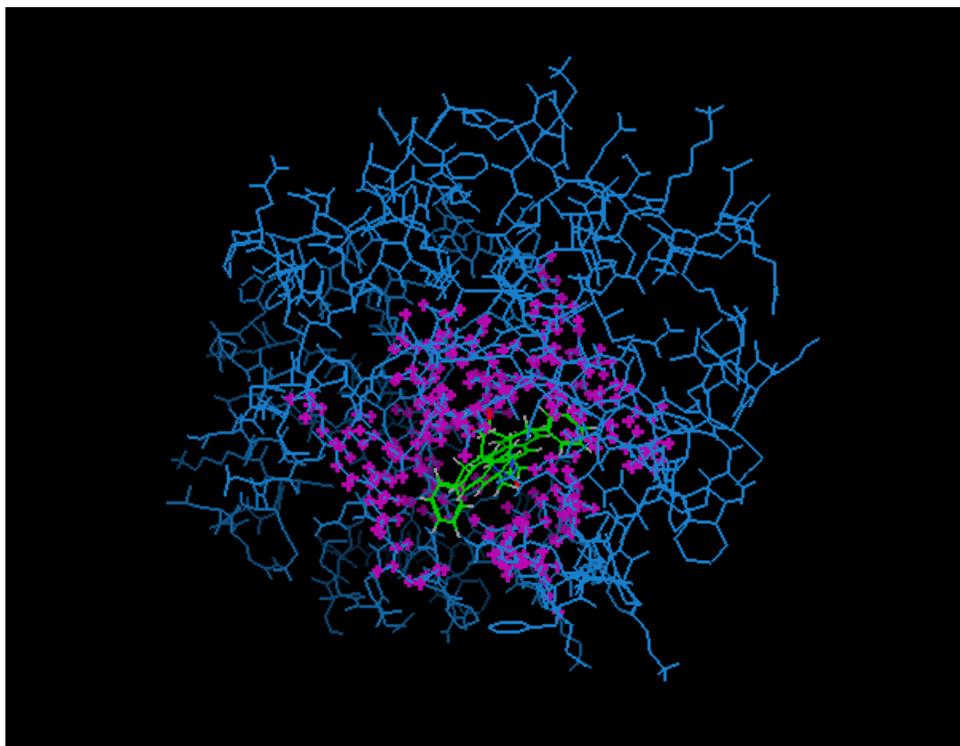
This window provides a wide range of tools that aid in the visualization and interpretation of the results of your calculations. You can view single or multiple conformations of each ligand in 3D along with the protein. You can simultaneously view quantitative energy information on the right as well as a graph of a selected quantity over all available conformations. Comprehensive controls for labeling and view control are at the left side and at the bottom right are buttons that provide a number of other useful tools. See the full documentation for details, available in the **Help** menu.

There are very large number of things that can be done from this window. For now we will look at just a few of the basics. When you arrive at the window it will be showing the docked confirmation for the selected ligand (shown in the **Available Ligands** box at the bottom center) with the lowest potential energy.

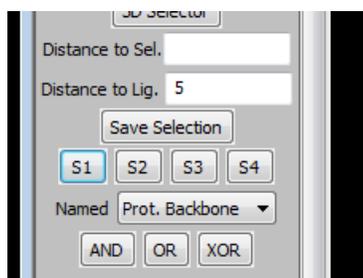
To make things a little easier to see, let's display only the portion of the protein that is within 5 Ang of the ligand. To do this, type 5 into the **Distance to Lig** field on the left in the **Atom Selection** panel and hit enter.



You will see all protein atoms within 5 Ang of the ligand highlighted with purple crosses.



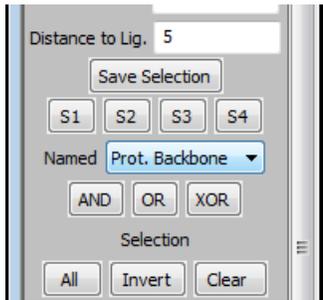
Now, let's save this selection for use later. Select the **Save Selection** button just below where you entered the distance based selection. Then click **S1** to save it in that memory location.



The **Atom Selection** panel allows you create complicated selections very easily by assembling them from simple 'building-block' selections using logical operations like **AND**, **OR**, and **XOR** in combination with the four selection memory locations **S1-4**

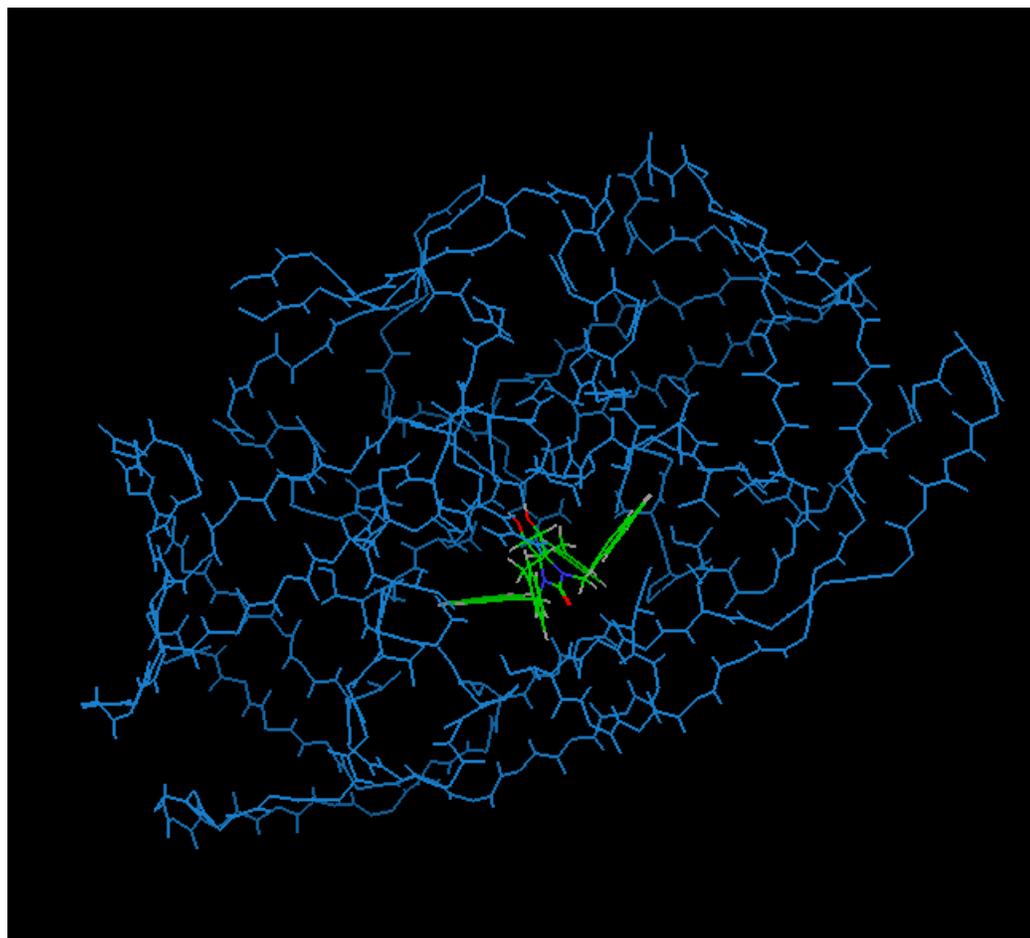
Let's see how this works by creating a selection that contains all atoms within 5 Angstroms of the ligand as well as all other atoms in the protein backbone. This will provide needed detail near the ligand while still providing enough the rest of the protein structure to help maintain your frame of reference.

To do this, use the drop down menu below the memory buttons to select **Prot. Backbone**

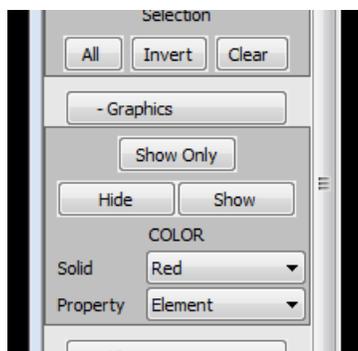


Now, click the **OR** button and then click **S1**. This will take the current selection, the protein backbone, and combine it with the selection in **S1** (atoms within 5 Ang of the ligand) using a logical **OR** operation. This is equivalent to a union set operation.

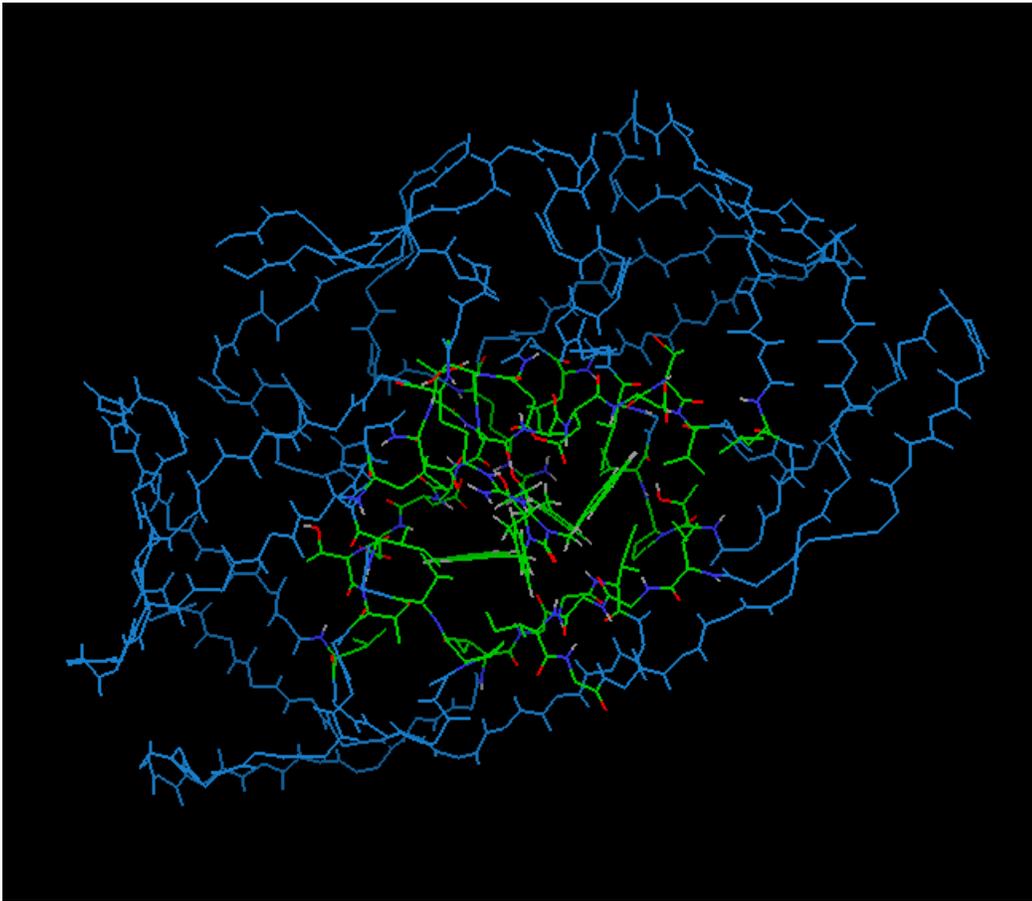
Now scroll down slightly using the scroll bar on the left to reveal the **Show Only** button on the **Graphics** panel and click it. This will show only the atoms in the current selection, that is all atoms either in the protein backbone or within 5 Ang of the ligand.



