

Supporting information for

A multi-disciplinary team-based classroom exercise for small molecule drug discovery

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Ligand docking and visualisation instructions

Software required

ChemOffice (including Chem3D)

Preparing the ligand

The molecule you wish to dock is known as the ligand. In order to dock it, you will need to generate the structure in 3D and in the correct format – this can all be done in ChemDraw / Chem3D.

- 1) First, draw your structure in ChemDraw. Save it. Make sure that you have checked for stereocentres and have correctly assigned the stereochemistry you want – if you don't do this, Chem3D will make a decision for you...
- 2) Select the structure in ChemDraw and copy it. Open Chem3D (available as part of the ChemOffice suite) and paste your structure. It will appear in 3D in the window in front of you.
- 3) From the bar above the 3D structure click on the MM2 with the arrow below it. This will carry out rounds of energy minimisation to give you the 3D structure in a low energy (physically likely) conformation



- 4) Save your structure as a .sdf file (File -> Save As -> .sdf). You may receive a warning to say that these files cannot be read/edited by Chem3D – if you think you might want to reopen the 3D structure, it might be handy to save the in the original Chem3D format first.
- 5) Your molecule is now ready is now ready to dock using GOLD.

Docking your ligands

In this section, you will use GOLD to dock your ligand against the binding site on Chk1 kinase. You will need three additional files (supplementary files S14-S16): Chk1.pdb, gold.conf and cavity.atoms.

- 1) *cavity.atoms* and *Chk1.pdb* are reference files which GOLD will use (you just need to save them someone on your computer).
- 2) *gold.conf* is a configuration file which contains all the instructions that GOLD needs to dock your compounds. Open *gold.conf* using WordPad.
- 3) Scroll down to the line starting 'cavity_file =' (in the 'FLOOD FILL' section) and change the path to the folder containing *cavity.atoms*.
- 4) Scroll down to the 'DATA FILES' section and change the paths for each of the 'ligand_data_file' lines to point to the folder where you have saved your .sdf files. Remember to include the correct filename (including .sdf) at the end of the path. Delete any ligand_data_file lines that you are not using. At the end of each line there should be a space, then a number (10). This tells GOLD to dock this compound 10 different times.
- 5) Scroll down to the 'PROTEIN DATA' section and change the path to point to the folder where you have saved *Chk1.pdb*.
- 6) Save and close *gold.conf*

- 7) Go to the Start Menu on the computer and scroll down to CCDC. Open the program GOLD 5.8.1
- 8) In the GOLD Setup window load *gold.conf* into the 'Conf file' line. You should see the protein on the GOLD screen.
- 9) Click on 'Run GOLD' at the bottom of the GOLD Setup window. A load of extra files should appear in your folder, along with a folder for each ligand.
- 10) When GOLD has finished running – it should take less than two minutes – close GOLD.
- 11) Your results are all saved in a new subfolder called *Results*. The dockings for each compound will be in a separate folder within the *Results* folder.
- 12) Take a look at *bestranking.lst*. This file contains (among other things) information on the highest ranking docking run for each compound and the docking score of this compound. Note the number of the highest ranking run for each compound.
- 13) Open *Chk1.pdb* in pymol. In the same window, go to File -> Open and open the highest ranking docking for each of your compounds. Have a look at the way in which the compound fits in the binding site and the interactions it makes.