Drug Design Teaching

Answers to Exercises 5 and 6 (Practice Session 2)

Exercise 5. Docking of a discovery compound into the protein c-Met with SwissDock

- *How many docking solutions are proposed?*

The answer can be slightly different from one calculation to the other. Two reasons for this: i) the parameters for the docking can vary a bit (e.g. the exact position of the box defining the search space), and ii) the search algorithm of AutoDock Vina is non-deterministic. This means that some of the steps include random numbers. The objective of such stochastic processes is to accelerate the convergence to a solution. One of the consequences is that two calculations initiated from the exact same starting point can return different results. In practice however, in standard dockings like those you perform here, convergence is obtained for about 9 docking runs out of 10. To control this effect, it is advised to run 2 or 3 times the same docking and confirm convergence of results.
For the docking ran as described in the booklet, 12 docking solutions were returned.

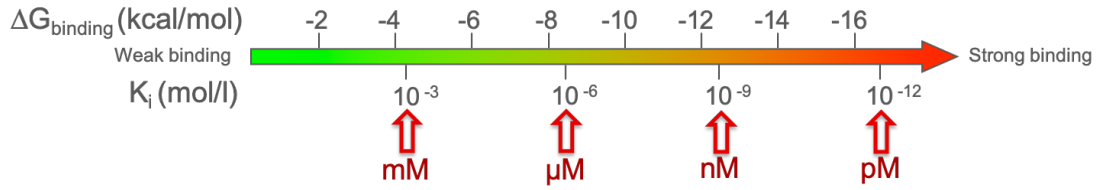
- *Are they well accommodated in the envisaged cavity?*

Yes, all atoms of all poses are inside the defined volume encompassing the inhibitor binding pocket. If not, something went wrong and you should re-define your search space.

- *What is the best score? In what range of Ki corresponds this score?*

Here again, for the same reasons as in question 1, the scores can vary slightly from one run to the other. By default, ViewDockX sorts the docking solutions from the best scored (most negative, as it is a (very approximate) estimation of the free energy of binding ($\Delta G_{binding}$)) to the less well scored. Thus, for the docking presented in the booklet, the best score is -10.441 (in kcal/mol).

The following scale helps you estimate the inhibition constant (K_i) from the calculated $\Delta G_{binding}$.



The discovery molecule you have docked has a predicted K_i for the inhibition of c-MET in the range of two-digit nM.

- *How many intermolecular H-bonds are proposed for this first docking solution?*

For the docking presented in the booklet, two hydrogen-bonds can be found between the best scored pose and the residues of c-MET.

- *Note the residues involved, if the polar atom belongs to the backbone or to the side chain of the amino acid, and if it is a H-bond donor or an acceptor*

The backbone of Asp1222 donates an H-bond to one nitrogen of the fused tetrazole of the central core of the ligand.

The sidechain of Asn1167 donates an H-bond to the oxygen of the methoxy aromatic substituent of the ligand.

- *Give two examples of hydrophobic interactions.*

Leu1157 with the central core. Ala1226 with the central core. Ala1108 with the quinoline. Ile1084 with the quinoline. Val1092 with the quinoline. Met1211 with the central core and the quinoline. But also Arg1208 with the phenol.

- *Can you spot intermolecular aromatic interactions?*

The most obvious is Tyr1230 making π-stacking with the central core.
Tyr1159 is also in favorable aromatic interaction with the quinoline.

- *Can you identify salt-bridges?*

There is no salt-bridge or ionic interaction between c-MET and your molecule as docked.

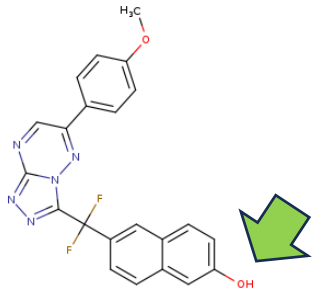
- *Propose one targeted mutation that could validate the predicted binding mode of your compound in c-MET.*

The residues whose side chains are involved in specific interactions with your molecule. For instance: Asn1209 → Leucine, Tyr1230 → Methionine or Glutamine

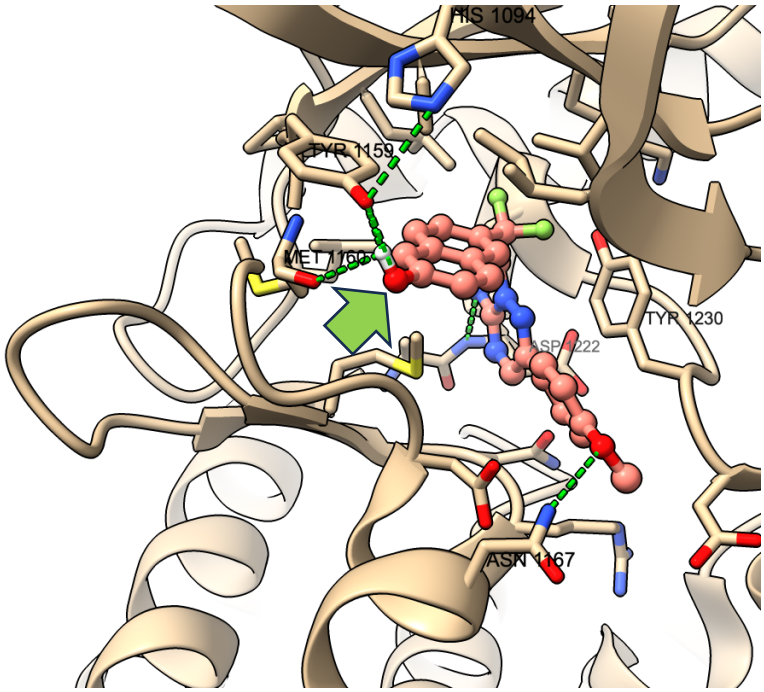
Exercise 6. Structure-based design in c-Met

There are of course many different possibilities to modify the first design compound to make it potentially better recognized by c-MET binding site.