You can alter this display to color all the atoms within 5 Ang of the ligand by element to make things easier to interpret. To do this, select the **S1** button where you saved the 5 Ang distance based selection earlier. Now, on the **Graphics** panel, to the left and just below the **Atom Selection** panel find the color by **Property** dropdown menu and select **Element**



This should be the result:



The **Atom Selection** panel offers many ways to construct simple selections which then may be saved and combined using logical operations to create very precise and complex selections. These can in turn be used to tailor the display in many different ways.

For example, one could highlight the positions of all ASP residues in the protein. First, select **All** at the bottom of the **Atom Selection** panel, then on the **Graphics** panel on the **Solid** dropdown, pick **Blue**. This just resets the color of all atoms (other than the ligand) to blue.

Now, type 'ASP' into the **Res Name** field of the **Atom Selection** panel and hit enter:

Mouse Click Selection

Atoms Residues

Res Num

Res Name ASP

Atom Num

Atom Name

3D Selector

Distance to Sel.

Distance to Lig. 5

Save Selection

S1 S2 S3 S4

Named Prot. Backbone

AND OR XOR

Selection

All Invert Clear

- Graphics

Show Only

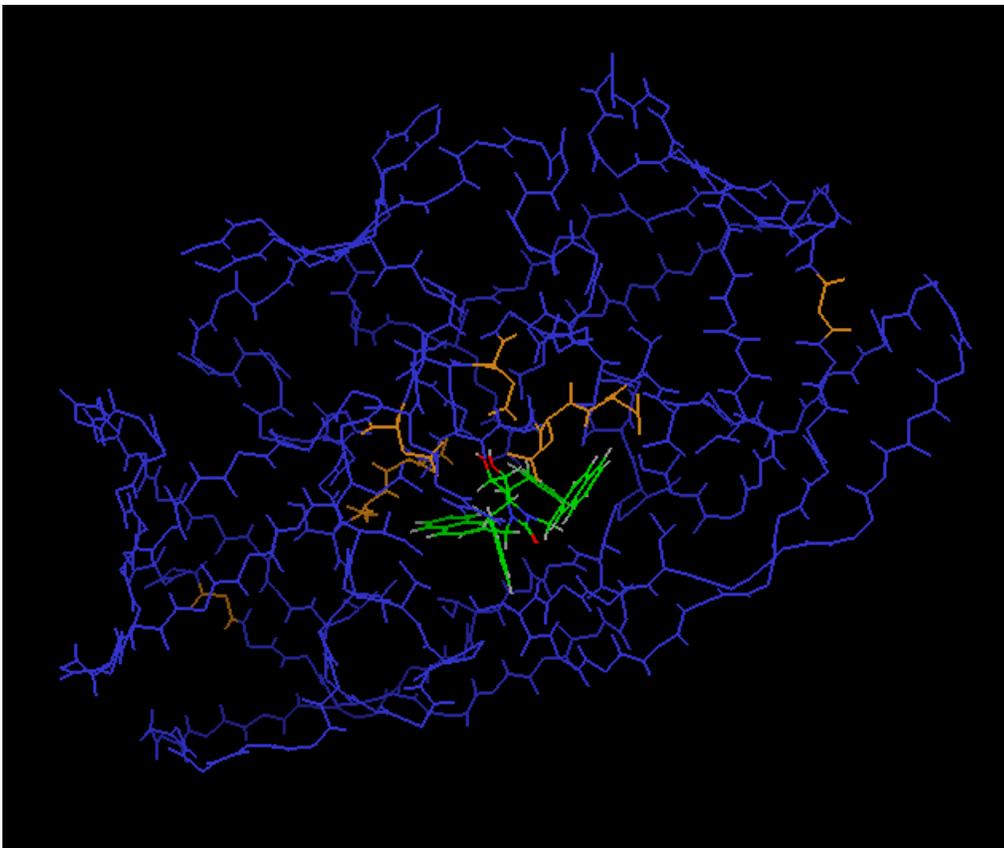
Hide Show

COLOR

Solid Blue

Property Element

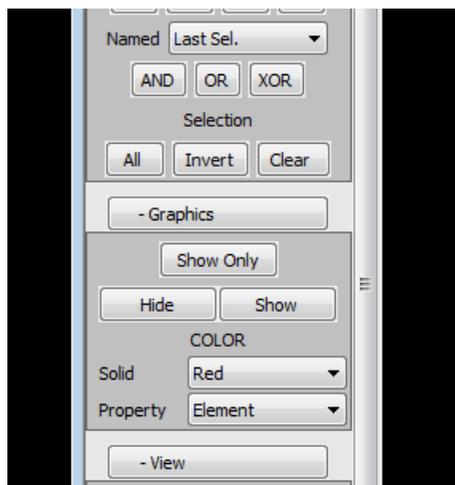
Now find the **Solid** dropdown on the **Graphics** panel and select **Orange**



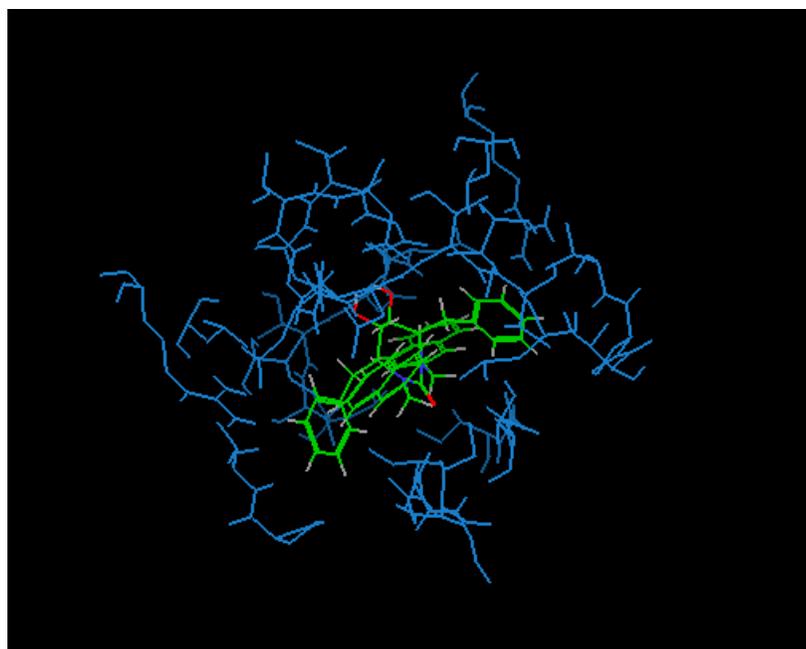
There are numerous other combinations that could be made. Remember that you can use the **S1-4** buttons to

save and return to different selections.

Lets return to just looking at the area near the ligand. Select the **S1** button. This will recall the 5 Ang distance-based selection you made earlier. Now, on the **Graphics** panel, select **Show Only**

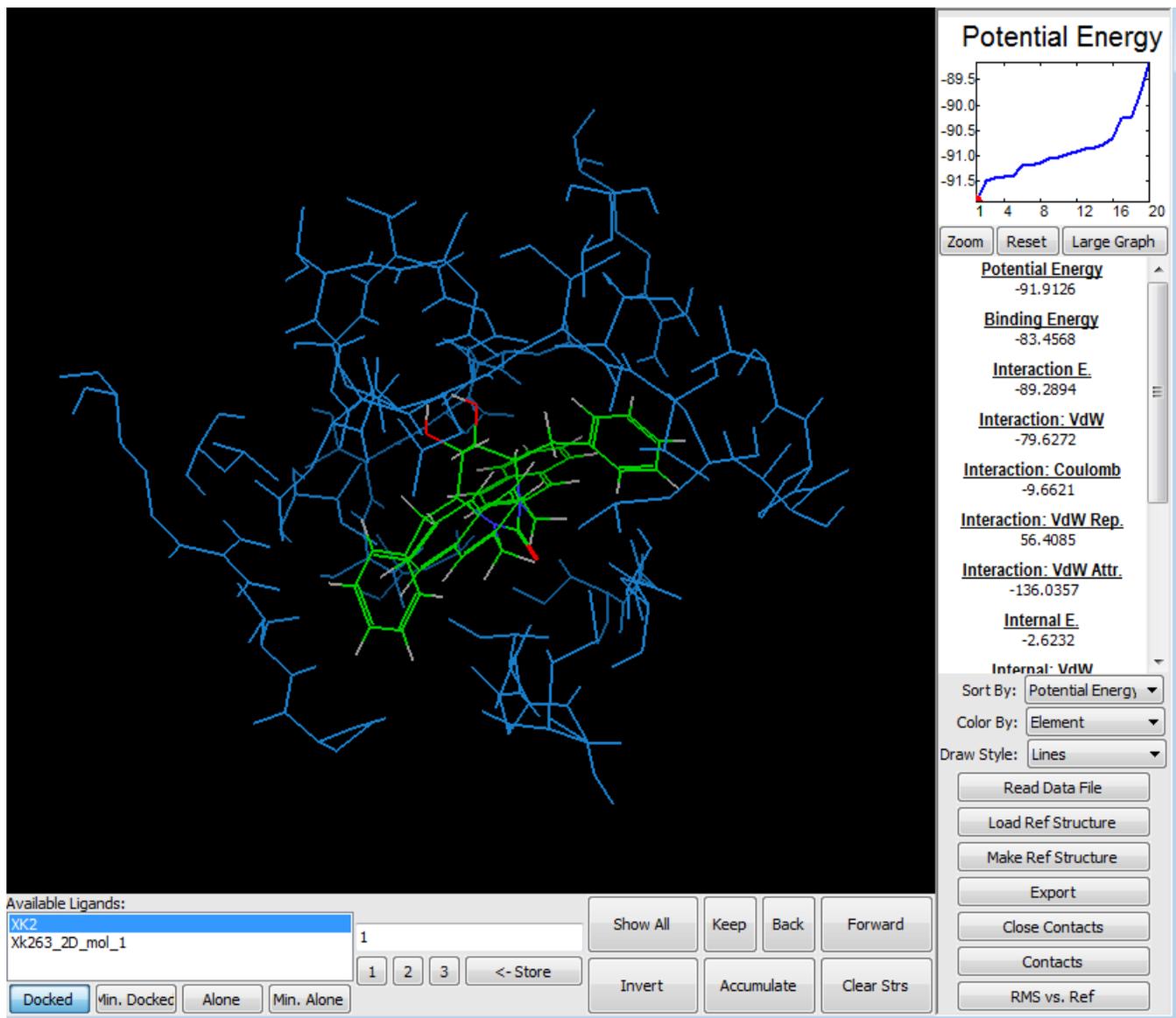


This will change the 3D view to display only the ligand and atoms that you selected (those within 5 Ang of the ligand)



If you wish to restore all atoms to view in the future, click the **All** button at the bottom of the **Atom Selection** Panel then the **Show** button on the **Graphics** panel.

