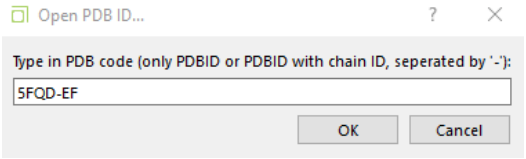
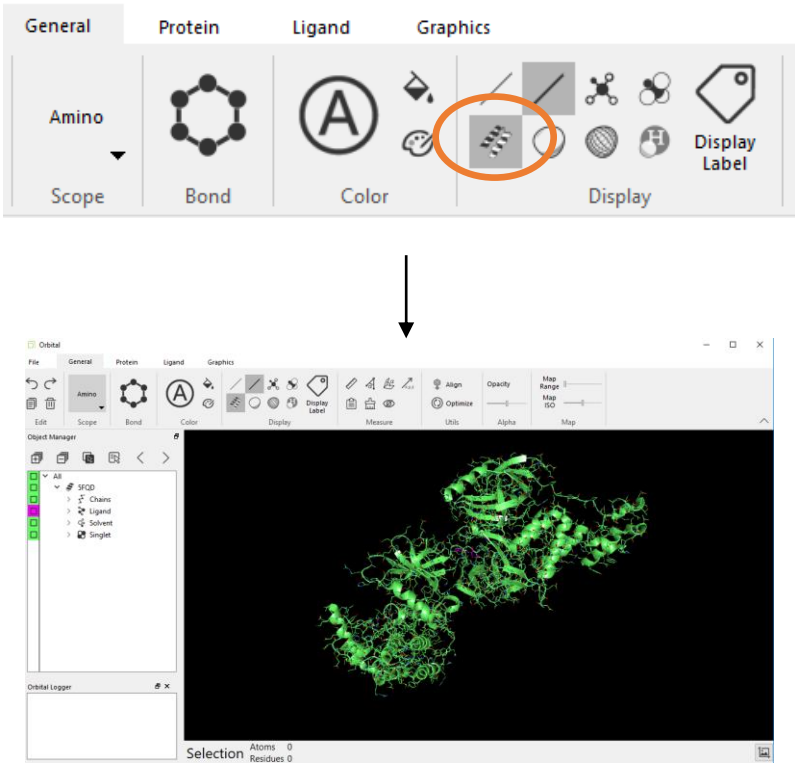
Incremental Docking Tutorial

1. **Open** Orbital and select **File** → **Open PDB ID** (or the hotkey **Ctrl+P**) to open the pop up window:



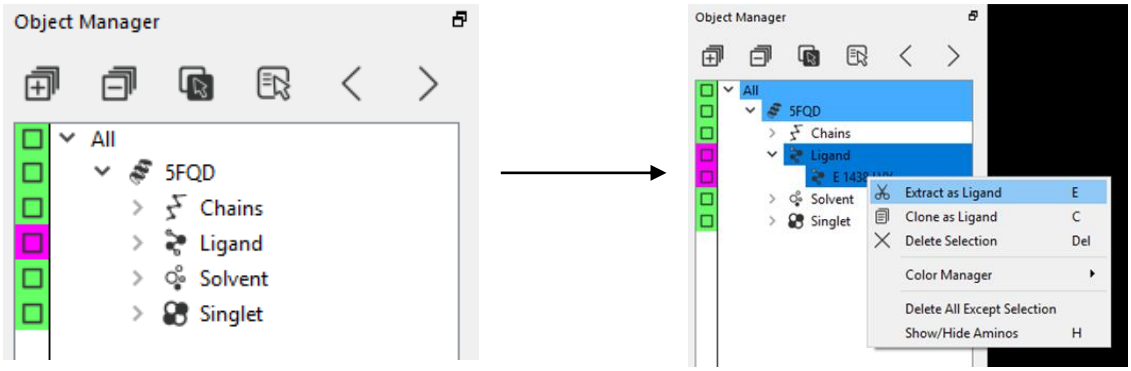
2. Enter the PDB file name 5FQD-EF and click OK to load the structure of CRL4^{CRBN} ubiquitin ligase in complex with lenalidomide.

3. Under the **General** tab select the **Cartoon** setting in the **Display** panel in order show the protein in its cartoon structure.

