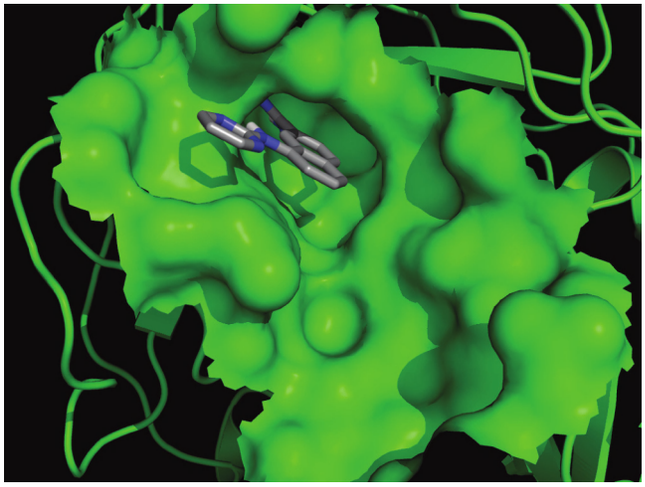


Figure 7.7. Docked pose for compound uk.1-7 fills extra subpocket near S1.

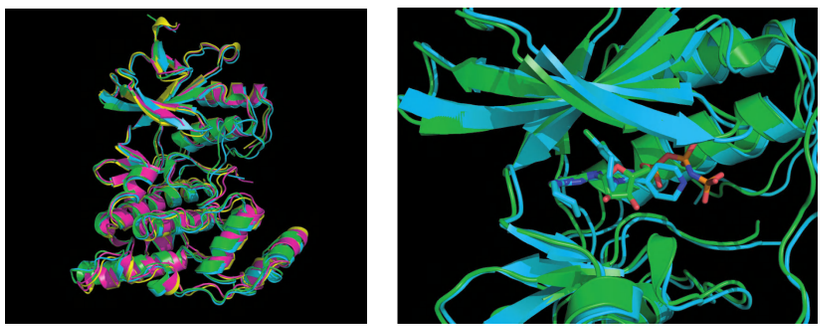
below the 95% confidence interval for all docked ligands, and the manual predictions are at or below the average automated prediction for all but three molecules. Of these three less-well-docked molecules, one was a small, fragmentlike compound with an acylguanidine arginine mimic; none of the larger acylguanidine-containing molecules were particularly well docked so there was no good starting point in the S1 pocket for this small fragment. For the second of the less-well-docked compounds, the predicted pose for the solvent-exposed portion of the molecule is tilted to the left of the binding site when compared to the crystallographically determined poses illustrated in Figure 7.3(b); in this case, a more careful comparison of this docked pose to others in the set of ligands would almost certainly have resulted in a better prediction. The third of the less-well-docked compounds contained a positively charged nitrogen; the lack of electrostatic screening in the Flo/qxp scoring function dominated the bound conformations, resulting in the arginine mimic being pulled slightly out of the S1 pocket. In this instance, I would likely have found a better docked pose if I had not protonated the basic nitrogen when docking using Flo/qxp.

Conversely, there were three molecules for which the manual prediction was better than one σ below the mean automated prediction. One of these three, shown in Figure 7.7, is a branched molecule that fills the extra pocket highlighted in Figure 7.3(b). The final two of the well-docked molecules (uk.1-2 and uk.1-19) are similar to the 1owd ligand, so the starting conformations generated by Rocs overlay are likely to be close to the correct answers. Strangely, however, the 1owd ligand itself was contained in the set to be docked, but the prediction for that molecule was worse than the predictions for uk.1-2 and uk.1-19. The 1owd ligand also contains a basic nitrogen; it is therefore my expectation that the lack of electrostatic screening in the Flo/qxp scoring function is again the culprit and has again resulted in the arginine mimic being pulled slightly out of the S1 pocket.

JNK3 protein kinase

JNK3 is a serine/threonine protein kinase that phosphorylates Ser63 and Ser73 in the transcriptional activation domain of c-Jun. I personally have not supported a JNK3 drug discovery effort, but I have directly carried out computational design for more than five kinase programs, and members of GSK Computational Chemistry US have supported more than twenty-five kinase programs. I therefore have a substantial amount of kinase drug discovery experience and have closely examined hundreds if not thousands of kinase-ligand crystal structures and docking models.

Two public JNK3 structures (PDB codes 1jnk and 1pmq) were provided as part of the virtual screening challenge and an additional two structures provided as part of the cross-docking challenge. A sequence- and structure-based alignment of the four structures is shown in Figure 7.8(a); the structures were aligned to emphasize the overlay of backbone atoms for the hinge residues, the catalytic lysine, and the DFG motif. As would be expected for most kinases, there was a substantial amount of variation in backbone conformation among the four structures. The activation loop in particular exhibited a wide conformational variance; for the virtual screening structures the activation loop packed against the glycine-rich loop and closed off the right side of the ATP binding site, while for the cross-docking structures there was missing density and therefore an undefined conformation of the activation loop. The glycine-rich loop itself exhibited a span of conformations; in the virtual screening structures these two beta strands were lifted away from the ATP binding site relative to the cross-docking structures. Structures 1jnk and 1pmq each contained a ligand bound in the ATP binding site [Figure 7.8(b), 2D structures shown in Figure 7.9]. Both the nonhydrolyzable ATP mimetic AMPPNP of 1jnk and the aminopyrimidine of 1pmq fill the binding site and make hydrogen bonds



a) b)

Figure 7.8. (a) Overlay of JNK3 crystal structures provided for virtual screening (in green and cyan) and cross-docking challenges (in magenta and yellow); **(b)** ligands from structures 1jnk (green carbons) and 1pmq (cyan carbons) in cognate crystal structures.