Now, let's take a look at the rest of the **View Results** interface:

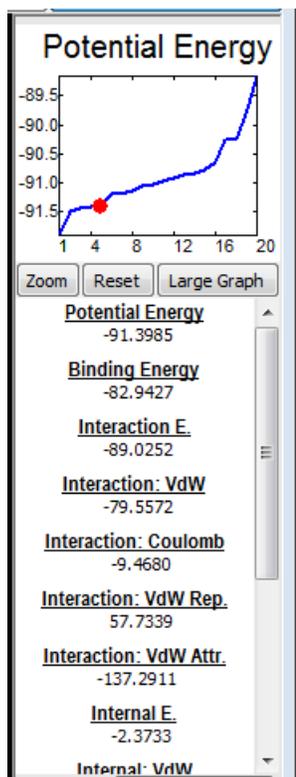


The **View Results** interface provides a wide range of tools for visualization and analysis of your results. At the bottom are controls that govern which ligand and which of the found conformations for the ligand to display in the 3D window.



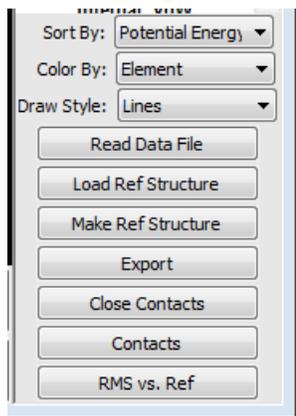
Select the ligand of interest from the **Available Ligands** list. This will display the lowest energy docked conformation found for that ligand. The rest of the conformations found are available, in order from lowest to highest energy as well. You can move through them using the **Forward** and **Back** buttons. As you move through the conformations you will see the rank number of the conformation update in the center bottom and if you would like to view all of them at once, select **Show All**.

Along the right side is a graph of potential energy over all conformations as well as a table of energy components and possible other properties for the ligand currently in view. You can graph any of the properties in the table by clicking on the underlined titles.



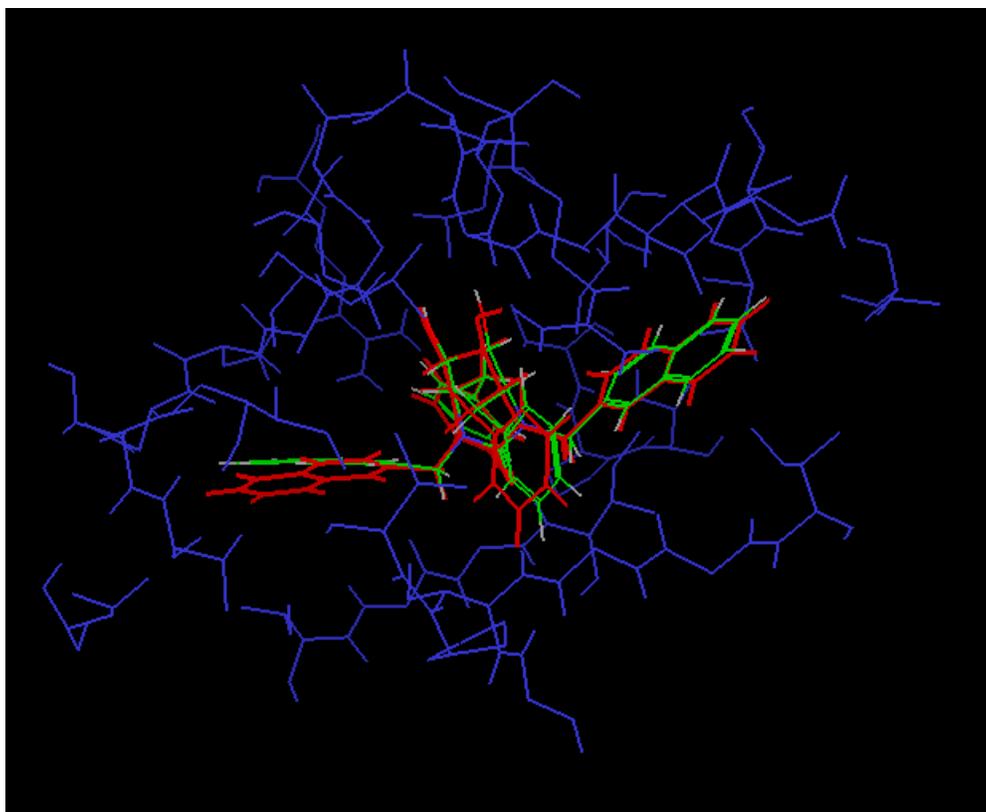
Note that what is referred to in the table as **Binding Energy** is just the potential energy of the complex minus the potential energy of the ligand by itself (available only if the ligand alone calculation has been carried out) This adjusts for the change in ligand energy that occurs as it moves from free in solution to bound. The protein conformation does not change during binding, unless some side chains have been mobilized, so in most cases this is the only adjustment needed to convert the potential energy of the complex to a rough estimate of binding energy. Since the energy of the ligand alone is the same for all bound conformations this does not change the relative energy between docked conformations, it only effects the magnitude. This is just a potential and not a free energy and the approximations made in the energy model, especially for solvation are significant. This is not expected to be a useful estimate of actual binding energy, only a rough measure of the strength of the binding as indicated by the energy model used for docking. The purpose of Vdock is to find good, low energy, candidate conformations for protein ligand systems. It is not intended to predict binding affinity. For prediction of true free energies of binding for host-guest and protein-ligand systems please see VeraChem's VM2 software package at <https://www.verachem.com/products/vm2/>

Below the energy component and property table are a number of other controls that allow you to change the order in which the conformations are sorted, their display characteristics, load reference structures for comparison, calculate RMS vs a reference, export conformations for use in other applications, and display two different types of VdW contacts.



Let's load a reference structure to use in evaluating the docking results. Very often you will have at least some 3D structural information about binding to your receptor. This can be useful in evaluating and understanding the results even if, in the majority of cases, you will be docking ligands for which you have no experimental data on binding conformation.

In this case one of the source structures we used for the ligands is, in fact, the ligand taken directly from a co-crystal structure. To load this as a reference structure click the **Load Ref Structure** button at the bottom right and select the `XK2_model1.sdf` file.



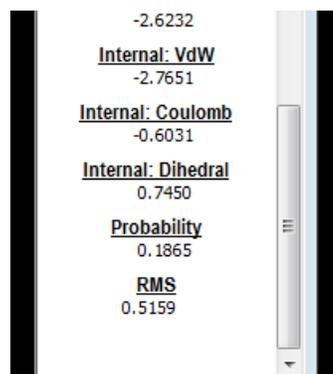
As you can see, the reference structure is rendered in red and the lowest energy docked conformation is quite similar to it. We can quantify this similarity by calculating the root mean squared (RMS) difference between the reference structure and each of the 20 docked conformations.

It is currently only possible to do this if the number and order of the atoms in the reference structure matches those in the ligand. This is the case now. So, click on the **RMS vs. Ref** button at the bottom right.

VDock correctly accounts for symmetry when computing RMS and will not be 'fooled' by cases in which symmetric

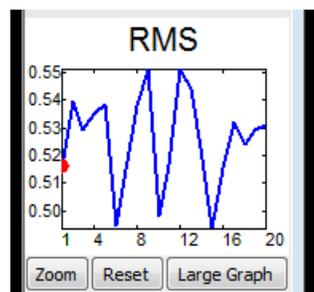
groups have been flipped or when the entire symmetric ligand might be bound rotated relative to the reference.

The RMS values of each ligand conformation can be viewed in the Property table (you may need to scroll the list down to reveal it):



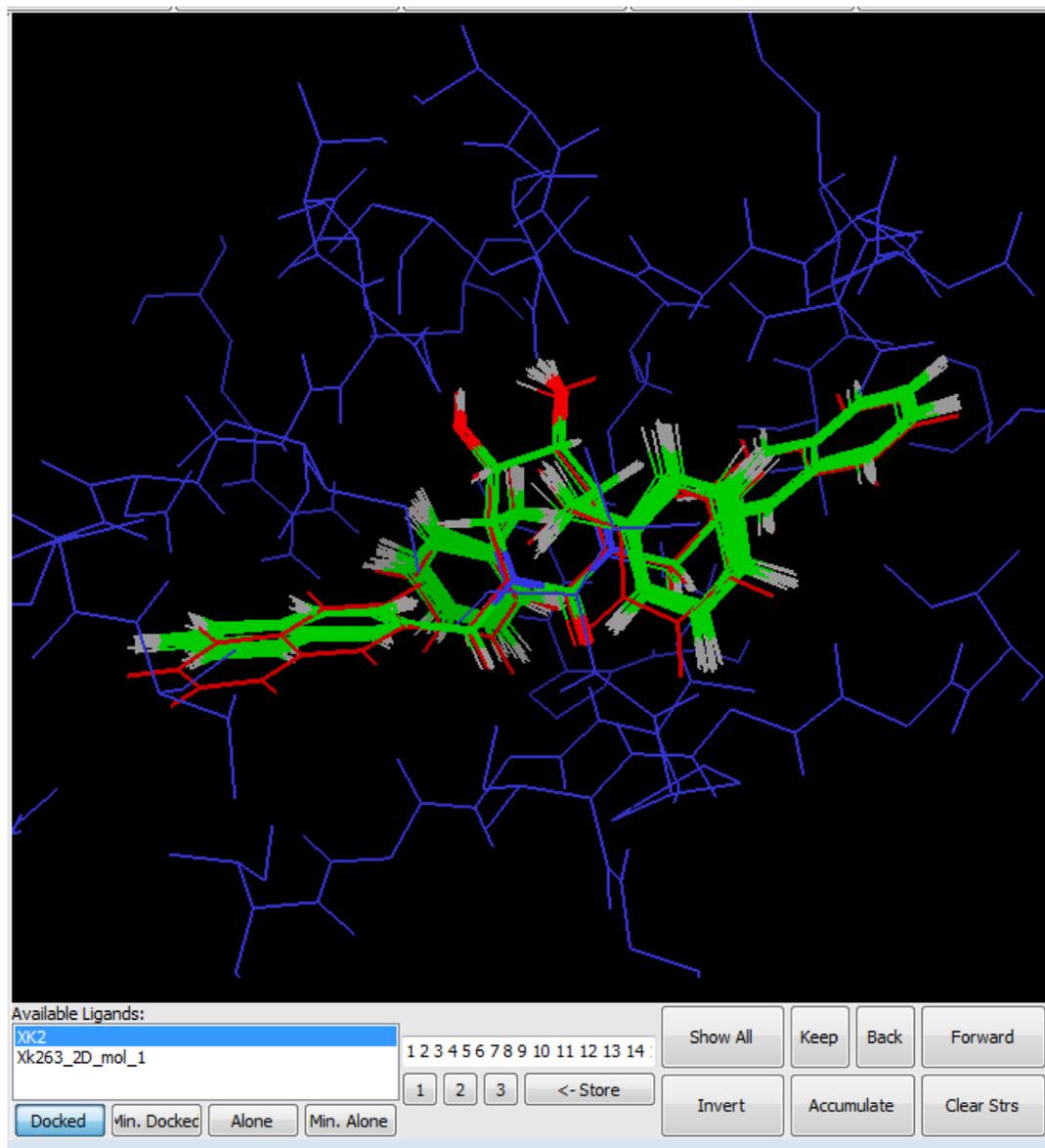
-2.6232
Internal: VdW
-2.7651
Internal: Coulomb
-0.6031
Internal: Dihedral
0.7450
Probability
0.1865
RMS
0.5159

Click on the title in the table, **RMS** to update the graph at the upper right to show the RMS values for all 20 docked conformations.