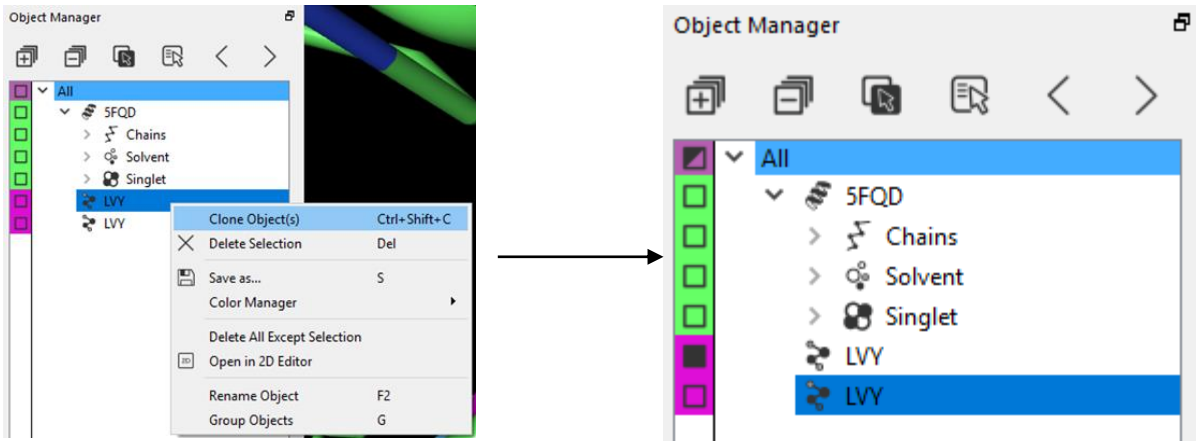


4. Next, open the dropdown menu for 5FQD in the **Object Manager** by selecting the downward facing caret next to the name.

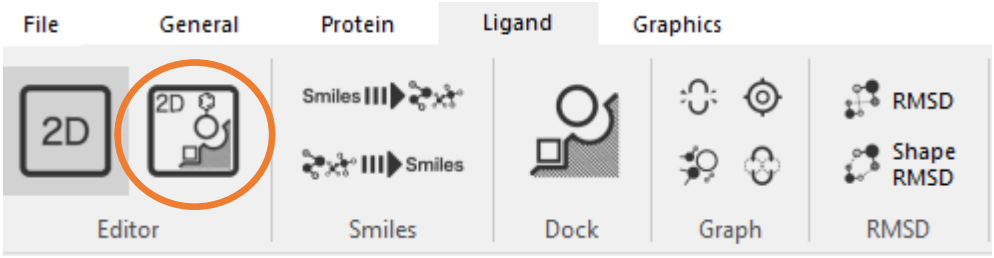
5. Select the ligand tab and right click **E1438 LVY** and select **Extract Ligand** (E).



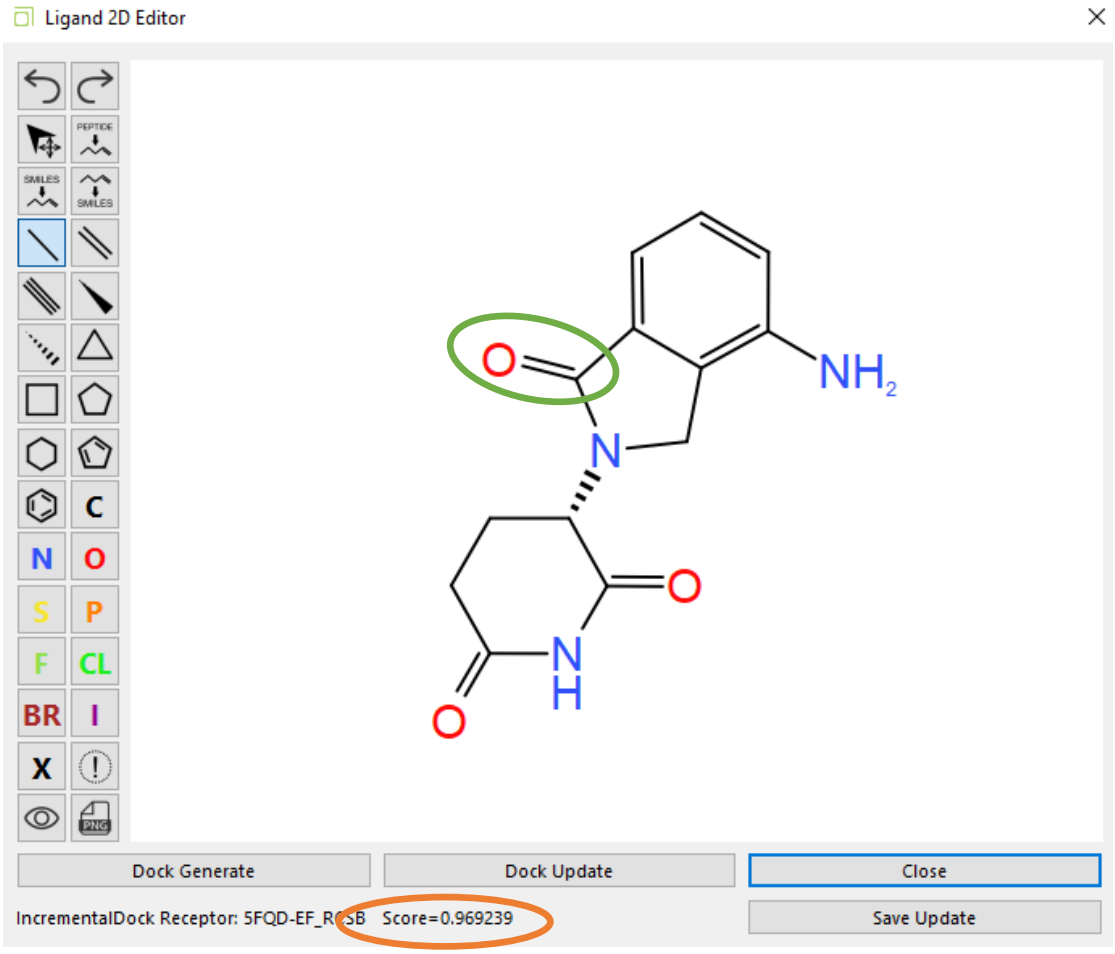
6. Right-click on LVY and select **Clone Object**. Deselect the original ligand and select the clone.