According to the docking best docking solution presented in the booklet, the quinoline is located in a polar region where the backbone carbonyl of Met1160 and the side chain of Tyr1159 are possibly free to make hydrogen-bonds. To the end, we have modified the quinoline in ß-naphthol, whose -OH function is capable to accept and to give H-bonds. A Vina docking towards 4wgj with SwissDock (identical parameterization as for the first molecule) returned a best scored docking pose well superposed to the binding mode predicted for the first molecule with all nominal specific interaction maintained. Moreover, the naphthol is superimposed with the quinoline showing the polar function involved in H-bonding network with the targeted backbone carbonyl and the phenolic side chain of the tyrosine as hypothesized. The scoring function of Vina considered these additional polar interactions as favorably stabilizing the reformed complex with c-Met with a decrease of ~0.5 [kcal/mol] compared to the first molecule.

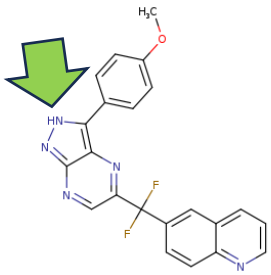


Design2

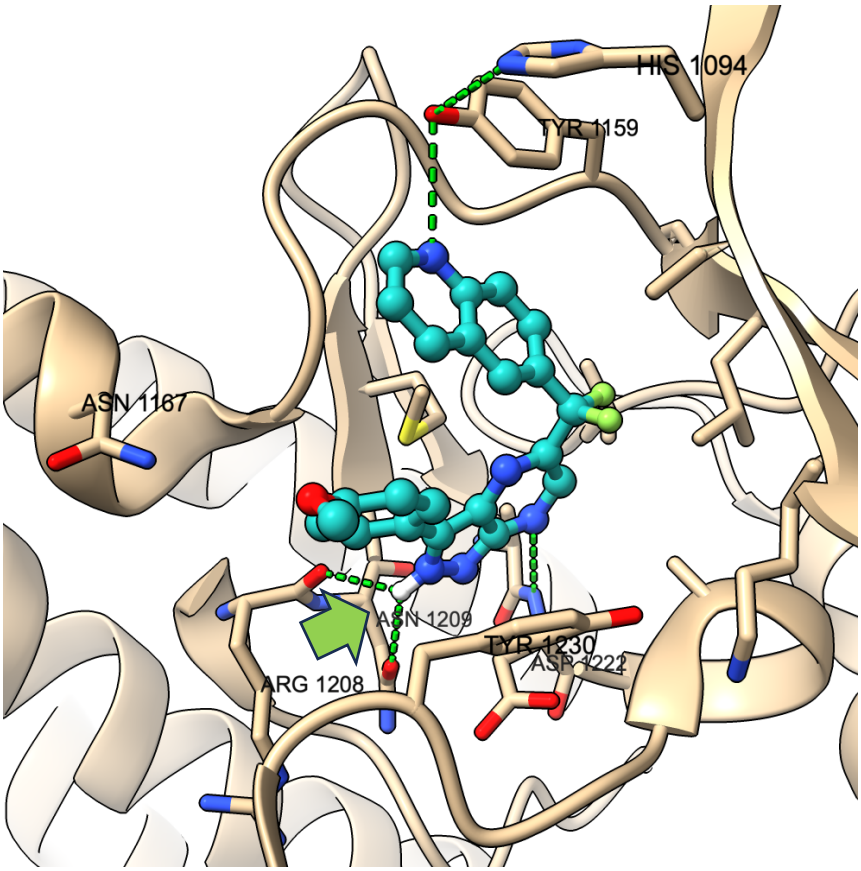


Another design strategy was to try to donate an hydrogen-bond to the side chain of Asn1209, which appears free and well oriented. For this, the central core was inverted and slightly modified to to include an H-bond donating heteronitrogen in the fused 5-membered ring.
The docking predicted a most favorable binding mode validating the hypothesis. The introduced H-bond donor atom interacts with the oxygen of Asn1209 and also maybe with the backbone carbonyl of Arg1208. Moreovre, the favorable H-bond with the

backbone nitrogen of Asp1222 is maintained. The position of the quinoline is slightly shifted so that it can accept an H-bond from the phenol of Tyr1159. However, the interaction between the methoxy group of the ligand and the Asn1167 is not found any more. Finally though, this binding mode is evaluated as very favorable by the Vina with this best posed scored -11.3 representing an descrease of 0.9 kcal/mol compared to the original molecule.



Design3



Other design strategies could be attempted. Getting a salt-bridge with one of the charged side-chains at the entrance of the cavity, or increasing π-π interaction with Tyr1159, or exchange the gem-difluoro with more hydrophobic moitey to be better accomodated in the hydrophobic zone of the cavity, and probably many more…

Don't forget that these designs shoud i) be evaluated for other properties (ADME, Tox, IP, …) and ii) must be experimentally assayed before going further with your drug discovery project!