In this case, since we started the docking for the ligand XK2_model from coordinates that were directly taken from a co-crystal structure docking was very successful in finding the 'right' conformation, and all 20 are quite close to the experimental reference.

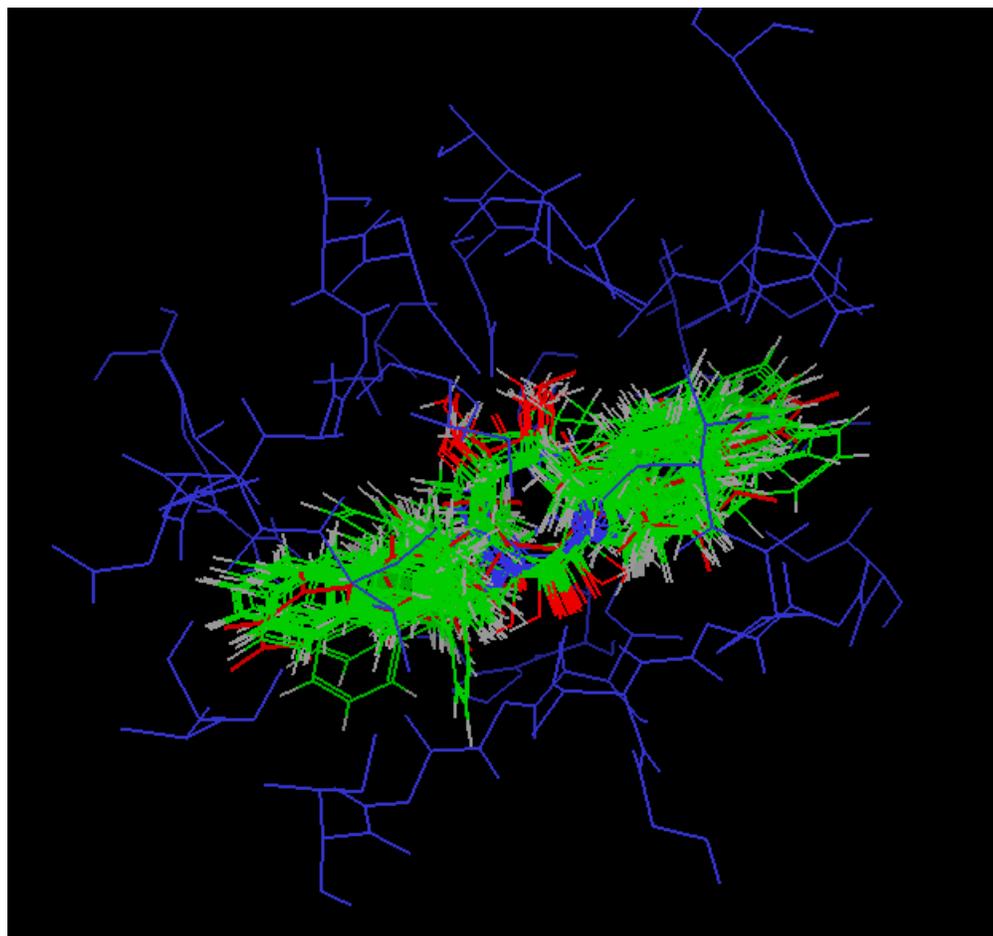
You can also see this by selecting the **Show All** button at the bottom center.



This high accuracy and low variance in the conformations located by VDock is mostly due to the unusual case of using a ligand from a crystal structure, in which all the bond lengths and angles are precisely what they were from the experimental structure. VDock only varies rotatable bonds during the search. In the case of HIV Protease and cyclic urea inhibitors like XK263 here, the ligand fits very tightly and precisely into the active site so there is little room for variation. That also contributes to the degree of success observed.

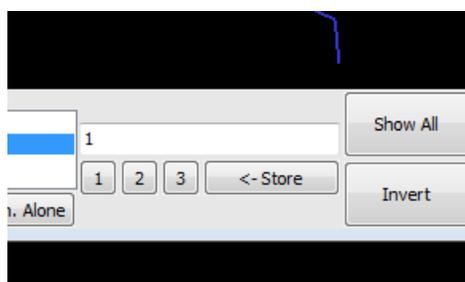
Let's take a look at the more realistic and usual case: when you are docking a ligand that you have drawn from scratch in 2D and then converted to 3D for docking.

From the **Available Ligands** list at bottom center, select Xk263_2D_mol_1. Now select **Show All**



You can see that the variation is much larger. This is a much more challenging case than with XK2 and gives you some idea of how big an impact having prior experimental structural information about ligands can have.

Select the **Clear Strs** button at the bottom right and then replace the 20 in the center entry field with a 1:



This will display only the conformation with the lowest potential energy. You can type any set of numbers, separated by spaces into this field to display the corresponding structures. For example, to see the first four lowest energy conformations, type '1 2 3 4' and hit enter.

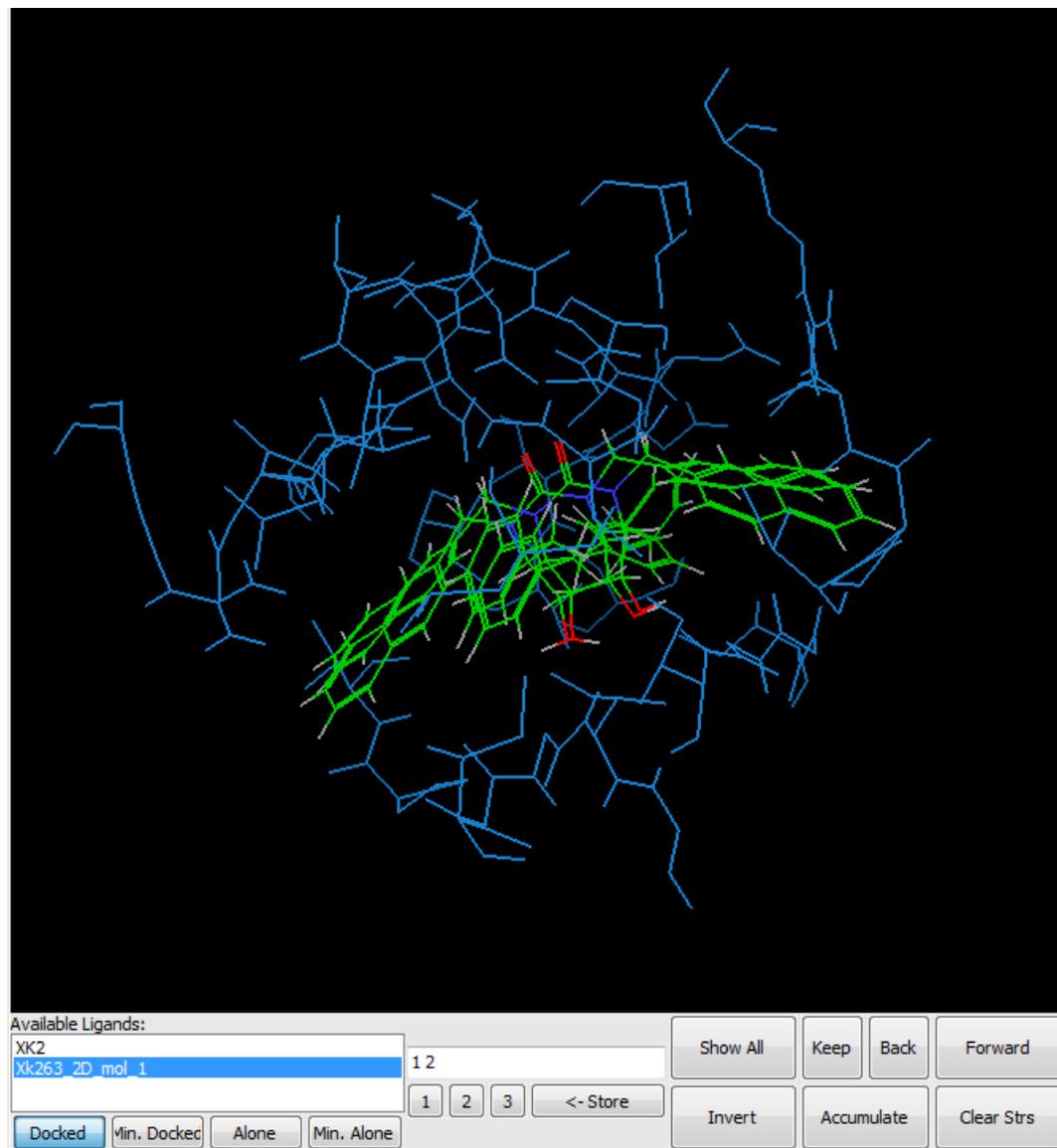
For now, go back to just structure 1.

This is the conformation with the lowest potential energy. Let's say you would like to compare this one with the other structures that were found, but viewing them all at once is too much. The **Keep** button allows you to designate structures that you wish to remain in view even as you move to others using the **Forward** and **Back** buttons.

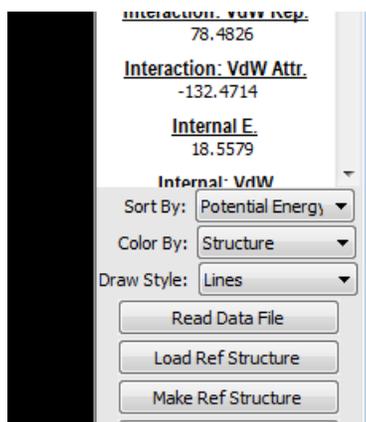
Try it now, select **Keep**. You will see the numbers field now contains **1 1** instead of just **1**.