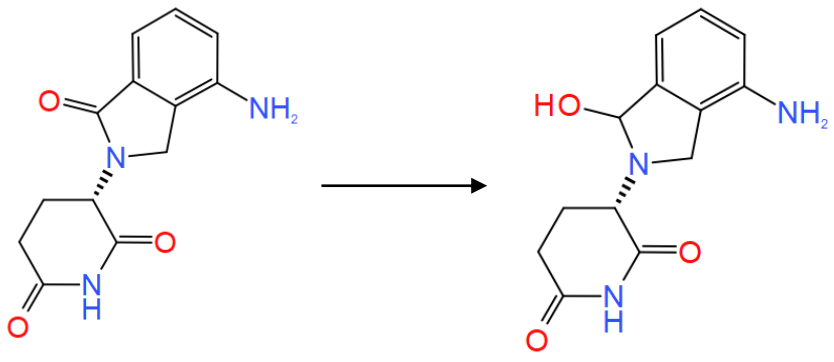
7. Open the **Incremental Dock** editor under the **Ligand** tab shown below:



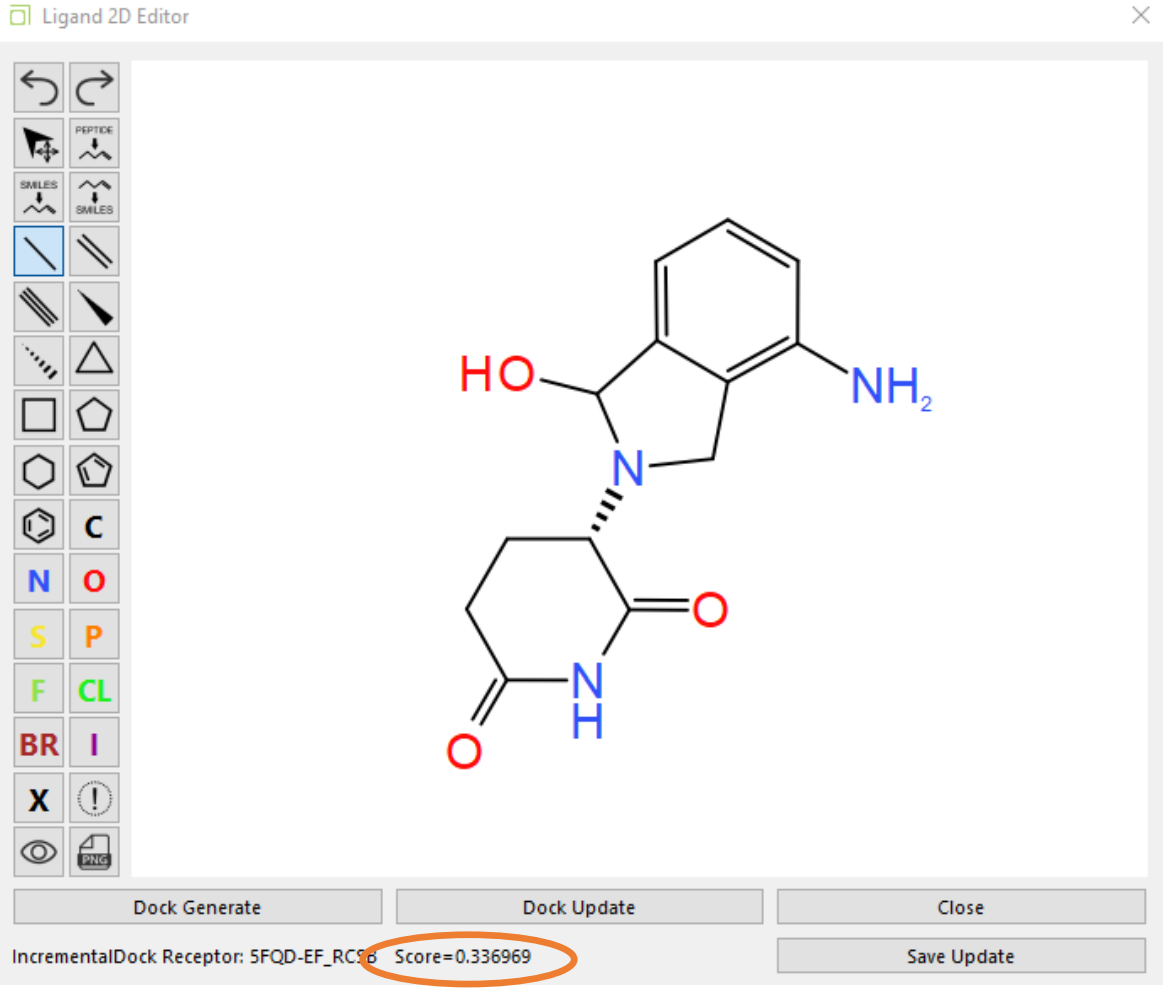
8. In the 2D editor it is possible to modify the structure of the ligand and re-dock it into the protein structure. The Incremental Dock Score at the bottom of the pop up will be adjusted with each update. In general, a larger number is better.

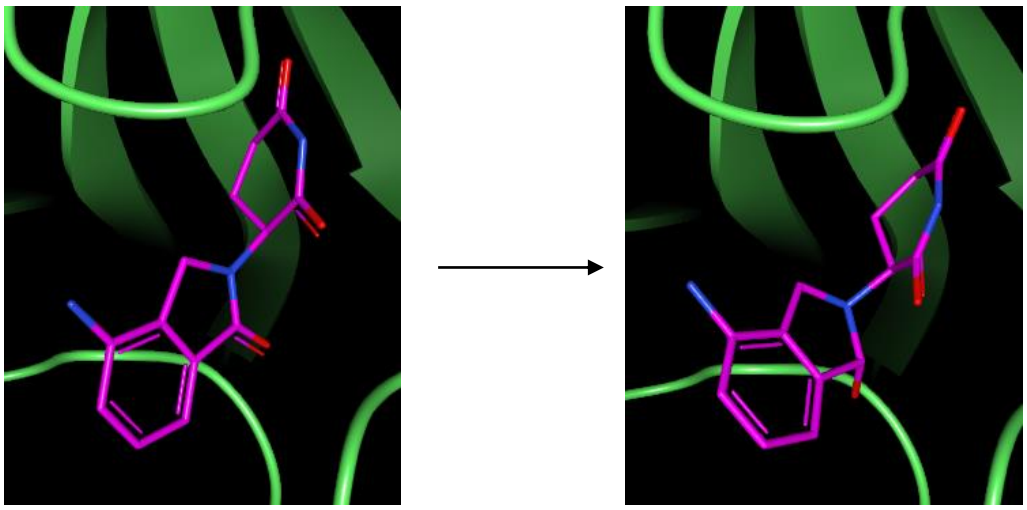


9. The current score for LVY is 0.969239. To further increase the score for the docking we can try to convert the amide carbonyl on the indole ring (circled in green) to a hydroxyl group and update the docking. We can do this by choosing "Bond Tool" and right clicking on the carbonyl double bond to convert it to a single bond.



10. Finally, select **Dock Update** in order to re-dock the new structure. The new Score is now 0.336969





11. The updated docking score suggests the product of this round ligand modification is less favorable compared to starting ligand.