Now try clicking **Forward**

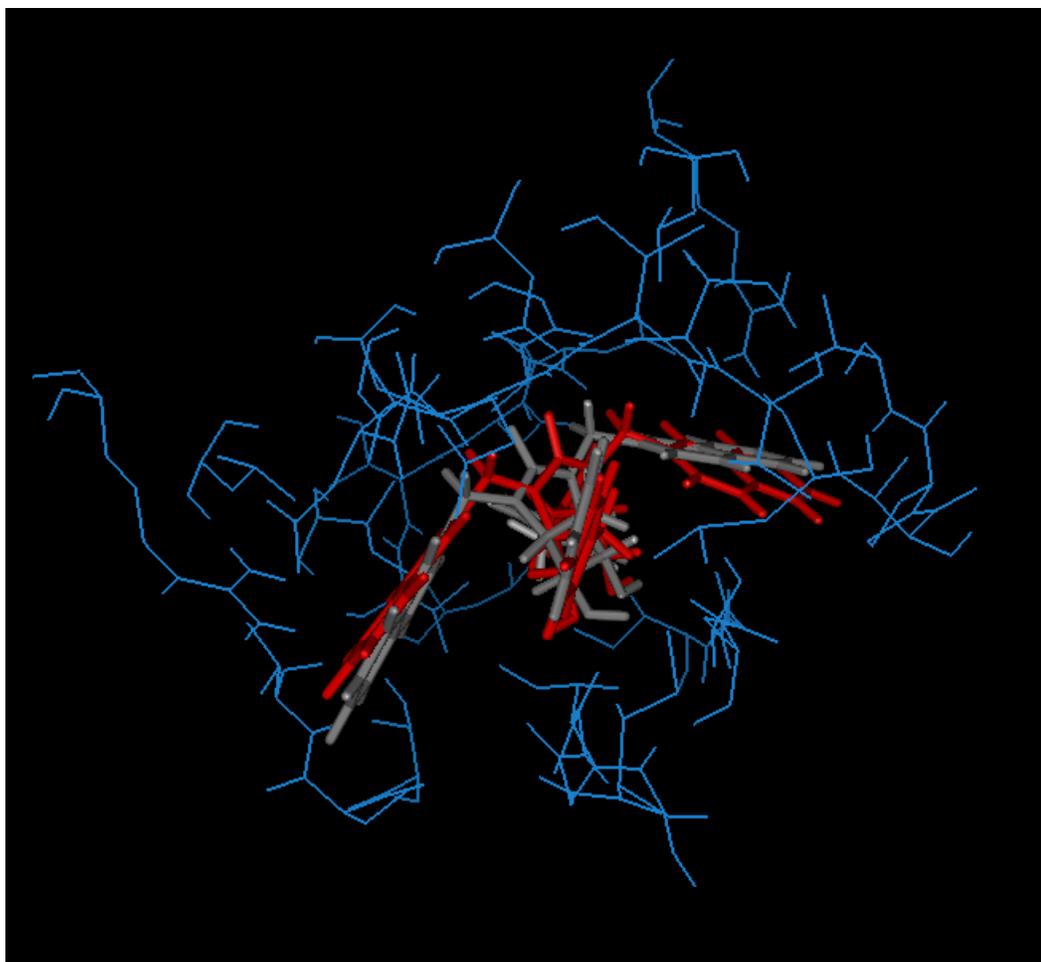


The numbers / ranks to display field now contains **1 2** and both structures 1 and 2 are displayed in the 3D window. You can make the structures easier to separate by selecting **Color By** and **Structure** on the right:



To make the ligand even easier to see try selecting **Tubes** in the **Draw Style** dropdown (found right below the **Color By** control that you just used.)

This should be the result:

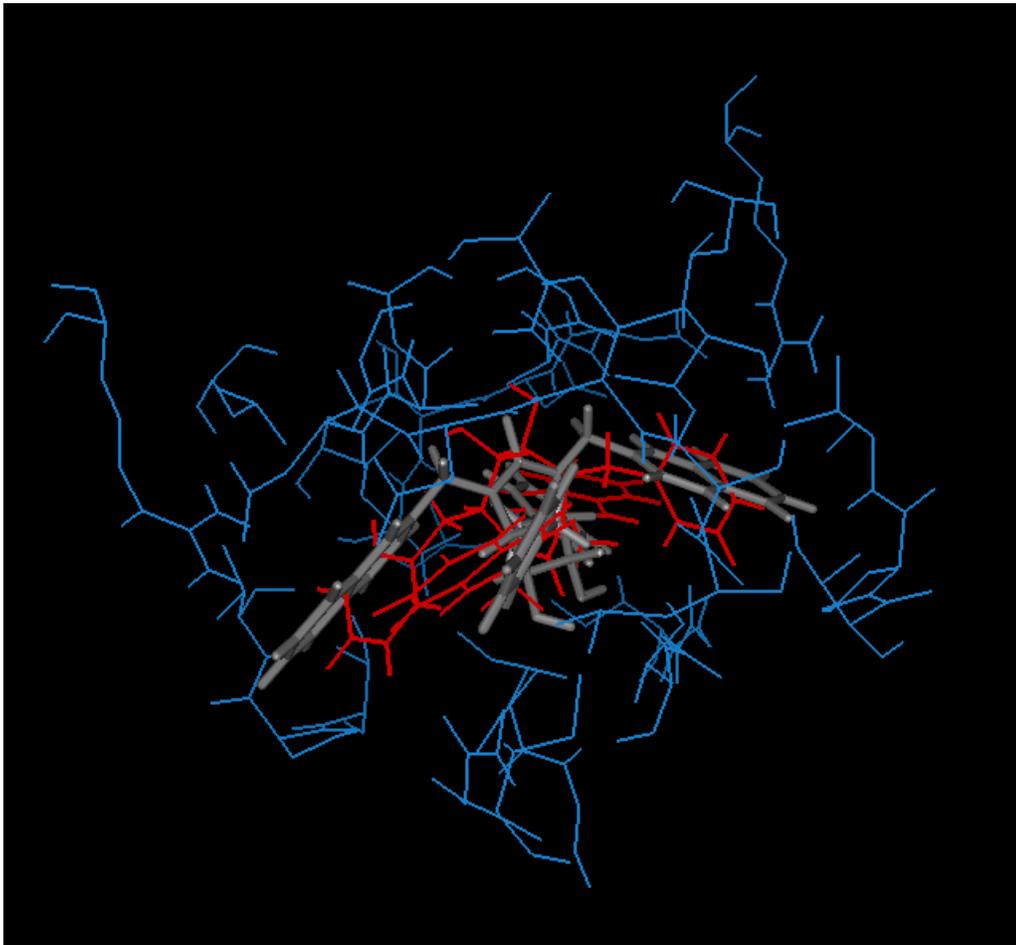


Now let's load up a reference structure to evaluate the docking of this set of ligands. Remember that the ones we are viewing now, **Xk263_2D_mol_1**, were not taken from an experimental crystal structure like **XK2** but instead were drawn in 2D, then converted to 3D and docked.

Change the display to show only docked conformation 1 by deleting the current contents of the center structure field (currently containing **1 2**) and typing in just **1** and hitting enter.

Now, select the **Load Ref Structure** button on the right and then pick the file **XK2_mode1.sdf**

This is what you should see:



The reference structure is shown as a red line rendered structure. Notice that the lowest energy docked conformation, in grey, is actually in a conformation upside down relative to the correct structure (represented by the reference we just loaded, which is from the pdb crystal structure for the complex)

In fact, if you move through the conformations using the **Forward** button you will see that the 'correct' structure is the 3rd in terms of potential energy. This is a good lesson. The energy function used for docking and the model used specifically in this implementation is not accurate enough to reliably rank conformations at a detailed level. This is partly because of approximations made in the molecular mechanics force field and partly because of other factors. These include the fact that the protein-ligand interaction energy is interpolated off of a 3D grid to speed evaluations during the search. Also, only degrees of freedom involving rotatable bonds (dihedrals) are optimized in the search, bond lengths and angle remains as they were at the start. Protein side-chains that are not specifically selected for search are also kept rigid. The model for solvation used, a very simple distance dependent dielectric, is not sufficiently accurate for fine distinctions between ligands. Also, it is not the potential energy that determines conformations in any case, it is the free energy. Evaluation of the free energy is a much more difficult and time-consuming task as it requires a careful consideration of entropic effects.

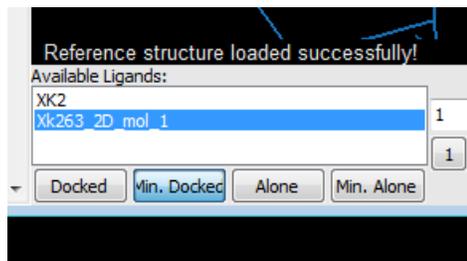
These are all beyond the scope of VDock, which is designed rather to provide a reasonable set of good conformations for docked ligands in a rapid and efficient manner. It is often capable of locating a structure similar to the actual one, somewhere within the set of low energy conformations that are located, but it will quite often not be the one with the lowest potential energy.

The output of VDock is therefore most useful for use in a qualitative sense, or as the starting point for further

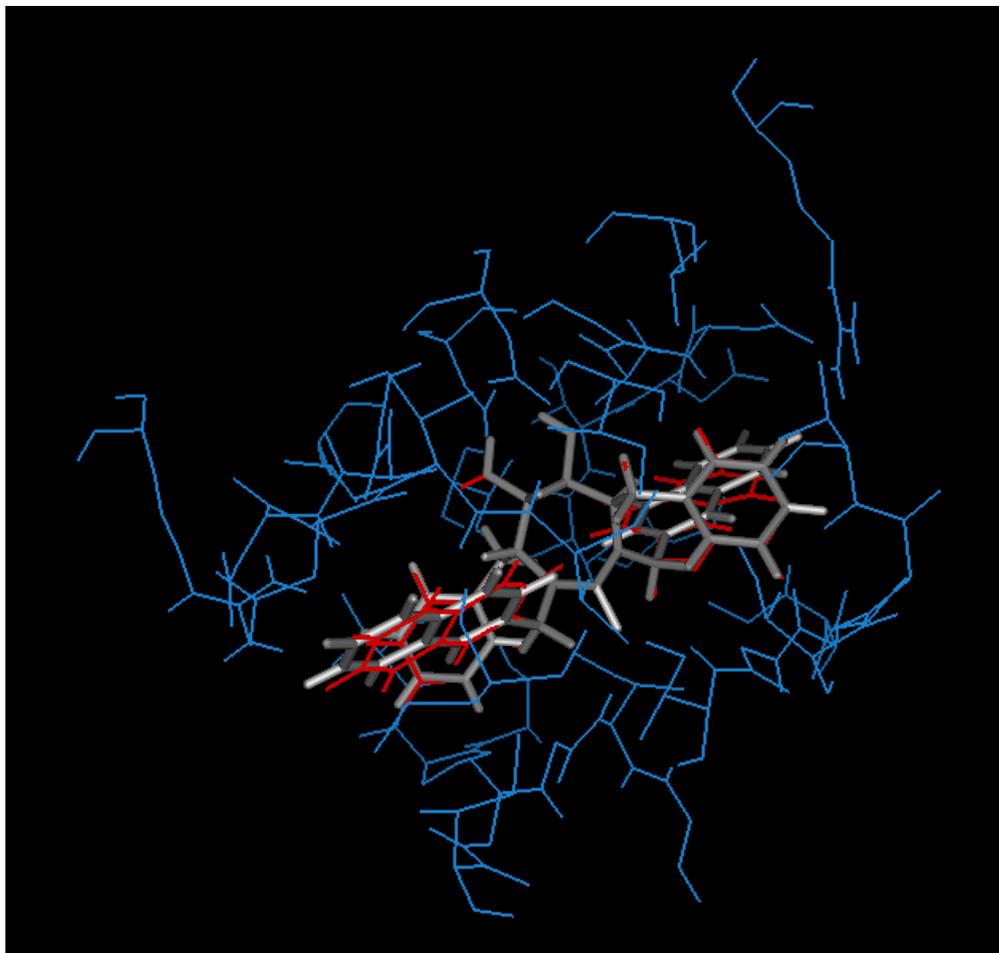
calculations. For example, VDock can be an excellent source of a diverse range of high quality starting conformations to use with the **VM2 free energy package**. Starting from reasonable conformations can greatly accelerate the VM2 calculation.

VDock does offer some simple additions that can help with the ranking problem however. For example, when you ran all the calculations in the **Run Docking** tab, you requested that the docking conformations located all be minimized in all-degrees of the freedom and without the 3D gridded and interpolated interaction energies.

The results of this minimization can be explored by selecting the **Min. Docked** button at the bottom, under the **Available Ligands** box.



This is what you should see (you may need to select **Tubes** from the **Draw Style** control on the right, again, after selecting **Min. Docked**).

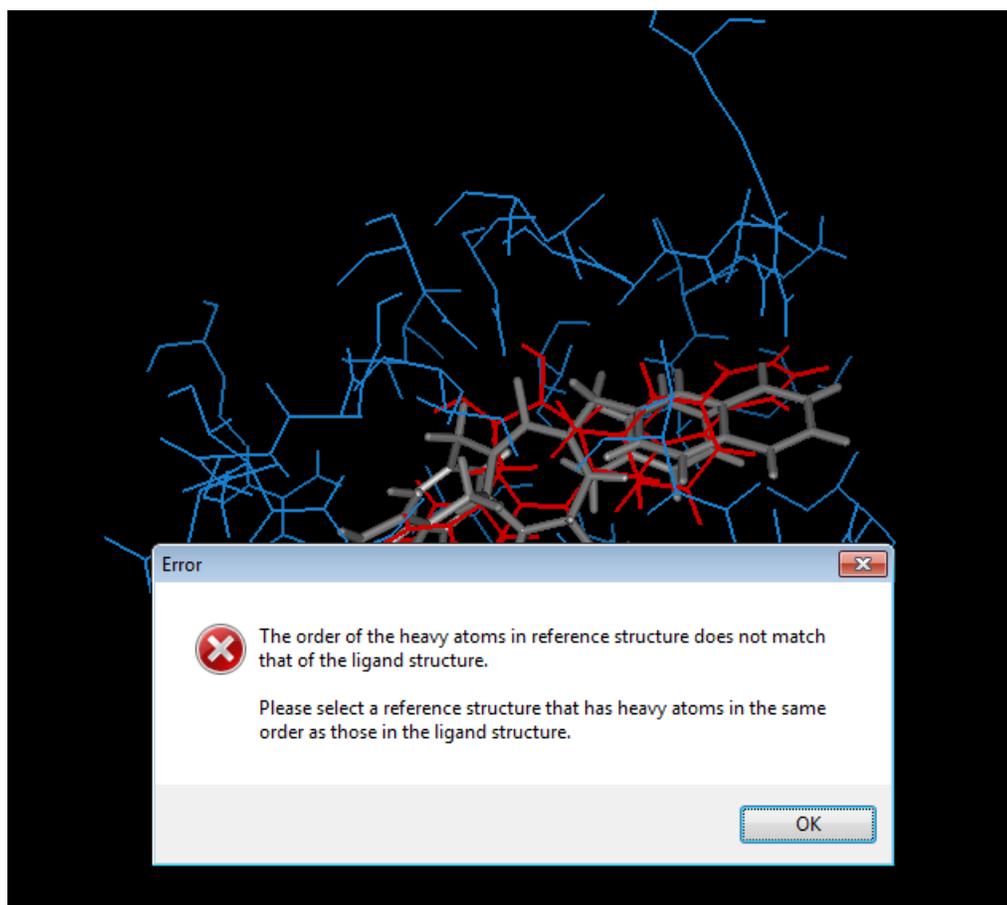


Notice that the lowest potential energy structure is now very close to the reference! In fact, now the first upside-down structure is ranked 18th!. This is a much better ranking.

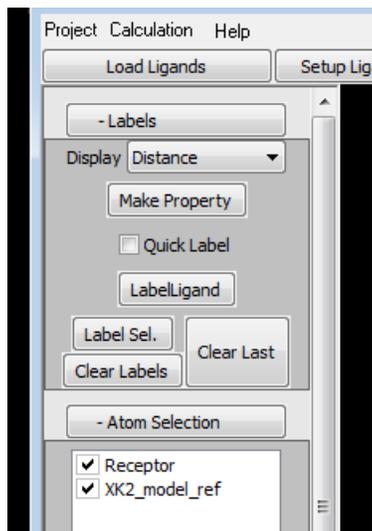
So, you can see that even a little extra calculation can greatly improve the results. Starting from a 2D, sketched, structure VDock is capable of locating conformations very close to the actual crystal structure and, following minimization, able to rank them reasonably well too. It is very important to keep in mind that this extra minimization was required however, and also that results this good will not always be obtained. Again, VDock generally will find something close to the actual structure, somewhere in the batch of structures it generates, but they might not be the ones scored the 'best', that is they may not be those with the lowest potential energy.

For this case, using the ligand drawn in 2D and not directly from the crystal structure, it is not possible to compute and RMS relative to the reference structure as we did above. This is because the atoms are in a different order in the ligand and reference structure files. VDock does not yet have the capability to find the correct corresponding atoms on its own. This is something that we are working on.

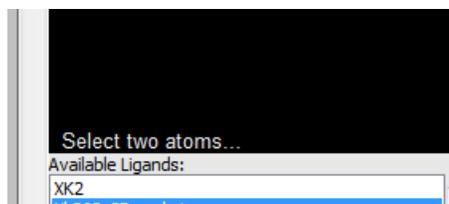
If you do try to compute RMS vs the reference structure (using the **RMS vs. Ref** button) you will see an error message about the mismatch in atom order:



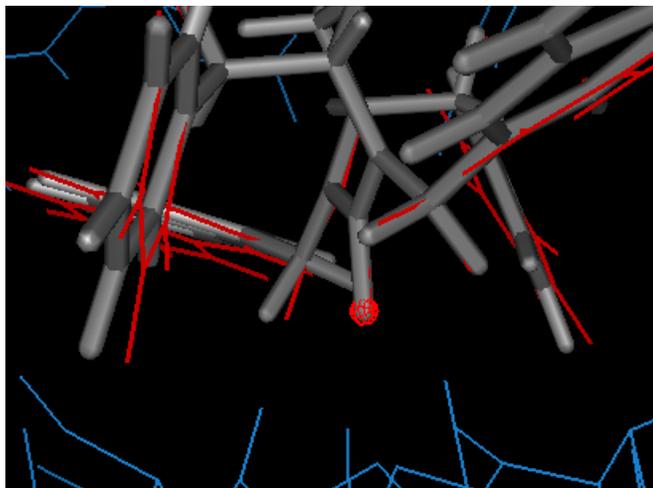
Let's consider two other features that are useful now. The first of these is the ability to measure distances between atoms. To do this, go to the **Labels** panel at the top left. You may need to scroll the control panels in order to reveal it. Then select **Distance** from the **Display** dropdown menu.



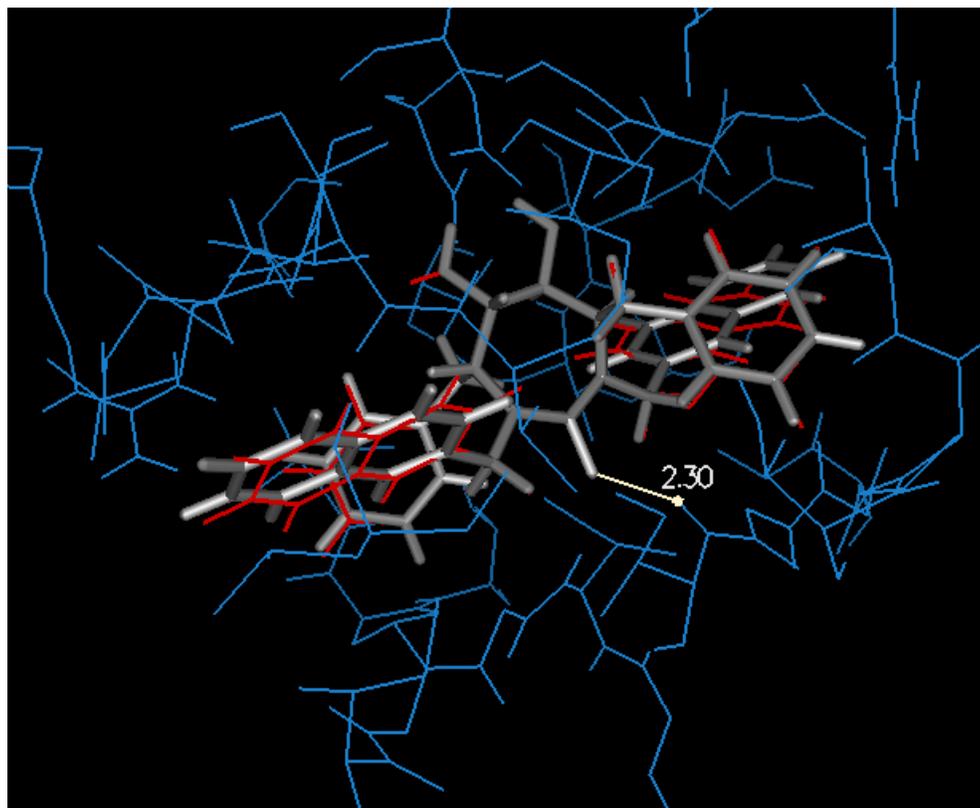
When you do this, you will be prompted on the 3D window status bar to select two atoms:



You can select atoms by **Shift-Left-Click** on them in the 3D window. Try this now, first picking one atom from the ligand and then another from either the protein or the reference structure. When an atom is selected it will be drawn as a small, red, sphere.

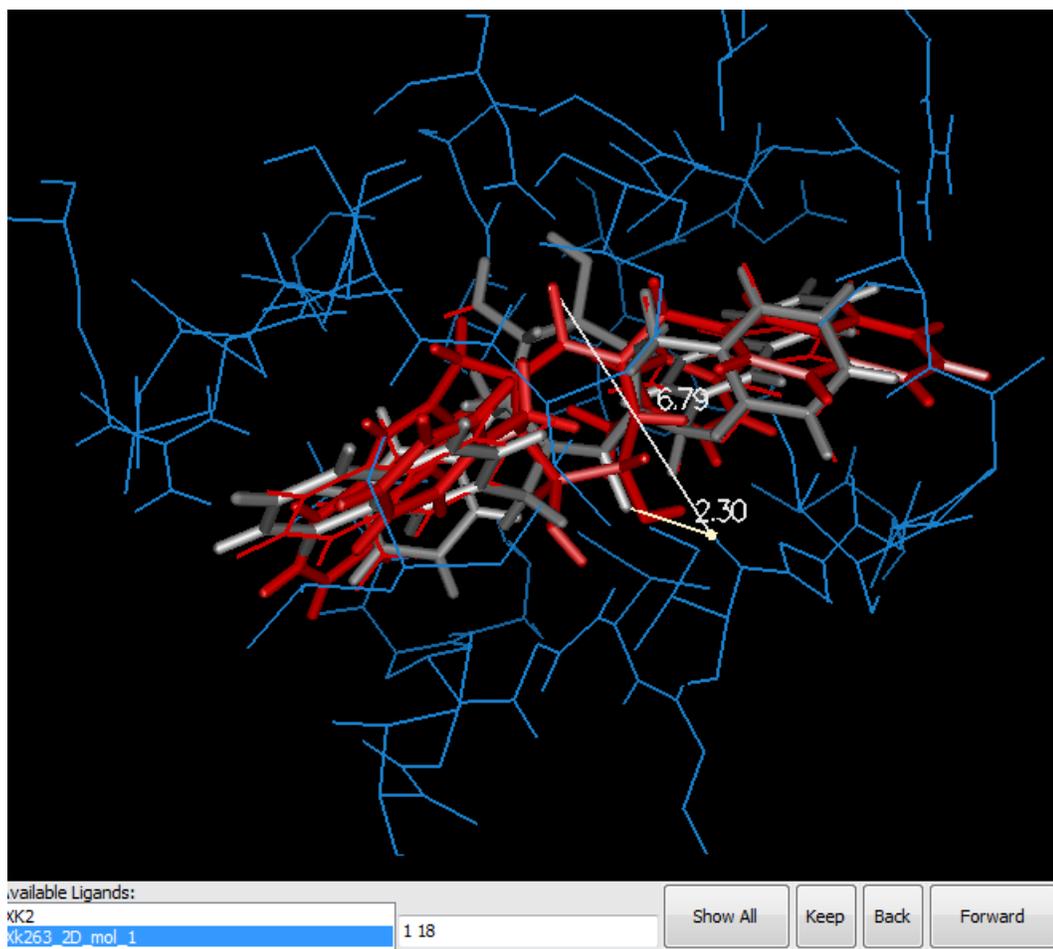


If you wish to deselect an atom you can just **Shift-Left-Click** it again. In this case pick two atoms. When the second atom is selected the distance between them will be calculated and displayed. It is interesting to pick two atoms similar to those in the following example:



Now you can move through the ligand conformations and the distance label will update to show the distance correct for the conformation that is being displayed. If you display more than one conformation then both distance will be displayed.

Try this by typing **1 18** and hit **enter** in the structure number field in the center just below the 3D window.

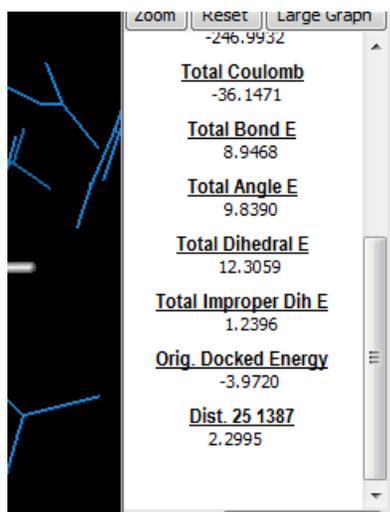


This can be a nice way to look for structures that differ from each other in some key way. In order to make this easier it is also possible to convert the distance label into a property, which then be displayed in the conformation properties area on the right. It will then also be possible to both graph by that property and even to sort the structures by that value as well.

To do this, go back to the **Labels** panel at the top left. Then click on the **Make Property** button.

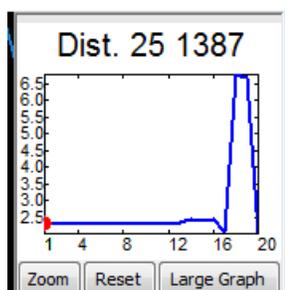
If this button is disabled and light grey it probably means that neither of the atoms you selected are from the ligand. If this happens then try clicking **Clear Last** and then selecting two more atoms, one of which should be from the ligand.

Now, you should be able to find the distance on in the property table on the right. You might have to scroll to find it as it will probably be at the bottom of the list.



Here the property is titled, Dist. 25 1387 as it is the distance between atom 25 of the ligand and atom 1387 of the protein.

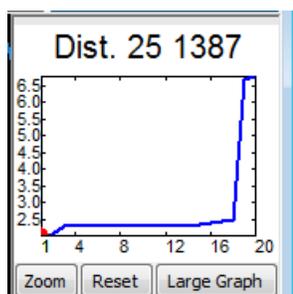
Now, left click on the title **Dist. 25 1387** in the property table. This will update the graph at the top right to display this distance.



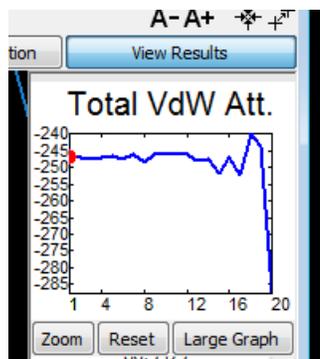
This makes it very easy to observe the way that the property in question, in this case the distance, varies across all of the conformations found by VDock. In this case, you can see which conformations are 'upside down' relative because this results in a larger distance (structures 18 and 19 in this case). Note that you can left click on a portion of the graph to jump to the corresponding conformation in the 3D window.

You can also sort the conformations by any of the properties in the table. Try this with the distance. Go to the **Sort By** control just below the property table and select **Dist. 25 1387** (or whatever the title is for the atoms you selected) from the dropdown list.

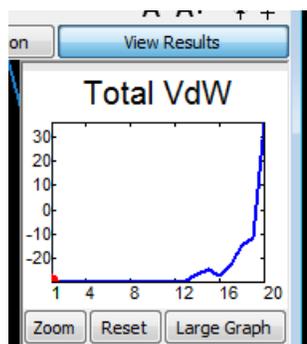
The conformations will now be sorted from lowest to highest by that property. Structure **1** will now be the conformation with the lowest value for that property. You can see the impact of the sorting by the graph at the top right.



You can check for correlations between different properties by sorting by one and then graphing another. This should reveal any links between them. For example, sort by **Potential Energy** and graph **Total VdW Att.** and the graph should look something like this:

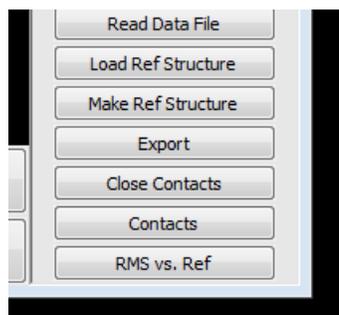


You can see that there is no real correlation between overall potential energy and just the attractive portion of the VdW potential. This is a somewhat contrived example as one wouldn't necessarily expect a such a correlation. It is the total VdW, the sum of the attractive *and* repulsive components that is more likely to be correlated. You can click on the **Total VdW** property to graph that.



Now let's look at how you can export conformations found by Vdock for use in other software. To do this display the conformations you wish to export in the 3D window. This can be done any way you prefer, either by navigating to them with the **Forward** and **Back** buttons, using the **Keep** button to build a set, or by directly entering the structure numbers you wish to display in the text field at bottom center. If you wish to export all of of the conformations you can use the **Show All** button.

After displaying the structures you wish to export, select the **Export** button on the right.



This will open a dialog in which you can select a location, filename, and file format to use. The supported formats at the moment are multi-structure pdb, sdf, the trj format (a modified multi-structure pdb file), and numbered, separate crd files.

I hope you have found this tutorial helpful to you. There is more to explore in the interface and with VDock in general. Please refer to the main documentation file, accessible in the **Help** menu at the top.

Feel free to experiment with different settings to see their effect on the results. In order to change input settings, add ligands, or change run parameters you will need to clear the current results. This will unlock all the of the buttons and controls that are grey and disabled when results are present. This happens as the interface acts as a record of the setting used to generate the current results. You can close and open the same project file and look back at the contents of each of the tabs to see how the calculation was set up and run. Disabling changes when results are present prevents the setting from getting out of sync with the results.

If you wish to clear results to make changes, you might also wish to save a copy of the current state for reference later. To do this, go to the **Project** menu at the top left and select **Save Copy**. Then select a location and name to use. It is best to place this copy in its own directory as there will be a number of files, not just one. The name you choose will form the basis for the filenames in that directory. So, if you pick **project_xk263** then all the files will be named that, with various suffixes.

Name	Size
project_xk263.dpr	1.29 MB
project_xk263-Xk263_2D_mol_1-minimized.trj	115 KB
project_xk263-Xk263_2D_mol_1-minimized.out	17.5 KB
project_xk263-Xk263_2D_mol_1-conformation.trj	150 KB
project_xk263-Xk263_2D_mol_1-conformation.out	71.6 KB
project_xk263-Xk263_2D_mol_1-docking.trj	150 KB
project_xk263-Xk263_2D_mol_1-docking.out	70.3 KB
project_xk263-Xk263_2D_mol_1-minimizedLig.trj	115 KB
project_xk263-Xk263_2D_mol_1-minimizedLig.out	16 KB
project_xk263-XX2-minimized.trj	115 KB
project_xk263-XX2-minimized.out	17.5 KB
project_xk263-XX2-conformation.trj	150 KB
project_xk263-XX2-conformation.out	76 KB
project_xk263-XX2-docking.trj	150 KB
project_xk263-XX2-docking.out	77.9 KB
project_xk263-XX2-minimizedLig.trj	115 KB
project_xk263-XX2-minimizedLig.out	16 KB
project_xk263_grid.out	6.35 KB
project_xk263_nbdc.grd	12.6 MB
project_xk263_nbdb.grd	12.6 MB
project_xk263_nbda.grd	12.6 MB

Now, navigate to the **Load Ligands** tab and you can clear the current results by going to the **Project** menu at the top left and selecting **Clear** and then **Results** and then **Non-Bonded Grid**. You should now be free to make any changes you wish and then run the calculations again.

One thing you might wish to try is to start a new project entirely (close the interface and the restart it) and then, in **Load Ligands** select the file **Xk263_from_2D_mol_1_confs.sdf** instead of **XX2_model.sdf** or **Xk263_from_2D_vconf.sdf**

This file contains the nine lowest energy energy conformations found when the 2D sketch of xk263 was converted to 3D by VeraChem's **VConf software**. If you remember, the file we used earlier, **Xk263_from_2D_vconf.sdf** contained just a single structure from the 2D sketch. That was the lowest of the nine in this new file. Sometimes it can be good, especially since VDock only searches rotatable bonds, to start from a number of different conformations of the ligand, if you have some means (like VConf) of generating them. You could then dock all of them and pick the lowest energy conformations found across all of the runs.

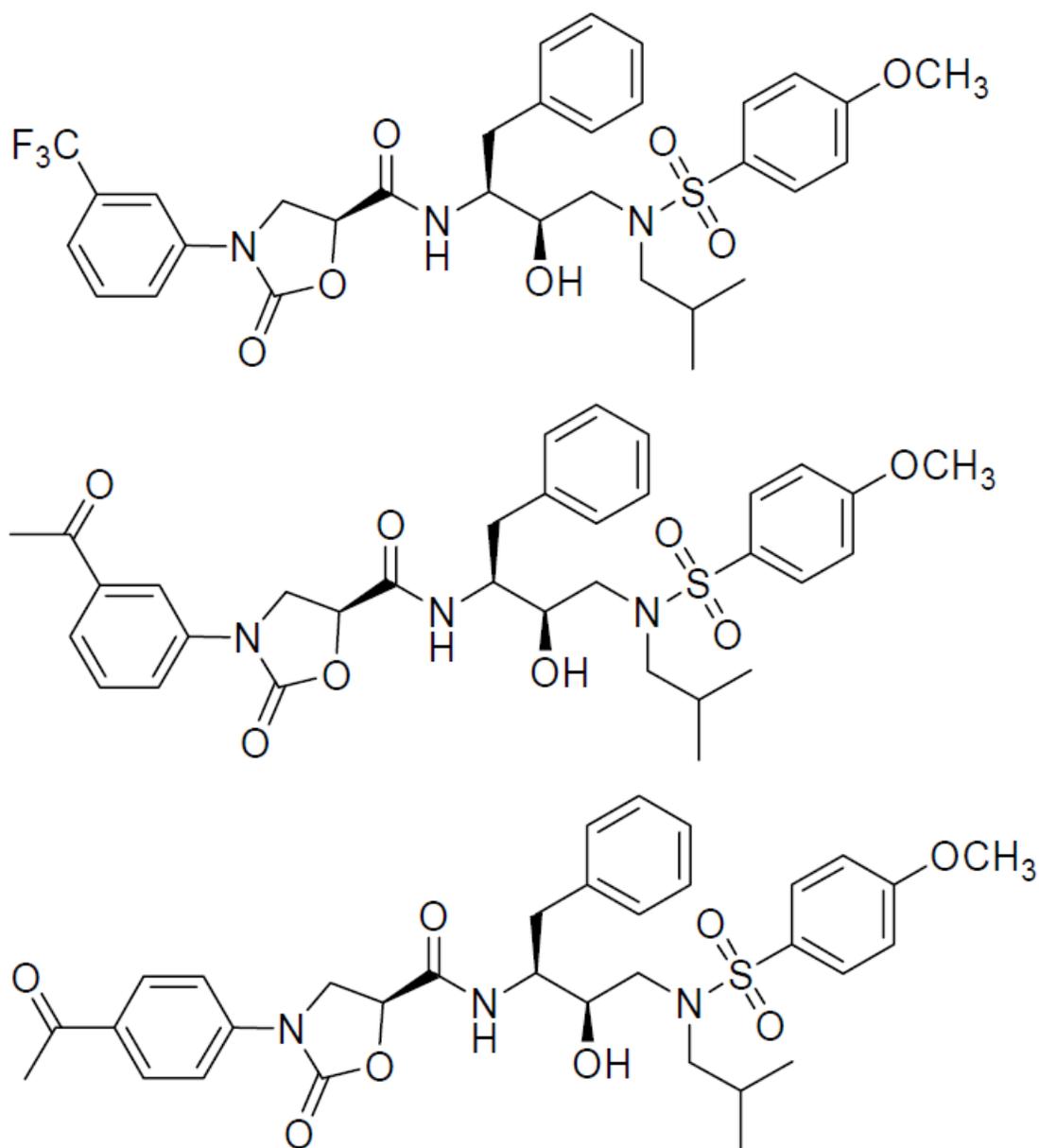
This concludes the tutorial / example involving HIV Protease and the inhibitor XK263.

HIV Protease and the UMASS series of ligands

The second example provided with your installation of Vdock involved HIV Protease again, but this time with a series of 40 ligands developed at the University of Massachusetts:

Ali, A.; Reddy, G. S. K. K.; Cao, H.; Anjum, S. G.; Nalam, M. N. L.; Schiffer, C. A.; Rana, T. M. Discovery of HIV-1 Protease Inhibitors with Picomolar Affinities Incorporating N -Aryl-Oxazolidinone-5-Carboxamides as Novel P2 Ligands. *J. Med. Chem.* 2006, 49 (25), 7342–7356. <https://doi.org/10.1021/jm060666p>.

These ligands are all quite large and very different from the cyclic urea inhibitor XK263 that we looked at in the first example. Here are a few examples from the set:



These ligands are a greater challenge to dock properly than the cyclic ureas because they are large, relatively flexible and less 'pinned' down by specific electrostatic interactions with the receptor.

Vdock can still be quite successful with them however.

I will not go through the entire process of setting things up and docking them here as it is very similar to that used for XK263.

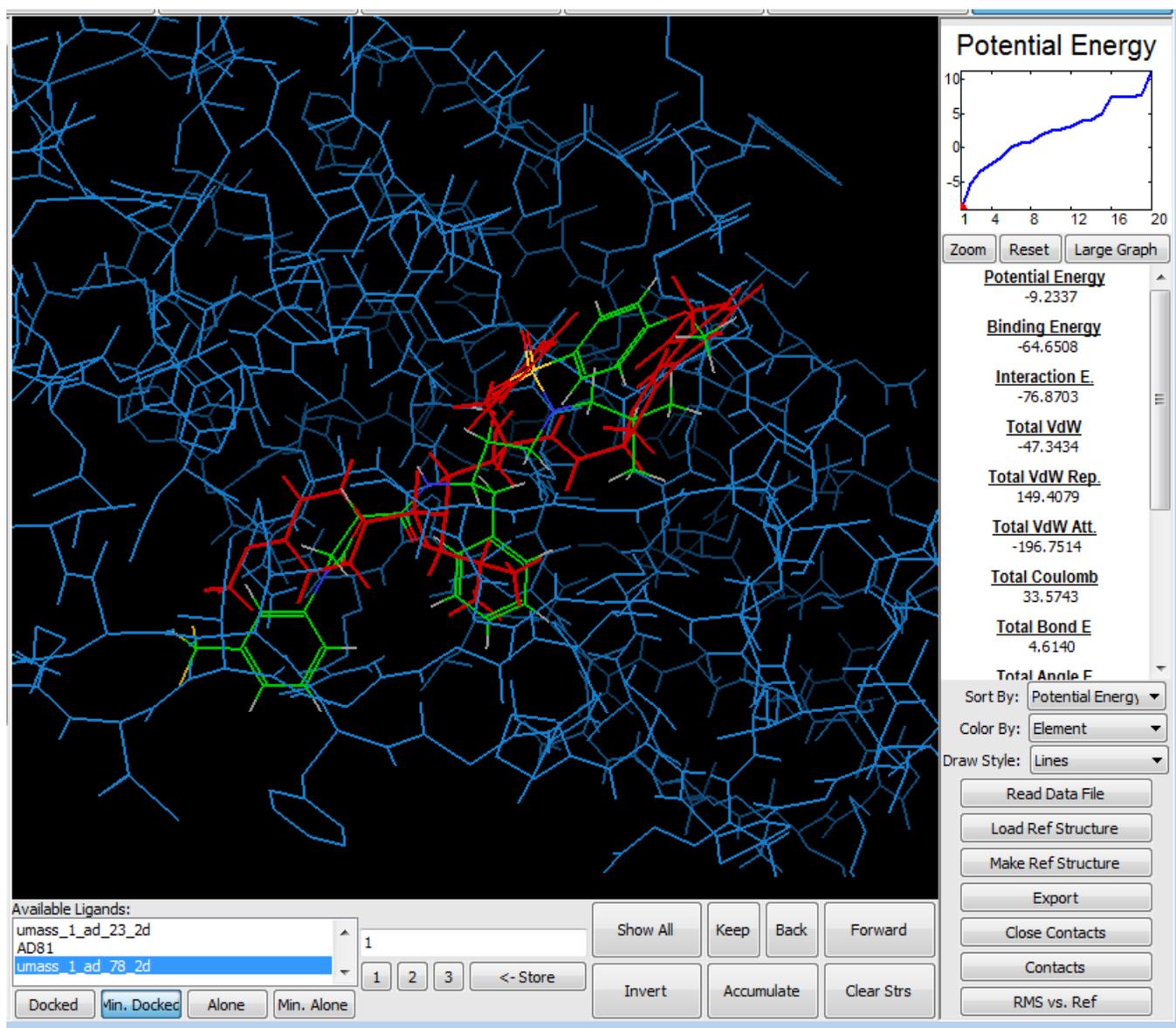
You can follow the same process as for XK263 only you should navigate to the `vdock_examples\2i0d_ad_81` directory and create a project there.

Then use the files `ad_81_model.sdf` and `ad_81_from_2D.sdf` in place of `XK2_model.sdf` and `Xk263_from2D_vconf.sdf`. These are both the ligand AD81 and the first is in the conformation taken directly from the crystal structure of its complex with HIV protease. The second is AD81 drawn in 2D and then converted to 3D using VeraChem's [Vconf software](#).

Remember that you can load `ad_81_model.sdf` as the reference molecule in **View Results** to compare the docked conformations to that from the actual crystal structure.

Once you get a feel for the type of ligand represented by AD81 you can try out the other 40 members in the series by loading them from the file `umass_1_vconf.sdf`

Explore the results obtained from the docking (remember that minimization in all degrees of freedom (**Min. Docked** in **View Results**)) often gives better results than the unoptimized docked structures.



Shown here is the ligand AD78 compared to the crystal structure of AD81.

This concludes the Vdocking tutorial / examples. I hope you found these examples interesting and helpful in learning about Vdocking and how to apply it effectively. We appreciate your interest and hope you go on to do interesting things with the software!